An assessment of the efficacy of compression bandaging on blood loss and acute pain following total knee arthroplasty;

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Abstract

This thesis has been undertaken to assess whether compression bandaging can deliver improvements in important short-term outcomes such as blood loss and pain following total knee arthroplasty within an enhanced recovery setting.

To achieve this, a thorough appraisal of the literature has been undertaken, with a robust systematic review and meta-analysis being performed. From these results and appraisal of the literature a relevant clinical trial has been performed.

To analyse any potential reductions in acute post-operative blood loss and pain, due to a hypothesised tamponade like effect, a randomised controlled trial (RCT) was performed using a complete compression bandage system (Coban 2, 3m) as the intervention. This was compared to the current 'standard' care of a single layer of wool and crepe bandage. Further assessment and analysis of both tourniquet use and any potential correlation between blood loss and pain is also presented. As an embedded sub-study within a larger trial (KReBS), which will assess long term outcomes of compression bandaging, the results from this study could provide an explanation for any findings observed later in the main study.

The results from the trial, following multiple linear regression analysis, were surprising, with a statistically significant increase in blood loss (107mls) observed with compression bandage use. There were no statistically significant differences in pain scores or breakthrough analgesia use, although early removal, due to reports of pain were observed.

This is currently the largest RCT performed and is the only one to include the effects of tourniquet use. Set within an enhanced recovery setting it provides evidence that compression bandaging should not be used following TKA.

This thesis presents a new hypothesis to explain the unexpected blood loss results, suggesting excessive pressure from the compression bandaging resulting in increased haemolysis. The role of free fatty acids released during surgery and increased oxidative stress is also explored to explain the increase in hidden blood loss observed with compression bandaging.

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Authors declaration

'I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised'.

1 Introduction

1.1 Aim

Total knee arthroplasty (TKA) is currently the gold standard of care for managing painful knee joints which exhibit wear, often due to arthritis.

However, the surgery is not without risks and adverse effects, including substantial blood loss and acute pain. These two factors can have detrimental effects on the patient journey and experience, as well as on institutional factors, such as cost and length of stay.

Enhanced recovery after surgery (ERAS) aims to minimise the effect of the operative intervention on individual patients and is now widespread, challenging long held beliefs and dogma.

Operative blood loss and acute pain remain a concern for both patients and surgeons alike and cost effective, low risk interventions are likely to encourage uptake and be acceptable to both patients and surgeons. This thesis will assess the effects of one such low risk intervention, a compression bandage system, which will be trialled within an ERAS setting following TKA.

The current literature will be analysed with a systematic review and meta-analysis and a trial will subsequently be performed with the key aim of assessing the effect of compression bandaging on post-operative blood loss and acute pain.

Secondary aims such as effect on length of stay, transfusion rates and complications will also be analysed.

1.2 Total knee arthroplasty

Major elective lower limb orthopaedic surgery consists predominantly of TKA and total hip arthroplasty (THA) operations, whereby damaged and painful joints are replaced with

prostheses. The main indication for this type of surgery is persistent pain and with it, a reduction in a patient's mobility. By replacing the affected joint a patient can undergo a significant reduction in the volume of pain experienced and can thus see an improvement in their mobility. This is concisely summed up by Thomsen et al. who state; "The primary goals of joint arthroplasty in the treatment of arthritic disease are pain relief and restoration of function and health-related quality of life" (1). As such TKAs and THAs have the ability to transform people's lives.

During a TKA, a diseased or damaged knee joint and articular cartilage is completely resected and replaced with a metal and polyethylene prosthesis. This is sometimes augmented with the use of bone cement. A patient's native bone and cartilage are removed during surgery and a tibial and femoral prosthetic component inserted in their place as a new load bearing surface, allowing movement and mobilisation.

Within the United Kingdom, between 1st January 2015 and 31st December 2017, 272,133 primary TKAs were performed, equating to approximately 90,000 operations per annum. 56.8% of these replacements were for female patients and the median age at operation was 69 years (Interquartile range 63 to 76 years) (2). The majority of these, 97.3%, were performed for osteoarthritis; a condition characterised by chronic pain and with it, a loss of function.

TKA is the most commonly performed inpatient surgical procedure in the United States of America and numbers are projected to continue rising. Projections from the United States of America vary from a conservative estimated rise of 143% by 2050 and a 601% rise by 2030 (3, 4). This picture is also set to be mirrored within the United Kingdom (5). This predicted increase in incidence is heavily linked to an ageing and increasing population, however, it is also due to the raised expectations of the population for an ongoing active life and a broadening of indications for performing TKA (6).

TKA is seen as a successful operation, with overall satisfaction rates quoted as being 81.8% 2007 (7). However, it carries a significant economic burden, with current estimates putting the annual cost in the United States of America at approximately $10.2 billion (£8.3 billion) (8). These figures are driven primarily by the cost of the implant, operating room time and length of hospital stay.

With such a large economic impact and an increasing population eligible for TKAs, ways to improve operative efficacy and efficiency and overall patient outcomes should be sought. Within the National Health Service (NHS) cost effective measures are especially pertinent. As such, justification for any changes to practice must be backed up by robust evidence and bring with it, clear clinical benefit.

To ensure arthroplasty patients have an optimum outcome, strategies have been developed to help standardise care and target specific aspects which are known to increase the risk of poor outcomes and complications. These aspects can occur in the pre-operative, peri-operative and post-operative settings. Now grouped together under the umbrella term 'enhanced recovery after surgery' (ERAS) or fast-track protocols, strategies include 'patient-centred, evidence-based, multidisciplinary team developed pathways for a surgical specialty and facility culture to reduce the patient's surgical stress response, optimise their physiologic function, and facilitate recovery' (9). These pathways have gained credence for their reported improvement in patient outcomes and subsequent cost effectiveness for healthcare providers. Within orthopaedic surgery, in lower limb arthroplasty particularly, there are many specific factors which need addressing to help optimise the overall outcomes for patients and to help reduce subsequent economic impact.

1.3 Enhanced recovery after surgery within orthopaedics

The model of ERAS was first pioneered in colorectal surgery and is now utilised across the wide variety of surgical specialities. By analysing the separate stages within the surgical journey that affect individual patients; robust clinical evidence can be applied to challenge existing dogma, improve outcomes and subsequent benefits in efficiency and costings can be achieved.

As a speciality, 'trauma and orthopaedics' has utilised the concept of ERAS and its use is now widespread. It has been applied predominantly with regards to major joint surgery such as TKA and THA. Continued improvements in surgical technique, anaesthesia and the

understanding of the body's response to trauma have all contributed to helping improve patient outcomes.

As surgical techniques and prosthetic implants have evolved, the long-term outcomes and longevity of lower limb arthroplasty has increased with 15-year implant survivorship now as high as 96.4% (10). Indeed, even in those below 55 years old, survival and satisfaction rates remain high (11). With these significant long-term improvements, emphasis is now being focused on short-term or acute outcomes, especially as early enhancements can also bring long-term improvements. One example of this is the move to commence post-operative rehabilitation in a more efficient and time effective manner, thus improving the patients overall experience whilst also decreasing the reliance on long hospital stays and expensive inpatient care. Other financial factors such as bundled payment programs, where a single payment to hospitals for a pre-defined episode of care, are also providing substantial incentives to create more efficient TKA protocols (12). Factors which negatively impact upon a patient's overall length of stay therefore need to be addressed. By doing this, not only will the economic burden lessen, but patient satisfaction will also increase.

Several variables have been highlighted as being predictive of a longer hospital stay. Some of these are modifiable, and others are fixed, with some being surgical factors and others being patient factors. The main patient factors are; age, co-morbidities and obesity, with type of anaesthesia, pre-operative anaemia, and blood transfusion being the key surgical factors (13, 14). Importantly, these surgical factors can be thought of as modifiable and as such their alteration can significantly affect length of stay.

Following TKA, the expected length of stay has fallen steadily from 16.0 days (95% CI 14.9 to 17.2) in 1997 to 5.4 (95% CI 5.2 to 5.6) in 2014 (15). For this, 'a key driver of the efficiency gains in joint replacement has likely been a move towards 'fast-track' arthroplasty', rather than changing patient demographics and overall health status (15). Within the United Kingdom, in many orthopaedic units, the average length of stay is now below three days(16).

Larsen et al. conducted a randomised controlled trial (RCT) assessing the efficacy of an ERAS protocol against the standard peri-operative care and rehabilitation protocol. The trial highlighted a significant reduction of three days in the length of stay following both TKA and

THA. A study by Stowers et al. supports that of Larsen et al. where decreased length of stay had no associated increase in readmissions or complications with the introduction of an ERAS pathway (17). In multiple other studies, these same reductions in length of stay with an ERAS pathway, are also seen following lower limb arthroplasty (18-20). Importantly, these studies not only highlight a significant reduction in length of stay but that ERAS pathways are safe to implement and do not appear to increase post-operative complication or re-admission rates.

Jones et al. also conducted a review of orthopaedic ERAS, with a focus on patient satisfaction (21). The review found that patients prefer a shorter length of stay, and as such, their satisfaction was higher following a quicker discharge from hospital. Having assessed 4,500 consecutive THAs and TKAs, Malviya et al. found a significant reduction in mortality, length of stay and allogenic blood transfusion rates when a multimodal enhanced recovery programme was initiated (22).

Enhanced recovery in an orthopaedic setting, has been shown to be beneficial for both patients and for a health care system as a whole when applied to THA and TKA. Further improvements can be made, resulting in better outcomes with fewer complications, and thus a greater patient experience and cost effectiveness. As stated by Henrik Kehlet, a colorectal surgeon who first outlined a multi-modal approach to recovery, ‘if such surgical sequelae are controlled, one may ask if patients could undergo major surgery on an ambulatory or semi-ambulatory basis’ (9). At present there is an increasing desire amongst orthopaedic units to reduce length of stay further with many aiming for day one or day zero post-operative discharges. This of course must not occur with any compromises on subsequent patient care, outcomes or safety.

With specific regard to orthopaedics, a consensus statement from the European ERAS society stated ‘work is still required in order to understand how to reduce the inflammatory response post-operatively; reduce pain; reduce impairment of physical activity and improve function quicker postoperatively; how to better identify patients at high risk of complications owing to psychiatric disorders, chronic renal failure, and orthostatic intolerance; anaemia and transfusion thresholds; post-operative urine retention and urinary bladder catheterization; and how to improve sleep’(23). Henrik Husted, an orthopaedic surgeon who is a key proponent of ERAS, has also highlighted specific research

areas including improvements in pain treatment, blood saving strategies, fluid plans, reduction of complications, avoidance of tourniquet and concomitant blood loss, improved early functional recovery and muscle strengthening to further improve outcomes (24). Within an ERAS setting, by focusing on these areas for improvement, length of stay and complication rates can be reduced further and with them, outcomes optimised further.

In an effort to help achieve shorter lengths of stay, barriers to efficient rehabilitation need to be overcome. Decreasing the need for allogenic blood transfusions and hence blood saving strategies are key to achieving this in conjunction with providing adequate post-operative pain relief.

As the incidence of TKAs continues to rise and with it, the subsequent economic burden, on-going, consistent improvements in care and efficiency need to be sought. Robust research should be undertaken to highlight improvements to aid post-operative rehabilitation by reducing blood loss and post-operative pain following TKA to aid overall outcome advances. These will not only help individual patients but also the entire healthcare system.

1.4 Early mobilisation following total knee arthroplasty

Early mobilisation after surgery is a key concept within ERAS regardless of surgical speciality. The importance of this is further emphasised within orthopaedics, particularly following joint replacement whereby outcomes are directly linked to mobility. By starting the rehabilitation process early, such as day zero, many significant benefits have been revealed.

Following TKA and THA, early mobilisation has been shown to significantly decrease the patient's length of stay. Tayrose et al. observed a significant reduction in length of stay when rehabilitation started in the recovery room following surgery compared to the day after surgery (25). Guerra et al. additionally performed a meta-analysis of five available randomised controlled trials and also highlighted a significant reduction in length of stay when patients were mobilized within 24 hours of surgery (26). These positive findings have also been found by a further meta-analysis performed by Masaracchio et al. (27). Importantly, they did not find an increase in the incidence of adverse reactions but

positively noted a subsequent lower overall cost, linked to the reduced length of stay.

By mobilising patients earlier, the negative impact of bed rest and venous stasis, which can include serious complications such as deep vein thrombosis and pulmonary embolism, can also be reduced. Pearse et al. saw a thirtyfold reduction in the risk of post-operative deep vein thrombosis when adjusted for other risk factors between the control group and early ambulators (28). Early mobilisation has also been shown to be an effective and cost- effective method of reducing thromboembolic events by Chandrasekaran et al. (29).

Multiple after-effects of surgery can be managed effectively by the multimodal approach intrinsic to ERAS pathways. To allow early mobilisation, after-effects, such as post-operative pain, need to be controlled (30). As pain is a complex pathway linked to many exacerbating factors, inhibitory reflexes and actions, there are many ways in which to limit its effect.

These include diverse physical and psychological factors, addressed with methods such as pre-operative education and risk stratification (31) . Pain following joint replacement not only affects the local operative area itself but has been shown to increase the body's stress response and therefore by alleviating pain, it may decrease the stress responses systemic effect and improve overall outcomes as stated by Kehlet et al. (32).

Other significant factors shown to inhibit early post-operative mobilisation include post-operative nausea and vomiting and allogenic blood transfusion requirement, linked to symptomatic anaemia (33). Post-operative nausea is strongly linked to opiate consumption and therefore post-operative pain (34). The ability to limit opiate consumption will hence improve post-operative nausea and vomiting, again allowing early mobilisation to occur. Key to reducing consumption is the management of pain and the use of multi-modal analgesia, including local anaesthetic and non-opiate containing spinal anaesthesia, a variable also linked to increased length of hospital stay (13).

Allogeneic blood transfusions, as a result of symptomatic anaemia not only inhibit early mobilisation, Monsef et al. also observed the need for post-operative transfusion and a patients age as the two strongest, independent predictors of an increased length of stay (35). Age is a fixed, patient factor whereas allogenic blood transfusion can be seen as a modifiable surgical factor. As the population ages, increased numbers of older patients will

be requiring TKAs. Modifiable factors such as reducing allogenic blood transfusion rate and by proxy, blood saving strategies coupled with ways to decrease post-operative pain are of paramount importance to improve outcomes further, increase early mobilisation and reduce hospital stay.

1.5 Operative blood loss and blood saving strategies

Blood loss management is one of the most modifiable factors that significantly impacts on patient outcomes including length of stay and overall satisfaction.

Through previous studies, anaemia has been shown to have significant detrimental effects for patients following surgery (36). This has been highlighted across the surgical specialities including orthopaedic surgery, especially following joint arthroplasty (37). As such, the ability to limit anaemia and hence any potential blood loss with blood saving strategies are key areas within orthopaedics and lower limb arthroplasty.

1.5.1 Anaemia

Oxygen is transported around our body's within blood via red blood cells. The oxygen molecules bind to the red blood cells via Haemoglobin (Hb), which in turn utilises iron as a key substrate for its formation. Hence, low levels of Hb result in decreased levels of Oxygen delivery to tissues and end organs.

A reduction in Hb levels, termed anaemia, is defined by the World Health Organisation as an Hb less than 13 g/dL in men and Hb less than 12 g/dL in women (38). Although multifactorial, with variations between countries and socio-economic classes, the main causative factor for anaemia worldwide is iron deficiency (39).

In broad systemic terms, anaemia can lead to symptoms of lethargy, fatigue, palpitations and insomnia (40). The depletion of available oxygen also has deleterious effects following surgery. Anaemia has been shown to increase the risk of complications, length of stay and

decrease patient outcomes (41). In their large, retrospective study, Wu et al. observed that anaemic patients undergoing major, non-cardiac surgery were at a significantly higher risk of thirty day complications and mortality than those with normal Hb levels (42).

1.5.2 Blood loss in total knee arthroplasty

TKA is an invasive procedure causing damage to the body's tissues in and around the knee joint. It involves the incising of skin and soft tissues as well as the resection of bone and joint surfaces from both the femur and tibia. This inevitably results in bleeding and blood loss.

Surgical blood loss is divided up into visible and hidden blood loss and when combined they give a total blood loss volume. Visible blood loss is from observed sources such as through surgical drains inserted peri-operatively and from the surgical wound itself at the time of surgery. This can be measured through suction devices, visual estimation, direct measurement, gravimetric and photometry methods such as the weighing of surgical swabs (43).

Hidden blood loss follows closure of the operative wound and is not accounted for by the volumes observed within surgical drains. This hidden loss occurs due to several proposed factors including; extravasation into the surrounding tissues, haemolysis of the red blood cells and by peroxidation damage of membrane molecules of red blood cells due to free fatty acids (44-46).

Sehat et al. calculated that the mean total blood loss following TKA, with the use of a tourniquet was 1474 ml (47). From this study they also concluded that 50% of the blood loss was visible and the remaining volume was attributed to hidden blood loss. Prasad et al. calculated the hidden loss seen in their study as 38% of the total blood loss of approximately one litre (48). Hu et al. similarly recorded a total blood loss of 1346ml (SD 671ml) following TKA with 465ml (SD 358ml) being recognised as hidden blood loss (49). As such, it can be assumed that patients undergoing TKA will lose between 1 to 1.5l of blood in total with between a third and a half occurring invisibly or due to hidden losses.

From these stated figures and utilising the recognised estimate of 70ml/kg for circulating

blood volume, patients will experience significant levels of blood loss following TKA (50). For some patients this will equate to one third of their circulating blood volume. As a result, patients are being subjected to the associated risks of anaemia and surgical blood loss.

1.5.3 Effects of blood loss

As TKA can result in a significant volume of blood loss due to incisions and damage to soft tissues and bone, the effects of this acute blood loss can be felt by those patients undergoing this major surgery.

Blood loss has many systemic effects and these effects increase as the volume of blood loss similarly increases. A systematic review by Van Remoortel et al. states that following a one unit, approximately 400ml to 500ml, donation of blood, the body's exercise tolerance and Hb levels drop in the first two days following donation (51). As such, we can expect similar effects following a comparable volume of blood loss after surgery.

Acute blood loss can also lead to the same symptoms and signs as chronic anaemia; namely fatigue, lack of energy and lethargy by decreasing the body's oxygen carrying capability. This in turn can have a deleterious effect on the rehabilitation potential of a patient and potentially increase their length of hospital stay and inhibit outcomes (35).

For fracture neck of femur patients and not in the elective arthroplasty setting, Foss et al. and Lawrence et al. independently found a correlation between post-operative anaemia and functional recovery following hip fracture repair (52, 53). Following multivariate analysis integrating the type of surgery, medical complications and pre-fracture function, Foss et al. highlighted that anaemia at the time of physiotherapy was an independent risk factor for not being able to ambulate. Within elective orthopaedic surgery, Conlon et al. also found a distinct correlation between low post-operative Hb levels and functional outcome following THA (37).

There is some debate as to whether overall quality of life is affected by post-operative anaemia with Conlon et al. showing a correlation between blood loss and worse quality of life scores, whereas both Wallis et al. and Vuille-Lessard et al. independently found no

correlation between a post-operative Hb drop and a patient's quality of life scores following arthroplasty (54, 55). Wallis et al. found that it takes approximately one month post-operatively for two/thirds of patients Hb levels to return to their 'normal' level and for the remaining one/third of patients the return occurred over two months post-operatively, often leading to iron deficiency anaemia.

Blood loss following surgery is also strongly linked to an increase in length of stay (56). Coupled with operative time, Andersen et al. also cite relative blood loss as a predictor of length of stay (57). Along with blood loss, an increase in length of stay is also associated with decreased overall mobility and outcomes, as well as increased economic cost (15).

In addition to these effects, perhaps the biggest outcome of significant blood loss following surgery is the increased risk of needing an allogenic blood transfusion and the important risks and costs associated with these.

1.5.4 Allogenic blood transfusions

With the potential significant volume of blood loss following TKA, there is a recognised need for allogenic blood transfusions. These blood transfusions come with several risks, both major and minor, and additional costs associated with them.

The indications as well as triggers or limits for a post-operative blood transfusion differ between institutions and as such the incidence also differs. There has, however, been an overall downwards trend in observed transfusion rates over recent years. Between 2007 and 2015, Bedard et al. showed a significant decrease in transfusion rates following TKA, down from 17.3% to 4.4% (58). This has potentially occurred due to pathways such as ERAS, with the multimodal interventions included, being introduced. Carling et al. have also reported an 11% transfusion rate from their prospective observational study for TKA; lower than the rate of 16% following THA (59). Baker et al. have also shown a lower rate of transfusion following TKA at 7%, than for THA in their retrospective study analysis (60). Similarly, from Boutsiadis et al. an overall post-operative transfusion rate of 13% was quoted (61). With these figures, although the rate is falling, the possibility of requiring a

transfusion post-operatively remains significantly high.

Allogenic blood transfusions come with risk for the patient receiving them and are also known to have an association with worse outcomes. Adverse effects are broad ranging and can result in increased mortality.

Many of these risks are generic and are associated with the risk of receiving the blood product themselves, regardless of the indication for transfusion. The adverse events and risks following blood transfusion are commonly split into early and late, relating to the timeframe that the adverse event is experienced. Early complications include haemolytic reactions, acute transfusion related lung injury, thrombophlebitis and allergic reactions. Late events include bacterial and viral infections due to contaminated blood products, graft vs host disease and immune sensitization (62). Acute transfusion related lung injury is the major cause of mortality and morbidity following blood transfusion and its incidence is between 1 in 5000 to 1 in 1100 transfusions given (63).

As well as the generic risks, there are also specific outcomes associated with receiving a blood transfusion following a lower limb arthroplasty. A cohort study by Naseer et al. found that primary TKA patients who were subsequently transfused had an independently higher risk for surgical complications and readmissions at both thirty and ninety days, and increased mortality within two years (64). Taneja et al. have also found that post-operative blood transfusions significantly increase the risk of both deep and superficial infections following TKA (65). It has also been stated that the use of allogenic blood transfusions following THA or TKA increases the risk of any post-operative infection, be it a lower respiratory tract or a peri-prosthetic infection associated with the arthroplasty itself (66). With regards arthroplasty, the study from Everhart et al. identified a dose-dependent association between allogeneic red blood cell transfusion and surgical site infections, with the infection rate increasing as the transfusion dose increased (67). Similarly, a meta-analysis which included data on 21,770 patients by Kim et al. reports that allogeneic blood transfusion is a significant risk factor for increasing the surgical site infection rate after both THA and TKA (68).

Furthermore, Monsef et al. have shown allogenic blood transfusions to be independently associated with longer lengths of stay and are therefore contributing to the overall increased costs of THAs and TKAs (35, 69). As such, the need to have robust blood

management strategies is apparent, not only to help improve outcomes but also as a cost saving strategy.

Coupled with the afore-mentioned risks for patients involved in blood transfusions and the association with increased length of stay, there is also an individual cost attached to them, both for the product and in its administration, without taking any potential complication or increased hospitalisation into account (70, 71). With the 7% to 16% transfusion rate highlighted post TKA, a reduction in transfusion rate would also enable a real cost saving, in addition to those seen with a reduction in length of stay.

This body of evidence promoting the significant impacts seen with allogenic blood transfusions stresses the need for optimising blood conservation strategies and limiting the volume of blood lost during surgery and thus the potential need for transfusion. This multi-modal approach to blood saving encompassed by ERAS, has led to a significant reduction in transfusion rates and their incidence following TKA is now relatively low (72). However, there is still a recognised need and risk associated with transfusions. Therefore, methods which can be used in addition to those currently in place within ERAS, which are able to achieve a reduction in operative blood loss, even if modest in size, are worth considering especially if inexpensive and low risk.

1.5.5 Blood saving strategies

As blood loss following TKA has significant risks and adverse effects associated with it; it is a concern for both patients and surgeons alike. Indeed, the PREPARE study shows the incidence of post-operative anaemia following orthopaedic surgery. Across seventeen centres in Europe, anaemia prevalence increased from 14.1% pre-operatively to 85.8% post-operatively and with it the transfusion risk and the associated post-operative complication rate (73).

As such, there are a multitude of strategies available to help limit blood loss and hence prevent the associated complications. Pragmatically, these interventions are split into pre, peri and post-operative domains.

Pre-operative strategies revolve around modifiable patient factors such as co-morbidity optimisation, anaemia recognition and correction including iron supplementation and erythropoietin (EPO) as well as management of anti-coagulants.

Peri-operative methods include hypotensive anaesthesia, the use of tranexamic acid or other pharmacological agents and blood salvage techniques.

Post-operative techniques involve robust transfusion guidelines and limits in addition to modalities to prevent ongoing bleeding such as cryotherapy and compression.

Combined, these methods aim to reduce the overall requirement for post-operative blood transfusions whilst limiting the volume and effect of operative blood loss.

1.5.5.1 Pre-operative techniques

As with other aspects of enhanced recovery, blood loss management starts with optimising the patient in readiness for surgery and the resulting insult to the body. The two key-ways highlighted to improve outcomes for patients following TKA with blood saving strategies are pre-operative anaemia screening and its subsequent correction and appropriate anti-coagulant management.

Anaemia surveillance, management and correction

A key modifiable patient risk factor linked to longer lengths of stay and risk of transfusion is pre-operative anaemia (72). This has been shown in several studies and has also been observed to significantly increase the risk of post-operative complications (74). As a result of this correlation, pre-operative anaemia screening and its optimisation is performed as part of the work-up towards joint replacement surgery within ERAS and has been shown to have a significant effect (72). These programmes have shown a substantial decrease not only in complications and allogenic blood transfusion rates but also an associated cost saving. Patients deemed to be anaemic pre-operatively aim to have their blood Hb levels improved

prior to surgery predominantly with the use of iron supplementation.

Pre-operative anaemia in the orthopaedic population is still prevalent with levels of approximately 20% cited by Saleh et al. prior to arthroplasty (75). This compares favourably with figures cited for non-cardiac surgery of between 31% and 26% by Baron et al. but remains a concern (76).

Multiple studies have highlighted pre-operative anaemia as a predictor of increased lengths of stay and rate of post-operative complications following arthroplasty surgery (74, 77-79). Jans et al. noted that pre-operative anaemia, found in almost 12% of their patients was independently associated with the post-operative transfusion rate and increased overall morbidity (77). Similarly, Viloa et al. in their large cohort study found a significantly higher risk of post-operative complications and mortality when pre-operative anaemia was present (74).

It is thought that pre-operative anaemia leads to these increased risks as it can be a marker of poor overall health and decreased functional reserve. Also, as the patients starting volume of Hb is at a much lower level, any subsequent blood loss from surgery will have a much more significant impact, enhancing any negative effects seen.

As a result of the continued prevalence within the arthroplasty population and its association with significant risks; strategies to detect and correct pre-operative anaemia have been developed and refined. Protocols exist that follow a coherent system and pattern although the exact details often differ between institutions and units.

In order to correct any potential pre-operative anaemia, blood results are taken from patients approximately one month prior to surgery as recommended by the European Society of Anaesthesiology (41, 80). This allows sufficient time for the correction of any blood levels deemed to be anaemic.

The protocol also aims to identify the cause of anaemia at this time, assessing for common pathologies being iron deficiency and dietary conditions affecting vitamin B_{12} absorption. Pathways differ in the exact mechanisms utilised for correction of this anaemia but there is a consensus that it should be done using medication such as oral or intravenous (IV) iron, EPO or other dietary supplements where necessary (81). This is instead of pre-operative blood transfusions as has been used previously, being seen as a more efficacious, safer and

cost-effective measure.

The use of oral Iron has been shown to be highly effective in managing the commonly diagnosed, iron deficient anaemia, prior to arthroplasty surgery and has been shown to reduce the rate of post-operative blood transfusions (82). Lately, the use of IV Iron transfusions has increased, as it is deemed to have fewer side effects and better tolerance and adherence from patients than its oral alternative (83).

Another important adjunct is synthetic EPO which controls the proliferation, differentiation, and maturation of red blood cells (84). It is predominantly used for those patients with anaemia of chronic disease or due to renal insufficiency and stimulates the production of further red blood cells from the bone marrow, thus helping increase Hb level (85). Although licensed for use pre-operatively within orthopaedics, its use remains limited, and it should also be used in conjunction along with iron supplementation (86). This is likely to do with overall cost and the prevalence of iron deficient anaemia.

Following correction of the anaemia, and potentially any further underlying pathology, patients can then undergo elective arthroplasty surgery. The successful implementation of a screening and correction pathway has been shown to have several benefits for patients undergoing arthroplasty surgery as well as cost savings. Following the enactment of a pre-operative anaemia screening programme, Pujol-Nicholas et al. showed an average cost saving of £162 per patient, as well as a significant reduction in post-operative transfusion rates, overall length of stay and readmissions (72).

Anti-coagulant management

Anti-coagulants are medications whose actions are to limit the effects of the body's clotting cascade. This reduces the body's efficacy in forming clots and hence can increase bleeding. They are usually prescribed to aid prevention of thrombotic events such as deep vein thrombosis, cerebrovascular events and myocardial infarctions from occurring in at risk individuals.

Commonly used agents include warfarin and low molecular weight heparins as well as more

novel medications termed DOACs or direct oral anti-coagulants (87).

A patients' clotting profile is analysed and the risks of any surgery and the risks of omitting the medication are assessed. This is often done in consultation with a haematologist and there are national guidelines to support these decisions (88). It is important to understand the risks involved and the medications chemical properties. To enable surgery to be safely performed, it is often necessary for anti-coagulant medication to be stopped several days prior to surgery.

Any medications that are withheld during the peri-operative period are usually recommenced once the risk of bleeding has diminished, usually within the first two days following surgery (89). Being aware of the pharmacokinetics and half-life of medication can allow a patients' clotting profile to normalise prior to surgery and as a result the risk of excess blood loss minimised.

1.5.5.2 Peri-operative techniques

Following optimisation of the patient prior to elective surgery the surgeon and anaesthetist must utilize techniques which help minimise blood loss during the operation.

Technological advances have aided in achieving this, as has evolving surgical technique. Included below are several ways in which surgical technique is continuing to develop, to reduce the amount of blood lost during surgery and limit the harmful impact it can have. These include controversial areas such as minimally invasive surgery and tourniquet use as well as more robustly supported methods including the medication tranexamic acid.

Diathermy and meticulous surgical technique

Electrosurgery or diathermy is utilised to coagulate cut blood vessels and incise tissues to achieve haemostasis during surgery. By using a high frequency, A/C electric current, the precise use of high temperatures is able to be utilised to coagulate tissues and blood

vessels alike. By coagulating blood vessels and tissues during surgery, peri-operative blood loss as well as on-going blood loss can be reduced (90). By recognising bleeding vessels and handling tissues with care throughout surgery this effect can be optimised.

Femoral canal block

When performing a TKA, the femoral intramedullary canal is breached by a metal rod. This rod enables correctly orientated cuts to be made to the bone by the operating surgeon. However, this trauma to the vascular medullary canal can result in blood loss. To occlude the canal, a simple measure of utilising bone offcuts' during surgery can be employed.

Li et al. noted a significant improvement in the calculated blood loss, hidden blood loss, transfusion requirements, drainage volume and Hb levels when comparing canal occlusion to no occlusion (91). Another randomised controlled trial by Ko et al. also showed similar beneficial results for reducing Hb loss and transfusion requirements with the use of a femoral canal block (92).

With these reductions in blood loss, from a quick and cheap intervention with a low complication profile, it is now commonplace for surgeons to utilise this technique in routine practice (93).

Fibrin sealant

Fibrin sealant is a surgical tissue adhesive and is used during surgery to help achieve haemostasis. It utilises fibrinogen and thrombin to 'seal' damaged vessels and tissues, mimicking the final steps of the physiological coagulation cascade to form a fibrin clot (94). It is currently used within many surgical specialities including orthopaedics.

Multiple randomised controlled trials have been performed to assess the efficacy of fibrin sealant use in TKA. Subsequently these randomised controlled trials have been combined in meta-analyses. Wang et al. noted a reduction in blood transfusions and drainage volume,

but not in overall blood loss (95). These findings were also expressed by Yang et al. in their systematic review and meta-analysis (96). Neither of these two studies observed an increase in thrombo-embolic or other significant complication rates with fibrin sealant usage.

The use of a fibrin sealant varies widely within TKA and it carries with it a high financial cost, indeed, Kluba et al. note that any reduction in transfusion rates or blood loss saving are negatively offset by the overall cost of the sealant (97). Although studies have shown some benefit with its use, other randomised controlled trials do not support its use over more cost-effective measures such as tranexamic acid as described by both Gao et al. and Aguillera et al. following their randomised controlled trials (98, 99).

Minimally invasive surgery

Minimally invasive surgery is a term used to describe a variation to the traditional surgical approach whereby incisions and soft tissue trauma are attempted to be minimised. To achieve this, specifically designed instruments are utilised but due to the reduced amount of surgical exposure achieved, it is not suitable for all patients (100).

With TKA, the incision length over the front of the knee is reduced, ideally to less than 14cm. This has been reported to help reduce blood loss, post-operative pain and cosmesis (101). Minimally invasive techniques also aim to reduce deep tissue trauma by limiting incisions to the surrounding muscles and tendons. Techniques termed quadricep sparing and minimal sub-vastus approaches have therefore been developed, whereby soft tissue trauma is restricted.

There is, however, some apprehension surrounding the adoption of minimally invasive surgery within TKA. Mal-positioning of the knee prosthesis has been reported by Yuan et al. and subsequently Kazarian et al. backed up this finding in their meta-analysis whilst additionally showing no improvement in knee function with a quadricep sparing approach compared to a conventional method (102, 103).

Tourniquet

The use of a tourniquet during TKA is another controversial subject. Prior to the skin being incised, a pneumatic tourniquet can be inflated around the patient's thigh. It is released at different timepoints according to a surgeons wishes, usually once the prostheses have been implanted or following application of dressings.

The advantages of its use include the maintenance of a blood less operating field which aids prosthesis implantation, especially with the use of cemented prostheses, as well as increasing operative efficiency and hence a reduction in operative time (104).

Opponents of their use, however, cite increased post-operative pain around the thigh, bruising, blisters and the potential for metabolic disturbances and neurovascular injury with extended use (105).

Crucially, there is also controversy surrounding the tourniquets efficacy in helping limit bleeding and therefore the amount of blood loss. Several meta-analyses have been conducted to try and answer this question. Zhang et al. concluded that no tourniquet use was preferential due to a lower complication rate without there being any significant difference in total blood loss with or without tourniquet use (106). Tai et al. similarly noted no difference in total blood loss and also, an increased risk of thrombo-embolic complications with tourniquet use (107).

Conversely, a meta-analysis from Alcelik et al. showed a reduction in both the observed and total blood loss without a significant increase in thromboembolic events when using a tourniquet compared to without (108). Ten trials were used in this review compared to thirteen by Zhang et al, with eight trials used in both reviews. The differences in opinion come from the methods employed to define blood loss, in addition to the different trials included. Alcelik et al. used intra-operative and post-operative measurements added together for total blood loss, whereas Zhang et al. used estimated blood loss calculations. Due to study heterogeneity, the meta-analysis from Zhang et al. was sub-divided further, therefore only using two and three studies, only one of which was included in the review by Alcelik et al. Following analysis of 1,040 TKAs by Smith et al. a higher intra-operative blood

loss was also seen without tourniquet use, but without an observed difference in blood transfusion or complication rates (109).

There is no clear consensus on whether a tourniquet reduces the overall volume of blood loss and concerns remain around post-operative complications. As such, whether or not to utilise them during surgery comes down to individual surgeons' preference.

Tranexamic acid

As a potent fibrinolysis inhibitor, tranexamic acid helps prevent the breakdown of clots and reduce bleeding (110). It does this by inhibiting plasminogen and thereby slows the conversion of plasminogen to plasmin (111).

There have been a multitude of RCTs and systematic reviews analysing its effectiveness with positive results regarding its efficacy in reducing blood loss and importantly, no significant increase in thromboembolic events following TKA (112, 113). Its use is now widespread throughout arthroplasty surgery and beyond.

Gandhi et al. showed through their meta-analysis a significant reduction in total blood loss and transfusion requirements with its use and no significant difference in thromboembolic events (114). Concurrent findings have been published by Alshryda et al. and Yang et al. in their meta-analyses of fourteen and fifteen suitable randomised controlled trials respectively (115, 116). From the available evidence it is quite evident that tranexamic acid use does reduce surgical blood loss.

Although the overall clinical benefits of tranexamic acid have been well documented its optimum use is not certain. It can be administered either orally, intravenously, topically or in combination. Wang et al. showed no significant difference in outcomes when comparing topical administration vs intravenous, although both forms of administration saw a reduction in blood loss (117). The same outcome was reached by both Sun et al. and Fu et al. following their respective meta-analyses (118, 119).

Further research into the optimal timing, dosage and subsequent route of administration, coupled with its use in patients with a high thrombo-embolic risk, needs to be addressed to

fully garner the full potential of tranexamic acid.

1.5.5.3 Post-operative techniques

Surgical blood loss occurs not only during surgery but also following wound closure. This can account for up to half of the total blood loss and is often termed ‘hidden blood loss’ (69). Indeed, both Prasad et al. and Hu et al. have observed hidden blood loss accounting for approximately a third of overall loss following TKA (48, 49). Hernandez-Vaquero et al. also saw similar losses with 573mls in total blood loss and a post-operative measurement through suction drainage of 364mls highlighting a significant proportion of blood loss occurring post-operatively (120). These volumes and measurements show that a significant proportion of blood loss occurs following wound closure and in the post-operative period. This can subsequently lead to an increased use of transfusions whilst also inhibiting post-operative rehabilitation and recovery due to increased swelling and oedema and the effects of anaemia. As such, multiple methods to control this have been initiated and are currently used by surgeons.

The initiation of peri-operative methods detailed previously, including meticulous haemostasis and tranexamic acid, also have the potential to reduce the volume of post-operative bleed loss.

Many post-operative interventions to decrease blood loss, such as cryotherapy and compression, have also been implemented to help reduce post-operative pain. Often, they are relatively simple measures, usually lower cost and carrying fewer potential complications than those seen during the pre-and peri-operative time periods.

Cryotherapy

The use of a cold compress has been utilised for centuries to help combat the effects of inflammation and swelling. Indeed, its use is advised to help aid functional recovery

following an injury to the musculoskeletal system (121).

The rationale for its use is varied and it remains popular following TKA. By utilising cold temperatures around the knee joint following surgery, local blood flow is reduced due to vasoconstriction of the blood vessels and this in turn helps limit the amount of swelling and localised inflammatory response experienced (122). Concurrently, the decreased temperature can suppress the level of tissue metabolism occurring and thus, is associated with a reduction in enzymatic activity, preventing further tissue damage caused by hypoxia (123). The cold temperatures have also been reported to slow down nerve conduction velocity and can thus help decrease pain (124).

Evidence to robustly support its on-going use is, however, limited. Su et al. found a reduced amount of opioid analgesia usage in the two weeks post-operative when using a cold compressive device but no significant difference in range of movement or knee girth measurements (125). However, Thienpont et al. did not find the same benefits in opioid consumption or pain relief with cryotherapy usage (122). A reduction in the quadriceps arthrogenic muscle inhibition (AMI), characterised by a lack of knee joint extension and impaired contraction of the quadriceps muscle post-operatively has also been observed. A reduction in swelling via cryotherapy use and thus an improvement in overall strength of the quadriceps has been found by both Ewells et al. and Rice et al. (126, 127). This improvement in strength could therefore aid patient rehabilitation post-operatively.

Importantly, a Cochrane review was performed in 2012 to analyse the potential benefits put forward by multiple studies. Adie et al. concluded that the quality of evidence from these studies was low or very low and that there was likely to be little or no clinical benefit with regards blood loss, pain or range of movement to justify its ongoing use (128).

Limb position

Perhaps the simplest and most cost-effective method to potentially limit post-operative blood loss is the limb position itself. The knee can be positioned throughout its arc of movement from a fully extended, straight position to one of full flexion where it is fully

bent. Venous blood flow velocity has been found to be faster in a flexed limb compared to a fully extended limb following TKA. This has translated clinically into a reduction in post-operative knee swelling and hidden blood loss (129). Yang et al. have similarly shown a significant reduction in calculating blood loss, hidden blood loss and post-operative knee circumference with a flexed knee position. Importantly, negative factors such as infections and deep vein thromboses were also reported to be comparable between the extended and flexed knee groups in the trial (130).

Multiple meta-analyses have also been performed on the subject, consistently highlighting a significant reduction in blood loss and a decreased need of allogenic blood transfusions with the limb being in a flexed position post-operatively (131-133).

To achieve this reduction in operative blood loss, the meta-analyses advises keeping the knee in a flexed position for greater than 24 hours, optimally, up to 72 post-operatively. This restriction, is against the ethos of ERAS, limiting the ability for early post-operative rehabilitation and a timely discharge. By mobilising patients early, even on the day of surgery, it has been shown that length of stay can be reduced and a higher proportion of patients are discharged home, rather than to a rehabilitation centre (13, 25). As such it can be argued that early mobilisation, whilst utilising other interventions that could help limit blood loss, would confer even greater benefit than a flexed knee for greater than 24 hours. The need for a prolonged period of flexion to achieve a reduction in blood loss is likely detrimental to overall patient outcomes, length of stay and finances within an ERAS setting where early rehabilitation is key.

Compression Bandaging

Another simple method, currently utilised by some surgeons, to help limit post-operative blood loss is the use of a compressive bandage or stocking. Concurrently, their use may also aid post-operative pain control.

By using an external stocking or bandage to increase the pressure around the knee, a tamponade like effect may help to limit blood loss and swelling. Compression stockings and

bandages have been used successfully for this effect following lower limb venous surgery (134). This compression effect can be achieved by in-elastic or elastic bandages or indeed by simple wool and crepe bandages wrapped in multiple layers, as has been used for many years (135).

The use of compression bandaging following TKA may have benefits in limiting blood loss. It could also confer advantages in post-operative pain, knee function and as a result, decrease length of stay.

There is currently no overall consensus on the efficacy and indeed safety on the use of compression bandaging following TKA.

Compression bandaging has been used extensively in the management of venous leg ulcers and lymphoedema. The technique aids the reduction in swelling by improving the efficacy of the calf muscle to act as a pump during ambulation, thereby aiding venous return (136). By this method, it has also been envisaged that post-operative swelling can be decreased. However, in practice this reduction in limb size has not been observed (137).

Charalambides et al. observed a reduction in length of stay, an improvement in overall flexion and a quicker recovery on patients managed with compression bandages (138). Similarly, Cheung et al. highlighted improved post-operative function and mobility with their use(139).

The effect of compression bandaging on blood loss and pain is also unclear with conflicting reports. Andersen et al. have reported a significant improvement in post-operative pain scores when using compression bandaging in conjunction with local anaesthetic (140). However, both Pinsornsak et al. and Pornrattanamaneewong et al. conversely found comparable results between compression and non-compression bandaging in their respective RCTs (141, 142). Yu et al. have also concluded that compression bandaging does not confer a beneficial blood loss saving over conventional bandaging (137).

There is also a degree of concern regarding the use of compression following TKA and as such care needs to be taken to ensure benefits out-weigh any potential complications. Cutaneous complaints, such as bruising and blisters, as well as more serious nerve palsies have been muted (141).

Yamaguchi et al. have analysed the effects of externally applied compression with elastic bandages on the peripheral circulation of the distal portion of the lower limb (143). They found with increasing amounts of compression, to 50mmHg and upwards to 70mmHg, significant differences in limb temperatures and peak pulsatile flow were observed. This is in keeping with earlier work conducted by Landis et al. and later by Ogata et al. who stated that excessive external pressure can lead to tissue ischemia by obliterating the blood flow to subcutaneous tissue (144, 145). Compression bandaging has however been consistently used with a good safety record within tissue viability (146).

There is no clear evidence to support or refute the use of compression bandaging following TKA and as such the utilisation of this modality is varied within orthopaedics. To help maximise cost benefits for institutions and health care providers low morbid, cost effective interventions should be sought and evidence used to highlight their effectiveness.

Compression bandaging has been shown to be a low morbid, low cost intervention that could help limit post-operative blood loss further in conjunction with other methods as part of a blood saving strategy (147).

Studies are limited and there is no available literature on long term outcomes. An in-depth evaluation of the current evidence and further targeted and robust research could further delineate if they should be incorporated as part of post-operative care following TKA within an ERAS setting.

2 Current knowledge of the effects of compression bandaging following total knee arthroplasty

The use of compression bandaging and compressive forces around a joint post-operatively is not a modern thought. Bandages, applied for compression following surgery or injury in the form of Robert Jones bandages (RJBs), have been detailed in the literature for decades with Sir John Charnley describing and attributing it to Sir Robert Jones in the 1950s (135).

As such, there have been several studies and trials performed, assessing the efficacy and safety of compression bandaging following TKA.

It is therefore necessary to evaluate the available literature on the subject of compression bandaging post TKA, prior to commencing any further research in this area to ensure a suitable, robust and worthwhile study is designed and conducted. Shortcomings with studies and gaps within the known literature will help guide appropriate research and hypotheses. As such, a systematic review and meta-analysis has been conducted to help elicit this.

2.1 Systematic review and meta-analysis

2.1.1 Background

Compression bandaging and compressive force has been used within a variety of clinical settings for many years. It is a well-recognised, safe and effective method of managing venous leg ulcers, lymphoedema and following varicose vein surgery (146).

The use of compression has also been employed within orthopaedic surgery to help prevent swelling following trauma and after surgical interventions.

The use and optimal mode of compression bandaging varies and the potential benefits that come from their continued use are not fully understood.

To perform a TKA, whether through standard surgical approaches or through minimally invasive approaches, trauma to tissue occurs. From the skin, through the adipose layer into the muscles and tendons, to the femoral and tibial bones; all of these tissues and structures receive traumatic insults. From this trauma, bleeding occurs.

In conjunction to the systemic effects seen with blood loss such as anaemia which can lead to higher transfusion rates and subsequently, prolong inpatient hospital stays, localised bleeding into a joint and the surrounding tissues can also result in swelling. This swelling around the knee joint can have its own significant effects.

McNair et al. have shown that an effusion or fluid within the knee joint negatively impacts the quadriceps muscle and hence inhibits the ability to mobilise (148). This was also observed by Fahrer et al. who noted an improvement in quadriceps strength following joint aspiration (149). Further work, by Rice et al. expanded this topic and the term arthrogenic muscle inhibition (AMI) is now often used. AMI is caused by a change in the discharge of articular sensory receptors due to local factors such as swelling, inflammation, joint laxity, and damage to joint afferents (150). These factors all occur to a greater or lesser degree following TKA and can thus result in quadriceps weakness.

The effects of limiting ongoing blood loss and post-operative swelling could be widespread. Around the joint, decreased swelling could result in less AMI of the quadriceps, in turn improving the rehabilitation potential. Less swelling could also reduce post-operative pain and analgesia requirements (151). With improved pain control and more effective rehabilitation overall hospital lengths of stay could also decrease. As stated by Monsef et al. transfusion of allogeneic blood is independently associated with increased hospital stay after total hip arthroplasty, and as such, blood management strategies are a viable way of improving hospital lengths of stay (35). This brings with it, potential cost savings and could additionally lead to improved overall patient satisfaction.

Henrik Husted, a key proponent of fast track hip and knee arthroplasty surgery, has highlighted several key areas for ongoing development and research within lower limb arthroplasty. These areas for improvement include pain management, blood saving strategies, fluid plans, reduction of complications, avoidance of tourniquet and concomitant blood loss, improved early functional recovery and muscle strengthening

(24).

Compression bandaging has the potential to tackle many of these highlighted key areas following TKA by utilising a relatively low cost and low morbid intervention.

2.1.2 Method for undertaking review

Prior to embarking on this systematic review, a thorough search of published and on-going systematic reviews was performed to ensure new and relevant information was being analysed without undue duplication. Searches were conducted of the Cochrane Database of Systematic Reviews, Pubmed and PROSPERO for published, registered or on-going systematic reviews assessing compression bandaging following TKAs on 3rd November 2018. No such reviews were identified under the terms 'Compression bandage' or 'compression' within TKA.

A protocol for this systematic review was published on PROSPERO, International prospective register of systematic reviews 17th December 2018. The preliminary searches had been completed at registration.

2.1.2.1 Criteria for considering studies for this review

2.1.2.1.1 Types of study

Studies were eligible if they were available as full text, published RCTs (those that used pseudo-randomised methods of treatment allocation such as participant date of birth or order of recruitment would be excluded). Parallel, cross-over and factorial trials were eligible.

No restrictions were placed on date or language of publication. Non-English texts would be translated fully utilising Google translate.

2.1.2.1.2 Types of participant

Patients undergoing primary TKA in the elective setting. Revision and unicondylar arthroplasties were excluded as were primary TKAs for acute trauma.

Patients undergoing bilateral simultaneous TKAs were also excluded.

The type of prosthesis, use of cement and the surgical approach used were irrelevant as was any surgical intervention performed on the patella such as re-surfacing.

Osteoarthritis and Rheumatoid arthritis were both eligible indications for undergoing TKA.

2.1.2.1.3 Types of interventions and comparators

Intervention

A compression bandage was defined as either a specifically designed and manufactured bandage or stocking used intentionally for achieving compression (e.g. Coban, Actico or other elastic or inelastic type bandages) or as a standard wool and crepe bandage applied in a specified way to achieve planned compression.

An example of a standard bandage being used to apply definitive compression is the RJB which utilises several layers of wool and crepe (135). The specific compression bandage could also be described as having inelastic or elastic (short or long stretch) properties.

The intervention would be applied following TKA on the day of surgery.

If the primary purpose of the compression bandage or stocking was defined as deep vein thrombosis prophylaxis rather than post-operative pain relief, blood loss or swelling control, the studies were not subsequently used.

Comparator

A valid comparator was defined as a non-compression bandage or the use of no post-operative bandage at all. A non-compression bandage consists of single layers of wool and crepe bandage and is not described as being applied specifically for compression or in the form of an RJB.

2.1.2.1.4 Types of outcome measure

Main outcomes

i. Blood loss: defined as the volume measured from a surgical drain, the drop in Haemoglobin (Hb) or Haematocrit (HCT) from pre-operative to post-operative values, or by other validated methods that estimate blood loss volumes.
ii. Transfusion rate: measured as the proportion of patients requiring a blood transfusion during the acute post-operative stay in hospital or the volume or units of blood transfused.
iii. Post-operative pain: measured post-operatively using a subjective pain scale such as the visual analogue scale or analgesia usage.
iv. Knee swelling: circumference as measured at a set point around the knee.
v. Knee range of motion: measured as the number of degrees of flexion and extension of the knee.
vi. Knee function: measured using an available validated knee score.

Other outcomes

i. Cost benefit analysis: potential quality adjusted life years (QALYs) gained or cost effectiveness calculations
ii. Length of hospital stay: days spent in acute hospital following surgery
iii. Activity level: measured using a validated system such as pedometer, walking speed test or patient self-reported diary/questionnaire.

iv. Adverse effects, including i) withdrawals due to adverse events, and ii) the total number of adverse events.

2.1.2.2 Search methods for identification of studies

2.1.2.2.1 Electronic searches

The following electronic databases were searched on 12th December 2018.

Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE via OVID; EMBASE via OVID and the Physiotherapy evidence database (PEDro). The full text of the electronic search strategies are available in the appendix (A 1.1).

2.1.2.2.2 Searching other resources

Electronic databases for protocols and ongoing RCTs including, International Standard Randomised Controlled Trial Number (ISCRTN) registry and the clinical trials register maintained by the US National Institute of Health- ClinicalTrials.gov were also searched for potentially eligible studies not on the aforementioned databases.

The reference lists of all included eligible articles were subsequently checked for other potentially eligible studies.

2.1.2.3 Data collection and analysis

2.1.2.3.1 Selection of studies

Two independent reviewers JK and RM assessed the title, abstract and key words from studies following the conclusion of searches. Any disagreements for study inclusion were discussed and any that were unresolved were further discussed with a third reviewer MR for arbitration. Full texts of studies deemed to be potentially eligible were then assessed and reasons for subsequent exclusion documented.

2.1.2.3.2 Data extraction and management

Two independent reviewers (JK and RM) extracted data from all included and eligible studies utilising a standardised proforma based on the 'Cochrane Collaboration data Collection Form'. The data collected included:

- General study characteristics: size, location, inclusion and exclusion criteria and design type.
- Participant details: gender, age, operative indication.
- Intervention characteristics: type, duration, when applied and any other adjuncts used.
- Control characteristics: type, duration, when applied and any other adjuncts used.
- Outcome data: number of events and percentage for dichotomous outcomes and means and standard deviations for continuous outcomes.

Any discrepancies between the two authors were first discussed and then arbitrated by a third author (MR) if no resolution was forthcoming.

2.1.2.4 Assessment of risk of bias in included studies

Utilising the Cochrane Collaboration's tool for assessing risk of bias; the risk of bias was

assessed by two independent authors (JK and RM). A third author (MR) arbitrated, as necessary.

Domains assessed included: selection bias with random sequence generation; allocation concealment; performance bias with blinding of participants and personnel; detection bias with blinding of outcome assessment; attrition bias with incomplete outcome data; reporting bias with selective reporting; and any other sources of bias.

Each domain was graded either low risk of bias if the criterion was met, high risk of bias if the criterion was not met, or unclear risk of bias if there was insufficient information to determine if the criterion was met.

2.1.2.4.1 Baseline heterogeneity

As true randomisation produces treatment groups that differ only by chance; a meta-analysis of a baseline measurement should produce no overall difference and hence zero heterogeneity (152).

Baseline heterogeneity of included studies was assessed. A meta-analysis with age as a baseline variable was performed and trials systematically removed, starting with those with the largest t-statistic, until the I^2 measure of heterogeneity became 0%. As a sensitivity check, the outcome meta-analysis was repeated, excluding the trials causing the heterogeneity.

2.1.2.5 Measures of treatment effect

Continuous outcomes

The mean and standard deviation (SD) of the intervention and control group were extracted for continuous outcomes. Where studies used identical units of measurement to measure

an outcome, the pooled mean difference (MD) was calculated directly.

When units of measurement differed, where appropriate, these were converted to one common measurement to aid analysis. An example of this is with post-operative analgesia use where dosage of morphine is utilised for the meta-analysis as mg/kg/48hour. Where a total mean dosage of morphine was given in the original study this was subsequently divided by the mean participant weight and thus converted to mg/kg. This was performed for Andersen et al. and Pornrattanamaneewong et al. Where values were given as the median with interquartile ranges, by utilising calculations from Hozo et al. these were converted to the mean and standard deviation (SD) (153). These values were then incorporated into the pooled mean difference.

Where values were given in graphical form, the results were extrapolated as accurately as possible. This was following unsuccessful attempts to contact authors for numeric results.

Dichotomous outcomes

For dichotomous outcomes, the number of events in the intervention and control groups were extracted, and the relative risks (RR) were calculated with 95% confidence intervals (CI).

2.1.2.6 Dealing with missing data

Where studies reported outcomes with incomplete follow up, the data was extracted using the total number of patients initially assigned to that group.

Where standard deviations were not reported for continuous outcomes, they were calculated by means of an available standard error, p-value, or 95% CI. If this was applied, the most conservative measure was used (for example, for a p-value reported as <0.05, 0.05 was used). If measures of uncertainty were not supplied in trial reports, and contacting trial authors was not successful, we imputed the missing standard deviations using available data

(154). This was only performed if the majority of studies reported a measure of uncertainty; then the average of the standard deviations in that group was used. This was utilised for analysis of Gibbons et al. including blood loss, analgesic use, pain scores and length of hospital stay (figures 4, 7, 9, 10, 14, 16, 17, 18).

For standard deviations, estimates were applied using known values and input accordingly (154).

2.1.2.7 Assessment of heterogeneity

Heterogeneity was assessed using the chi-squared and I^2 tests. We used the following guide for interpretation of I^2:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity present.

2.1.2.8 Data synthesis

Where appropriate, we pooled results of comparable studies. As there was deemed significant clinical heterogeneity present in the studies the random effect model was our default. A fixed effect model was utilised only when the specific outcomes measured, the intervention utilised and the control were all deemed of sufficient homogeneity such as with analysing blood loss on day one post-operative utilising studies by Pinsorsak et al. Pornrattanamaneewong et al. and Yu et al. (figure 5).

Meta-analysis was performed using Metalight (V1.2.0) (155).

2.1.3 Results

2.1.3.1 Description of studies

Following the electronic database searches 12th December 2018, and the removal of duplicates, 463 records were identified. Screening of the titles and abstracts highlighted 12 potentially eligible papers (figure 1).

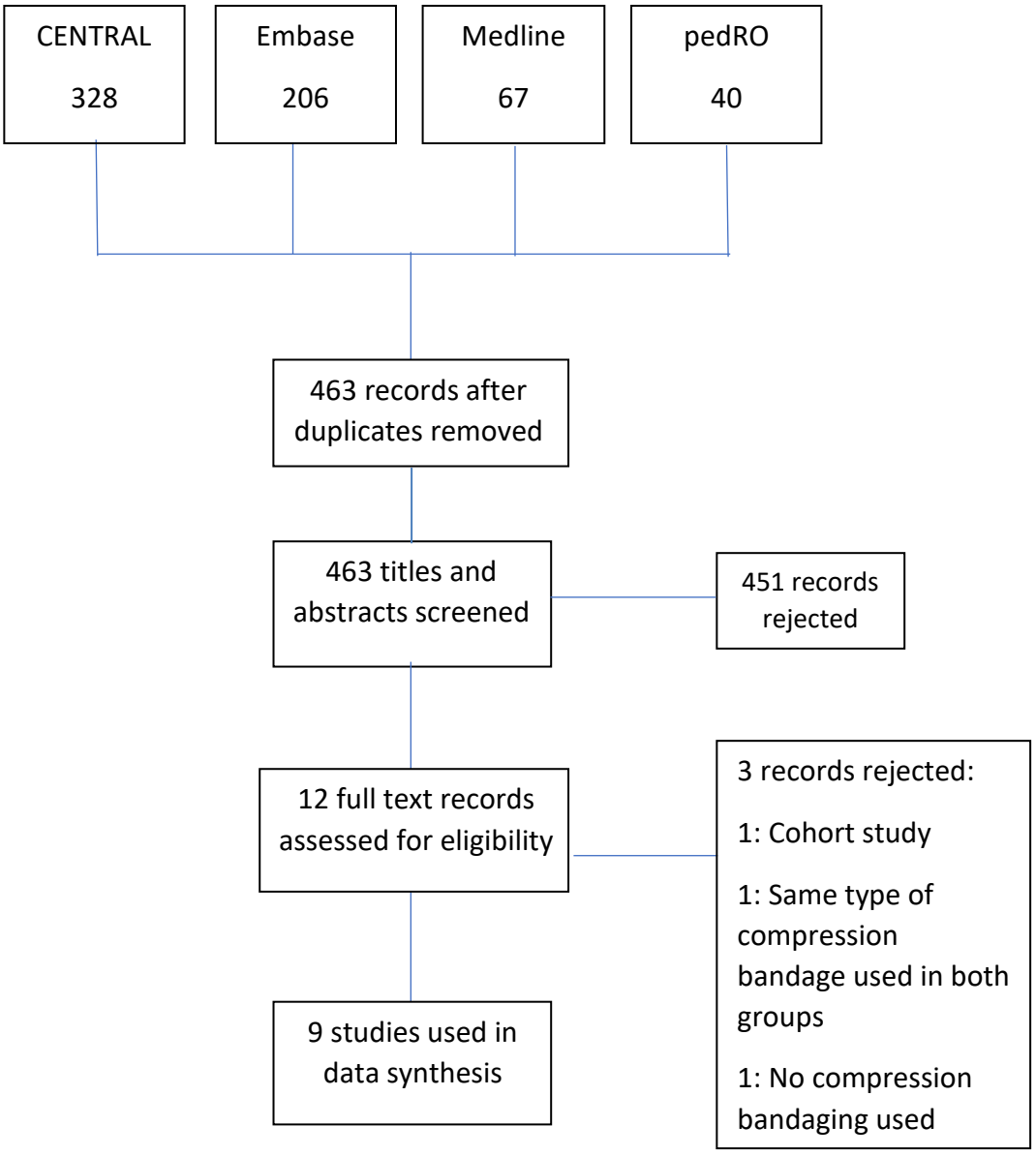

Figure 1: Systematic review flow diagram

From these, nine full text papers were deemed eligible for inclusion in the systematic review (Andersen et al. Brock et al. Gibbons et al. Munk et al. Pinsornsak et al. Pornrattanamaneewong et al. Smith et al. Stocker et al. Yu et al.) (137, 141, 142, 147, 156-160).

Following assessment of the full text, three potentially eligible papers were excluded for separate reasons: Charalambides et al. was rejected as it was a non-randomised cohort study (138). Kayamori et al. used the same type of compression bandaging, in both trial groups, assessing the addition of a 'compressive pad' and Webb et al. did not use compression bandaging in either group (161, 162).

From the trial registries, ISCRTN and ClinicalTrials.gov, one current on-going study was identified. At the time of writing, KReBS has completed recruitment and is currently completing follow up and hence is unable to be included in this systematic review.

Eligible papers displayed a clinically relevant age range, consistent with the known patient population undergoing TKAs. The studies average age for participants ranged from 64 to 72 years old. The median age for those undergoing primary TKA in the United Kingdom is 69 years as reported by the England, Wales, Northern Ireland and Ilse of Man National Joint Registry (16).

All studies looked at the efficacy of compression following TKA with each utilising a type of compression bandage. One study converted from a compression bandage to an elastic compression stocking the morning after surgery (Munk et al.).

There was a degree of heterogeneity in the types of bandaging used to achieve compression and the subsequent timeframe used for their application (table 1). A combination of a woollen inner layer and a purpose made compressive outer bandage was used by the majority of studies, seven of the nine, although the actual manufacturer of the bandage varied (Andersen et al. Brock et al. Munk et al. Pinsornsak et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.). The earlier studies (Gibbons et al. Smith et al.) used the more traditionally described method of a compression bandaging, with a modified RJB, using multiple layers of wool and crepe bandage. The exact constituency of the bandage differed between the two studies with different layering employed.

The class of bandage used to achieve compression and duration left in-situ varied between studies. Two studies used standard wool and crepe bandages (Gibbons et al. Smith et al.)

Elastic bandages from different manufacturers were applied by four studies (Andersen et al. Pinsornsak et al. Pornrattanamaneewong et al. Stocker et al.). Inelastic bandages were used by three studies (Munk et al. Brock et al. Yu et al.).

Study	Year	Inner layer	Outer layer	Type	Time in-situ
Gibbons	2001	3 layers wool	3 layers crepe	Standard	48 hours
Smith	2002	Thick wool	Crepe	Standard	24 hours
Andersen	2008	2 layers wool	Acrylastic (BSN)	Elastic	24 hours
Munk	2013	Coban 2 (3M)	Coban 2 (3M)	Inelastic	12-24 hours
Pinsornsak	2013	Thick wool	Elastic bandage	Elastic	24 hours
Brock	2017	Wool	Actico (Activa)	Inelastic	24 hours
Pornrattanamaneewong	2018	3 layers wool	2 layers elastic bandage	Elastic	24 hours
Stocker	2018	Wool	Comprilan (BSN)	Elastic	22hours/day for 5 days
Yu	2018	Thick wool	Coban 2 (3M)	Inelastic	24 hours

Table 1: Types of compression bandaging as used in included studies

There was a general consensus on the length of time the compression bandage was kept in-situ for, with 24 hours post-operative, the most commonly used (Andersen et al. Brock et al. Pinsornsak et al. Pornrattanamaneewong et al. Smith et al. Yu et al.). One study (Gibbons et al.) kept the bandage in situ for 48 hours and in another study (Munk et al.), the compression bandage was converted, on the day following surgery, to an elastic compression stocking which was subsequently kept in-situ for a further four weeks. The final study used a compression bandage for 22 hours a day with re-application daily for five days post-operatively (Stocker et al.).

There was also heterogeneity with the type of control utilised. A standard wool and crepe bandage (Andersen et al. Brock et al.), a sterile adhesive wound dressing only (Pinsornsak et al. Pornrattanamaneewong et al. Yu et al.) a sterile adhesive dressing following removal of compression bandage the morning after surgery (Munk el at.) and cold therapy with cryocuff/pad or ice packs (Gibbons et al. Smith et al. Stocker et al.).

Four of the studies utilised post-operative wound drains (Gibbons et al. Pinsornsak et al. Pornrattanamaneewong et al. Smith et al.) and the remaining five, did not (Andersen et al. Brock et al. Munk et al. Stocker et al. Yu et al.). By using drains, these studies were able to

directly measure blood loss volumes in the post-operative period. Tourniquets were used by all studies expect one (Yu et al.)

Studies were performed in a variety of different countries and healthcare systems. Six of the studies (Andersen et al. Munk et al. Brock et al. Pornrattanamaneewong et al. Stocker et al Yu et al.) included an ERAS type set-up and subsequently also utilised local anaesthetic (table 2).

A summary of the eligible studies and individual study characteristics are included in the appendix (A 3).

Study	Year	Country	ERAS	Local anaesthetic	Drains	Tourniquet
Gibbons	2001	UK	No	No	Yes	Yes
Smith	2002	Australia	No	No	Yes	Yes
Andersen	2008	Denmark	Yes	Yes	No	Yes
Munk	2013	Denmark	Yes	Yes	No	Yes
Pinsornsak	2013	Thailand	No	No	Yes	Yes
Brock	2017	UK	Yes	Yes	No	Yes
Pornrattanamaneewong	2018	Thailand	Yes	Yes	Yes	Yes
Stocker	2018	Switzerland	Yes	Yes	No	Yes
Yu	2018	China	Yes	Yes	No	No

Table 2: Clinical setting for included studies

2.1.3.2 Risk of bias in included studies

Following assessment with the 'Cochrane Collaboration's tool for assessing bias', there was a varying degree of risk of bias within the nine included studies (table 3).

For random sequence generation six studies utilised 'computer randomisation' (Andersen et al. Munk et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Yu et al.) and deemed low risk. A simple coin toss was used by one study (Smith et al.) which is considered at high risk of bias and not a suitable randomisation process (163). The remaining two studies (Gibbons et al. Stocker et al) did not highlight the methods used to achieve randomisation and are assigned as 'unclear risk of bias'.

Allocation concealment was achieved through the use of opaque, sealed envelopes for five studies (Andersen et al. Pinsornsak et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.). This method is subject to potential subversion and is therefore at high risk of bias (164, 165). Three studies (Gibbons et al. Smith et al. Munk et al.) did not state the methods of allocation concealment. One study (Brock et al.) utilised a centralised computer randomisation system to achieve adequate concealment.

Because of the type of interventions utilised, blinding of surgeons and participants was not possible. Data collection was, however, stated as being blinded in two studies (Stocker et al. Yu et al.).

All studies accounted for all included participants including drop- outs thus addressing any potential incomplete data. Flow diagrams detailing this were included for two studies (Brock et al. Pornrattanamaneewong et al.).

Seven studies had no conflicts of interest or funding bias stated (Andersen et al. Munk et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.). There were no statements included in the published papers for the remaining two studies detailing any potential conflicts of interest (Gibbons et al. Smith et al.).

Selective reporting was a potential concern for one study. Length of stay was measured and reported upon but not included in the original methods or design section, there is no published trial protocol for this study either (Gibbons et al.).

Study	Year	Random sequence generation (Selection bias)	Allocation concealment (Selection Bias)	Blinding (Performance bias and detection bias)	Incomplete outcome data (Attrition data)	Selection reporting (Reporting bias)	Free of conflict of interest (other bias)
Gibbons	2001						
Smith	2002						
Andersen	2008						
Munk	2013						
Pinsornsak	2013						
Brock	2017						
Pornrattanamaneewong	2018						
Stocker	2018						
Yu	2018						

Low risk of bias		Unclear risk of bias		High risk of bias	

Table 3: Risk of bias for included studies

Judgments of the risk of bias for each study is included in the appendix (A 1.2).

2.1.3.3 Baseline heterogeneity analysis

As an important predictor of outcomes, and a variable that can be used to overtly or covertly subvert allocations, Hicks et al. propose that age should always be used for assessing baseline heterogeneity when available (152).

Age was included in all eligible studies and as such a meta-analysis using a fixed effect model was performed to highlight any baseline heterogeneity. If this was highlighted; studies were systematically removed, starting with those with the largest t-statistic, until the I^2 measure of heterogeneity became 0%.

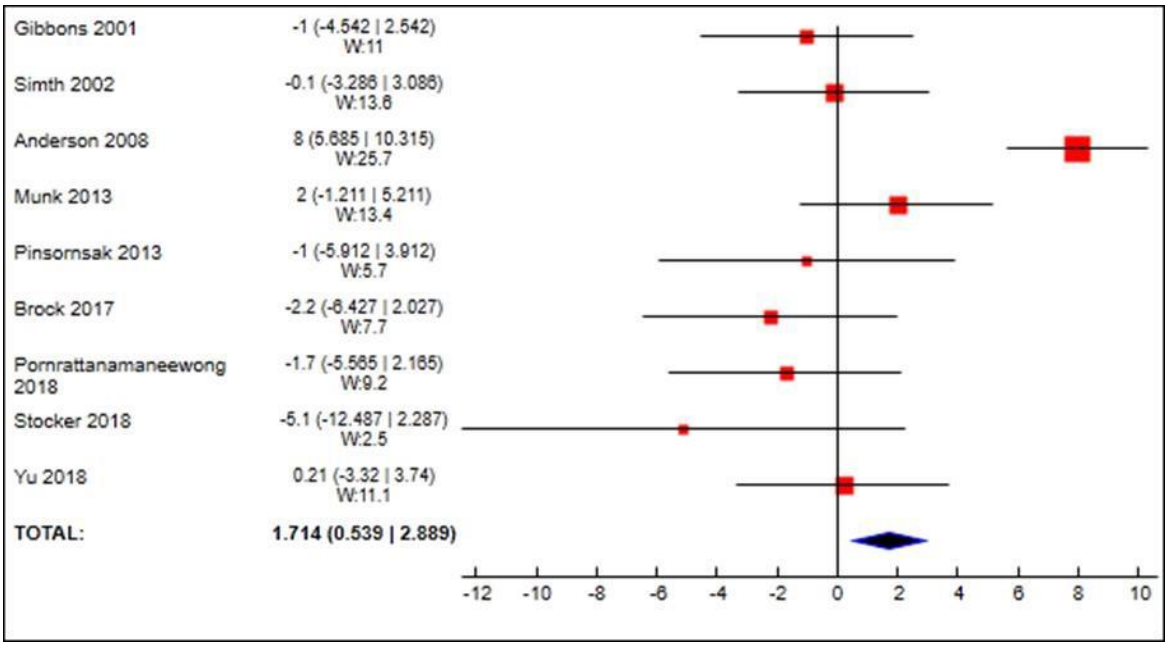

Figure 2: Baseline heterogeneity analysis- fixed effect model with all studies included.

The fixed effect meta-analysis with all studies included had an I^2= 81.5% highlighting significant heterogeneity in baseline characteristics (figure 2).

The study with the largest t-statistic was Andersen et al. and as such was removed prior to performing the analysis again.

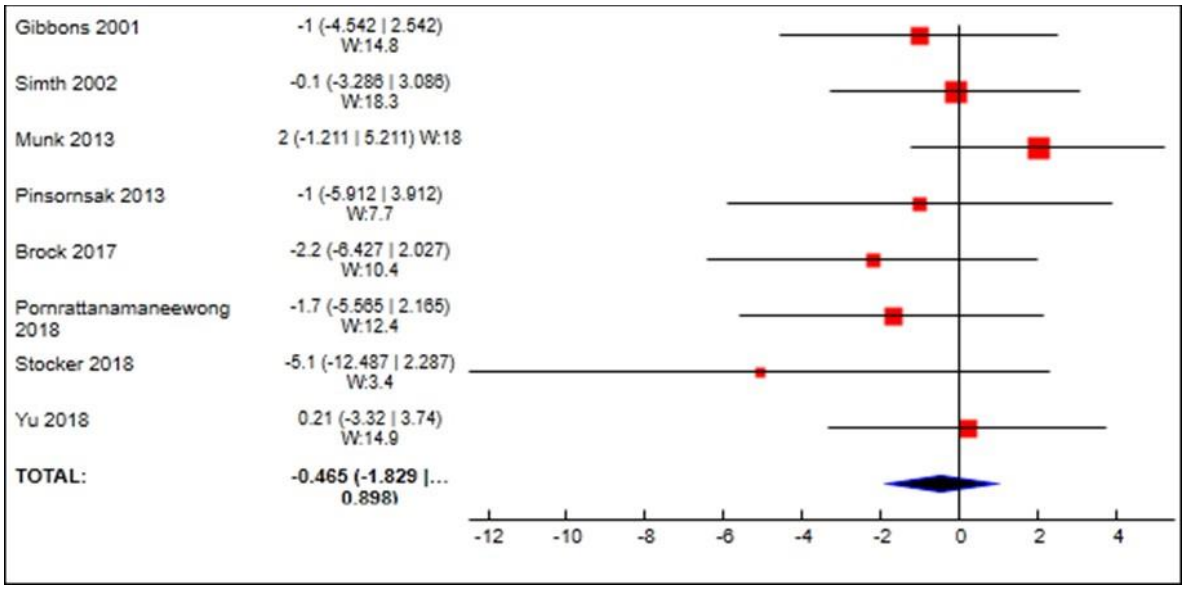

Figure 3: Baseline heterogeneity analysis- fixed effect model with Andersen et al. removed.

With Andersen et al. removed from the model, the I^2= 0%, showing no further significant baseline heterogeneity (figure 3).

This initial baseline heterogeneity suggests suboptimal randomisation of participants and as such the initially performed meta-analyses which included Andersen et al. were performed again with this paper excluded as a sensitivity analysis and are highlighted as such.

2.1.3.4 Effects of Interventions

2.1.3.4.1 Blood loss

Of the five studies that measured blood loss, four used direct measurement of blood loss through drainage of blood from surgical drains placed at the time of surgery (Gibbons et al. Smith et al. Pinsornsak et al. Pornrattanamaneewong et al.).

From these four studies, 284 participants were included. Blood loss for these four studies was recorded on day two post-operative (figure 4). The pooled mean difference (MD) from

the random effect meta-analysis was -6mls indicating a greater amount of blood loss in the control group (95% CI -118 to 106). Three of the four studies showed a small effect towards a decreased volume of blood loss with compression bandaging, however, their 95% CI all cross zero (Smith et al. Pinsornsak et al. Pornrattanamaneewong et al.). A single outlier showed a much larger and significant increase in measured blood loss with compression bandaging (Gibbons et al.). As such, moderate heterogeneity may have been present (I^2=50.9%).

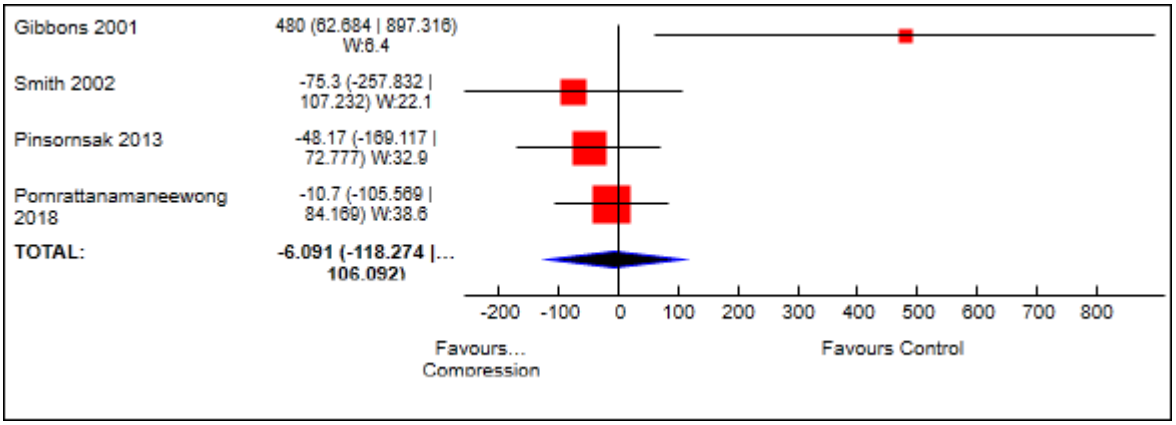

Figure 4: Meta-analysis- measured blood loss volume (mls) day two post-operatively

Heterogeneity: Q= 6.11, df= 3, p=0.106 I^2= 50.9%

A further study calculated a total blood volume loss (mls), utilising Nadler's calculation and the surrogate marker of overall Hb loss (Yu et al.). Post-operative Hb levels were taken at 24 hours and 72 hours post-operatively. Nadler's blood loss calculation is a validated method of calculating total blood volumes and therefore felt to be comparable to direct drain measurements when pre and post-operative blood parameters are measured.

A random effect meta-analysis was performed including drain measurements (Pinsornsak et al. Pornrattanamaneewong et al.) and the calculated total blood volume loss (Yu et al.) day one post-operatively. A total of 228 participants were included. The pooled MD using a random effect model was -8mls (95% CI -43 to 28) indicating a small but non-statistically significant reduction in blood loss with compression bandaging (figure 5).

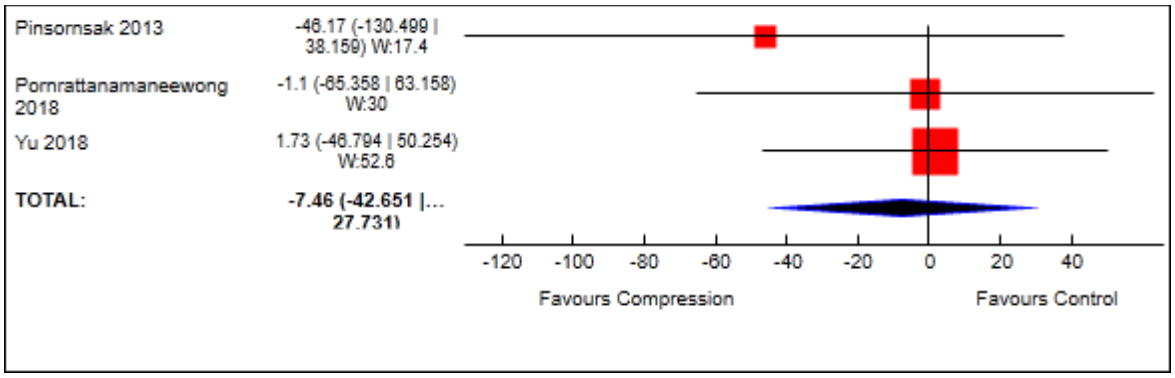

Figure 5: Meta-analysis- measured and calculated blood loss volume (mls) day one post-operatively

Heterogeneity: Q= 0.98, df= 2, p= 0.611, I^2= 0%

Blood markers were also measured by two other studies. Smith et al. noted no difference in recorded post-operative Hb levels (mean 13.9g/dl for both compression and control groups). Pinsornsak et al. observed a small but non-statistically significant difference in HCT loss favouring the control group (compression 3.4 l/l SD 2.6, control 2.6 l/l SD 3.1, p= 0.243).

2.1.3.4.2 Transfusion requirements

Transfusion requirements were analysed by five studies with 372 participants.

Three studies (Gibbons et al. Pinsornsak et al Yu et al.) recorded the number of participants requiring a blood transfusion; fourteen participants required transfusion in the compression group and thirteen in the control group. These give a mean transfusion rate of 0.134 with compression and 0.126 with control.

Transfusion volumes were recorded by two studies (Smith et al. Pornrattanamaneewong et al.). The pooled MD was -15.3mls (95% CI -91.1 to 60.4). This highlights a small decrease in the overall blood volume transfused in the compression group (figure 6).

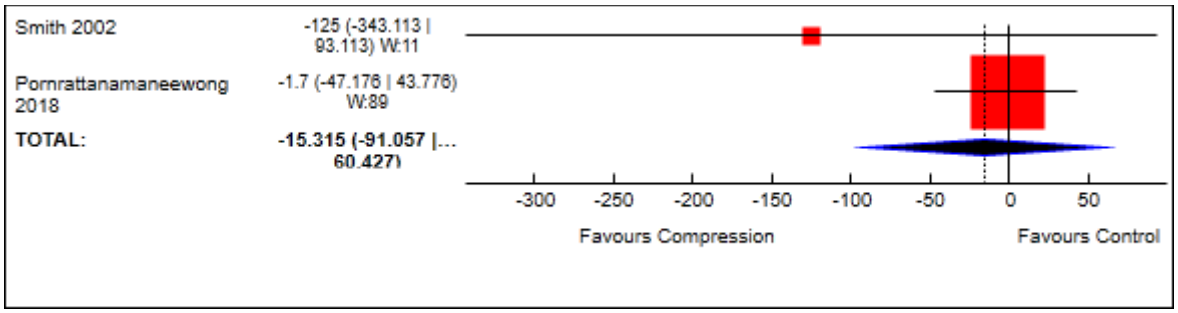

Figure 6: Meta-analysis- overall blood transfusion volumes (mls)

Heterogeneity: Q= 1.18, df= 1, p= 0.279, I^2= 15%

2.1.3.4.3 Post-operative pain

Pain scores were measured by all nine studies with a combined total of 574 participants. A visual analogue scale (VAS) was used to measure pain by eight of the studies of the studies, with one study utilising a numeric rank scale (Andersen et al.).

A 0 to 10 (no pain to worst pain) scale was used by six studies (Smith et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.) and a 0 to 100 (no pain to worst pain) scale was used by the other three studies (Gibbons et al. Andersen et al. Munk et al.).

Pain scores were recorded at variable timepoints.

Day one post-operative

All nine studies recorded pain scores on the first day post-operative.

Andersen et al. recorded pain scores as a median for groups, at multiple time points up to 24 hours with the knee in various positions. For analysis, the median scores were converted to mean scores and SD (153). The equates to a mean pain score for the compression group 3.5 (SD 2) and in the control group 4.5 (SD 3). As interquartile ranges were displayed only at

six-and eight hours post-operative, the later timepoint (eight hours) was used for the meta-analysis as it more closely followed the other included studies.

Munk et al. recorded pain scores and grouped the results into low (0 to 2), medium (3 to 5) and high (6 to 10) score groups for their analysis and outcomes. For the meta-analysis the group scores were converted to a mean value by assuming all participants in the low group (0 to 2) scored 1; moderate (3 to 5) scored 4; high (6 to 10) scored 8 (A 1.3).

The random effect meta-analysis showed a negligible improvement favouring the compression group (MD -0.04, 95% CI -0.50 to 0.41) (figure 7).

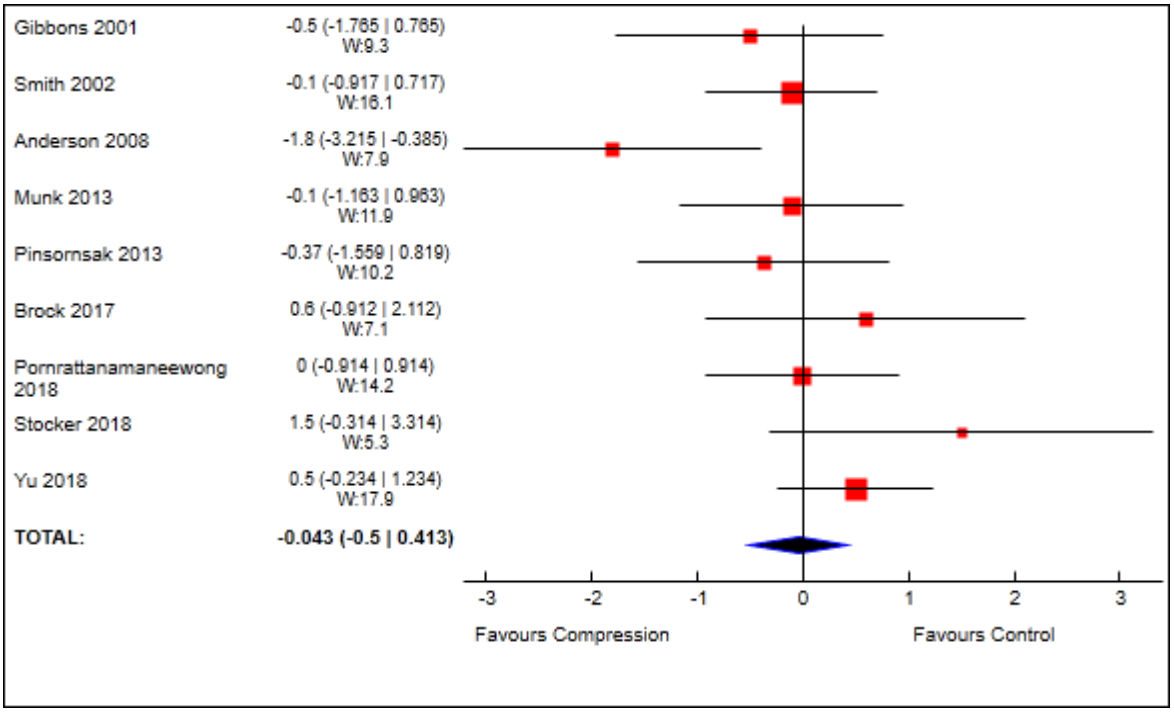

Figure 7: Meta-analysis- pain scores (points) day one post-operatively

Heterogeneity: Q= 12.3, df= 8, p= 0.138, I^2= 34.9%

Day two post-operative

Six studies with 378 participants recorded pain scores on the second day post-operative

(Smith et al. Munk et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Stocker et al.) providing a pooled MD 0.44 (CI -0.09 to 0.98). This shows a decreased pain score with the control group (figure 8).

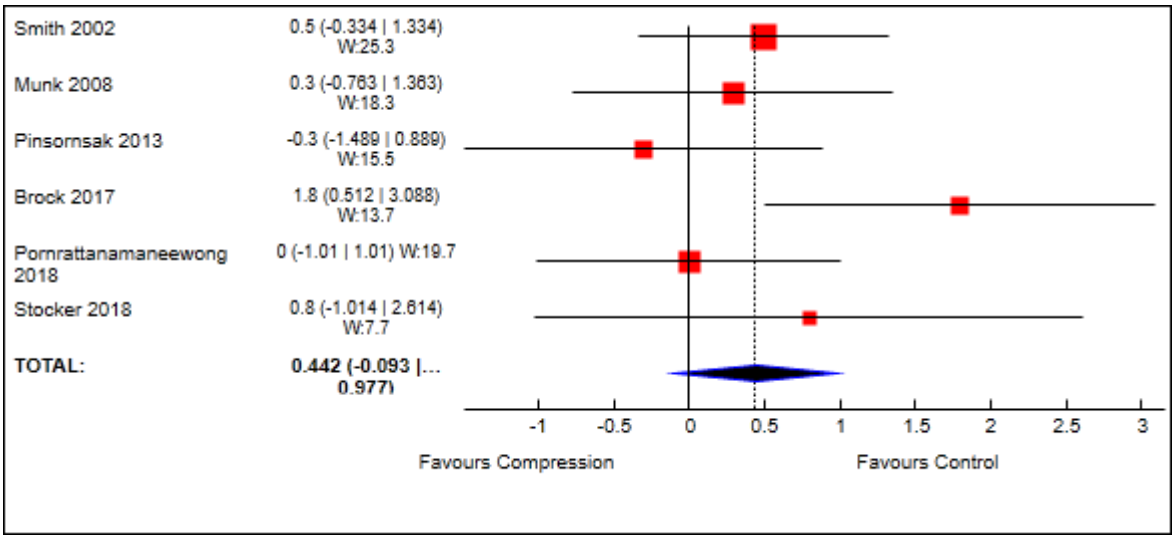

Figure 8: Meta-analysis- pain scores (points) day two post-operatively

Heterogeneity: Q= 6.73, df= 5, p= 0.241, I^2= 25.8%

Day three post-operative

Four studies recorded pain scores on the third day post-operative with 248 participants (Gibbons et al. Smith et al. Stocker et al. Yu et al.). Random effect Pooled MD -0.1 (95% CI -0.41 to 0.22) indicating a decreased pain score with compression (figure 9).

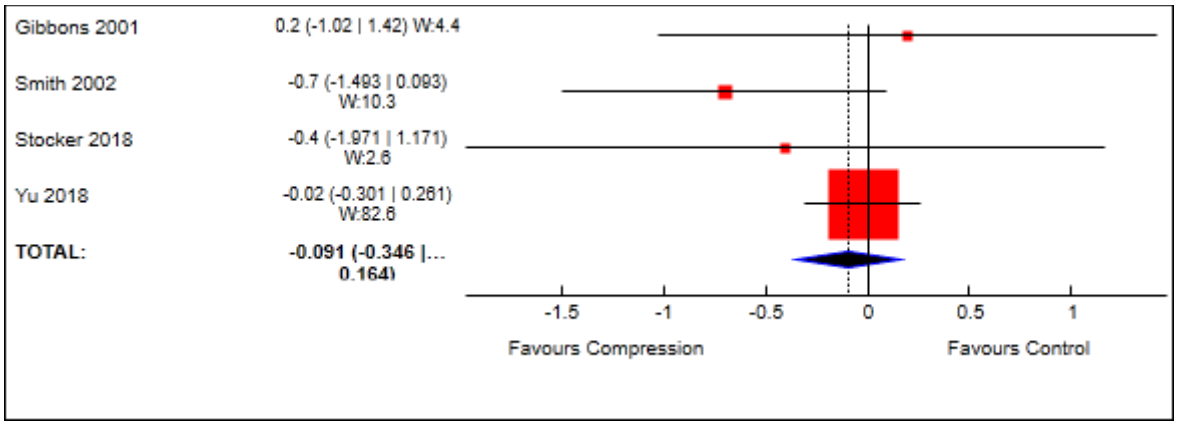

Figure 9: Meta-analysis- pain scores (points) day three post-operatively

Heterogeneity: Q= 2.88, df= 3, p= 0.411, I^2= 0%

Additional time points

Brock et al. recorded pain scores at six weeks post-operative in addition to days one and two. Gibbons et al. recorded pain scores at five, seven and nine days post-operative as well as days one and three. Munk et al. measured pain scores at seven days, two weeks and one-month post-operative, in addition to days one and two. At all these time points, no statistically significant differences were noted between the compression and control groups.

2.1.3.4.4 Analgesia use

Four studies analysed post-operative analgesia use, with acute (24 to 48 hours post-operative) analgesia consumption being recorded (Gibbons et al. Smith et al. Andersen et al. Pornrattanamaneewong et al.). The analgesia used was all opiate based with Gibbons et al. used Patient controlled analgesia' Morphine. Smith et al. used Morphine and Pethidine where the Pethidine usage was converted to a Morphine equivalent unit by dividing the volume used by 7.5. Oxycodone was used by Andersen et al and Morphine only by Pornrattanamaneewong et al. All of these types of analgesia are classed as strong opiates.

Two studies recorded consumption as mg/kg/48hours (Gibbons et al. Smith et al.). For the

meta-analysis, the Morphine usage, originally recorded as mg/48hour by Pornrattanamaneewong et al. was converted to mg/kg/48hours by dividing the mean morphine consumption by the baseline participants weight (Kg). A similar method was used for the values recorded by Andersen et al. which were over 24 hours. It was felt that combining the one set of values recorded at 24 hours, and the three 48 hours values for analysis, would not significantly affect the overall outcome as both are deemed to be assessing acute post-operative analgesia requirement.

Pooled MD -0.02mg/kg (95% CI -0.04 to -0.002) highlights a modest, statistically significant reduction in the amount of analgesia used by the compression group (figure 10).

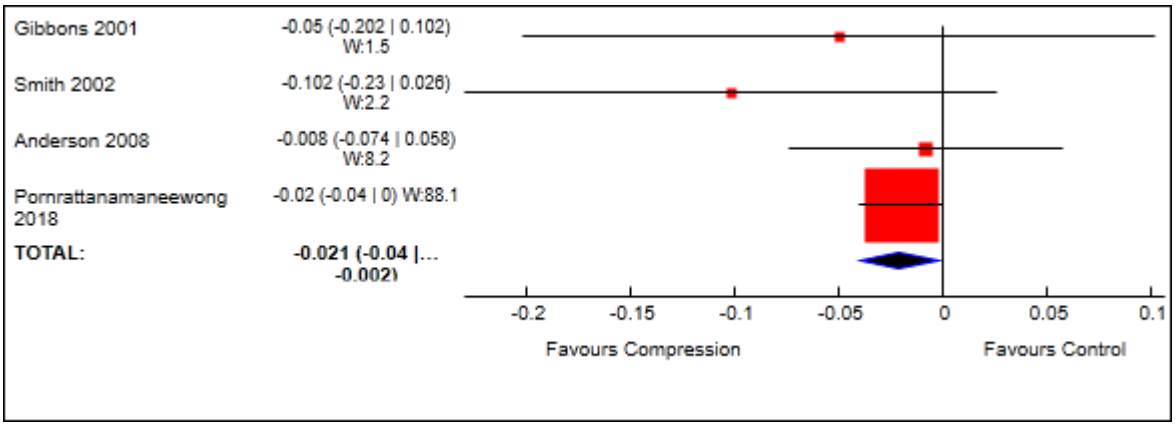

Figure 10: Meta-analysis- acute analgesia use (Morphine mg/kg)

Heterogeneity: Q= 1.83, df= 3, p= 0.608 I^2= 0%

2.1.3.4.5 Knee swelling

Six of the studies with 386 participants measured post-operative swelling at set points around the knee (Smith et al. Munk et al. Pinsornsak et al. Brock et al. Stocker et al. Yu et al.).

Multiple measurements at different timepoints and at different anatomical locations were taken in the studies (table 4). All six studies included measurements on day one post- operative. Four studies (Munk et al. Brock et al. Stocker et al. Yu et al.) observed

the amount of swelling present at least three weeks post-operatively.

Study	Year	Measurement location	Timepoint
Smith	2002	Knee	Day one, day two
Munk	2013	Patella, calf, ankle	Day one, day two, day seven, day fourteen, One month
Pinsornsak	2013	Leg, thigh	Day one
Brock	2017	Thigh, knee, calf	Day one, day two, six weeks
Stocker	2018	Knee joint line and 5cm, 10cm, 15cm proximally and 15cm distally	Day one, day three, day six, six weeks
Yu	2018	Patella (Superior, middle, inferior aspect), thigh	Day one, day three, three weeks

Table 4: Anatomic location and timepoints for knee swelling measurements

As multiple anatomic locations were used, with no overall consensus, the closest description between all studies was utilised for analysis. For Smith et al. there was only one measurement which not precisely defined. Other measurements used were the patella (Munk et al.), thigh (Pinsornsak et al.), knee (Brock et al.), knee joint line (Stocker et al.) and middle aspect of patella (Yu et al.). It was felt that by utilising a random effects model, these areas would give a suitable representation of post-operative swelling.

Brock et al. did not include the absolute figures recorded, displaying them as a chart, as such, the results were extrapolated from this. On day one post-operatively we determined knee swelling as 43.5cm (interquartile range 39 to 47cm) for control and 44cm (interquartile range 40 to 48.5cm) for the compression bandage. Standard deviations were then estimated at 2 and 2.125 respectively (A 1.4).

Following analysis, the result was MD 0.11cm (95% CI -0.66 to 0.88) indicating a small decrease in swelling with the control group (figure 11).

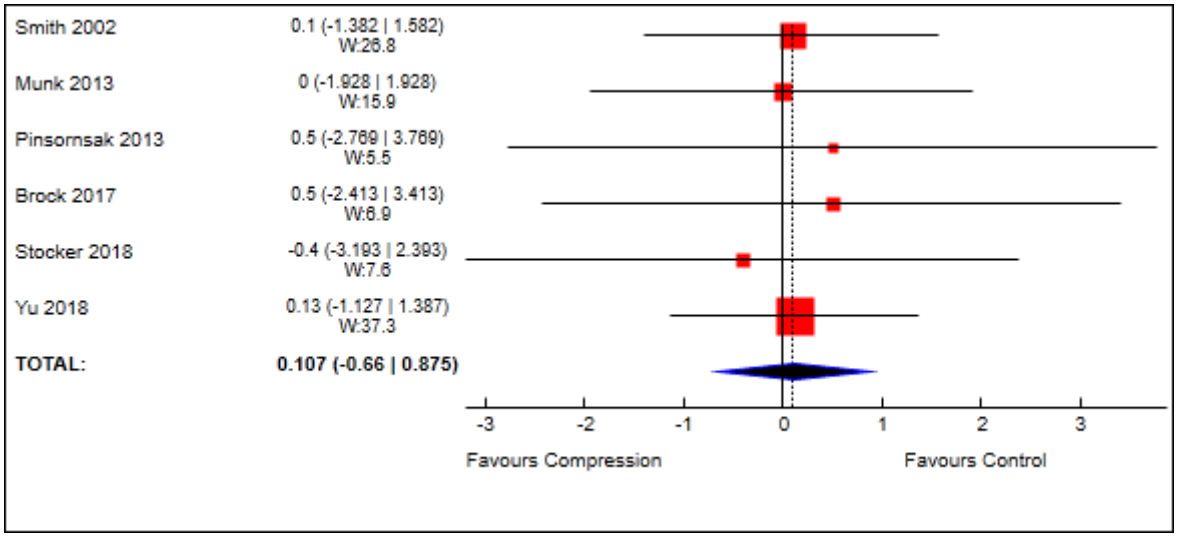

Figure 11: Meta-analysis- swelling (cm) as measured around the knee day one post-operatively

Heterogeneity: Q= 0.26, df= 5, p= 0.988, I^2= 0%

2.1.3.4.6 Knee range of movement

Knee range of movement was recorded by eight studies (Gibbons et al. Smith et al. Munk et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.) at one time point as a minimum.

Day one post-operative

Five studies (Smith et al. Munk et al. Brock et al. Stocker et al. Yu et al.) recorded knee flexion measurements on day one post-operative with 326 participants included.

Munk et al. recorded median scores for knee flexion. This was converted to mean values and SD, with compression group being converted to 60° (SD 16.3) and control group 58° (SD 20.8).

Following random effects analysis, pooled MD 0.5° (95% CI – 3.1 to 4.1) (figure 12).

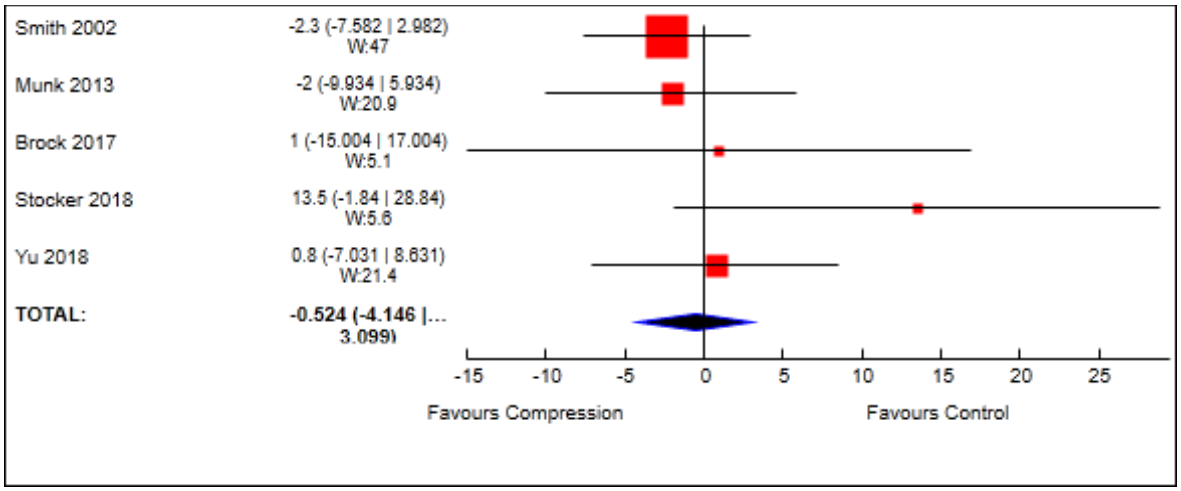

Figure 12: Meta-analysis- knee range of movement (degrees flexion) day one post-operatively

Heterogeneity: Q= 3.92, df= 4, p= 0.417, I^2= 0%

Knee flexion was also measured at discharge by two studies (Pinsornsak et al. Pornrattanamaneewong et al.)

Pinsornsak et al. recorded a flexion range; 1° to 94° in the compression group and 1° to 97° in the control group. Pornrattanamaneewong et al. measured mean flexion of 84.9° (SD 10) in the compression group and 85.3° (SD 10.4) in the control group.

Gibbons et al. measured knee range of movement at ten days post-operatively and found no statistically significant difference between the two groups.

2.1.3.4.7 Knee function

Three studies included validated knee function scores (Munk et al. Brock et al. Yu et al.).

Both Munk et al. and Brock et al. used the 'Oxford knee score' (OKS), scored 0 to 48, where a higher score indicates better knee function. Scores were recorded at one month by Munk et al. and six months post-operatively by Brock et al. The change in scores from pre-operative to post-operative were used for random effect analysis, pooled MD -0.3 (95% CI -

2.8 to 2.1) (figure 13).

Yu et al. utilised the 'Hospital for Special Surgery' knee score, scored 0 to 100, where a higher score indicates better function. However, no timeframe of analysis was stated and only the post-operative scores and no baseline scores were available. No statistically significant difference was found between the two groups (compression 80.55 ± 5.36, control 79.34 ± 4.66, p <0.26).

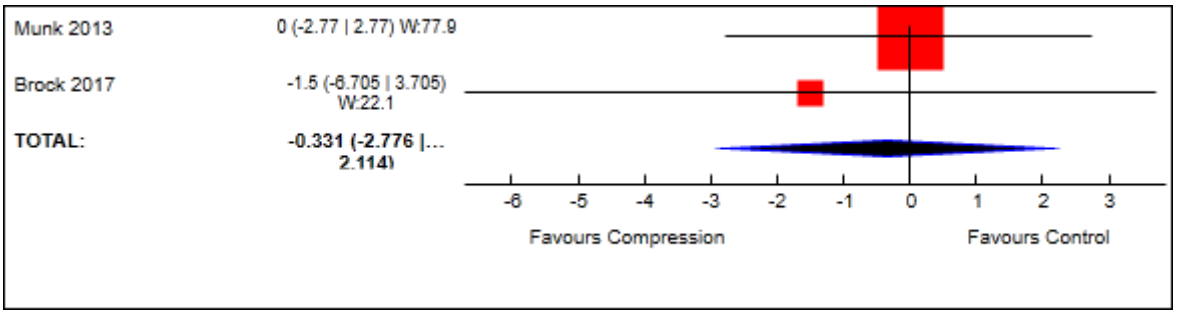

Figure 13: Meta-analysis- change in OKS (points) from pre-operative to post-operative scores

Heterogeneity: Q= 0.24, df= 1, p= 0.618, I^2= 0%

2.1.3.4.8 Length of hospital stay

Length of hospital stay was assessed by five studies (Gibbons et al. Smith et al Andersen et al. Brock et al. Stocker et al. with 257 participants included. Pooled MD -0.1 days (95% CI -1.1 to 0.9), highlighting a minimal difference in length of stay, favouring compression over control group (figure 14). Considerable statistical heterogeneity was also identified (I^2= 80.6%).

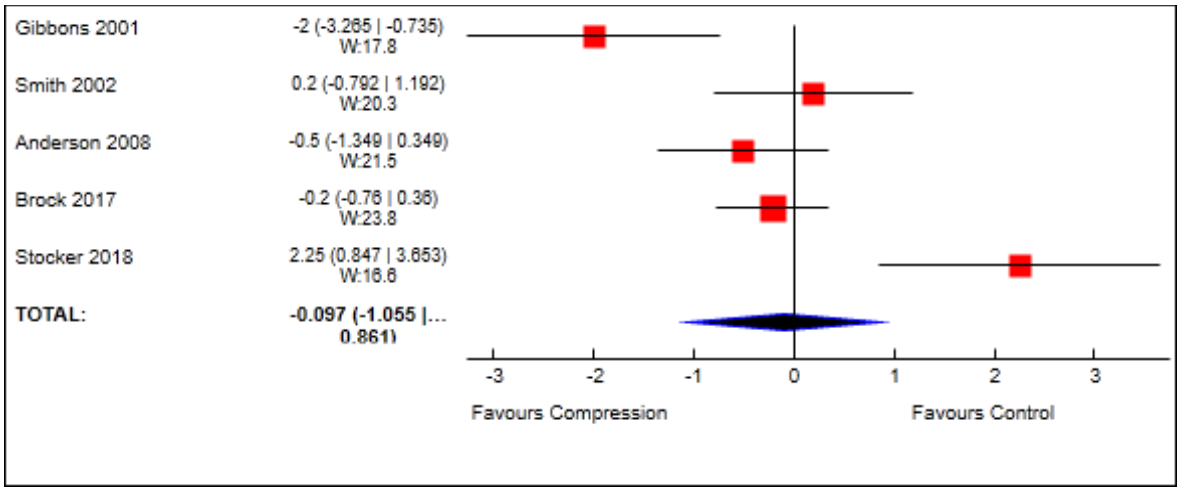

Figure 14: Meta-analysis- length of hospital stay (days)

Heterogeneity: Q= 20.6, df= 4, p= 0.0004, I^2= 80.6%

2.1.3.4.9 Adverse reactions

Adverse reactions were recorded in seven studies (Gibbons et al. Munk et al. Pinsornsak et al. Brock et al. Pornrattanamaneewong et al. Stocker et al. Yu et al.) with 442 participants. In total, ten adverse reactions were recorded in the compression group and eight in the control group giving a relative risk 1.25 (95% CI 0.503 to 3.105). The most commonly cited adverse reaction was bruising or ecchymosis, accounting for nine of the ten events in the compression group and six of the eight events in the control group. There were no recorded deaths in any of the studies.

2.1.3.4.10 Quality of life

One study (Brock et al.) with fifty participants analysed quality of life. Utilising the EQ-5D-3l questionnaire, scored from 5 to 15 points, an improvement in scores at six months post-operative favouring compression over control was highlighted (p = 0.057; point estimate= 0.147; 95% CI −0.328 to 0.005).

2.1.3.4.11 Walking speed test

A walking speed test was used as a secondary outcome by one study (Stocker et al.). Walking speeds were measured at six days and six weeks post-operative. Analysis shows a narrowing of the 95% CI occurring at the same time as the differences between groups also converge (figure 15).

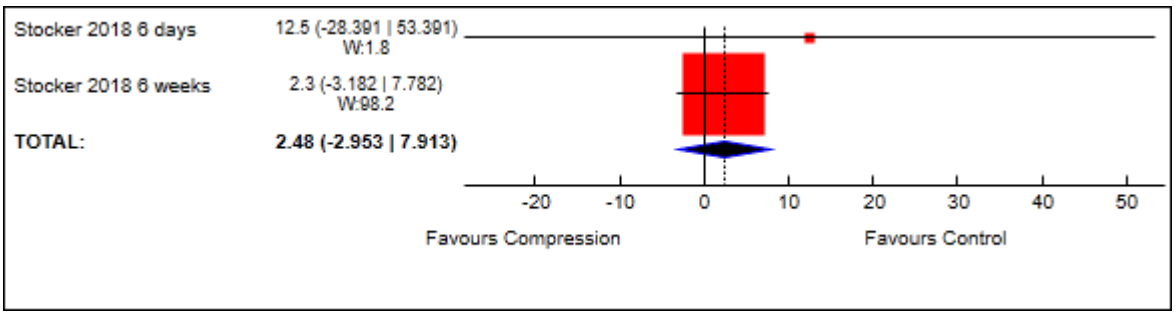

Figure 15: Meta-analysis- walking speed test (seconds)

2.1.3.4.12 Cost comparison

One study (Smith et al.) used a narrative cost comparison. For this, only basic assumptions and not economical heath statistics and actual values were used. Points raised were, the increased initial cost of cryotherapy and the potential for more intensive nursing needs than with compression bandaging alone.

2.1.3.5 Effects of interventions with Andersen et al. excluded

Initial meta-analyses performed which included data sets from Andersen et al:

2.1.3.4.3 Day one post-operative pain (figure 7).

2.1.3.4.4 Analgesia use (figure 10).

2.1.3.4.8 Length of hospital stay (figure 14).

2.1.3.5.1 Day one post-operative pain

Eight studies are now included in the meta-analysis. The random effects model showed a small improvement favouring the control group (MD 0.05, 95% CI -0.32 to 0.41) (figure 16).

This compares with the initial random effect meta-analysis showing a small improvement favouring the compression group (MD -0.04, 95% CI -0.50 to 0.41) (figure 7).

The heterogeneity (I^2) with Andersen et al excluded has been substantially reduced.

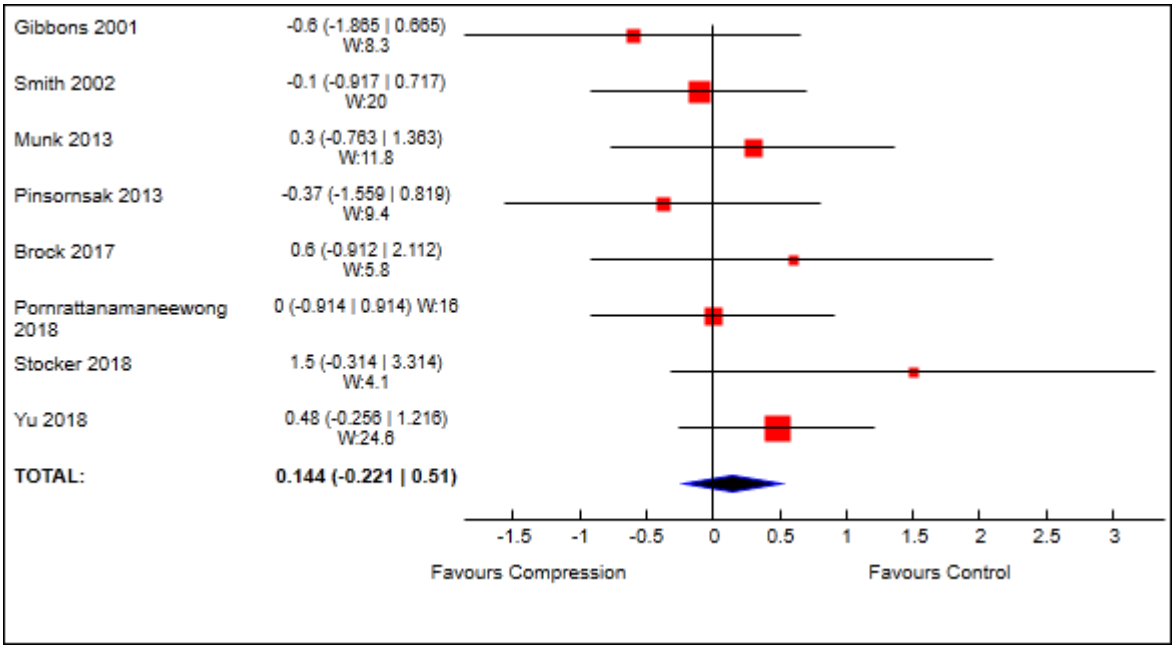

Figure 16: Meta-analysis- pain scores (points) day one post-operatively. Andersen et al. excluded

Heterogeneity: Q= 5.86, df= 7, p= 0.556, I^2= 0%

2.1.3.5.2 Analgesia use

Three studies are now included for meta-analysis with 204 participants.

Previously, the pooled MD was -0.02mg/kg (CI -0.03 to -0.002) highlighting a statistically significant reduction in the amount of analgesia used by thecompression group (figure 10).

Following exclusion of Andersen et al. the heterogeneity remained zero and the pooled MD -0.02mg/kg (-0.04 to -0.003), sustaining statistical significance (figure 17).

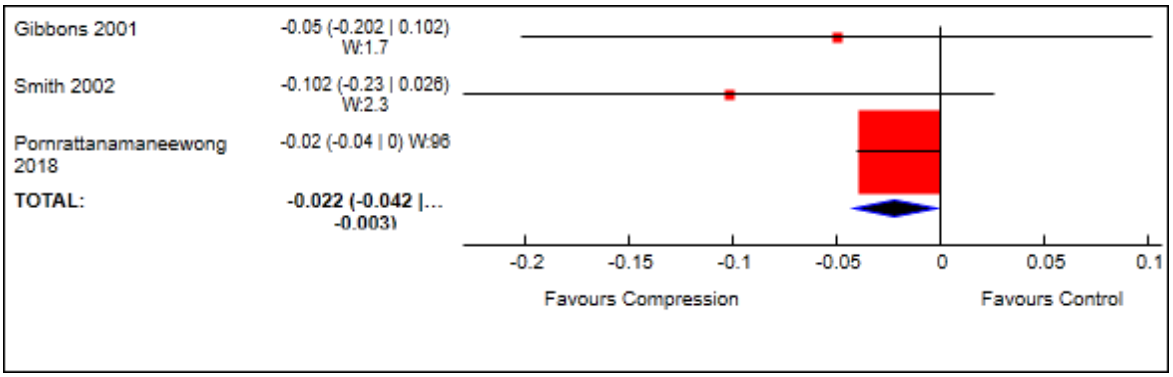

Figure 17: Meta-analysis- acute analgesia use (Morphine mg/kg). Andersen et al. excluded

Heterogeneity: Q= 1.89, df= 2, p= 0.428, I^2= 0%

2.1.3.5.3 Length of hospital stay

With Andersen et al. excluded, four studies were subsequently analysed for length of stay giving a pooled MD of 0.03 (95% CI- 1.69 to 1.74) indicated no significant difference (figure 18).

With Andersen et al. included, the pooled MD was -0.12 (CI -1.22 to + 0.98) favouring compression over control in reducing length of hospital stay, although without statistical significance (figure 14).

Considerable heterogeneity remained (I^2= 81.8%).

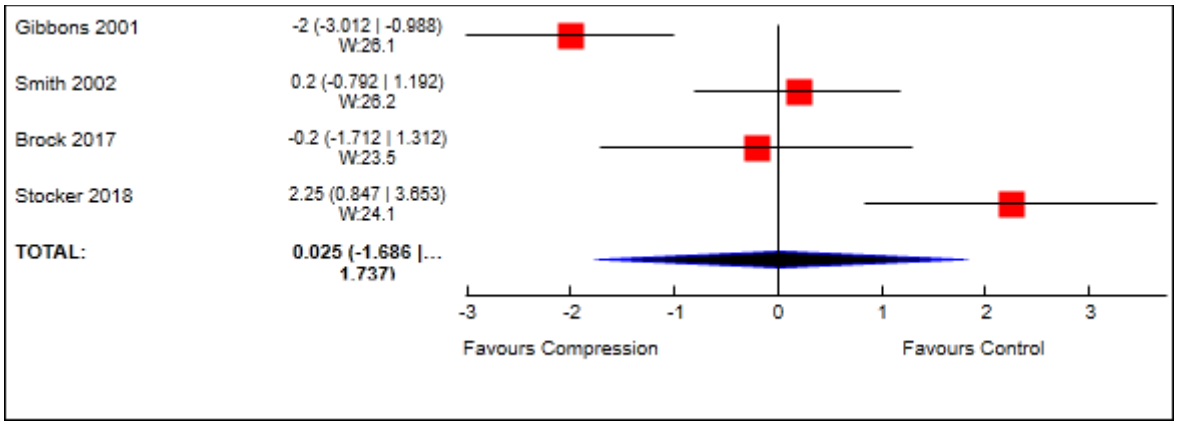

Figure 18: Meta-analysis- length of hospital stay (days). Andersen et al. excluded

Heterogeneity: Q= 16.5, df= 3, p= 0.0009, I^2= 81.8%

2.1.3.5.4 Overall

With Andersen et al. excluded from the meta-analysis there were subtle changes to overall outcomes. Pooled MDs for length of stay and day one post-operative pain scores shifted marginally towards the control group but did not gain statistical significance. For post-operative analgesia use, the modest but statistically significant difference favouring the compression group remained.

Considerable statistical heterogeneity remained following length of stay analysis but was substantially reduced following further analysis of day one post-operative pain.

2.1.4 Discussion

2.1.4.1 Summary of main results

The systematic review and meta-analysis included nine studies and 574 participants. The earliest paper included was published in June 2001 and the most recent in October 2018.

Due to our systematic review design and inclusion criteria, primary TKAs were used in all studies, and as a result, the characteristics of the study populations were similar and accurately portray the current clinical picture with ages and BMI values stated, enhancing the studies applicability. The included studies average age for participants ranged from 64 to 72 years old, with the United Kingdom average for TKA currently stated as 69 years old (16).

Interventions were either in the form of an elastic compression bandage system or a multi-layer wool and crepe bandage used for compression and were kept in-situ for at least 24 hours.

Included studies used multiple domains and outcome measures which have subsequently been analysed and assessed. Overall, following meta-analysis, there was one statistically significant effect noted. Acute analgesia use (Morphine mg/kg) was less within the compression group than the control group, with pooled MD 0.02mg/kg. This was true with Andersen et al. included and excluded from analysis. Over 24 hours this modest difference is unlikely to be clinically or indeed cost significant, unless combined with other adjuncts in an enhanced recovery setting helping minimise its use further. It could however benefit those who are more susceptible to post-operative nausea and vomiting, a common side effect of strong opiate use. A reduction in morphine consumption and its associated post-operative nausea and vomiting is a key proponent of enhanced recovery and any reduction in its consumption is a positive finding.

Following analysis of blood loss at different time points and the resultant post-operative transfusion rate, no statistically significant differences were observed.

Additionally, there were no statistically significant differences in pain scores highlighted. Indeed, on day two post-operative the control group had lower overall pain scores and, conversely on day three post-operatively the compression groups scores were lower. This may have coincided with the removal of compression bandages at 24 hours and a rebound effect or an increase in the volume or workload due to the post-operative physiotherapy regime.

By excluding Andersen et al. following assessment of baseline heterogeneity, a change in pain scores and length of stay was seen with a trend towards the control group, although

neither achieved statistical significance. This was an expected effect as Andersen et al. concluded that compression bandaging conferred significant benefits to improving analgesia and pain relief with local anaesthetic infiltration technique and as such, their outcomes favoured compression bandaging over standard bandaging. However, due to the baseline heterogeneity highlighted, there is the potential for selection bias in their study.

Importantly, adverse events were relatively low throughout the groups and non-serious in nature. This highlights the use of compression bandaging as a safe intervention with a similar recorded incidence of low morbid adverse effects as the control group.

With these outcomes following meta-analysis, there is little significant benefit highlighted in using a compression bandage over standard bandages or dressings following TKA. The statistically significant difference in morphine consumption (mg/kg) is not likely to confer clear clinical significance.

This study has highlighted that compression bandage use has some tendencies towards an improvement in outcomes such as analgesia use, knee function and quality of life whilst being safe to use with no significant increase in adverse events or side effects, although any improvements are modest in scale.

2.1.4.2 Overall completeness and applicability of evidence

The evidence presented within this review is broad and many outcomes have been addressed. Due to the relatively small number of included studies and subsequent participant numbers, several outcomes contain few studies for meta-analysis. However, statistical heterogeneity was low and meta-analyses were able to be conducted on all of the main outcomes. Evidence from these results can therefore be confidently applied elsewhere.

Post-operative pain analysis was the most complete outcome with all nine eligible studies including at least one analysis of pain scores at a minimum of one time point.

As such, overall completeness for analysis of the stated outcomes was good, however, only one study looked at quality of life scores and there were no complete cost comparisons included. As a result, this does limit the reviews overall clinical applicability.

Included studies are published between 2001 and 2018 and from different healthcare systems around the world. As such clinical heterogeneity was evident. There is also an evolution of care within the clinical setting as well as research methodology and study design. The more contemporary studies were often performed in an enhanced recovery setting and displayed a more robust clinical methodology as evident in the risk of bias table (table 2.2). This review therefore gives a broad understanding of the outcomes analysed but clinical judgment will still be necessary in their application.

2.1.4.3 Quality of the evidence

Nine studies were included and had results extracted for review and analysis. Two of these were 'pilot' studies with one (Stocker et al.) including sixteen participants in total. As the number of eligible studies was relatively low, the strength of evidence for some outcomes is low. Indeed, transfusion rate analysis was only able to include two studies.

The risk of bias also varied with several papers displaying moderate to high risk in multiple domains. No included studies were able to demonstrate a low risk of bias in all domains, with all studies displaying a high risk of performance and detection bias. This is due to the nature of the intervention used which excluded the ability to blind both participants and researchers alike. Six of the nine studies used adequate random sequence generation, with concern about three studies.

Only one included study (Brock et al.) used an adequate allocation concealment and randomisation procedure. Due to opaque envelopes being inadequate forms of concealment, five studies were deemed at high risk of selection bias (164, 165).

Due to baseline heterogeneity (participant age), there was also concern regarding selection bias with Andersen et al. As such, for sensitivity analysis and increasing the robustness of this review, further meta-analyses were performed with this paper excluded.

2.1.4.4 Potential biases in the review process

Bias was attempted to be minimised throughout this study by utilising a published protocol on PROSPERO and the electronic searches used are also available. Additionally, electronic searches and data extraction was independently undertaken by two individuals and there was no time or language limit set on included papers, allowing all applicable papers to be included.

Limitations are the lack of grey literature included in our searches and the small overall number of papers available for review. This meant certain outcomes were not able to undergo meta-analysis and other domains only had two studies included.

2.1.4.5 Agreements and disagreements with other studies or reviews

Other reviews looking at post-operative adjuncts such as cryotherapy have found minor improvements in some domains such as blood loss and two-week range of movement but not in other domains such as pain and analgesia use. The systematic review by Adie et al. stated that 'the potential benefits of cryotherapy on blood loss, postoperative pain, and range of motion may be too small to justify its use, and the quality of the evidence was very low or low for all main outcomes' (128).

Overall, no significant difference in knee function or flexion was highlighted in this review which is in contrast to results presented by Charalambides et al. (138). There, the use of compression bandaging is concluded to have beneficial effects for knee function and improving length of stay. Being a cohort study of three series of fifty patients, it was ineligible for the systematic review.

Cheung et al. also found favourable outcomes for compression bandage use with improved mobility post-operative (139). Statistically significant improvements in both straight leg raise ($p= 0.017$) and mean knee flexion at discharge ($p=0.04$) are stated. Walking aid use was also improved and mean length of stay decreased. However, this paper is open to significant bias

with surgeons able to choose participant allocation and bandage type and hence no method of randomisation or concealment was used. Additionally, no power calculations were performed, and the recruitment process was not clearly described throughout.

Overall, any improvements in outcomes with post-operative adjuncts and compression bandaging are modest and not statistically significant. This is in keeping with other systematic reviews including on cryotherapy. There are, however, conflicting results and outcomes from individual studies including non-randomised studies, ineligible for the systematic review. Potential for bias in the included studies raises some doubt on the outcomes observed.

When completed and published, KReBS will add significantly to this presented body of evidence. The primary outcome measure of knee function as measured by the OKS will greatly increase our current knowledge and guide on-going recommendations as there is limited data currently available on this particular outcome and no long-term outcomes assessed.

2.1.4.6 Applicability of evidence

The findings from this systematic review and meta-analysis can be applied to current clinical practice. However, there are key areas to consider prior to this. Not all of the included studies were performed in the same healthcare system, and not all were performed in an ERAS setting. Current arthroplasty practice, particularly in the United Kingdom, is for an ERAS type pathway (22). There was also varying use of drains and tourniquets throughout.

Further ways in which to increase our knowledge can thus be initiated.

Yu et al. did not use a tourniquet within their study. However, no direct comparison of the use of a tourniquet with compression bandaging has been performed. It has been surmised by Yu et al. that compression bandaging is not necessary following TKA without tourniquet (137).

There is also significant heterogeneity with the types of bandages used within the studies and to a lesser degree in the controls. Hence, the best type of bandage or most effective way of achieving compression is not fully appreciated.

From the included studies and those looking at other post-operative adjuncts such as cryotherapy and continuous passive movement, it is unlikely that a minimal clinically important difference in outcomes such as blood loss, stated as 300mls by Kalairajah et al. or a change of three points for OKS, will be seen with a low impact intervention such as compression bandaging when analysed in isolation (166).

From this review's findings, compression bandaging is a safe intervention that could still have benefits for patients, especially within a multi-modal ERAS setting, although such findings are likely to be small scale. As such, a well-designed, and robust RCT, powered to detect modest but clinically significant improvements in post-operative outcomes within an ERAS setting should be initiated. Specific areas to also focus upon, include tourniquet use and the type of bandage used to achieve compression.

3 Randomised controlled trial design and methodology

3.1 Introduction

From the conclusions drawn from the systematic review and meta-analysis there remain ways in which to expand upon our current knowledge and understanding of compression bandaging use following TKA.

Within an enhanced recovery setting, where multiple small improvements brought about by several interventions can have a more prominent overall effect, compression bandaging may confer clinically relevant benefits for patients.

As such, the large, multi-centred, randomised controlled trial KReBS has been conducted. At its centre is the role that compression bandaging may have in helping improve patient reported outcome measures (PROMs) and quality of life as represented by the primary outcome measure of OKS at twelve months post-operative.

The objective of KReBS is to determine the effectiveness and cost-effectiveness of a two-layer compression bandage compared with a standard wool and crepe bandage applied post-operatively on patient-reported outcomes in TKA patients.

This chapter describes a trial embedded within KReBS, which will act as an explanatory study for the findings and conclusions observed within the main study.

KReBS aimed to recruit 2600 participants and was powered to show a relatively small improvement in PROMs of a one-point difference in OKS. This sub-study, looking closely at acute pain and blood loss, could provide the potential mechanism for any improvements observed within KReBS. It also has the potential to highlight any significant factors which either detract or enhance the effects seen with compression bandaging and could help stratify their ongoing use.

The hypothesis is that a tamponade like effect with compression bandaging will reduce post-operative blood loss and acute pain. As such, efficient, early rehabilitation will also be attained, potentially improving patient outcomes which will be assessed in KReBS.

This embedded RCT has therefore been designed and conducted to address the following question:

Within an enhanced recovery setting, does the use of a compression bandaging system reduce overall blood loss and acute pain following total knee arthroplasty?

As such the null hypothesis tested was:

There is no difference in acute blood loss or pain with the use of compression bandaging over standard bandages following total knee arthroplasty.

3.2 Outcome measures

3.2.1 Primary outcome

Post-operative blood loss

The primary outcome for this trial is the difference in Hb(g/dl) from pre to post-operative levels between the compression and non-compression groups.

As stated by Koch et al. a primary outcome must be unambiguous, reliably assessable and clinically relevant (167). The primary outcome also dictates the necessary sample size for a given power. To enhance the study's suitability and robustness the primary outcome must satisfy this description. Hb levels are routinely taken pre- and post-operatively, are reliably measured, easily recorded and highly clinically relevant.

There are multiple methods of measuring blood loss following TKA and there is not currently a gold standard for measurement of surgical blood loss (168). Methods have their own merits and drawbacks and the ability to accurately quantify blood loss is critical for a trial's validity as well as in clinical practice. Methods include direct and indirect measurements. The direct method consists of intra-articular drains, and swab weighing, with indirect methods including blood levels and blood loss estimation calculations. Within the

systematic review different methods including Hb and HCT levels, as well as drainage volumes were used and there is no agreed standard.

Following TKA it has been observed that 90% of blood loss occurs following skin closure and the first day post-operative (168, 169). Overall blood loss occurs due to a combination of bleeding during surgery and the hidden blood loss following skin closure from extravasation into the joint and surrounding tissues and additionally by fibrinolysis and haemolysis (170). As such it is paramount to account for all these aspects of blood loss and not just that which occurs during surgery itself. Indeed, Sehat et al. have shown that approximately 50% of the total blood loss following TKA is due to the hidden loss (171). As such, a surrogate marker for blood loss, taking account of both the visible and hidden losses needs to be used rather than measurements of visible blood loss only.

Surgical drains are not routinely used following primary TKA within Northumbria NHS Foundation trust. A Cochrane review published in 2007 appraised the evidence and concludes that there is insufficient evidence from RCTs to support the routine use of closed suction drainage in orthopaedic surgery (172). It has also been highlighted that blood loss and infection rates may be increased by their use (11, 173). Importantly, surgical drains also fail to address and measure the total volume of blood loss seen due to ongoing hidden losses, into tissue not directly connected to the drain.

Throughout major surgery, including TKA, patients often receive IV fluids to restore circulating volume. This in turn can lead to a ‘dilution’ of the components within blood. The effect of this dilution is dose dependent, and work by Grathwohl et al. showed that maintenance fluid did not alter Hb or HCT concentrations (174). A significant fluid bolus however can change the concentration resolving over time. This effect will be evident in both the intervention and control groups, likely only in small numbers. With a sufficient sample size, the difference in Hb loss between the two groups should represent the true loss and not be affected by dilutional effect, especially with post-operative bloods being taken on day one post-operative.

Hb loss as an outcome carries significant clinical value with its day to day use. It is used routinely by clinical staff to assess blood loss in a ward environment and it is utilised as a marker and trigger for subsequent blood transfusions or initiation of anaemia treatment. As

such it forms part of routine post-operative clinical care. Patients routinely have blood levels taken pre-and post-operatively, as such unnecessary or further tests do not need to be performed. It is also a low morbid intervention and well accepted by patients.

Measuring Hb loss, from pre to post-operative levels, will give a meaningful representation of overall blood loss by accounting for hidden losses, thus enabling the research question to be answered.

3.2.2 Secondary outcomes

i. Difference in HCT (l/l) loss from pre to post-operative levels between the compression and non-compression groups.
ii. Difference in estimated blood loss volume (mls) as calculated by the Hb-balance method between compression and non-compression groups.
iii. Allogenic blood transfusion rates (units) whilst an inpatient.
iv. Difference in pain scores (Numerical rating score (NRS)) between the compression and non-compression groups including mean and highest recorded score within 24 hours post-operatively.
v. Difference in breakthrough analgesia requirement (Oramorph, mg) between the compression and non-compression groups over 24 hours post-operatively.
vi. Length of stay (days)
vii. Complications including, deep vein thrombosis (DVT), pulmonary embolism (PE) and myocardial infarction (MI) that required hospitalisation; readmission and death rates within 30 days of surgery.

HCT levels will be taken as part of routinely taken pre-operative bloods at pre-assessment clinic and on day one post-operative following surgery at the same time as Hb levels.

The Hb-balance method will be utilised to estimate a volume (mls) for overall blood loss.

This is described in section 3.2.3.

Allogenic blood transfusion rates will be assessed between the two groups. Each transfusion utilised within the trust is recorded by the trust blood transfusion service database and can be retrieved as appropriate.

Acute pain scores will be assessed with the NRS. The NRS is currently used by most hospitals in the United Kingdom for routinely taken pain scores. This is due to its validity, reliability and ease of use. This is also true of Northumbria NHS trust. Williamson et al. state that the NRS is the best tool for clinical practice and is also favoured by patients (175). With these key factors considered, the 0 to 10 NRS was utilised to measure pain scores in this trial.

From work by Salaffi et al. the minimal clinically important difference (MCID) for the NRS has been recognised as one-point or a 15% change in score (176). This will help guide any conclusions made from our findings in this study.

NRS pain scores from the first 24 hours post-operative will be retrieved from patients' observation charts that are recorded by recovery and ward nurses as part of routine post-operative care. Each individual pain score in this timeframe will be transcribed, giving the ability to formulate averages, totals, frequency and highest recorded scores.

As part of the multimodal pain regime currently in place, a short acting opiate such as 'Oramorph' is used to combat breakthrough pain. This is given on an 'as required' basis as an oral medication and is both offered by nursing staff and requested by patients. The dose is often 5mg to 10mg and safe prescribing limits the use to two hourly consumption (177). As breakthrough medication and 'as required', patients' requirements and intake will vary and should mirror perceived pain. Any introduction of an intervention to control pain more effectively should concurrently decrease the requirement of breakthrough analgesia.

The total requirement of Oramorph (mg) within the first 24 hours post-operative will be retrieved from patients' drug charts and records.

Participants length of stay post-operatively (days) will also be recorded. This is retrieved from 'hospital episode statistics' (HES) data.

Significant post-operative complications associated with TKA including DVT, PE and MI that

required hospitalisation or readmission within 30 days of surgery will be collected as will any deaths in this timeframe. These figures will be collected from HES data.

3.2.2.1 Estimated blood loss calculations

The use of a volume of measurement carries clinical significance as it gives a readily transferable finding in an easy to apply and understand unit (mls) for both clinical and non-clinical personnel. By using an indirect method of recording blood loss such as Hb or HCT levels, an estimate of volume loss can be calculated.

There are multiple methods available to calculate and estimate blood loss volumes. The accuracy of these has been debated and there is not one that is routinely used as the gold standard.

To assess the total blood volume loss ($V_{loss\ total}$) we first need to know the estimated blood volume (EBV). The average adult has approximately five litres of circulating blood volume but this volume is dependent on variables such as weight, height and gender (178). Hence, these are taken to account with the calculation, to estimate an individual's circulatory volume more accurately. The standard calculation was developed by Nadler et al. and published in 1962 (figure 19) (179).

Men:	$EBV = (0.3669 \times H^3) + (0.03219 \times W) + 0.6041$	H= Height (m)
Women:	$EBV = (0.3561 \times H^3) + (0.03308 \times W) + 0.1833$	W= Weight (Kg)

Figure 19: Estimated blood volume calculation by Nadler et al.

From the EBV, blood loss can then be calculated in a variety of ways. These can be split into those that use HCT and those that use Hb.

HCT estimates include calculations from; Gross, Mercuriali, Bourke, Ward, Lisander and the OSTHEO formula (180-186).

Hb volume calculations include the Hb-dilution and Hb-balance methods (185, 187).

These different methods of estimating blood loss have been assessed by several authors to try and establish which is the most accurate. Gao et al. and Gibon et al. have specifically assessed these methods with regards to blood loss measurements following TKA (188, 189).

Gao et al. compared the Hb-balance, OSTHEO formula, Hb-dilution, and Gross equation methods following unilateral primary TKA. The results from each method varied widely with the Hb-balance and the Gross methods giving similar estimated volumes, with the Hb-dilution formula likely to underestimate blood loss and the OSTHEO method likely to overestimate it. They conclude that the Hb-balance method is likely to be the most accurate and reliable method. Indeed, the Hb-balance method has been used by several contemporaneous orthopaedic studies due to its supposed higher accuracy and intuitive expressiveness (187).

Gibon et al. assessed predominantly HCT methods, including those form Gross, Mercuriali, Bourke, Ward, and Lisander. As a comparison, the Hb-dilution method, as well as the weighing of swabs and measuring drainage volume as a direct measure was used. In a similar finding to Gao et al. the Hb-dilution method was found to underestimate blood loss. Although used by Yu et al. prospectively, when calculating blood loss with compression bandage use, they also state that the Gross formula is better used for autologous blood donation calculation rather than for prospective or retrospective studies. From the findings presented, the Mercuriali method was highlighted as the most accurate. However, this depends on a day five post-operative HCT level. Within an enhanced recovery setting, participants length of stay, as reported within Northumbria NHS trust, the mean stay of 3.2 days will not allow this measurement to be routinely taken (147).

Following appraisal of the aforementioned methods, the Hb-balance method appears the most accurate and reliable calculation for use within this particular study and timeframe, giving an applicable measure of blood loss volume (figure 20).

i. $Hb_{loss\ total} = EBV \times (Hb_{pre} - Hb_{post}) \times 0.001 + Hb_t$

ii. $V_{loss\ total} = 1000 \times Hb_{loss\ total}/Hb_{pre}$

$Hb_{loss\ total}$ (g)- Total Hb loss

EBV (ml)- Estimated blood volume from Nadlers calculation (figure 19)

Hb_{pre} (g/dl)- Pre-operative Hb value

Hb_{post} (g/dl)- Post-operative Hb value

Hb_t (g)- Blood transfusion value

$V_{loss\ total}$ (ml)- Blood loss total

Figure 20: Hb-balance method for calculating blood volume loss

3.3 Timeframe

It is important to ascertain a clinically relevant timeframe for assessing blood loss associated with TKA. The use of a compression bandage will be applied from the time of surgery for 24 hours and the hypothesis is that a tamponade like affect will occur, thus limiting the amount of bleeding that will occur.

As stated previously, approximately 90% of overall blood loss occurs within the first 24 hours post-operatively and from Cuenca et al. the use of Hb levels at 24 hours post-operative is an accurate indicator of blood loss after TKA (81, 169). As such, samples taken on the first day post-operative will give a reliable measure of overall blood loss and any statistically significant difference between the groups is likely to be down to the bandage allocation.

Blood samples are also routinely taken as part of post-operative care on the first day post-operative. This will ensure no excess tests are unethically or unnecessarily performed on participants as the blood result information provided will have real-time clinical benefit as well as measurements for the trial.

Pre-operative blood levels will be taken at a surgical pre-assessment clinic allowing modifiable risk factors to be identified and corrected prior to surgery. This includes the identification and correction of pre-operative anaemia.

Hb levels pre-operatively and 24 hours post-operatively will be retrieved from the trust pathology results system (ICE; Sunquest Information Systems [Europe] Ltd.).

The assessment of acute pain is also maximal following surgery and any potential benefit from utilising the compression bandage is likely to be observed within the first day post-operative. As such, pain scores will also be assessed throughout the first 24 hours post-operative.

3.4 Setting

As an embedded trial within KReBS, this was a prospective RCT. Although set within KReBS; data collection and subsequent analysis, as well as the write up has been kept separate. It aims to assess the clinical effectiveness of a compression bandage system within an enhanced recovery setting by analysing post-operative blood loss and acute pain following TKA.

The trial was registered on 20th February 2017 with the International Standard Randomised Controlled Trial Register (ISRCTN 87127065). A trial protocol for KReBS which includes this sub-study was published online on 8th May 2019. Ethical approval was granted by North East – Newcastle & North Tyneside 2 Research Ethics Committee (16/NE/0400) in February 2017.

The study participants were all recruited from within Northumbria NHS foundation trust with orthopaedic surgeons operating at three trust sites: Hexham General Hospital, North Tyneside General Hospital, and Wansbeck General Hospital as part of KReBS.

3.5 Participant recruitment into main ‘KReBS’ trial

Patients due for primary TKA were approached to be recruited into KReBS and assessed for eligibility. A detailed 'patient information sheet', which clearly explains the risks and benefits of trial participation was given to each patient by a research nurse. The participants were also given a contact phone number enabling clinical staff to answer questions relating to the study. Each participant was given at least 24 hours from receiving initial information to reaching a decision on whether to take part. Participants were also given the opportunity to discuss the trial with research staff of treating surgeon prior to their surgery. Patients were approached at a variety of locations including pre-operative education classes, surgical pre-assessment clinic and following orthopaedic clinic consultations.

Following confirmation of eligibility, written informed consent was obtained by research staff prior to surgery.

3.5.1 Eligibility

3.5.1.1 Inclusion criteria

Patients were eligible for the KReBS trial if they fulfilled all the following criteria:

i. Scheduled for primary total knee arthroplasty.
ii. Aged 18 years and over.
iii. Willing and able to provide written informed consent.

3.5.1.2 Exclusion criteria

Patients were ineligible for the KReBS trial if they fulfilled one or more of the following criteria:

i. Unable or unwilling to provide informed consent.

ii. Had a history of peripheral vascular disease.

iii. Had a history of peripheral neuropathy.

iv. Had a history of, or current, venous ulceration on the operative limb.

v. Had absent foot pulses

vi. Planned same-day discharge joint replacement patients.

vii. Scheduled for revision knee arthroplasty

viii. Scheduled for unicondylar or patellofemoral joint knee arthroplasty

ix. Scheduled for bilateral knee replacement.

x. Prescribed regular concomitant high-dose anti-coagulant medication (patients on routine thromboprophylaxis can be included)

xi. Lacked mental capacity and were therefore unlikely to comply with data collection

3.5.1.3 Inclusion into embedded sub-study

Participants recruited into KReBS within Northumbria NHS trust were routinely included within this sub-study. As such, the first one hundred and fifty-six eligible participants for KReBS were included. The sample size calculation is included in section 3.7.1. No time limit was put on the recruitment phase for the embedded study due to the significantly smaller sample size than the main trial.

3.6 Randomisation

Simple, equal randomisation without stratification or blocking was used to generate the treatment allocation schedule. As the sample size of the trial exceeds one hundred there is no loss of statistical efficiency using simple randomization compared with using more

complex (restricted) randomisation methods (190). Following assessment of eligibility and informed consent, participants were randomised into the KReBS trial in a 1:1 ratio of compression to non-compression groups via a secure online randomisation system at the York Trials Unit (YTU), University of York. This ensured adequate concealment and immediate unbiased allocation.

Due to the nature of the intervention, no blinding for surgeons or participants could reasonably occur. Surgeons, however, were informed of treatment arm allocation following closure of the surgical wound by the research nurse and were not involved in the eligibility assessment or randomisation of participants. They were also not part of data collection, synthesis or analysis.

3.7 Surgical procedure

Although part of a larger pragmatic trial and the surgery being undertaken by twelve orthopaedic surgeons, due to the full enhanced recovery set-up within a single NHS trust's orthopaedic unit, much of the surgical procedure was uniform.

A midline skin incision was used throughout with the on-going approach through the deeper layers of the knee being surgeon's preference and due to clinical need. Patients received spinal anaesthesia (low-dose spinal anaesthesia: 2 to 3 mL of 0.25% Bupivacaine (plain) or 2 mL of 0.5% Bupivacaine (heavy)) with or without sedation. At induction of anaesthesia, IV antibiotics (gentamicin 3 mg/kg and teicoplanin 400 mg IV) and tranexamic acid (30 mg/kg IV up to 2.5 g) were also routinely administered.

A Nexgen (Zimmer, Swindon, United Kingdom) cruciate-retaining total knee prosthesis was used in conjunction with Palacos, Refobacin and Gentamicin bone cement (Heraeus Medical, Newbury, United Kingdom). Local anaesthetic, in the form of intra-operative periarticular injections of 100 ml 0.125% bupivacaine, was infiltrated prior to skin closure.

Skin closure was down to the surgeon's particular inclination and consisted of either surgical clips, absorbable sutures or a combination of the two. A sterile hydrocolloid dressing (Aquacel Surgical, Convatec Ltd., Flintfield, UK) was used for the wound dressing. Bandages

were then applied according to randomised group allocation.

Tourniquet use was down to the individual surgeon's preference and was recorded throughout. Electrocautery and routine haemostasis were performed during the surgery. Surgical drains were not used as is the routine practice within the Northumbria orthopaedic fast track unit.

Post-operative care was identical regardless of group allocation. Bandages were removed at 24 hours leaving the hydrocolloid dressing in-situ and cryocuffs subsequently applied.
Full weight bearing and mobilisation with physiotherapy input on the day of surgery was aimed for as standard and discharge to home once the patient was independently mobile with the help of appropriate walking aids and pain well controlled. Within the ERAS setting, early range of movement and mobilisation was aimed for and encouraged with no limitation applied.

Post-operative analgesia included Gabapentin (300 mg twice daily for five days) and Oxycontin (5 mg to 20 mg twice daily for two days) with Oramorph (5 to 10mg as required, up to two hourly) as breakthrough analgesia.

The trigger for a blood transfusion was an Hb level of 8.0 g/dL or less or between 8.0 and 10.0 g/dL if the patient was symptomatic after hospital policy and national guidelines. Low molecular weight heparin (Clexane, Sanofi-Aventis, France, 40mg) was administered for the first fourteen days post-operative on a daily basis as routine thromboprophylaxis.

3.7.1 Intervention group

Following application of the sterile adhesive dressing, the Coban 2 (3M) compression bandage system was applied.

The foam inner layer was applied from the metatarsal heads upwards to the mid-thigh being careful not to apply tension; instead, laying it onto the limb. An approximate 10% overlap was used to reduce overall bandage bulk and still allow knee flexion and therefore not inhibit early mobilisation and rehabilitation.

The outer compression layer was then applied; from the foot upwards to aid venous return. As per manufacturers guidance the bandage was 'tightened' and stretched taught, then wrapped around with 50% overlap to ensure adequate compression was achieved.

When a tourniquet is utilised, the lower leg is first wrapped and then the tourniquet deflated and removed prior to the thigh and upper leg being wrapped with the bandage.

All surgeons had undergone bandage application training prior to partaking in the study with face-to-face training and video tutorials.

3.7.2 Control Group

Following application of the sterile adhesive dressing a single layer of soft wool bandage (Sofban, BSN Medical Ltd.,Brierfield, UK) was applied approximately 10cm above and 10cm below the patella with approximately 50% overlap. Over this a further layer of crepe bandage was similarly applied.

The bandages are removed at 24 hours post-operative up to 48 hours post-operative leaving the adhesive dressing in-situ.

3.8 Statistical analysis

3.8.1 Sample size calculation

The primary outcome for the study has been defined as the change in Hb (g/dl) from pre-to post-operative levels between the two bandage groups. As such the sample size calculation is powered to detect a statistically significant difference in this.

In order to accurately determine a sample size, relevant studies and their respective results have been assessed to ensure both statistical and clinical significance is achieved. Since this

trial lacks a placebo arm, we wanted to ensure that the effect of routine treatment was also accounted for over no treatment when determining the limit of equivalence.

A recently published, prospective RCT by Subramanyam et al. assessing the efficacy of intravenous and intra-articular tranexamic acid on post-operative blood loss following TKA has been utilised to help determine the significant level of Hb drop (191). This study uses a 0.35g/dl difference as the level of significance. This was justified by a Delphi consensus having assessed previous studies with blood loss interventions. From previous studies, compression bandaging is deemed to be low-cost and at low risk of morbidity, there is value in detecting a small difference in resultant Hb levels. By using work from Prasad et al. a 0.35g/dl difference in Hb is almost equivalent to 20% of the overall Hb drop observed post-operatively following TKA (A 2.1) (48). Within an enhanced recovery setting, this percentage saving with a low cost, low morbid intervention would carry clinical significance.

In a previous cohort study of an anaemia optimisation programme within Northumbria NHS trust, the mean pre-operative Hb value among 1,006 TKA patients was 13.7 g/dl (SD 1.3) and on day one post-operative it had decreased to 12.0 g/dl (SD 1.3) (72). The correlation between pre-and post-operative values was 0.78. As such, we will assume a slightly more conservative pre-post correlation of 0.7 for this trial.

The anaemia optimisation programme was performed in the same clinical setting as this blood loss and compression bandage trial and as such is deemed eminently transferable. Both studies will involve a similar patient population, operating surgeons and study setting, with the same NHS trust and enhanced recovery setting being used.

The 1,006 participants were operated on by sixteen different surgeons, each operating on between 1 and 110 patients (mean 63, median 70). The intra-cluster correlation (ICC) coefficient associated with day one post-operative Hb values within surgeon was <0.001.

In order to limit the possibility of a type II error from occurring the power has been set at 90% and an alpha value set at 0.05%. To account for any potential loss to follow up a 10% attrition rate has been included.

As such, a sample size of 156 participants (78 in each group) will give us 90% power to detect a difference in post-operative Hb level (the primary outcome measure) between the compression and non-compression groups of 0.35 g/dl (SD 0.7, equates to an effect size of

0.5), assuming a pre-post correlation of 0.7, 10% loss to follow-up, an average of sixty procedures per consultant (from KReBS) and an ICC of 0.01.

3.8.2 Statistical analysis plan for outcomes

Statistical analysis will be performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

Baseline characteristics for the overall cohort, compression and non-compression groups will be presented as number, mean and SD for continuous variables and as number and percentage for categorical variables.

Operative data will be presented with the same arrangement.

Analyses will be conducted following the principles of intention-to-treat with outcomes analysed according to the patients' original, randomised group irrespective of deviations based on non-compliance, and significance tests will be two-sided at the 5% level.

The primary analysis will consist of day one post-operative Hb levels as the dependent variable in multiple linear regression, adjusting for age, bandage allocation, gender, pre-operative Hb level and tourniquet use.

Secondary analysis of HCT and blood volume loss will be analysed similarly, substituting pre-operative HCT level for pre-operative Hb level as a variable when post-operative HCT is assessed.

Secondary analysis of pain scores will consist of mean 24 hour pain scores as the dependent variable in multiple linear regression, adjusting for age, anxiety, bandage allocation, depression, gender, low back pain, previous TKA and tourniquet use. Treatment effects in the form of an adjusted mean difference will be presented with an associated 95% CI and p-value. Highest 24 hour pain score and breakthrough analgesia use, as a volume (mg), will be analysed in the same format.

Complications, defined as a DVT, PE or MI requiring hospital admission, re-admission to hospital or death within thirty days of the index TKA will be analysed using a logistic regression model adjusting for age, American Society of Anaesthesiologists (ASA) grade,

bandage allocation, gender and tourniquet use. The treatment effect in the form of an odds ratio will be presented with an associated 95% CI and p-value. Allogenic blood transfusion rates will be similarly analysed.

Length of hospital stay in days will be analysed via a mixed effect Poisson, or negative binomial, regression model as appropriate, adjusting for age, ASA grade, bandage allocation, gender and tourniquet use and presented as an incidence rate ratio, 95% CI and p-value. Separate scatter plots will also be used to assess and observe specific trends between Hb drop and mean 24 hour pains scores with length of stay.

Post-hoc analysis

Following the initial multiple linear regression analysis of the primary outcome and secondary outcomes, a further regression analysis was performed assessing for an interaction between tourniquet and compression bandage use. The was performed for the primary outcome and the secondary outcome, mean 24 hour pain scores. This analysis was performed as both tourniquet use and compression bandages were statistically significant predictors of post-operative Hb levels. For mean pain scores, both tourniquet use and compression bandages had modest but non statistically significant increases in scores. A synergistic effect of tourniquet use and compression bandaging for both pain scores and blood loss could not be discounted without further analysis and would provide additional valuable detail.

Linear regression analysis was performed with post-operative Hb as the dependent variable adjusting for age, gender, bandage allocation, pre-operative Hb, tourniquet use and a bandage/tourniquet interaction. For mean 24 hour pain score adjustments were made for age, anxiety, bandage allocation, depression, gender, low back pain, previous TKA, tourniquet use and bandage/tourniquet interaction. Treatment effects in the form of an adjusted mean difference are presented with an associated 95% CI and p- value.

3.9 Compression bandage

To assess the efficacy of compression bandaging following TKA, an appropriate compression bandage needs to be chosen as the intervention. Compression bandaging can take many different forms and as such there is not one particular type available. Indeed, the use of simple, non-compression wool and crepe bandages can be utilised in a 'compressive' manner, as initially described (135).

To satisfy the demands of patients, surgeons and healthcare systems the compression bandage must fulfil several criteria. Namely, tolerability and comfort, ease of application, be non-restrictive and allow adequate range of movement and effective rehabilitation.

To assess our research question, the compression bandage must also be able to exert sufficient pressure to the limb, potentially decreasing post-operative blood loss and acute pain.

As such, an appropriate compression bandage has been chosen for KReBS and this trial.

3.9.1 Types of compression bandages

To satisfy the important criteria set out above, appraisal of current compression bandaging methods is necessary.

Charalambides et al. assessed compression bandage use following TKA whilst also measuring intra-articular pressures (138). Tourniquets were used and they observed intra-articular pressures rising consistently following their release, plateauing after 30 minutes. Within 5 minutes of release, the mean pressure was approximately 35mmHg. As such, to create sufficient tamponade effect, a minimum pressure of 30mmHg to 40mmHg has been hypothesised and hence any compression bandage utilised to achieve adequate compression post-operatively should achieve this level.

Pressure transducers have also been used by Melhuish et al. to demonstrate significant variability in sub-bandage pressures, ranging from 21 to 67 mm Hg (192). The main factors said to create this variability included the number of layers used, the surface hardness of

the limb and the radius of the surface being bandaged. As such, any compression bandage used within this trial must achieve a reproducible and consistent level of pressure following application even though the surface hardness and radius of the limb may vary.

A key element of ERAS is efficient and timely rehabilitation. To achieve this, the compression bandage should not be restrictive and hence allow uninhibited range of movement. It is envisaged that the use of a compression bandage may have benefits with post-operative blood loss, analgesia use and functional outcomes. In order to maximise these outcomes, the bandage should not inhibit or delay post-operative rehabilitation.

Indeed, within an enhanced recovery setting, rehabilitation aims to commences on the day of surgery. The compression bandage should therefore limit the amount of material used and overall bulk, particularly within the popliteal fossa which could limit flexion.

With this crucial rehabilitation goal, the use of a bulky, RJB consisting of multiple layers of wool and crepe bandage has been discounted. It is also highly user dependent to achieve both equal and reproducible sub-bandage pressures.

From the information attained from the systematic review and other relevant studies, post-operative compression can be achieved by a variety of methods and different types of bandages. These include standard, elastic and inelastic constructs (table 5). The earlier studies by Gibbons et al. and Smith et al. used RJBs with wool and crepe and not a specific compression layer. Later studies have since used either an elastic or inelastic layer to achieve compression.

Compression bandages have traditionally been classified according to their inherent elasticity. Bandages with a maximal extensibility of < 100% are called ‘short stretch’ or inelastic and those with > 100% stretch are termed ‘long stretch’ or elastic (146). However, these properties can change, if for example, multiple layers of an elastic bandage are applied, it invariable behaves in an inelastic manner.

Study	Year	Inner layer	Outer layer	Type	Time in-situ
Gibbons	2001	3 layers wool	3 layers crepe	Standard	48 hours
Smith	2002	Thick wool	Crepe	Standard	24 hours
Charalambides	2005	2 layers wool	Septopress (Molnlycke)	Elastic	24 hours
Andersen	2008	2 layers wool	Acrylastic (BSN)	Elastic	24 hours
Munk	2013	Coban 2 (3M)	Coban 2 (3M)	Inelastic	12-24 hours
Pinsornsak	2013	Thick wool	Elastic bandage	Elastic	24 hours
Cheung	2014	Wool	Actico (Activa)	Inelastic	24 hours
Brock	2017	Wool	Actico (Activa)	Inelastic	24 hours
Pornrattanamaneewong	2018	3 layers wool	2 layers elastic bandage	Elastic	24 hours
Stocker	2018	Wool	Comprilan (BSN)	Elastic	22hours/day for 5 days
Yu	2018	Thick wool	Coban 2 (3M)	Inelastic	24 hours

Table 5: Types and use of compression bandaging in previous studies

3.9.2 Participant tolerability and side effects

In addition to providing compression, the bandage must also satisfy other important criteria. The chosen bandage must be well tolerated by patients as it is likely to be in situ for a minimum of 24 hours and should not cause un-due discomfort. Discomfort will limit the bandages tolerability and decrease patients overall experience.

Side effects, such as skin complaints, should also be kept to an absolute minimum, as too should more significant complications, such as deep vein thromboses and nerve palsies, which carry significant morbidity and invariably lead to increased hospital stays and poorer outcomes.

Study	Year	Complications
Gibbons	2001	Nil
Smith	2002	Not recorded
Charalambides	2005	Blisters 3 Bruising 4
Andersen	2008	Not recorded
Munk	2013	Nil
Pinsornsak	2013	Blisters 3 Bruising 1
Cheung	2014	Not recorded
Brock	2017	Nil
Pornrattanamaneewong	2018	Bruising 5 Haematoma 1
Stocker	2018	Superficial infection 1
Yu	2018	Blister 1 Bruising 1

Table 6: Recorded complications following compression bandage use in previous studies

Three of the studies did not record complications or side effects. Of those that did record them, there were no significant complications such as deep vein thromboses, pulmonary embolisms or deep infections. More minor and superficial skin complaints, such as blisters and bruising, were recorded by five of the eleven studies (table 6).

There was a distinct correlation between the type of bandage used and the number of side effects seen. Complications appear to be more frequent when using an elastic bandage and less likely to be observed when utilising an inelastic bandage (table 7).

Bandage type, n	Blisters	Bruising	Haematoma	Superficial Infection	Overall
Elastic, 115	6	10	1	0	17
Inelastic, 120	1	1	0	1	3

Table 7: Type of compression bandage and recorded complications and side effects

With this information identified, the side effect profile appears to be greater for elastic rather than inelastic bandages following TKA, however, no significant complications were noted.

Brock et al. as a pilot study which preceded KReBS reported that the inelastic bandage was well-tolerated by patients, with no reports of discomfort or restriction (147). Furthermore, there were no highlighted problems with bandage application by the operating surgeons.

Yu et al. is the only other study that assessed tolerability or perceived comfort with the use of compression bandages. A comfort level questionnaire regarding the feeling of the operated lower limb was used by asking participants to rate their comfort, ranging from very uncomfortable to very comfortable. A statistically significant difference between compression and non-compression groups at 24 hours post-operative ($p=0.03$) which subsequently declined by 72 hours post-operatively was presented.

Yu et al. used an outer layer of Coban 2 (3M) with a thick inner layer of 'winner' cotton wool bandage. Coban 2 (3M), is an inelastic, short stretch bandage that is designed as a complementary two-layer system with specific inner and outer layers. As such, it is possible that the perceived increase in discomfort could result from not using the correct inner layer as part of the synergistic system as intended by the manufacturer. There is no justification from the authors detailing this decision to use cotton wool bandage in preference to the Coban 2 inner layer.

3.9.3 Inelastic versus elastic bandages

In addition to the observed increase in minor complications with elastic bandage use following TKA, there are other differences between elastic and inelastic bandages. Much of this knowledge arises from studies assessing their application with regards to chronic venous leg ulcers, lymphoedema and tissue viability.

Inelastic bandages are able to generate larger dynamics, or amplitudes underneath the bandage than elastic bandages. This increase is then able to achieve a greater degree of compression (193).

Additionally, the more rigid compression system generated by an inelastic bandage are able to distribute muscle contraction forces more equally, thus improving the muscles efficacy as a pump and subsequently reducing oedema. Indeed, Partsch et al. also state that inelastic

material is more effective at reducing deep venous refluxes than elastic bandages in patients with venous ulcers and hence reduce the accumulation of tissue oedema (194).

As patients undergoing TKA will be mobilising on the day of surgery and partaking in early rehabilitation, the increased efficacy of the muscles as a pump could have a large impact on outcome. The use of inelastic bandages following TKA are likely to be preferable as they have a low, tolerable resting pressure but a more effective activation of the deep venous system and calf-muscle pump with ambulation compared to their elastic counterparts (195). By mobilizing early and incorporating the calf muscle pump, the accumulation of fluid may be effectively reduced, whilst the lower pressures at rest should improve concordance.

As fewer side effects have been observed, along with higher dynamic pressures, participant tolerability from the pilot study and with evidence of increased muscle efficiency, an inelastic compression bandage system was deemed to have the best profile for improving outcomes following TKA.

3.9.4 Coban 2 (3M) compression bandage system

Coban 2 is a two-layer compression bandage system manufactured by 3M. It consists of an inner foam layer and an outer compressive layer consisting of short-stretch inelastic material working together.

It provides tolerable resting compression pressures of 35mmHg to 40mmHg, and, due to the inelastic properties further enhances venous return and effectively the recruits the calf muscle as a pump with ambulation. Muscle contraction during ambulation produces peaks in pressure due to resistance of the rigid inelastic properties of the compression bandage (figure 20). Intermittent pressure peaks are therefore seen, creating a massage like effect. As the muscles relax and the pressure drops between each muscle contraction the intermittent squeezing of the veins during walking further enhances deep venous return and limb swelling (196).

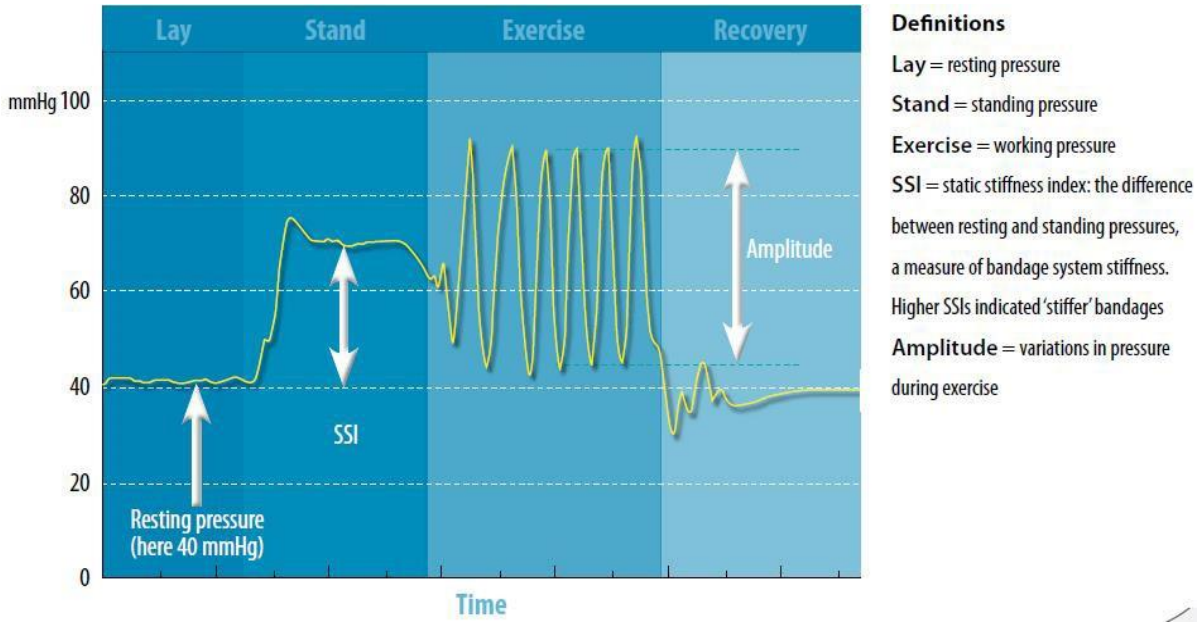

Figure 21: Coban 2 sub-bandage pressures highlighting peak pressures with ambulation from Vowden et al. (196).

This compression bandage system has been used for many years within tissue viability for the management of lymphoedema and the treatment of chronic venous ulcers. Indeed, the manufacturer states it application is 'For management of venous leg ulcers, oedema, lymphedema and other clinical conditions where compression is appropriate' (197).

Amongst the purported benefits of Coban 2, the overall profile of the product is said to be thinner than other products available, thus allowing patients to wear their normal clothes and shoes. This positively contributes to quality of life and importantly to compliance, whilst also potentially leading to more effective therapy through ambulation (198). This reduction in bulk is perhaps even more important when utilising a compression bandage following TKA. It is imperative to commence post-operative rehabilitation in a timely manner. Indeed, within an enhanced recovery setting, range of movement exercises and rehabilitation often occurs on the day of surgery. As such there should be no impediments to this and any bandage applied to specifically aid recovery should allow the knee to move and flex without restriction. An overall thinner bandage will allow more flexion to occur.

As the bandage has been designed as a synergistic two-layer system it also experiences less slippage than other bandages, and hence remains in place applying consistent pressure

(198). This should again allow a greater freedom of movement around the knee as the bandage is less prone to bunching (200). This is achieved by the inner layer having a cohesive surface which allows the outer compression layer to attach to it when applied.

Notably, the application of the bandage is also said to be reproducible and consistent. In a study involving thirty-two 'experts' and an artificial leg model, the Coban 2 two-layer compression system was reported to be easier to learn and provided more consistent pressure values than other bandages tested (199). This is a significant factor for ensuring homogeneity within the clinical trial. The bandages will be applied by multiple surgeons and it is important that they are able to reproduce sufficient and accurate sub-bandage pressures following each application. The ease of using an intervention in routine care following a trial is also important to consider with regards the widespread uptake of any significant outcomes produced by a clinical study (200).

With these factors in mind the Coban 2 compression bandage system was chosen for the trial intervention group. Two other clinical trials have used Coban 2 when assessing outcomes following TKA (table 3.3). Yu et al. used the outer compressive layer with an inner layer of thick wool bandage, whereas Munk et al. used the complete two-layer system. However, Munk et al. removed the compression bandage on the morning the day after surgery and replaced it with a class II medical elastic compression stocking. At present no studies have utilised the Coban 2 compression system for 24 hours assessing both acute blood loss and pain, or longer-term outcomes such as those being assessed by KReBS. 3M, the manufacturer of the Coban 2 compression bandages, provided funding for the main study KReBS. This included the procuring of the bandage system itself and in extension, this sub-study also utilised the industry funding and hence, the choice of bandage was influenced by this connection. Other than the monetary funding and hence compression bandage choice, 3M did not influence the study design or have any involvement with the sub-study itself.

3.9.5 Coban 2 application

In order to achieve homogeneity throughout the application of the compression bandages,

the operative surgeons involved will need sufficient education and training. Following on from the work by Brock et al. where surgeons found compression bandage application to be acceptable and re-producible, the use of face-to-face tutorials and a training video are to be utilised (147). This combination of face-to-face training in combination with a video, to help confirm and cement good practice whilst being an on-going point of reference, has been shown to be effective elsewhere. Park et al. have demonstrated video learning to be just as effective when learning asthma inhaler technique as face-to-face sessions. The benefit of face-to-face tuition is the ability to give real time feedback and answer any questions there and then. As the Northumbria orthopaedic unit has twelve eligible surgeons partaking in this trial, it is feasible to perform face-to-face training individually and to reaffirm this training with readily accessible videos and information leaflets. The compression bandage application takes simple steps and as such is also amenable to proformas and aide memoirs. The steps, as depicted in section 3.6.2, describe the process and a leaflet explaining the entire bandaging method was also produced and made available to all surgeons and in the theatres themselves (A 2.2).

Prior to partaking in the study, surgeons underwent face to face training and were directed to the readily accessible application video and leaflet. I was also able to support the surgeons throughout this study with further training and clarification of the technique, as necessary.

4 Post-operative blood loss and acute pain correlation

Both blood loss and significant pain are commonly observed following TKA. For improved patient satisfaction and outcomes, controlled pain and decreased blood loss are paramount. By improving individual outcomes such as post-operative pain and blood loss, more complex overall outcomes such as length of stay and quality of life could also be improved, impacting on the cost burden of surgery and its consequences to patients and the NHS. As an extension of assessing the efficacy of compression bandages post TKA, we additionally investigated the potential correlation between acute blood loss and pain following TKA.

4.1 Pain

Pain is a highly individual and complex experience. It has been classified into three broad categories; nociceptive, inflammatory and pathological (201).

Nociceptive: Part of an 'early warning' system and stimulated by noxious stimuli such as heat, cold or sharp objects. This triggers a withdrawal reflex via the autonomic pathway which helps prevent further injury. A painful stimulus triggers a nervous response, experienced as pain.

Inflammatory: A further protective mechanism which heightens sensory sensitivity. Along with the physical effects of inflammation, such as swelling, the pain experienced limits movement and discourages physical contact. It is mediated by the immune response and chemical mediators and occurs after injury, such as surgery.

Pathological: An abnormal response that is not protective and occurs due to abnormal

nervous system function. This can be classed as neuropathic or dysfunctional pain. Conditions which fall into this category include fibromyalgia and irritable bowel syndrome.

Following TKA, the key acute manifestations of pain are nociceptive and inflammatory in nature due to the tissue damage sustained during the operation and the body's subsequent immune and inflammatory response. An unwanted and often catastrophic progression of acute to chronic pain can develop into pathological pain. The use of a compression bandage, as assessed in this study, is likely to reduce pain, which is inflammatory in nature, if an improvement is observed. With the hypotheses of a tamponade like effect, swelling and the release of local pro-inflammatory mediators may be reduced, decreasing perceived pain.

Pain is a well-recognised outcome following TKA. Indeed, significant post-operative pain is experienced or described by almost half of patients undergoing TKA (202). This acute pain can have significant effects, not only on a patient's short-term experience and perception of recovery, but also on long-term outcomes and overall function. Acute pain can lead to increased morbidity, impaired physical function and quality of life, slowed recovery and increased cost of care (203). Post-operative pain also increases the use of analgesia and the potential side-effects associated with this including prolonged opioid use during and after hospitalization. Patients requiring more analgesia at home following discharge tend to have experienced increased post-operative pain and required higher amounts of opiates during their inpatient stay (204).

As a highly complex experience, ways in which to manage post-operative pain could have significant long-reaching effects in addition to improving a patient's short-term experience. On-going pain following TKA leads to significant patient dissatisfaction with their overall result (205).This is highlighted in questionnaires sent to patients asking them to assess overall satisfaction and 'success' of their knee replacement in addition to other PROMs and quality of life questionnaires. Ongoing pain limits a patients' function and their ability to return to activities and employment resulting in dissatisfaction with the surgical procedure itself (206).

Dissatisfaction also arises as most TKAs are performed with the explicit objective being pain

relief or at least a significant reduction. If this is not achieved, then patient expectations are not met and dissatisfaction ensues (207). This finding is corroborated by the work from Bryan et al. that showed a direct correlation between ongoing pain and a patient's subsequent dissatisfaction and their expectations prior to surgery (208).

Following TKA, 15 to 20% of patients report being dissatisfied with their outcome following their procedure (206-208). This dissatisfaction remains even when surgical factors and complications such as implant instability, mal-alignment and infection are taken into account. As TKA rates increase worldwide, the number of patients experiencing dissatisfaction is equally going to rise.

Following major joint surgery there are of course dissatisfied patients. There is however a significant discrepancy between the levels seen following TKA and THA. In a study by Varacallo et al. 24% of their TKA patients were noted to be dissatisfied with their total joint arthroplasty compared to only 2% in the THA group (209). Studies have looked at the reasons as to why this dissatisfaction occurs with post-operative functional outcome and relief of pain being paramount determinants for achieving satisfaction (210).

Baker et al. utilised a postal survey of 10,000 patients post TKA to analyse this. With a high response rate, an 81.4% patient satisfaction rate following primary TKA was highlighted. The most predictive factor for dissatisfaction was post-operative pain (7).

This finding is borne out in a 2010 prospective study by Scott et al. Dissatisfaction, as expected, is multifactorial, with mental health, pre-operative expectations and other musculoskeletal pain all influencing outcome. However, the biggest determinant was the degree of improvement in pain following the procedure (211). This is likely due to patients' expectation of it being a successful, pain-relieving operation.

As well as being highly predictive of patient dissatisfaction, acute pain can subsequently develop and contribute to the formation of chronic pain. The causes of chronic pain after TKA are complex and are not yet fully understood. Research interest is however developing, and it is evident that this chronic pain has a multifactorial aetiology, with a wide range of possible biological, surgical and psychosocial factors that can influence pain outcomes (212). Pain is linked to a patient's overall experience and post-operative symptoms and thus their pre-operative expectations also have a role to play.

Post-operative pain will negatively impact on physical activity and general mobility, whilst additionally having a deleterious impact on a patient's mental health, amplified in those who already have a depressive condition (213). Factors highlighted as having a significant role to play in the development of chronic pain post TKA include pain catastrophising, other musculoskeletal pain, high intensity knee pain, poor mental health and significant co-morbidities (214).

4.2 Current pain relief strategies within enhanced recovery after surgery

Factors influencing pain can be modifiable or fixed and can present before, during or after surgery. As such, pain relieving strategies cover a wide scope and vary considerably in their application.

As discussed in section 1.4, for lower limb arthroplasty, methods include pre-operative education especially for 'at risk' patients who have depression or anxiety, minimally invasive surgery may have a role to play and multimodal pain relief pathways, including non-opiate containing spinal anaesthetic and a 'cocktail' of analgesia pre, peri and post-operative which contains low side-effect profiles have shown excellent results (215). The inclusion of local anaesthetic infiltration appears to have a great benefit for arthroplasty patients (216).

The methods employed within ERAS aim to improve patient outcomes, by directly decreasing pain, setting appropriate patient expectations and allowing efficient timely return to function.

4.3 Does post-operative blood loss influence acute pain?

Following TKA, outcomes such as length of hospital stay and transfusion rates have continued to fall following the initiation of ERAS protocols, however, the incidence of chronic pain and subsequent dissatisfaction of around 15 to 20% remains (7). This is not the case following THA where satisfaction rates are incredibly high, reported as 90% to 93%

(217, 218). This disparity remains even though TKAs and THAs are performed on a similar patient demographic, predominantly for pain relief due to osteoarthritis, by the same surgeons within the same ERAS pathways.

As the level of overall dissatisfaction following TKA remains high, and is heavily linked to acute pain, effective ways in which acute pain can be managed have the potential to help improve outcomes and overall patient satisfaction.

Although we know some predictive factors for pain, it remains a subjective and complex emotion and further work to identify modifiable factors should continue.

With local tissue damage and subsequent inflammation occurring, we understand that pain is an expected outcome following surgery, especially one which involves both soft tissue and bone resection, such as TKA. However, could the volume of blood lost during surgery and within the post-operative period also have a role to play when managing acute pain? Could blood loss be a modifiable factor and as such could blood loss prevention also be a way of reducing pain?

To evaluate this theory an assessment of the current evidence as well as understanding the body's response to blood loss and the potential ways this could induce pain is necessary.

4.3.1 Acute blood loss

Sehat et al. state that TKA patients sustain a mean total blood loss of 1498 ml, with the hidden loss, occurring following surgery, accounting for 765 ml (49%) (171). From Kalairajah et al. a similar mean total volume loss of 1351 ml was observed (166). With the use of tranexamic acid, the total volume of blood loss observed by Good et al. reduced down to a total of 1045 ml. The overall contribution of the hidden blood loss, however, remained unaffected and also accounted for approximately 50% of the total volume (219). These overall and hidden blood loss totals are significant volumes.

It is important to consider the timeframe of this blood loss and therefore when it is likely to maximally exert any potential effect. Kumar et al. analysed the rate of blood loss post-

operatively by utilising drainage volumes. They recorded that 84% of the total blood drained was collected within the first 12 hours and 94% within 24 hours post-operatively (220).

Yang et al. corroborate this rate of blood loss with findings from their study showing 37% loss in the first 2 hours, 55% in the first 4 hours and 82.1% within 24 hours post-operative (116). These findings again highlight the significance of the first 24 hours post-operatively when assessing the effects and outcomes of overall blood loss. Any significant effects are therefore more likely to occur within the first post-operative day.

4.3.2 Physiological response to blood loss

The average adults circulating blood volume is approximately 5 litres (178). Utilising the previously cited mean total volumes lost following TKA (1-1.5 litres), mean blood loss volumes could be approximated as approximately 20% to 30% of the total circulating blood volume. This percentage loss would be classified as class 2 haemorrhagic shock and as such this a loss of this volume has the potential to initiate systemic and physiological effects (221). The effects observed in a ward setting following TKA are usually less severe than those presenting with acute haemorrhagic shock following trauma and this is likely due to the extended timeframe that the blood loss occurs, from minutes to days.

As a compensatory mechanism to this fall in blood volume, heart rate and myocardial contractility increases. The sympathetic nervous system is also activated and blood vessels also constrict, decreasing overall peripheral volume. This readies the body to conserve central and end organ blood flow and is often referred to as the flight or fight response.

The sympathetic response also consists of substantial hormonal release. This includes catecholamines such as Dopamine, Adrenaline and Noradrenaline. There is also Arginine vasopressor, Angiotensin 2 and an increase in Renin activity. Through these hormones, the effects of increased heart rate, contractility and vasoconstriction are seen amongst other widespread physiological responses.

The body’s response to stress, trauma and blood loss is complex, as too is its perception of

pain. Cortisol is released by the body as part of the stress response due to trauma. Cortisol is known to affect our perception of pain and is designed to help prevent further damage following injury. A higher level of cortisol is known to increase our perception of painful stimuli (222).

As such, following surgery and subsequent blood loss, a patient may experience symptoms such as anxiety and pain as well as clinical signs such as increased heart rate and a drop-in blood pressure. We also understand that a chronic disease process such as osteoarthritis can modulate our pain perception and pathways (223). This may sensitize local tissues to subsequent trauma and elicit a heightened effect to further tissue injury or hormonal signals. This may be further compounded by the body's acute response to this localised trauma and the occurrence of blood loss may exacerbate this further.

4.3.3 Current understanding of link between blood loss and acute post-operative pain

There have been significant numbers of studies directed at defining predictive factors for pain post TKA. Yang et al. performed a wide-ranging meta-analysis in 2019 (224). Pre-operative predictors of poor acute post-operative pain control were assessed. Within their study they highlighted nine significant, pre-operative predictors of increased acute pain. This was for all surgical patients, not just orthopaedic arthroplasty ones. These nine factors were smoking, raised BMI, young age, female gender, depressive symptoms, anxiety, sleep disturbance, pre-operative pain and pre-operative analgesia use. Some are modifiable like smoking and BMI whereas others such as gender are fixed. Liu et al. had similar findings within the THA and TKA populations and additionally stated that the severity of pre-operative pain was perhaps the most important factor (225). The role that blood loss could potentially have was not explored within either of these papers.

The inclusion of peri-operative adjuncts, such as local anaesthetic infiltration, have been shown to help reduce post-operative pain (226). Other interventions such as tourniquets have equivocal contemporary evidence for reducing pain and their influence in reducing overall blood loss is also controversial with studies reporting conflicting results (61).

In current literature there are only three papers that have explored the potential link between operative blood loss and pain following TKA, indeed, there has been very little exploration of this throughout all surgical specialities (table 8).

If there is a link between post-operative pain and blood loss it can be thought of as either; acute blood loss resulting in increased pain, or acute pain resulting in further or higher blood loss. As such, studies have analysed this potential link from both stand points.

Study	Year	Title	Key results
Guay et al.	2006	Post-operative pain significantly influences post-operative blood loss in patients undergoing total knee arthroplasty	Positive correlation between measured blood losses and; • morphine consumption at 12 to 18 hours (P = 0.006) • pre-operative mean arterial blood pressure (P = 0.01)
Kim et al.	2011	The effect of post-operative pain on post-operative blood loss after sequential bilateral total knee arthroplasty	Post-operative mean arterial pressures and blood loss were not different among the mild, moderate and severe pain score groups
Hegarty et al.	2015	The effect of peri-operative blood loss on post-operative pain following total knee arthroplasty	Increasing levels of peri-operative blood loss have no direct relationship with levels of post-operative pain

Table 8: Summary of studies assessing potential link between blood loss and pain following TKA

4.3.3.1 Acute pain influences blood loss

In the study by Guay et al. they state that for patients undergoing TKA, post-operative pain significantly contributes to post-operative bleeding (227). This conclusion was made from their prospective RCT evaluating three separate post-operative analgesia pathways,

including IV morphine patient-controlled analgesia (PCA) alone or IV PCA plus a continuous femoral (three-in-one) nerve block (CFNB) or a continuous posterior lumbar plexus (psoas compartment) nerve block (CPNB). TKAs were performed using normotensive spinal anaesthesia.

Intra-operative blood losses and total blood losses were measured and calculated as were pre- and post-operative Hb levels.

Their hypothesis centres around an increase in blood pressure due to pain subsequently causing increased blood loss. As such mean arterial pressures (MAP) were measured to assess this correlation.

Utilising stepwise regression, they found a positive correlation between increased morphine usage, an indirect surrogate for pain, and blood loss (Morphine usage between 12 to 18 hours and blood loss, p=0.006). From this, they drew their conclusion of pain significantly influencing post-operative blood loss. There was no direct analysis between the measured pain scores (VAS) and blood loss. There was also no reported significant difference between the groups MAPs. Mean intra-operative measurements were; IV PCA 91.7mmHg (SD 12), CFNB 88.3mmHg (SD 15.6), CPNB 88.3mmHg (SD 12.2) P >0.85.

From this study there is a suggestion that there is a relationship between blood loss and pain. The conclusion drawn, however, is not robustly supported by the VAS, a direct marker of perceived pain, and is not included in their analysis. This is a real draw-back of this paper and questions arise as to why no analysis was performed considering that the ‘aim of this study was to evaluate the effect of pain on perioperative blood losses of patients undergoing primary TKA’. The conclusion is drawn from a correlation between morphine usage within the first day post-operative (12 to 18 hours) and blood loss. As the study was looking at effectiveness of three different analgesic therapies, the more effective the therapy the lower the VAS and perceived pain and as such an increase in morphine usage needed to control pain could still be used to indicate a link with blood loss.

The number of participants used was also low (n= 60 split equally into 3 groups of 20) and with statistical analysis being performed between the three groups an increased risk of error is inherent. There is also no power or sample size calculation included to attribute the chosen sample size.

From this work they hypothesise that the correlation may occur as a result of sympathetic stimulation due to pain and thus an increase in arterial blood pressure and hence surgical blood losses. With a higher pressure, blood flow increases and normal clotting is less likely to occur; as stipulated by Virchow's triad, which is necessary for adequate blood coagulation (228).

A further prospective study by Kim et al. has also assessed the role that acute pain commands with increasing blood loss post TKA (229).

The intensity of post-operative pain was compared to blood loss following simultaneous bilateral TKAs in 91 participants. Bilateral TKAs were chosen due to their reported higher volume of blood loss to unilateral TKAs. In a similar method to Guay et al. MAPs were measured as was blood loss and pain scores for the first 24 hours post-operatively.

The working hypothesis surrounded hypotensive spinal anaesthetic and its role in helping prevent operative blood loss, and the fact that blood loss and pain is higher in bilateral rather than unilateral TKA.

For analysis, participants were split into three groups according to their VAS pain score at 6 hours (mild 0 to 4, moderate 5 to 6, severe 7 to 10).

As shown in previous studies, such as by Boutsiadis et al. the only predictive factor for overall blood loss was intra-operative blood loss ($p=0.001$)(61). With a mixed effect linear model post-operative pain score did not influence blood loss ($p=0.736$). Additionally, MAP and blood loss did not differ between the three groups and hence no correlation was identified. Thirty-three participants were included in the mild pain score group, twenty-four in the moderate and thirty four in the severe group, respectively. Median intra-operative blood loss was recorded as 200mls for each group (inter-quartile ranges: mild 150mls to 300mls, moderate 200mls to 350mls, severe 180mls to 320mls) and the mean MAP was; mild 94mmHg (SD 8), moderate 93mmHg (SD 10) and severe 91mmHg (SD 10).

As such, it was concluded that there was no direct link between post-operative blood loss, pain or MAPs.

4.3.3.2 Blood loss influences acute pain

A study from Hegarty et al. has assessed the correlation between blood loss and pain scores following TKA (230). In contrast to both Guay et al. and Kim et al. who hypothesised that acute pain, due to raised MAP, would cause increased blood loss, Hegarty et al. explored if blood loss itself influenced the amount of post-operative pain a patient experienced following TKA. Their hypothesis states that patients with increased blood loss would suffer increased pain. The potential, causal mechanism for this to occur was not suggested or described within the study.

Hegarty et al. combined data from two previous RCTs conducted by the same research team from 2006 and 2009 respectively, giving a total of 403 participants. These two separate RCTs were conducted to assess outcomes on two different total knee prostheses. The specific outcomes assessed in these two studies are not clearly detailed within the latest study.

Within the two RCTs used with for the latest study by Hegarty et al. VAS pain scores were collected within one week post-operative and then again at four and eight weeks, respectively. The precise time of the VAS pain score collection within the first week was not explicitly stated and remains an unknown, potentially occurring up to seven days post-operatively and at different timepoints for different participants. OKS were also collected in one of the two previous studies at 3 months and one-year post-operatively.

Day one and day two post-operative blood loss volume was calculated using the 'Gross formula' and thus estimated from HCT levels. This estimated blood loss was then used for subsequent analysis.

Of the 403 participants, thirty-one had inadequate pain diaries and twelve were missing full HCT values; therefore, the final analysis was based on a cohort of 360 participants. The null hypothesis of there being no correlation between blood loss and pain was accepted following analysis. At no measured time point was there a statistically significant correlation between estimated blood loss and VAS pain scores. Pearson's correlation was used for the analysis of the estimated blood loss on day one and day two post-operative and the respective VAS pain scores. This was not statistically significant at any stated time point. The data and values for average blood loss and pain scores were not included in the paper.

Further analysis of their results was performed by assessing patients whose blood loss results were one standard deviation from the mean on days one and two post-operatively. Similarly, no correlation was identified.

There was also no correlation between blood loss and the OKS, and hence overall function.

This is currently the only study that has assessed any potential effect that post-operative blood loss may have on post-operative pain. The main concerns with this study are the ceiling effect of the VAS pain score, recorded 0 to 10, with 10 being the worst possible pain, and the retrospective collection of data from two previous studies, not designed to assess or detect this potential correlation. A significant proportion of participants were scoring maximum scores of 10 with the VAS. Ceiling effects can be a problem with utilising VAS as a pain score, as stated by González-Fernández et al. (231). As such, a significant correlation between blood loss and pain may have existed but was not able to be shown as those experiencing high levels of pain and therefore scoring a maximum were not able to express any further increase. We are also unsure if the VAS was a one-off score or an average of pain scores collected through a particular time period such as 24 hours. A scatter plot was used to assess any correlation between blood loss and pain. Again, the actual data on VAS is not included in the paper so it is difficult to assess the actual pain scores and the numbers of participants measuring these maximum scores.

The participant cohorts were also retrospectively collected from two separate RCTs comparing different total knee prostheses. The initial RCTs were not designed to assess for a potential correlation between pain and blood loss and as such an element of bias cannot be excluded, especially with forty-three participants being excluded for incomplete data, over 10% of the initial cohort. The included data does not show values for the recorded outcomes and there is also scarce baseline characteristics included. Any accounting for baseline variables has not been highlighted if indeed they were used.

From these three papers presented, there is currently no robust evidence to confirm that blood loss and pain are linked post-operatively. However, there is also little evidence to firmly discount this as the papers have many flaws in their methodology and limitations. As such, blood loss may still have a role to play in the experience of acute pain following TKA.

4.3.3.3 Limitations of current studies and ways to improve knowledge

Study	Limitations
Guay et al.	• Three different types of post-operative analgesia analysed and small population (n=60 in total)- limits power • Arbitrarily estimated blood volume calculated as 65 mL/kg for men and 60 mL/kg for women • Assessed 'pain causing blood loss' by measuring blood pressure
Kim et al.	• Pain groups split unevenly: mild 0 to 4, moderate 5 to 6, severe 7 to 10 • Intra-operative blood loss measurements only- with tourniquet • Concern over accuracy of blood loss measurements • Assessed 'pain causing blood loss' by measuring blood pressure
Hegarty et al.	• Potential ceiling effect of VAS pain scores • Retrospective RCTs combined for new hypothesis • Significant baseline predictors of pain not used in analysis • Imprecise timeframe for pain scores (one week, four weeks, eight weeks) • Incomplete data (10%)

Table 9: Summary of limitations of studies assessing link between blood loss and pain following TKA

Further assessment of any potential correlation is justified as the limited evidence currently available also has identifiable gaps and flaws which can be improved upon.

Guay et al. and Kim et al. have opposing final conclusions following their respective studies, which both analyse the effect of pain on blood loss, with the assumption that pain would increase MAPs. Guay et al. conclude that there is a significant correlation, drawn from a statistically significant correlation between morphine usage post-operatively and subsequent blood loss volumes whereas Kim et al. did not identify any correlation between their outcomes.

Although 'hypotensive epidural anaesthesia' (HEA) has been shown to reduce overall blood loss in TKA, it is proposed to achieve this by reducing the MAP. This has been highlighted by

Juelsgaard et al. where intra-operative MAP was recorded as 48 mm Hg (HEA) versus 83 mm Hg (Spinal) and subsequent overall blood loss was measured as 1,056 mL (HEA) versus 1,826 mL (Spinal). From Guay et al. and Kim et al. there was no difference in either intra-operative or post-operative MAPs between the groups analysed. Additionally, the operations themselves were all performed under normotensive spinal anaesthesia. With this is mind it is unlikely that the conclusions drawn from Guay et al. 'through sympathetic stimulation, pain may increase arterial blood pressure and hence surgical blood losses, this might be particularly true in major orthopaedic surgery where hypotensive anaesthetic techniques have been used to decrease intraoperative blood losses' are valid.

Another limitation from Guay et al. is the use of an arbitrary figure of 65ml/kg (male) and 60ml/kg (female) for the estimated blood loss calculation rather than individual heights and weights.

For Kim et al. the significant limitations arise from the blood loss measurements being intra-operative with the use of tourniquet. With this method, no difference in blood loss is likely to be observed. By not assessing the 'hidden' blood loss, which equates to approximately 50% of the total volume, the volume of blood loss is being under-reported, and any correlation missed. Additionally, the blood volumes recorded are all rounded figures for each group (200ml, 200ml, 200ml) raising suspicions around the accuracy of the measuring and recording of the volumes. There was also no justification as to the cut-off points for the pain score groups.

The conclusions from Hegarty et al. may also be masking the true result due to the ceiling effect seen with their VAS results and although acute blood loss was measured at one and two days post-operatively the pain scores were recorded at a later date which is nebulous in its description; 'within the first week and subsequently at four and eight weeks'. Any effect from the acute blood loss may not have a significant effect on pain experienced at a later timepoint. We are also unsure if the stated VAS is the score for the highest pain levels experienced or an average score over a particular timeframe. The final data included in the paper is also sparse limiting our ability to assess it further.

As almost all blood loss occurs following TKA within the first 24 hours post-operative it is therefore reasonable to suggest that the maximal effect that blood loss would have on pain

is also likely to occur during this time (116, 220). No studies have yet analysed this particular timeframe and correlation. The earliest that Hegarty et al. analysed pain was vaguely described as 'within the first week'. The acute timeframe, around 24 hours, is undoubtedly the most important as any physiological effects of blood loss are likely to be at their strongest.

Although Hegarty et al. did analyse those patients with a blood loss one standard deviation away from the mean separately, further work can be done to stratify and correlate the effect of blood loss on pain. There may be a specific trigger or tipping point for when blood loss becomes critical and increases pain perception. Along these lines, an assessment of whether there is a notable threshold for volume of blood lost beyond which particularly high pain scores are associated could also yield important results, aiding further input for 'at risk' patients.

There are also recognised, key predictive factors for post-operative pain. From the previous studies it is unclear if these have been adequately accounted for, such as in the analysis by Hegarty et al. The baseline characteristics included were simply gender, BMI and age. It will therefore be paramount to include other noteworthy factors such as depression and anxiety, as well as smoking status, in any further analysis to account for their potentially positive predictive value for post-operative pain (203).

A way of combating the potential ceiling effect as observed in Hegarty et al. could also give a more accurate portrayal of any potential correlation. To help overcome this, the mean pain score over the first 24 hours post-operative, could be utilised as well as further analysis of the highest recorded score in the first 24 hour period. The mean score is highly unlikely to exhibit maximal scores throughout a 24 hour period and will hence give a more accurate picture of overall pain experience without as significant a ceiling effect. In conjunction with this, a surrogate marker for pain, such as breakthrough analgesia requirement, could also be analysed.

4.4 How might blood loss affect acute pain?

Pain is a highly complex and multifaceted response and although it is beyond the scope of this study to prove its mechanism of action, it is important to hypothesise the foundations as to why any correlation may occur between pain and blood loss.

There is a significant difference not only in post-operative pain but also in ultimate satisfaction rates for TKA and THA. From previous studies the total blood loss following both TKA and THA is a similar volume, although as stated, overall outcomes and satisfaction rates differ significantly. TKA is seen as a more destructive form of surgery with larger surface area of bone cuts, ligament disruption and soft tissue insult, resulting in higher post-operative pain scores (232). Due to the body's response to trauma, the locally traumatised tissues may become sensitised to the body's systemic response to blood loss and its release of hormones such as Cortisol. These may then increase a patient's perception of pain. This possible sensitisation may be exaggerated by the amount of blood loss due to a raising of a patient's anxiety levels and stress response, increasing pain perception further. This is, however, only likely to be seen in those with higher blood loss volumes approaching 15-20% of circulating volume.

With TKA, the large loss of blood also occurs within a relatively confined anatomical area, much different to the hip and thigh area for THA which can more easily accommodate this excess fluid. The concentration of tissue damage and blood loss together in this anatomical location may therefore also be a factor. A significant proportion of the blood loss occurs following surgery, within the 'closed' knee. As such the volume may exert a pressure type effect, resulting in further pain. It is this potential mechanism that may benefit from the use of compression bandages, potentially reducing extravasation into the surrounding tissues.

In addition, the larger the stress response, as with more blood loss following surgery, the higher the potential pain perception, as an exaggerated protective mechanism. This of course echoes the foundations of ERAS by attempting to reduce the body's stress response to help reduce overall pain and improve subsequent outcomes and allow an efficient return to function.

4.5 Analysis plan

With the limitations of studies and gaps in current knowledge highlighted, a robust study, could assess for a correlation between the volume of blood lost post-operatively and acute pain following TKA.

As such, the main hypothesis that is being tested is that the overall volume of blood lost positively correlates with the degree of pain experienced post-operatively throughout the entire participant cohort enrolled in the main trial.

To assess for a correlation between the blood loss and acute pain, there are several key questions to answer and potentially explore further.

The estimated volume of blood lost, rather than Hb or HCT will be used, as this is determined by a participant's height and weight, in addition to the Hb levels. As described in section 3.2.2.1, the blood loss will be calculated using the Hb balance method. To help combat the potential ceiling effect as seen in Hegarty et al. both the highest and mean 24 hour pain scores will be used separately for this analysis. Thus, no further measurements will need to be taken in addition to the main trial.

Additionally, a correlation of estimated blood loss with breakthrough analgesia use will also be an important outcome to analyse as it carries significant clinical relevance and is an indirect marker of pain and its perception.

If a correlation between post-operative blood loss volume and acute pain does exist, further analysis to highlight any potential 'at risk' groups or those with whom a lesser volume of blood loss may still lead to higher than average pain scores will also be performed. If any are highlighted this could help aid operative planning and risk stratification to improve reported outcomes. We are aware of specific factors which can affect the perception of pain such as anxiety and depression and with these, blood loss may form a synergistic effect.

As hypothesized, the link between blood loss and pain could occur due to the stress response and be mediated by hormonal release. Blood loss following TKA almost completely occurs within the first 24 hours post-operative, hence, any potential link between pain and blood loss is much more likely to be highlighted within this timeframe. So far, no work has been performed within the first 24 hours post-operative, on assessing the direct link between acute blood loss and acute pain.

For the analyses, key factors which have previously been shown to affect post-operative pain, including gender, anxiety, depression, smoking, BMI, age, and the use of tourniquet will be utilised (224). As stated by Chiang et al. smoking has been observed to increase opiate consumption post-operatively, as also found by Hussain et al. when assessing the impact of gender (233, 234).

4.5.1 Statistical analysis plan

The complete participant cohort, including both the compression and non-compression bandage groups, will be included in the analysis.

The estimated volume of blood lost and 24 hour pain score (highest and average) will both be treated as continuous variables for this analysis. A scatter plot of estimated volume of blood lost and pain score (highest and average included separately) will be produced and the Pearson's correlation coefficient calculated. The scatter plot will also enable us to assess whether there is a notable threshold for volume of blood lost beyond which particularly high pain scores are associated.

Linear regression analysis, adjusting for age, anxiety, BMI, depression, gender, smoking, tourniquet use and blood volume lost, will also be used to investigate the relationship between volume of blood lost and mean and highest pain scores with post-operative pain (mean and highest) as the dependent variable.

An independent t-test will be used to assess whether volume of blood lost differs between those patients that used breakthrough analgesia and those that did not.

The relationship between blood volume lost and breakthrough analgesia requirement will be examined with a linear regression analysis, adjusting for age, anxiety, BMI, depression, gender, smoking, tourniquet use and blood volume lost with breakthrough analgesia requirement is the dependent variable.

Definitions for variables to be used in regression analysis:

Gender: Dichotomous. Male/female

Anxiety: Dichotomous. Yes/no as stated in data collected during surgical pre-assessment

Depression: Dichotomous. Yes/no as stated in data collected during surgical pre-assessment

Smoking: Dichotomous. Yes/no as stated in data collected during surgical pre-assessment.

BMI: Continuous scale. Calculated from height and weight collected at surgical pre-assessment.

Age: Continuous scale. Age in years at time of surgery.

Tourniquet: Dichotomous. Yes/no. As stated in operation note.

A p-value <0.05 was deemed statistically significant throughout the analysis.

5 Analysis

5.1 Participant eligibility and flow

Between 13th March 2017 and 5th June 2017, 167 patients under the care of Northumbria NHS trust consultants partaking in KReBS were assessed for eligibility and inclusion. Subsequently, 156 participants were randomised and included in this sub-study as well as KReBS. Nine potential participants failed eligibility checks and two potentially eligible participants underwent surgery prior to randomisation as a result of administration errors and logistical reasons. Seven potential participants were ineligible due to a single reason and two due to multiple cited reasons (figure 22).

Of the 156 participants recruited into the study and randomised, 155 subsequently underwent TKA surgery.

The one participant who did not undergo surgery had an anaphylactic reaction during induction of anaesthesia and intravenous anti-biotics. As such, no post-operative data is therefore available.

In addition to this participant, other missing data includes; height and weight measurements, and therefore BMI values for four participants, all from the compression group. Smoking data was also missing from two participants from the compression group.

Missing post-operative pain data included; incomplete pain score measurements for five participants, with four from the compression group, as well as absent break through analgesia requirements for the same four compression group participants.

Missing blood data included pre-operative Hb and HCT levels for one participant in the compression group. This, combined with the missing height and weight data, resulted in five participants not being able to have blood volumes and total blood volume loss measurements calculated.

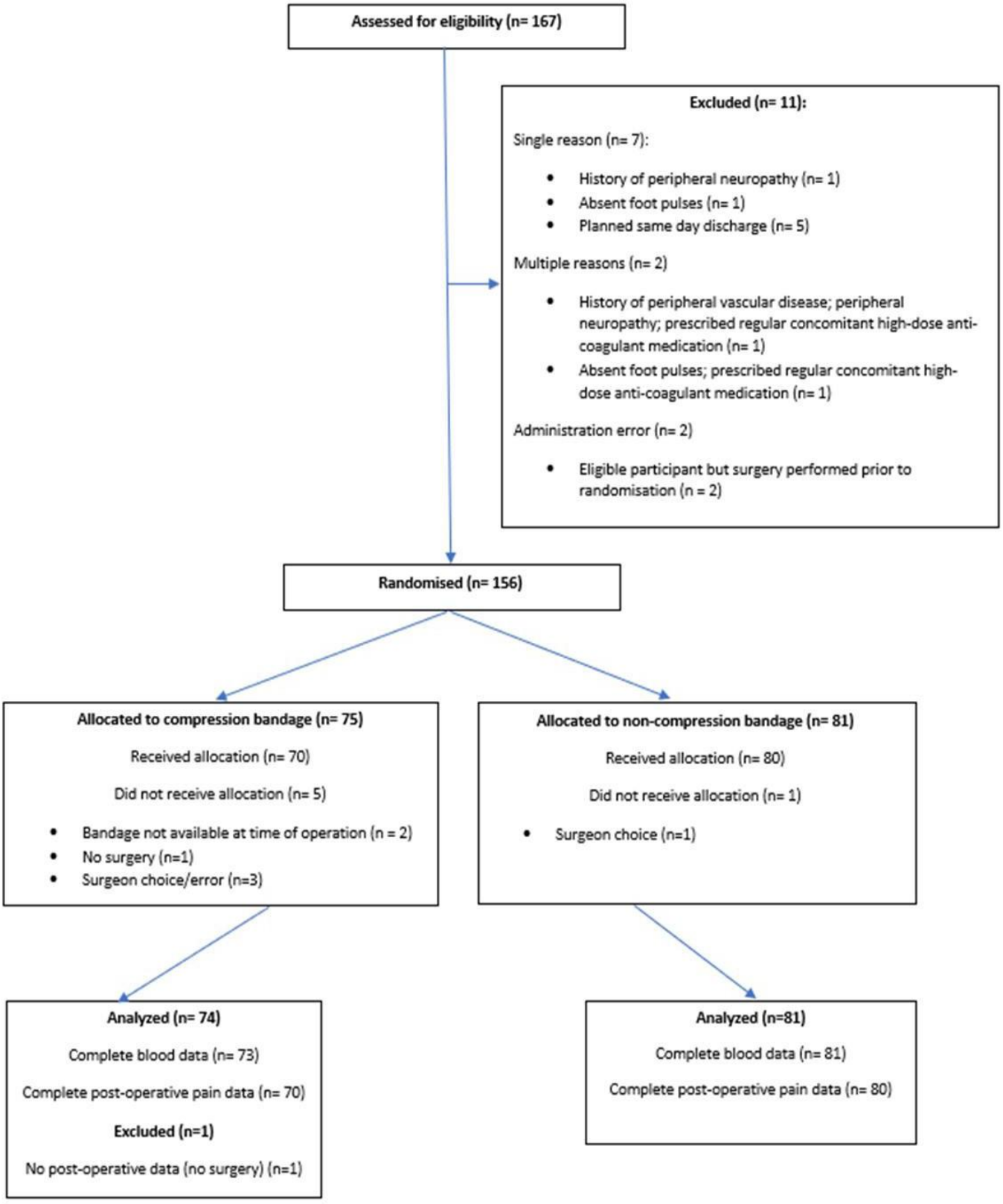

Figure 22: Consolidated Standards of Reporting Trials (CONSORT) patient flow chart

Total surgical times were not available for four participants, all from the compression group. For two of these participants tourniquets were also used and the timing of their use is also missing.

Data was missing from participant medical notes in addition to the electronically held records of the operative intervention. Records were searched at multiple time points for missing data.

No participants who were randomised and subsequently underwent surgery were lost to follow up. In total, five participants who underwent surgery had one or more missing data fields.

No missing values were added for absent data prior to statistical analysis. Five participants randomised to the compression bandage group did not get the treatment allocation following surgery in addition to the participant who did not undergo surgery. On two occasions the compression bandage was not available at the time of surgery. On another two occasions the surgical team erroneously applied the standard non-compression bandage and for one participant the surgeon did not want to use a non-sterile bandage. One participant in the non-compression group received a compression bandage, this was down to surgeon's choice at the time of surgery, although the precise reason given for this is not known.

5.2 Study characteristics

5.2.1 Participant characteristics

156 KReBS participants recruited from Northumbria NHS trust were included in this sub study: 75 (48.1%) in the compression group; and 81 (51.9%) in the non-compression group. The participants baseline characteristics are presented in table 10.

The mean age overall was 67.1 years (SD 8.4; range 47 to 91). The mean age of participants in the compression group was 67.8 years (SD 8.6; range 47 to 91) and in the non-compression group was 66.5 years (SD 8.6; range 49 to 84).

In total, 69 (44.2%) participants were male, with similar proportions in both the compression group (n=33, 44.0%) and non-compression group (n=36, 44.4%).

Weight, height and BMI was comparable between both groups. The average weight of participants was 90.0kg (SD 18.1) and average height was 1.67m (SD 0.09). As such, overall BMI was 32.1 (SD 5.5).

Pre-operative Hb, HCT and platelet levels were available for 155 participants (99.4%). The one participant (in the compression group) without pre-operative blood parameters did have their post-operative levels taken. This participant was likely to have been pre-assessed in another care group prior to their operation but the blood results were not transferred to the electronic system at Northumbria NHS trust and so were unavailable for data analysis.

Overall, the pre-operative blood parameters of Hb, HCT and platelet levels were comparable between the two groups.

Participants ASA grade was recorded to highlight overall health status and was similar between groups. ASA grade 2 was the most prevalent rating, accounting for 53 (70.7%) and 57 (70.4%) of participants in the compression and non-compression groups, respectively.

9 (5.8%) participants declared being an active smoker at their pre-operative assessment. 4 (5.4%) of the compression group and 5 (6.2%) of the non-compression group.

Characteristic	Compression (n=75)	Non-compression (n=81)	Overall (n=156)
Age, years			
Mean (SD)	67.8 (8.59)	66.5 (8.58)	67.1 (8.44)
Gender, n (%)			
Male	33 (44.0)	36 (44.4)	69 (44.2)
Female	42 (56.0)	45 (55.6)	87 (55.8)
Weight, kilograms	(n=71)		
Mean (SD)	88.9 (18.6)	91.0 (17.7)	90.0 (18.1)
Height, metres	(n=71)		
Mean (SD)	1.67 (0.09)	1.67 (0.09)	1.67 (0.09)
BMI	(n-71)		
Mean (SD)	31.8 (5.9)	32.3 (5.2)	32.1 (5.5)
Pre-operative haemoglobin, g/dl	(n= 74)	(n= 81)	(n= 155)
Mean (SD)	13.9 (1.12)	13.9 (1.22)	13.9 (1.17)
Pre-operative haematocrit, litre of cells per litre of blood (l/l)	(n= 74)	(n= 81)	(n= 155)
Mean (SD)	0.413 (0.033)	0.411 (0.035)	0.412 (0.034)
Pre-operative platelets,	(n= 74)	(n= 81)	(n= 155)
Mean (SD)	241 (69.7)	246 (61.3)	244 (65.3)
ASA grade, n (%)			
1.	11 (14.7)	16 (19.8)	27 (17.3)
2.	53 (70.7)	57 (70.4)	110 (70.5)
3.	11 (14.7)	8 (9.9)	19 (12.2)
4.	0 (0.0)	0 (0.0)	0 (0.0)
5.	0 (0.0)	0 (0.0)	0 (0.0)
Overall ASA grade			
Mean (SD)	2.0 (0.54)	1.9 (0.55)	2.0 (0.54)
Number of co-morbidities			
Mean, (SD)	1.3 (1.15)	1.2 (1.23)	1.2 (1.19)
Current smoker,	(n= 73)		(n= 154)
n (%)	4 (5.4)	5 (6.2)	9 (5.8)

Table 10: Participant baseline characteristics

The mean number of co-morbidities overall, as defined by those comorbidities included in table 11, was 1.2 (SD 1.19); 1.3 (SD 1.15, range 0 to 5) in the compression group and 1.2 (SD 1.2, range 0 to 6) in the non-compression group. The most prevalent co-morbidity overall was hypertension (n= 76, 48.7%); present in 40 (53.3%) participants in the compression

group and 36 (44.4%) in the non-compression group, showing a disparity between groups. There was also a discrepancy in prevalence of depression between compression group (n= 5, 6.0%) and non-compression group (n= 9, 11.1%). Prevalence of other co-morbidities was comparable between the groups and for many co-morbidities, low numbers of participants were affected, such as epilepsy and varicose veins.

Comorbidity, n (%)	Compression (n=75)	Non-compression (n=81)	Overall (n=156)
Hypertension	40 (53.3)	36 (44.4)	76 (48.7)
Diabetes	14 (18.7)	13 (16)	27 (17.3)
Epilepsy	0 (0.0)	3 (3.7)	3 (1.9)
Depression	5 (6.0)	9 (11.1)	14 (9.0)
Atrial fibrillation	3 (4.0)	6 (7.4)	9 (5.8)
COPD/Asthma	15 (20.0)	13 (16.0)	28 (17.9)
Cerebrovascular disease	1 (1.3)	2 (2.5)	3 (1.9)
Anxiety	2 (2.7)	1 (1.2)	3 (1.9)
Chronic low back pain	5 (6.7)	2 (2.5)	7 (4.5)
Varicose veins	0 (0.0)	2 (2.5)	2 (1.3)
Hypothyroidism	5 (6.7)	4 (4.9)	9 (5.8)
Ischaemic heart disease	9 (12.0)	6 (7.4)	15 (9.6)

Table 11: Participant co-morbidities

Baseline participant characteristics and pre-operative data were comparable between the two groups.

5.2.2 Operative characteristics

Twelve consultants operated on the 155 participants across the two groups (table 12). Eleven of the consultants operated on at least one participant from each group. The one consultant who did not, operated on participants allocated to the compression group only, following randomisation (n= 3).

Surgeon	Compression (n= 74)	Non-compression (n= 81)	Overall (n= 155)
A1			
Participants, n	1	1	2
% within surgeon	50.0	50.0	100.0
% within bandage	1.3	1.2	1.3
B2			
Participants, n	5	5	10
% within surgeon	50.0	50.0	100.0
% within bandage	6.7	6.2	6.5
C3			
Participants, n	2	5	7
% within surgeon	28.6	71.4	100.0
% within bandage	2.7	6.2	4.5
D4			
Participants, n	12	13	25
% within surgeon	48.0	52.0	100.0
% within bandage	16.0	16.0	16.1
E5			
Participants, n	4	11	15
% within surgeon	26.7	73.3	100.0
% within bandage	5.3	13.6	9.7
F6			
Participants, n	2	1	3
% within surgeon	66.7	33.3	100.0
% within bandage	2.7	1.2	1.9
G7			
Participants, n	8	9	17
% within surgeon	47.1	52.9	100.0
% within bandage	10.7	11.1	11.0
H8			
Participants, n	6	6	12
% within surgeon	50.0	50.0	100.0
% within bandage	8.0	7.4	7.7
I9			
Participants, n	3	0	3
% within surgeon	100.0	0.0	100.0
% within bandage	4.0	0.0	1.9
J10			
Participants, n	18	13	31
% within surgeon	58.1	41.9	100.0
% within bandage	24.0	16.0	20.0
K11			
Participants, n	5	3	8
% within surgeon	62.5	37.5	100.0
% within bandage	6.7	3.7	5.2
L12			
Participants, n	8	14	22
% within surgeon	36.4	63.6	100.0
% within bandage	10.7	17.3	14.2
Total			
Participants, n	75	81	156
% within surgeon	48.1	51.9	100.0
% within bandage	100.0	100.0	100.0

Table 12: Participant allocation by operative surgeon

The volume of participants operated upon by consultants ranged from two to thirty-one participants. Over half of the total participants (n=78, 50.3%) were operated on by one of three consultants (J10, D4, L12).

The median number of operations performed by a single surgeon in each group was five cases. Within the compression group, the highest number of individual participants operated upon by one single surgeon was eighteen and within the non-compression group this was fourteen.

Operative characteristics are summarised in table 13.
The left knee was operated upon in 76 (49.0%) participants. The split between left and right sides showed a mild discrepancy between the compression group and the non-compression group with 34 (45.9%) and 42 (51.9%) participants having a left sided operation, respectively.

The average overall operative time was 62 minutes (SD 18.1) with the shortest operation being 29 minutes and the longest taking 119 minutes. In the compression group the average time was 66 minutes (SD 18.8) with the shortest duration being 30 minutes and the longest being 113minutes. In the non-compression group, the average duration was 59 minutes (SD 17.1) and the range was between 29 minutes and 119 minutes.

Tourniquets were used by ten of the twelve consultants and not by the remaining two. There was no overlap between tourniquet use, all consultants either using or not using tourniquets for all participants they operated upon. This resulted in 113 (72.9%) participants having a tourniquet used throughout the operation and 42 (24.1%) without. There was a slightly lower use of tourniquets in the compression group (n=50, 67.6%) compared to the non-compression group (n=63, 77.8%).

For those cases where tourniquets were used the average time of inflation was 64 minutes (SD 20.1) with times of 69 minutes (SD 21.1) in the compression group and 61 (SD 20.3) in the non-compression group.

Participants who had previously undergone a TKA on the contralateral side totalled 33 (21.3%): the groups were comparable with 14 (18.9%) in the compression group and 19 (23.5%) in the non-compression group.

All participants undergoing surgery had a spinal anaesthetic as part of the Northumbria enhanced recovery protocol and local anaesthetic infiltrate. Zimmer Nexgen CR cemented protheses were used throughout.

All participants were mobilised on day zero or day one post-operative with no restrictions on range of knee movement.

Characteristic	Compression (n=74)	Non-compression (n=81)	Overall (n=155)
Operative side, n (%)			
Left	34 (45.9)	42 (51.9)	76 (49.0)
Right	40 (54.1)	39 (48.1)	79 (51.0)
Operative time, minutes	(n= 70)		(n= 151)
Mean (SD)	66 (18.8)	59 (17.1)	62 (18.1)
Tourniquet use, n (%)			
Yes	50 (67.6)	63 (77.8)	113 (72.9)
No	24 (32.4)	18 (22.2)	42 (24.1)
Tourniquet time, minutes	(n= 48)	(n= 64)	(n= 112)
Mean, (SD)	69 (21.1)	61 (20.3)	64 (20.1)
Previous TKA, n (%)			
Yes	14 (18.9)	19 (23.5)	33 (21.3)
No	60 (81.1)	62 (76.5)	122 (78.7)
Spinal anaesthesia, n (%)			
Yes	74 (100.0)	81 (100.0)	155 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)

Table 13: Operative characteristics

5.2.3 Bandage compliance

Bandage compliance data was collected on the 'Confirmation of treatment form' as part of KReBS.

Compression bandage

Compression bandages were intended to be in-situ for 24 to 48 hours. 17 (23.3%) participants in the compression bandage group had the bandage removed before 20 hours, deemed an acceptable cut off for 'early removal', with 11 (64.7%) of these occurring due to 'pain' (table 5.5). Of note, five of these 'pain' requests specifically name the bandage as the proposed cause of pain and six are cited as 'pain/uncomfortable (not specified as being due to bandage)' on the treatment confirmation forms. Of the five participants who had the bandage removed between 0 to 15 hours, four requested its removal due to pain. The remaining participant had the compression bandage removed at 11 hours due to 'damage occurring on the skin of the thigh'.

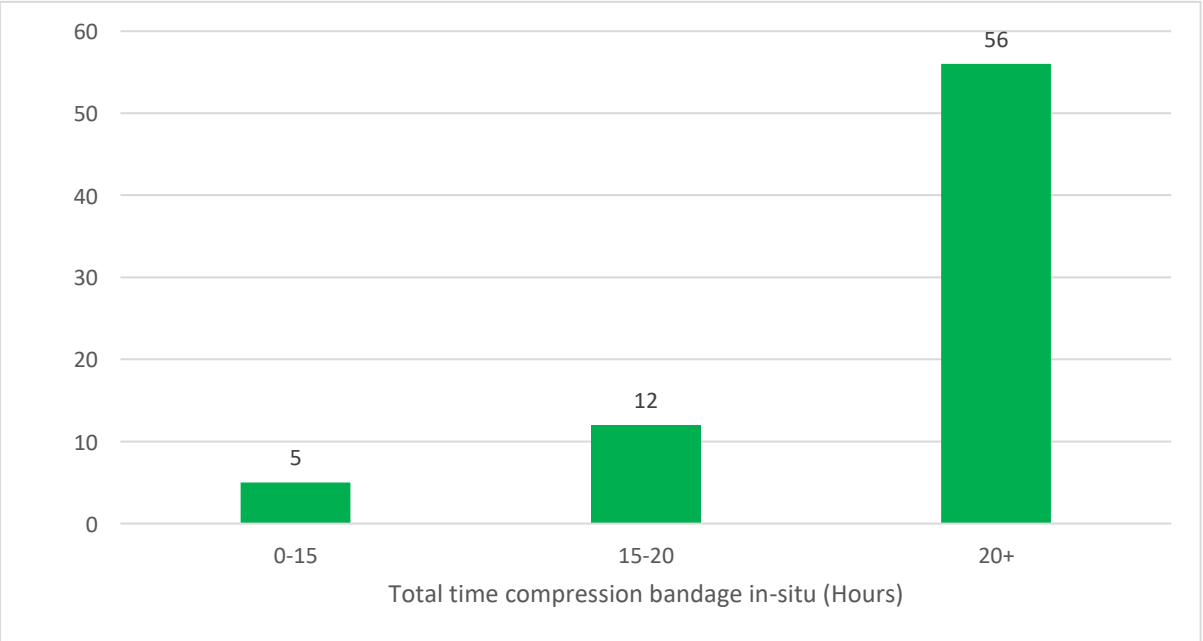

Figure 23: Total time compression bandage in-situ post-operative (hours)

For the twelve participants who had the compression bandage in-situ for 15 to 20 hours, seven requested its early removal due to pain, one 'at patients request' and the remaining four participants do not have a recorded reason for the early removal.

	0 to 15 hours	15 to 20 hours
Pain	4	7
Patient request	0	1
Unknown	0	4
Skin injury/damage	1	0

Table 14: Cited reason for early (less than 20 hours) removal of compression bandage

The earliest that a bandage was removed was 7 hours 45 minutes. The reason cited was 'severe pain' (figure 24). Intention to treat analysis was used for all outcomes including if the bandage was removed early or the wrong allocation of bandage received.

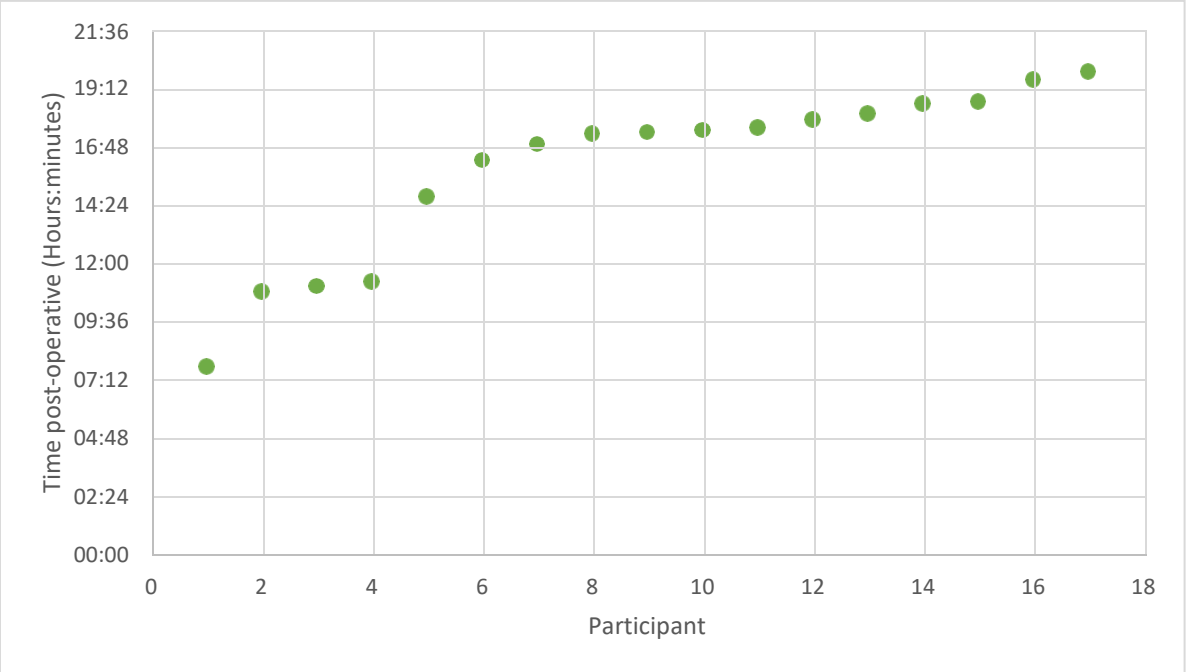

Figure 24: Time post-operatively (hours: minutes) when compression bandage removed early

Non-compression bandage

Within the control group, the non-compression bandage also had cases of early removal. There were 40 (49.4%) participants who had the non-compression bandage removed before 24 hours. The majority of these, 24 (60.0%), were documented as being for 'standard care'. Anecdotally, this would allow the application of a cryo-cuff and physiotherapy to commence the day following surgery. A further 9 (22.5%) were removed to allow a 'routine discharge'. 3 (7.5%) cases did not have a reason documented for the early removal. The remaining 2 (5.0%) bandages were removed due to 'pain'.

5.3 Trial results

5.3.1 Primary outcome

Difference in Hb(g/dl) from pre to post-operative levels between the compression and non-compression groups

Characteristic		Compression (n=74)	Non-compression (n=81)	Overall (n=155)
Haemoglobin, g/dl Mean (SD)	**Pre-operative**	13.9 (1.1)	13.9 (1.2)	13.9 (1.2)
	Post-operative	12.1 (1.3)	12.4 (1.4)	12.3 (1.4)
	Change (Pre to post)	1.8 (1.0)	1.5 (0.7)	1.6 (0.9)
Haematocrit, litre of cells per litre of blood (l/l) Mean (SD)	**Pre-operative**	0.41 (0.033)	0.41 (0.035)	0.41 (0.034)
	Post-operative	0.36 (0.038)	0.37 (0.041)	0.36 (0.040)
	Change (Pre to post)	0.05 (0.029)	0.04 (0.022)	0.05 (0.026)
Allogenic blood transfusion, units n (%)		0 (0.0)	1 (1.2)	1 (0.6)
Estimated blood volume loss, millimetres Mean (SD)		(n= 69) 635.0 (345.7)	(n= 81) 524.5 (267.7)	n=150 575.3 (309.9)

Table 15: Blood levels and transfusion rates

The mean post-operative Hb was 12.1g/dl (SD 1.3) in the compression group and 12.4g/dl (SD 1.4) in the non-compression group; with the overall average post-operative Hb being 12.3g/dl (SD 1.3). This resulted in an unadjusted overall average post-operative Hb drop of 1.6g/dl (SD 0.9); with 1.8g/dl (SD 1.0) in the compression group and 1.5g/dl (SD 0.7) in the non-compression group (table 15).

Variable	Adjusted mean difference (g/dl)	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	+0.01	0.01	-0.01	+0.02	0.441
Compression bandage	-0.30	0.13	-0.56	-0.05	0.020
Female gender	-0.39	0.16	-0.70	-0.08	0.013
Pre-operative Hb	+0.82	0.07	+0.68	+0.95	0.001
Tourniquet	+0.52	0.14	+0.23	+0.80	0.001

Table 16: Coefficients for multiple linear regression with post-operative Hb as dependent variable

Multiple linear regression was performed with age, bandage allocation (compression = 1, non-compression = 0), gender (female = 2, male = 1), pre-operative Hb level and tourniquet (used = 1, not used = 0) as predictor values of post-operative Hb. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.1) The Durbin-Watson value was 2.05, indicating no autocorrelation of the residuals.

Gender and pre-operative Hb levels are statistically significant predictors of post-operative Hb levels (table 5.7). Females tended to have a lower post-operative Hb level than males (adjusted mean difference -0.39 g/dl, 95% CI -0.70 to -0.08, $p<0.001$). An increase of 1g/dl in pre-operative Hb was associated with a predicted increase in post-operative Hb of 0.82 g/dl (95% CI +0.68 to +0.95, $p<0.001$).

There was evidence of a difference in post-operative Hb between the two bandage groups. On average, participants in the compression group had a post-operative Hb that was 0.30 g/dl lower than the non-compression group ($p<0.02$). The 95% CI indicates that the true population difference might be between -0.56 and -0.05 g/dl.

Tourniquet use is also a statistically significant predictor of post-operative Hb levels. The use of a tourniquet resulted, on average, in a higher post-operative Hb than when not used (adjusted mean difference +0.52 g/dl, 95% CI +0.23 to +0.80, $p<0.001$).

5.3.2 Secondary outcomes

5.3.2.1 Difference in HCT (l/l) loss from pre to post-op levels between the compression and non-compression groups.

The unadjusted mean post-operative HCT was 0.36 l/l (SD 0.038) in the compression group and 0.37 l/l in the non-compression group; with the overall average post-operative HCT being 0.36 l/l (SD 0.040).This resulted in an unadjusted overall average post-operative HCT drop of 0.05 l/l (SD 0.026) with 0.05 l/l (SD 0.029) in the compression group and 0.04 l/l (SD 0.022) in the non-compression group (table 15).

Variable	Adjusted mean difference (l/l)	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	0.000	0.000	0.000	+0.001	0.644
Compression bandage	-0.007	0.004	-0.015	+0.001	0.075
Gender	-0.011	0.005	-0.020	-0.002	0.021
Pre-operative HCT	0.834	0.068	+0.700	+0.967	0.001
Tourniquet	0.014	0.004	+0.006	+0.023	0.001

Table 17: Coefficients for multiple linear regression with post-operative HCT as dependent variable

Multiple linear regression was performed with age, bandage allocation (compression = 1, non-compression = 0), gender (female = 1, male = 2), pre-operative HCT level and tourniquet (used = 1, not used = 0) as predictor values of post-operative HCT. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.2). The Durbin-Watson value was 2.11, indicating no autocorrelation of the residuals.

Gender and pre-operative HCT are statistically significant predictors of post-operative HCT levels (table 17). Females tended to have a lower post-operative HCT level than males (adjusted mean difference -0.011 l/l, 95% CI -0.020 to -0.002, $p<0.021$). An increase of 1.0 l/l in pre-operative HCT was associated with a predicted increase in post-operative HCT of

0.834 l/l (95% CI +0.700 to +0.967, p<0.001).

Tourniquet use is also a statistically significant predictor of post-operative HCT levels. The use of a tourniquet resulted, on average, to a higher post-operative HCT than when not used (adjusted mean difference +0.014 l/l, 95% CI +0.006 to +0.023, p<0.001).

There was evidence of a difference in post-operative HCT between the two bandage groups, but this was not statistically significant. On average, participants in the compression group had a post-operative HCT that was 0.007 l/l lower than the non-compression group (p=0.075). The 95% CI indicates that the true population difference lies between -0.015 and +0.001 l/l.

5.3.2.2 Difference in estimated blood loss (mls) as calculated by the Hb-balance method between compression and non-compression groups.

Variable	Adjusted mean difference (mls)	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	-7.7	3.0	-13.7	-1.7	0.01
Compression bandage	107.6	49.0	+10.8	+204.3	0.03
Gender	-2.3	59.8	-120.4	+115.8	0.97
Pre-operative Hb	16.5	25.4	-33.7	+66.8	0.52
Tourniquet	-123.6	55.1	-232.4	-14.7	0.03

Table 18: Coefficients for multiple linear regression with estimated blood volume loss as dependent variable

Multiple linear regression was performed with age, bandage allocation (compression = 1, non-compression = 0), gender (female = 2, male = 1), pre-operative Hb level and tourniquet (used = 1, nor used = 0) as predictor values of estimated blood volume loss. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.3). The Durbin-Watson value was 1.96, indicating no autocorrelation of the residuals.

Age was a modest but statistically significant predictor of blood loss (table 18). Older participants tended to have a lower estimated blood volume loss (adjusted mean difference -7.7mls, 95% CI -13.7 to -1.7, p< 0.01).

There was evidence of a difference in estimated blood volume loss between the two bandage groups. On average, participants in the compression group had an estimated blood volume loss that was 107.6mls higher than the non-compression group (p=0.03). The 95% CI indicates that the true population difference might be between 10.8 and 204.3mls.

Tourniquet use is also a statistically significant predictor of estimated blood volume loss. The use of a tourniquet resulted, on average, to a lower blood volume loss than when not used (adjusted mean difference -123.6mls, 95% CI -232.4 to -14.7, p<0.03).

Pre-operative Hb and gender were not statistically significant predictors.

5.3.2.3 Allogenic blood transfusion (units) rates.

Within the total participant cohort, one unit of allogenic blood was transfused for one female participant. This was within the non-compression group and occurred five days post-operative.

The overall transfusion rate was 0.64%, with the transfusion rate being 1.23% within the control group (table 15).

Due to this small number, no further statistical analysis has been performed on this outcome.

5.3.2.4 Difference in pain scores (NRS) between the compression and non-compression groups including average and highest recorded score over 24 hours post-operative.

Characteristic		Compression (n=70)	Non-compression (n=81)	Total (n=151)
Pain, Numerical ranking score	**24 hour mean score,** Mean (SD)	n= 70 3.0 (1.5)	n= 80 2.6 (1.6)	n= 150 2.8 (1.5)
	24 hour highest score, Mean (SD)	n= 70 7.3 (2.4)	n= 80 6.5 (2.3)	n=150 6.9 (2.4)
Number of pain scores recorded, Mean (SD)		n= 70 11.0 (2.8)	n=80 10.7 (2.7)	n=150 10.8 (2.7)
Breakthrough analgesia required n (%)		n= 70 56 (80.0)	n= 81 64 (79.0)	n= 151 120 (76.9)
Breakthrough analgesia requirement, Oramorph (mg) Mean (SD)		n= 70 17.4 (13.3)	n= 81 18.0 (15.1)	n= 151 17.7 (14.2)

Table 19: Post-operative pain scores and breakthrough analgesia requirement

The mean overall average 24 hour pain score (NRS, 0 no pain to 10 most pain) was 2.8 (SD 1.5). This translates to a mean 24 hour pain score of 3.0 (SD 1.5) for the compression group and 2.6 (SD 1.6) for the non-compression group (table 19).

The mean overall 24 hour highest pain score (NRS, 0 no pain to 10 most pain) was 6.9 (SD 2.4) with the compression group scoring a mean of 7.3 (SD 2.4) and the non-compression group a mean score of 6.5 (SD 2.3).

The incidence of pain scores, defined as the number of occasions in the first 24 hours post-operatively a ward nurse recorded a participants pain score (NRS), was comparable for both groups; compression group mean 11.0 (SD 2.8) and non-compression group mean 10.7 (SD 2.7).

Variable	Adjusted mean difference (Points)	Standard Error	95% Confidence Intervals		P value
			Lower bound	Upper bound	
Age	+0.01	0.02	-0.04	+0.02	0.449
Anxiety	-2.06	0.89	-3.83	-0.30	0.022
Compression bandage	+0.43	0.25	-0.07	+0.93	0.088
Depression	+0.39	0.44	-0.48	+1.25	0.382
Gender	+0.51	0.25	+0.01	+1.01	0.047
Low back pain	+0.74	0.60	-0.46	+1.93	0.224
Previous TKA	+0.25	0.30	-0.35	+0.84	0.413
Tourniquet	+0.21	0.28	-0.34	+0.76	0.458

Table 20: Coefficients for multiple linear regression with post-operative mean pain scores as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1 no = 0), bandage allocation (compression = 1, non-compression = 0), depression (yes = 1, no = 0), gender (female = 2, male = 1), low back pain (yes = 1, no = 0), previous TKA (yes = 1, no = 0) and tourniquet (used = 1, no = 0) as predictor values of post-operative mean pain scores (NRS). Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.4). The Durbin-Watson value was 2.05 indicating no autocorrelation of the residuals.

Anxiety was a statistically significant predictor of post-operative mean pain scores (table 20). Participants who stated ‘anxiety’ in their past medical history at surgical pre-assessment tended to have a lower post-operative mean pain score (adjusted mean difference -2.06 points, 95% CI -3.83 to -0.30, $p< 0.022$).

Gender showed a modest but statistically significant difference. Females tended to have a higher post-operative mean pain scores than males (adjusted mean difference +0.51 points 95% CI +0.01 to +1.01, $p<0.047$).

Age, compression bandage, depression, low back pain, previous TKA and tourniquet use were not statistically significant predictors of post-operative mean pain scores.

Variable	Adjusted mean difference (Points)	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	+0.01	0.02	-0.04	+0.05	0.830
Anxiety	-3.47	1.37	-6.19	-0.76	0.013
Compression bandage	+0.72	0.39	-0.05	+1.48	0.066
Depression	+0.14	0.67	-1.19	+1.48	0.832
Gender	+0.89	0.39	+0.12	+1.66	0.024
Low back pain	+1.22	0.93	-0.61	+3.05	0.191
Previous TKA	+0.50	0.46	-0.41	+1.42	0.280
Tourniquet	-0.03	0.43	-0.88	+0.82	0.949

Table 21: Coefficients for multiple linear regression with highest 24 hour post-operative pain score as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1 no = 0), bandage allocation (compression = 1, non-compression = 0), depression (yes = 1, no = 0), gender (female = 2, male = 1), low back pain (yes = 1, no = 0), previous TKA (yes = 1, no = 0) and tourniquet (used = 1, no = 0) as predictor values of highest pain score recorded in the first 24 hours post-operatively (NRS). Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.5) The Durbin-Watson value was 1.98 indicating no autocorrelation of the residuals.

Anxiety was a statistically significant predictor of highest post-operative pain score (table 21). Participants who stated ‘anxiety’ in their past medical history at surgical pre-assessment tended to have a lower recorded value for the highest post-operative pain score (adjusted mean difference -3.47 points, 95% CI -6.19 to -0.76, $p< 0.013$).

Gender showed a modest but statistically significant difference. Females tended to have a higher post-operative mean pain scores than males (adjusted mean difference +0.89 points 95% CI +0.12 to +1.66, $p<0.024$).

Age, compression bandage, depression, low back pain, previous TKA and tourniquet use were not statistically significant predictors of post-operative mean pain scores. However, there was a trend for compression bandage users to have higher post-operative pain scores.

5.3.2.5 Difference in breakthrough analgesia requirement between the compression and non-compression groups over 24 hours post-operative.

In total, 120 (76.9%) participants required at least one dose of Oramorph as breakthrough analgesia. Within the compression group 56 (80.0%) required at least one dose and 14 (20.0%) did not. Within the non-compression group, 64 (79.0%) required at least one dose and 17 (21.0%) did not.

The average overall breakthrough analgesia requirement was 17.7mg (SD 14.2). The requirement of breakthrough analgesia was comparable between the two groups, with the compression group average being 17.4mg (SD 13.3) compared to an average of 18.0mg (SD 15.1) in the non-compression group (table 19).

In addition, the incidence of pain scores being recorded in the first 24 hours post-operatively was a mean of 10.8 (SD 2.7); 11.0 (SD 2.8) in the compression group and 10.7 (SD 2.7) in the non-compression group.

Variable	Adjusted mean difference (mg)	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	-0.12	0.14	-0.39	+0.15	0.375
Anxiety	-11.11	8.16	-27.24	+5.03	0.176
Compression bandage	-0.32	2.29	-4.84	+4.21	0.891
Depression	+11.14	4.01	+3.22	+19.06	0.006
Gender	+2.03	2.30	-2.52	+6.59	0.379
Low back pain	+5.27	5.50	-5.61	+16.14	0.340
Previous TKA	+5.24	2.76	-0.20	+10.68	0.059
Tourniquet	-3.71	2.55	-8.75	+1.32	0.148

Table 22: Coefficients for multiple linear regression with breakthrough analgesia requirement as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1 no = 0), bandage allocation (compression = 1, non-compression = 0), depression (yes = 1, no = 0), gender

(female = 2, male = 1), low back pain (yes = 1, no = 0), previous TKA (yes = 1, no = 0) and tourniquet (used = 1, no = 0) as predictor values of breakthrough analgesia requirement (Oramorph, mg). Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.1.6). The Durbin-Watson value was 1.91 indicating no significant autocorrelation of the residuals.

Depression was a statistically significant predictor of breakthrough analgesia requirement (table 22). Participants who stated 'depression' in their past medical history at surgical pre-assessment tended to have a higher requirement of breakthrough analgesia (adjusted mean difference 11.14mg, 95% CI +3.22 to +19.06, p< 0.006).

Gender showed a modest but statistically significant difference. Females tended to have a higher post-operative mean pain score than males (adjusted mean difference +0.89 points 95% CI +0.12 to +1.66, p<0.024).

Age, anxiety, compression bandage, gender, low back pain, previous TKA and tourniquet use were not statistically significant predictors of breakthrough analgesia requirement.

5.3.2.6 Length of stay

Overall, the mean length of stay was 2.6 days (SD 2.6) and was comparable between the two groups. Within the compression group the mean stay was 2.7 days (SD 2.0) compared to 2.5 days (SD 3.1) in the non-compression groups.

The overall median length of stay was 2 days (IQR 1 – 3); this was the same for both compression and non-compression groups.

Length of stay ranged from 0 to 26 days. The range in the compression group was 0 to 10 days compared to 0 to 26 days in the non-compression group (figures 25- 27).

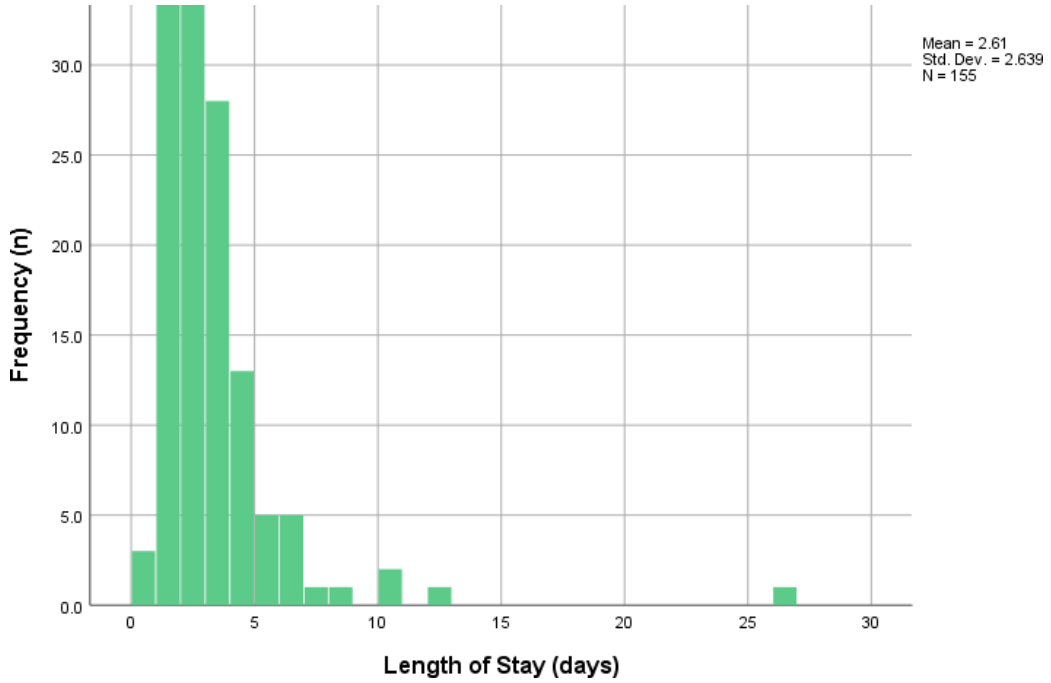

Figure 25: Simple histogram of length of stay (days) for entire participant cohort

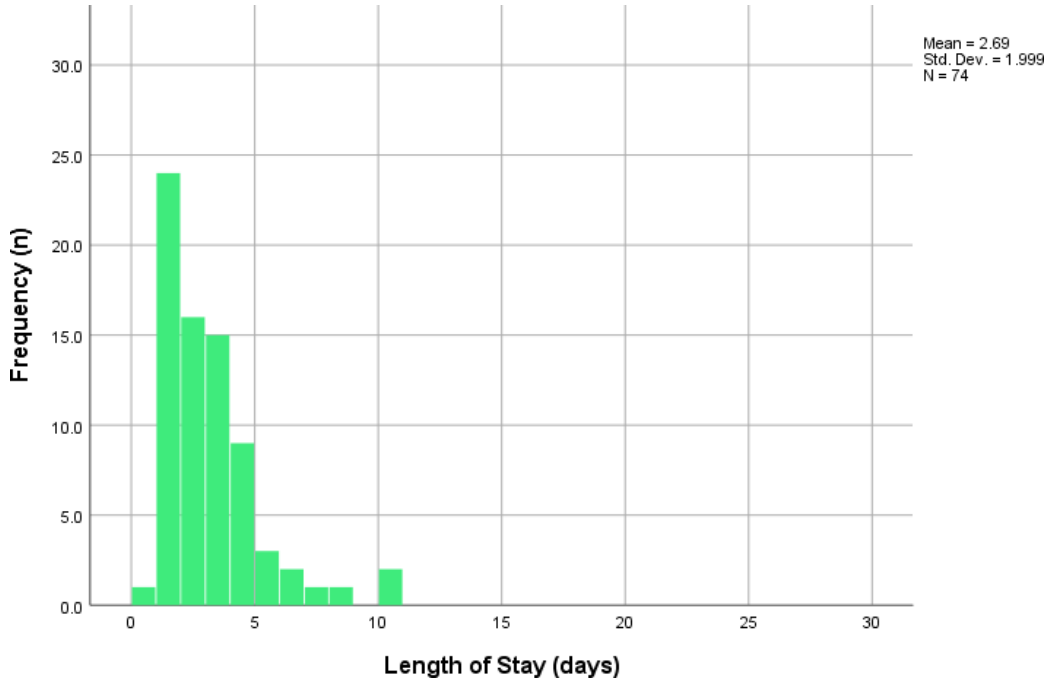

Figure 26: Simple histogram of length of stay (days) for compression group

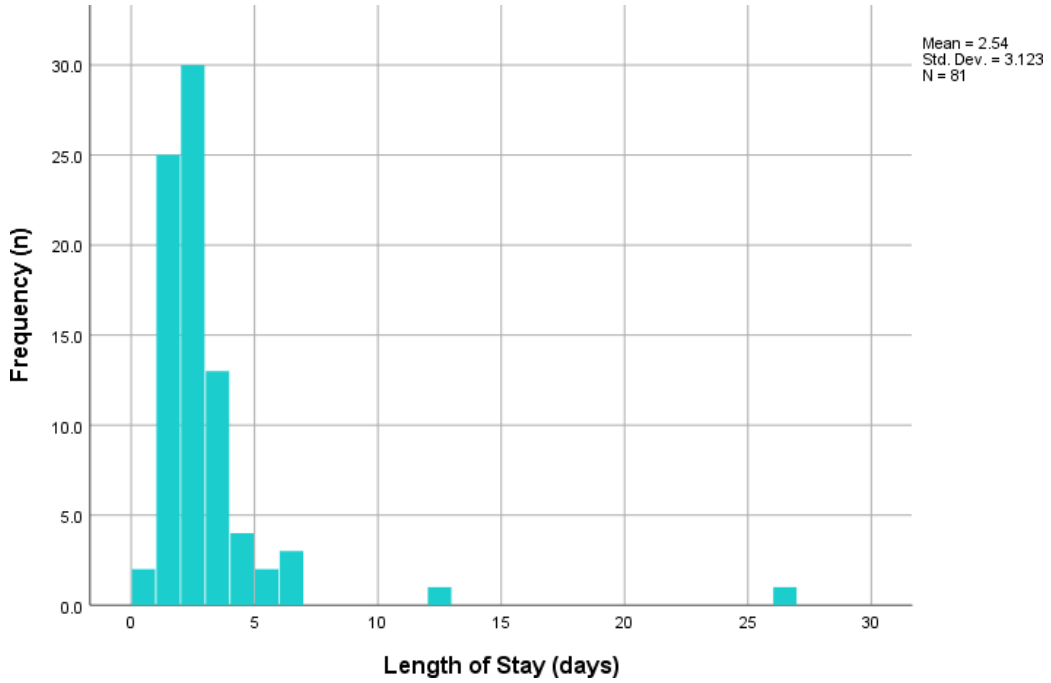

Figure 27: Simple histogram of length of stay (days) for non-compression group

A Poisson regression model was run to predict length of hospital stay (number of nights) based on participant age, ASA grade, bandage allocation (compression = 1, non-compression = 0), gender (female = 2, male = 1) and tourniquet (used = 1, not used = 0).

Using Pearson chi square test to assess the 'goodness of fit', there was significant evidence of overdispersion (value 1.88). A negative binominal model was subsequently run with a Pearson chi square test value of 0.51, showing the data fits the model.

With the negative binominal model, the only statistically significant predictor of length of stay was age. For each year increase in age the length of stay increases by 3% (incidence rate ratio (IRR) 1.03, 95% CI 1.01 to 1.05, p=0.03). Although, male participants and lower ASA grades had predicted shorter lengths of stay, these were not statistically significant (table 23).

There was no evidence of a difference in length of stay according to bandage allocation (IRR 0.98, 95 % CI 0.67 to 1.44, p=0.92) or tourniquet use (0.97, 95% CI 0.63 to 1.50, p=0.91).

Variable	Incidence rate ratio	95% Confidence Intervals		P value
		Lower bound	Upper bound	
Age	1.03	1.01	1.05	0.03
ASA grade 1	0.57	0.27	1.21	0.14
ASA grade 2	0.79	0.45	1.41	0.43
Non-compression bandage	0.98	0.67	1.44	0.92
Male gender	0.71	0.47	1.05	0.09
No tourniquet	0.97	0.63	1.50	0.91

Table 23: Coefficients for negative binominal model with length of stay as dependent variable

Separate, simple scatter plots of Hb drop and mean 24 hour pain scores were also performed. There was no relationship evident between either post-operative Hb drop or mean pain scores with length of stay (A 3.2)

5.3.2.7 Complications

In total there were five recorded complications (table 24). These were predominantly re-admissions within 30-days with one in the compression group and three within the non-compression group. There was one reported death within thirty days of the index operation; this was for a female participant allocated to the non-compression group. No thromboembolic episodes or myocardial infarctions were identified in either group. Due to the small numbers recorded, no further statistical analysis, as set out in section 3.7.2, was performed on this outcome.

Complication n (%)	Compression (n= 74)	Non-compression (n= 81)	Overall (n= 155)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)
Re-admission	1 (1.3)	3 (3.7)	4 (2.6)
Death	0 (0.0)	1 (1.2)	1 (0.7)
Total number of complications	1 (1.3)	4 (4.9)	5 (3.2)

Table 24: Post-operative complications

5.4 Correlation of post-operative blood loss and predictors for acute pain and the use of tourniquets.

5.4.1 Correlation of post-operative blood loss and acute pain

To assess for a correlation between post-operative blood loss and acute pain, Pearson's correlation was utilised. The post-operative blood loss measurements: Hb drop, HCT drop and blood volume lost were correlated with post-operative pain measurements; mean pain score, highest pain score and volume of breakthrough analgesia (table 25).

There were no correlations evident between the blood loss measurements and the post-operative pain outcomes. As expected, strong, positive correlations exist between the use of breakthrough analgesia and both mean and highest pain scores.

	Mean pain score	Highest pain score	Breakthrough analgesia
Hb drop	(n= 149)	(n= 149)	(n= 150)
Pearson correlation	-0.011	0.005	0.001
Significance (2-tailed)	0.897	0.953	0.986
HCT drop	(n= 149)	(n= 149)	(n= 150)
Pearson correlation	-0.101	-0.079	-0.116
Significance (2-tailed)	0.218	0.335	0.158
Blood volume lost	(n= 149)	(n= 149)	(n= 150)
Pearson correlation	-0.003	-0.025	0.360
Significance (2-tailed)	0.967	0.762	0.661
Breakthrough analgesia	(n= 150)	(n= 150)	
Pearson correlation	0.544	0.473	
Significance (2-tailed)	0.000	0.000	

Table 25: Correlation between post-operative blood loss and acute pain parameters

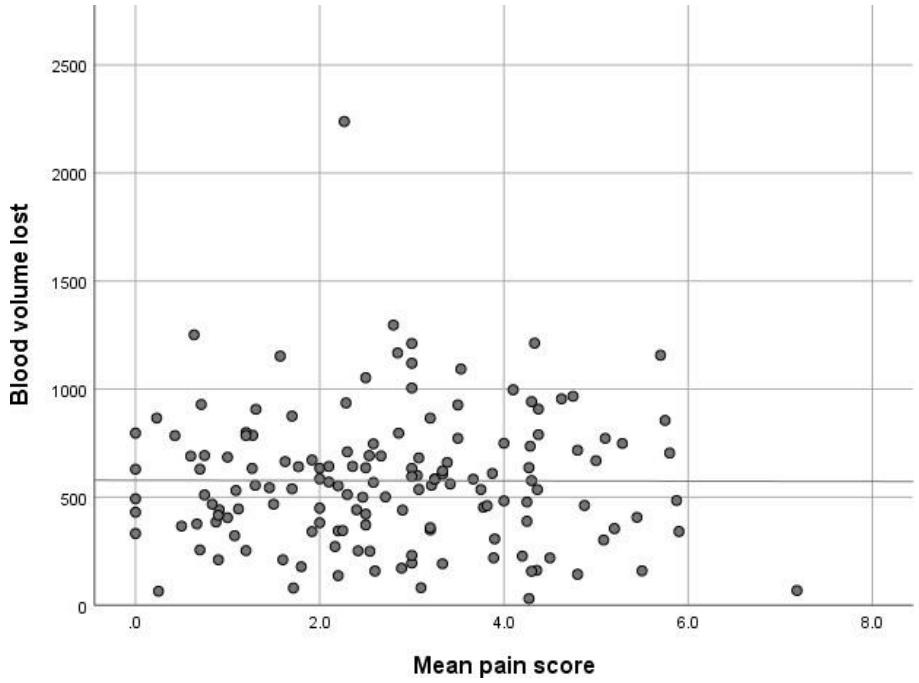

Figure 28: Simple scatter plot of estimated blood volume lost by mean pain score

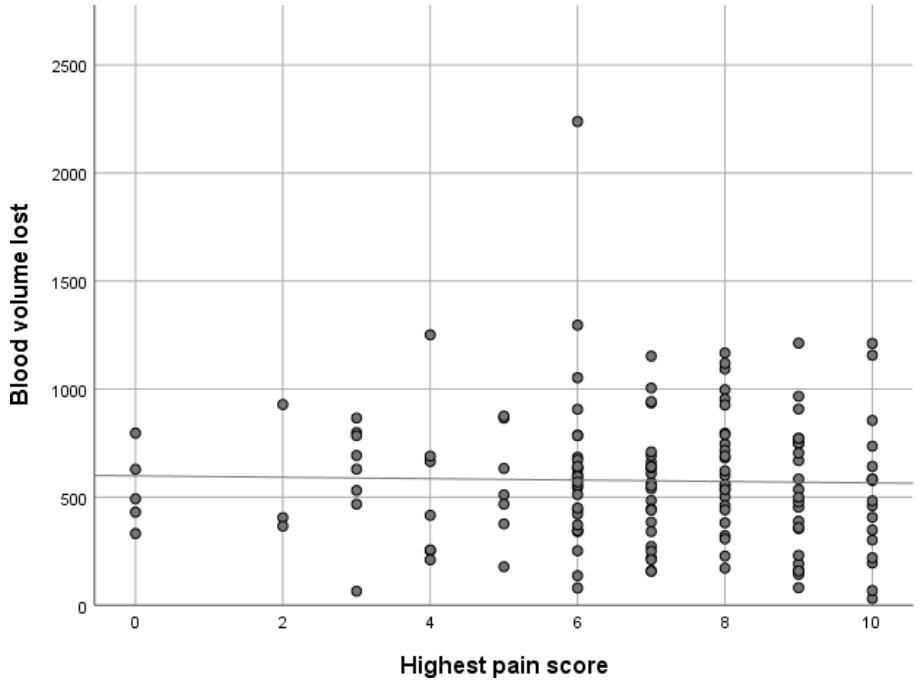

Figure 29: Simple scatter plot of estimated blood volume lost by highest pain score

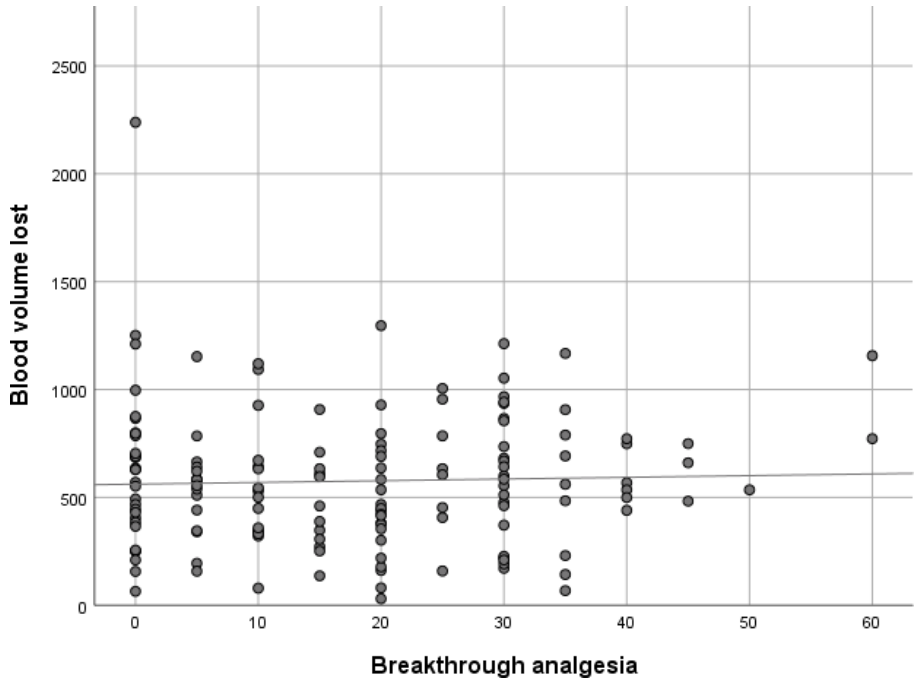

Figure 30: Simple scatter plot of estimated blood volume lost by mean breakthrough analgesia

From the simple scatter plots, there were no notable thresholds for estimated blood volume lost beyond which particularly high pain scores or analgesic requirements were associated (figures 28 to 30).

Variable	Adjusted mean difference	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	0.01	0.02	-0.02	+0.04	0.64
Anxiety	-2.22	0.92	-4.04	-0.39	0.02
BMI	0.07	0.02	+0.02	+0.11	0.01
Depression	0.23	0.44	-0.64	+1.11	0.60
Gender	0.50	0.26	-0.01	+1.01	0.05
Smoking status	0.43	0.53	-0.63	+1.48	0.42
Tourniquet	0.16	0.29	-0.40	+0.73	0.57
Blood volume lost	0.01	0.00	-0.01	+0.01	0.88

Table 26: Coefficients for multiple linear regression with mean pain scores as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1, no = 0), BMI, depression (yes = 1, no = 0), gender (female = 2, male = 1), smoking status (yes = 1, no = 0) tourniquet (used = 1, not used = 0) and estimated blood volume lost as predictor values of mean pain scores. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.3.1). The Durbin-Watson value was 2.04 indicating no significant autocorrelation of the residuals.

Of the predictors used in this model, anxiety and BMI were statistically significant. Estimated blood volume lost was not a statistically significant predictor. Those participants with a higher BMI had higher mean pain scores (adjusted mean difference 0.07, 95% CI 0.02 to 0.11, p=0.01) and those participants who stated ‘yes’ to anxiety in their pre-operative assessment had lower pain scores (adjusted mean difference -2.22, 95% CI -4.04 to -0.39, p= 0.02).

Variable	Adjusted mean difference	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	0.21	0.03	-0.03	+0.07	0.38
Anxiety	-3.54	1.46	-6.42	-0.66	0.02
BMI	0.05	0.04	-0.03	+0.12	0.22
Depression	-0.12	0.70	-1.50	+1.26	0.87
Gender	0.87	0.40	+0.07	+1.66	0.03
Smoking status	-0.01	0.84	-1.68	+1.65	0.99
Tourniquet	-0.13	0.04	-1.02	+0.77	0.78
Blood volume lost	0.00	0.01	-0.01	+0.01	0.76

Table 27: Coefficients for multiple linear regression with highest 24 hour pain scores as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1, no = 0), BMI, depression (yes = 1, no = 0), gender (female = 2, male = 1), smoking status (yes = 1, no = 0) tourniquet (used = 1, not used = 0) and estimated blood volume lost as predictor values of mean pain scores. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.3.2). The Durbin-Watson value was 1.95 indicating no significant autocorrelation of the residuals.

Of the predictors used in this model, anxiety and gender were statistically significant. Estimated blood volume lost was not a statistically significant predictor. Female participants experienced higher pain scores (adjusted mean difference 0.87, 95% CI 0.07 to 1.66, p=0.03) and those participants who stated ‘yes’ to anxiety in their pre-operative assessment experienced lower, peak pain scores (adjusted mean difference -3.54, 95% CI -6.42 to -0.66, p= 0.02).

Following analysis with an independent student t-test, there was no statistically significant difference in blood volume loss between those participants who required breakthrough analgesia and those who did not (mean difference 79.4, 95% CI -43.8 to 202.7, p= 0.21).

Variable	Adjusted mean difference	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	0.03	0.14	-0.24	+0.30	0.83
Anxiety	-12.61	8.23	-28.89	+3.66	0.13
BMI	0.83	0.21	+0.41	+1.25	0.01
Depression	9.84	3.94	+2.05	+17.63	0.01
Gender	1.34	2.28	-3.16	+5.84	0.56
Smoking status	0.26	4.76	-9.15	+9.66	0.96
Tourniquet	-4.29	2.55	-9.33	+0.75	0.09
Blood volume lost	-0.01	0.01	-0.01	+0.01	0.61

Table 28: Coefficients for multiple linear regression with breakthrough analgesia as dependent variable

Multiple linear regression was performed with age, anxiety (yes = 1, no = 0), BMI, depression (yes = 1, no = 0), gender (female = 2, male = 1), smoking status (yes = 1, no = 0) tourniquet (used = 1, not used = 0) and estimated blood volume lost as predictor values of mean pain scores. Model assumptions including homoscedasticity, linear relationship, normal distribution and independence of variables, were checked and deemed to be met (A 3.3.3). The Durbin-Watson value was 1.99 indicating no significant autocorrelation of the residuals.

Of the predictors used in this model, BMI and depression were statistically significant. Estimated blood volume lost was not a statistically significant predictor. Participants with higher BMI required more breakthrough analgesia (adjusted mean difference 0.83, 95% CI 0.41 to 1.25, p=0.01) and those participants who stated ‘yes’ to depression in their pre-operative assessment also required higher amounts of breakthrough analgesia (adjusted mean difference 9.84, 95% CI 2.05 to 17.63, p= 0.01).

5.4.2 Tourniquet use

5.4.2.1 Tourniquet use and post-operative Hb

The effect of tourniquet use on post-operative Hb was analysed in the main multiple linear regression model (Section 5.3.1 table 16). The use of a tourniquet resulted, on average, in a higher post-operative Hb than when not used (adjusted mean difference +0.52 g/dl, 95% CI +0.23 to +0.80, p<0.001).

A further multiple linear regression model was utilised to analyse any potential interaction between bandage use and tourniquet use with regards to blood loss. Age, bandage allocation (compression = 1, non-compression = 0), gender (female = 2, male = 1), pre-operative Hb level and tourniquet (used = 1, not used = 0) were individual predictors in addition to a bandage/tourniquet interaction for post-operative Hb.

The 'goodness of fit' Pearson's chi square value was 0.624.

Variable	**Adjusted mean difference (g/dl)**	**Standard Error**	**95% Confidence Intervals for B**		**P value**
			Lower bound	Upper bound	
Age	0.01	0.01	-0.01	+0.02	0.38
Male gender	0.38	0.15	+0.08	+0.68	0.01
Compression bandage	-0.22	0.14	-0.51	+0.07	0.14
Pre-operative Hb	0.82	0.07	+0.69	+0.95	0.01
Tourniquet	0.67	0.19	+0.29	+1.04	0.01
Non-compression bandage*No tourniquet	0.32	0.28	-0.24	+0.88	0.26

Table 29: Coefficients, including bandage allocation*tourniquet interaction for multiple linear regression with post-operative Hb as dependent variable

With this model, pre-operative Hb remains a statistically significant predictor of post-operative Hb levels (table 29). An increase of 1g/dl in pre-operative Hb was associated with a predicted increase in post-operative Hb of 0.82 g/dl (95% CI 0.69 to 0.95, p=0.01).

Tourniquet use is also a statistically significant predictor of post-operative Hb. Using a tourniquet resulted, on average, in a higher post-operative Hb level (adjusted mean difference 0.67 g/dl, 95% CI 0.29 to 1.04, p=0.01).

As with the main regression model, gender was also a statistically significant predictor, with male participants having 0.32g/dl greater post-operative Hb than female participants (95% CI 0.08 to 0.68, p=0.01).

The interaction between bandage allocation and tourniquet use was not a statistically significant predictor for post-operative Hb.

5.4.2.2 Tourniquet use and post-operative pain

The effect of tourniquet use on post-operative pain was analysed with a multiple linear regression model with 24 hour mean pain scores as the dependent variable for the overall participant cohort (Section 5.3.2.4 table 20). The use of a tourniquet resulted, on average, in higher post-operative pain scores than when not used but this was not statistically significant (adjusted mean difference +0.43, 95% CI -0.07 to 0.93, p=0.09).

A further multiple linear regression model was utilised to analyse any potential interaction between bandage allocation and tourniquet use with regards to mean pain scores. Age, anxiety (yes = 1 no = 0), bandage allocation (compression = 1, non-compression = 0), depression (yes = 1, no = 0), gender (female = 2, male = 1), low back pain (yes = 1, no = 0), previous TKA (yes = 1, no = 0) and tourniquet (used = 1, no = 0) were added as individual predictors in addition to a bandage*tourniquet interaction.

The ‘goodness of fit’ Pearson’s chi square value was 2.23.

Variable	Adjusted mean difference	Standard Error	95% Confidence Intervals for B		P value
			Lower bound	Upper bound	
Age	-0.13	0.15	-0.04	+0.02	0.39
Anxiety	-2.06	0.91	-3.83	-0.28	0.02
Compression bandage	0.45	0.29	-0.13	+1.02	0.13
Depression	0.34	0.43	-0.52	+1.20	0.44
Female gender	0.51	0.25	+0.01	+1.01	0.04
Low back pain	0.75	0.59	-0.40	+1.89	0.20
Previous TKA	0.25	0.29	-0.32	+0.83	0.39
Tourniquet	0.28	-0.38	-0.46	+1.02	0.46
Non-compression bandage*No tourniquet	0.14	0.55	-0.94	+1.23	0.79

Table 30: Coefficients, including 'bandage allocation*tourniquet' interaction for multiple linear regression with 24 hour mean pain scores as dependent variable

This model highlighted anxiety and female gender as statistically significant predictors of post-operative pain. Female participants experienced, on average, 0.51 points more pain than male participants (95% CI 0.01 to 1.01, p=0.04). Those participants with 'anxiety' reported lower post-operative pain scores (adjusted mean difference -2.06, 95% CI -3.83 to -0.28, p=0.02).

There was no evidence of a statistically significant interaction between tourniquet use and bandage allocation with regards post-operative pain (adjusted mean difference 0.14, 95% CI -0.94 to 1.23, p=0.79).

6 Discussion

There are several key findings from this trial regarding acute outcomes with compression bandage use following TKA. Along with the systematic review and meta-analysis, these outcomes will help shape both future research and clinical applications. The key findings include:

- Statistically significant differences in post-operative blood loss (Hb drop, HCT drop, blood volume loss), favouring non-compression bandaging.
- No statistically significant differences in the secondary outcomes of pain scores, analgesia requirements, length of stay, complication rates and allogenic blood transfusion requirements.
- No significant correlation between post-operative blood loss and post-operative pain scores or analgesic requirements.

With the overall outcomes from the systematic review and meta-analysis, coupled with the positive findings from this trial, the use of compression bandaging and in particular Coban 2, cannot be recommended in an ERAS setting following TKA.

6.1 Summary of key findings

This sub-study, embedded within the KReBS trial, included 156 participants from a single trial site, Northumbria Healthcare NHS Trust. This is the largest study to date to analyse compression bandaging following TKA on short-term outcomes. From these results, the use of compression bandaging following TKA in an ERAS setting cannot be supported, due to the increased blood loss observed.

The participant demographics are comparable with previous studies. The mean age in the analysed studies from the systematic review ranged from 64 to 72 years old; the mean age in this study was 67.1 years (SD 8.4). Similarly, the gender ratio (females 55.8%; males

44.2%) was very similar to that as reported in the latest National Joint Registry data for England, Wales, Northern Ireland and the Isle of Man (females 56.7%; males 43.3%)(16). This supports the overall generalisability and applicability of the findings. BMI was comparable between groups, with a mean of 32.1. Work by Joseph et al. described a patient cohort undergoing TKA as; 14% of patients having a BMI<25, 35% were overweight (BMI-25–30), 32% suffered from grade 1 obesity (BMI-30–35) and 19% had grade 2 obesity (BMI>35) (235). The National Joint Registry also reported a national average of 30.84 in 2018 (16). Currently, in the United Kingdom, TKAs need prior approval from 'clinical commissioning groups' for funding, with patients needing to satisfy certain criteria. Within this, BMI limits, due to the increased risks and complication profiles that may outweigh the functional benefits of total joint arthroplasty have been introduced (236). Patients with BMI above 30 are actively encouraged to engage in weight loss programmes and those above 40 will likely not receive funding without proving exceptional clinical need whilst accepting significantly increased risks.

The use of compression bandaging was associated with a statistically significantly lower post-operative Hb level. In a multiple linear regression with adjustment for pre-operative Hb, gender and age, compression bandage use was observed to be a statistically significant predictor of post-operative Hb levels (mean difference -0.367, 95% CI -0.63 to -0.10, p=0.007). The same was also highlighted with HCT levels. Following blood volume calculations, a statistically significant adjusted mean difference in blood volume loss of 108mls (95% CI +10.8 to +204.3, p=0.030) was also observed.

This study was powered at 90% to highlight a modest difference in Hb drop from pre to post-operative between the two groups of 0.35 g/dl, within its ERAS setting. This sample size was based on recruiting 156 participants, assuming a standard deviation of 0.7, pre-post correlation of 0.7, 10% loss to follow-up, an average of 60 procedures per consultant and an ICC of 0.01. We observed a difference greater than 0.35 g/dl, suggesting this is clinically relevant; however, the difference is in the opposite direction to that anticipated as it does not favour compression. The observed overall standard deviation in Hb change was 0.9, similar to the value of 0.7 assumed. The Hb analysis was based on 155 of the 156 participants, which equates to a lower loss to follow-up than the 10% planned for. We observed a correlation between pre-and post-operative Hb of 0.78 (p=0.001) which was

modestly stronger than the 0.70 anticipated. Twelve surgeons each operated on an average of approximately 13 patients. The ICC was 0.03, higher than the predicted value of 0.01.

Change in Hb levels was selected as the primary outcome in this trial because it is a validated and objective measure of blood loss whilst being clinically relevant. Primary outcomes from previous studies have varied, often focusing on post-operative swelling and pain. Both Pinsornsak et al. and Pornrattanamaneewong et al. had their primary outcome as blood volume loss and their sample size calculations reflected this (141, 142). They were powered to detect a blood volume loss of 150mls but with 80% power. This study, with 90% power, has reduced the potential for a type 2 error occurring. The adjusted blood volume loss calculated in this study, although statistically significant, remains below the 300mls cited by Kalairajah et al. as being the MCID (166). Indeed, the upper 95% CI of 204mls observed in this study suggests that although compression bandaging does seem to cause increased post-operative blood loss this difference is not clinically important. However, the average estimated blood loss of 107mls, does make up approximately 20% of the total average blood loss (575mls) observed in this study, a significant proportion.

Neither Pinsornsak et al. nor Pornrattanamaneewong et al. highlighted a statistically significant difference in mean post-operative blood loss between the two groups. One potential reason for this is the decreased power, sample sizes were sixty participants for Pinsornsak et al. and eighty with Pornrattanamaneewong et al. Both studies utilised surgical drains, which may give rise to the different results observed and additionally limit their applicability within an ERAS setting. Importantly they also both utilised thick woollen padding in several layers, prior to applying the compression bandage. This use of a thick wool layer could significantly limit the amount of compression achieved due to a lack of pressure on the limb tissues. Indeed, Pinsornsak et al. quoted ‘In usual clinical application, a modified RJB may not reach the pressure required for the tamponade effect’. As such, any positive or negative effect on blood loss could be ameliorated and the studies would not pick up any differences. The sub-bandage pressures achieved from the compression bandage was not measured in any of the studies so remains an unknown.

Of note, the only other study to highlight a statistically significant difference in blood volume loss between compression and non-compression groups was Gibbons et al. in 2001 (157). Gibbons et al. reported a significantly higher volume of overall blood loss (mean

960mls) than the volumes observed in our current study (mean 575mls). In Gibbons et al. the use of compression bandaging, corresponds with our study results, highlighting an increased volume of blood loss.

Pre-operative Hb level is a strong predictor of post-operative Hb level. As expected, patients with higher pre-operative level tended to have a higher post-operative level (in this study by 0.82 per unit increase 95% CI 0.68 to 0.95, p=0.001). This is in line with the current body of evidence that underpins pre-operative anaemia screening programmes in arthroplasty, such as that in use within the Northumbria orthopaedic unit (72). The success of these programmes and screening in general has also been stated by Maempal et al. and echoed by Jans et al. (77, 237). The recognition and correction of low pre-operative Hb levels has led to a significant improvement in a wide range of post-operative outcomes including transfusion rates, length of stay and subsequent complications following lower limb arthroplasty.

Overall, mean estimated blood loss in this study was 575ml (SD 309.9). This is considerably lower than the earlier studies such as from Gibbons et al. (2001) and Smith et al. (2002), who did not utilise an ERAS protocol or adjuncts such as tranexamic acid. Other contemporary studies, such as Yu et al. (2018), show comparable levels of blood loss. This highlights the effectiveness of ERAS and the blood saving strategies currently employed.

With the current ERAS system employing a pre-operative Hb screening programme and utilising tranexamic acid intra-operatively alongside a robust transfusion policy, the overall transfusion rate was also minimal. Within this study, only one participant (0.64%) required transfusion, utilising one unit of allogenic blood. As a significant factor in increasing length of stay and risk of complications, this is a major finding that again showcases that an effective blood saving strategy is already in place, resulting in improved patient and financial outcomes. This participant's resultant length of stay was 26 days; 14 days longer than the next highest participant's length of stay. Although only descriptive, this is in keeping with previously cited evidence of transfusions significantly increasing the length of stay (35).

The overall blood transfusion rate is significantly lower than the 2010 to 2014 transfusion rate of 13.9%, presented by Song et al. who did not use tranexamic acid and persisted with post-operative surgical drains (238). Newman et al. introduced an ERAS system incorporating blood saving strategies and observed a reduction in the need for transfusion

rates from 12.4% in 2009 to 2.1% in 2015 (239). It is also an improvement on the previously cited levels in the same trust from Malviya et al. where upon introduction of the ERAS pathway, transfusion rates dropped to 7.6% for both THA and TKA, which is in line with similar work from Frew et al. with transfusion rates of 0.5% following re-audit having introduced a blood management protocol (22, 240). Like blood loss, when compared to studies within the systematic review, transfusion requirements are comparable to more contemporary studies such as Yu et al., performed in an ERAS setting with tranexamic acid use (137). Earlier studies display significantly higher transfusion rates, along with more significant blood loss volumes (157, 159).

By adopting key blood saving strategies within an ERAS setting, such as pre-operative anaemia screening a judicious blood transfusion policy and widespread tranexamic acid use these results show that a transfusion rate of close to zero can be achieved.

No significant differences between groups were found in post-operative pain scores or in subsequent breakthrough analgesia requirement. Again, this is consistent with the majority of findings from the systematic review. From the meta-analysis, with and without Andersen et al., there was a statistically significant but likely to be clinically insignificant difference in breakthrough analgesia use favouring compression bandaging.

Mean pain scores for the first 24 hours post-operative were, on average, 3.0 (95% CI 2.6 to 3.3) in the compression group and 2.6 (95% CI 2.3 to 2.9) in the non-compression group ($p = 0.114$). Breakthrough analgesia requirement was also comparable. This is likely due to the effective multimodal pain pathway already in place within the ERAS setting, such as peri-articular local anaesthetic use and multi-modal analgesia.

Following analysis, compression bandage use was comparable to non-compression bandage use, with regards mean and highest post-operative pain scores. When a multiple regression model was utilised with bandage allocation as a predictor, the findings for acute pain were in keeping with previous studies. The key predictors of post-operative pain in this study were female gender (+0.51 points, 95% CI +0.01 to +1.01, $p=0.047$) and anxiety (-2.06 points, 95% CI -3.83 to -0.30, $p=0.022$). Participant age, however, was not found to be a significant predictor as previously stated by Singh et al. and Ip et al. (241, 242). Anxiety was analysed as a dichotomous variable, verified in surgical pre-assessment as part of the

participants past medical history. Three of the one hundred and fifty-six participants answered ‘yes’ to having anxiety. No formal anxiety scores were utilised to grade the severity of the participants’ anxiety. The degree of anxiety symptoms and their resultant correlation with post-operative pain was not able to be formally assessed or analysed further. This may be as a result of targeted pre-operative education which helped alleviate participant anxiety, although the numbers in the study are very small. Additionally, as no anxiety scale was utilised the severity of symptoms was not known and the three participants may only have mild symptoms and not require psychotropic medication which may be the true influence on outcomes (243).

For breakthrough analgesia requirement, depression was the sole statistically significant predictor and compression bandage use was not. The systematic review and meta-analysis by Yang et al. state that depressive symptoms increase the risk of poorly controlled post-operative pain (224). A sequalae of poorly controlled pain, would lead to an increase in breakthrough analgesia requirement, as observed in this study. Unlike this study though, Yang et al. additionally reported that anxiety also increases the risk of poorly controlled post-operative pain. Echetson et al. also found that depression increased opioid consumption following TKA, however, this was also linked to a significant increase in pain experienced, a finding not supported in our analysis (244). As such there is likely to be further interlinking psychosocial factors such as pre-operative consumption levels and perhaps even habits that result in increased consumption but not overall pain scores.

The results from our study show a low, overall length of stay whilst also displaying a low overall mortality and complication rate. There was, however, no significant difference in these outcomes between the compression and non-compression groups. This links in with the very low transfusion rates, as a result of effective blood saving strategies, equivalent between the two groups, which has been shown previously to be the strongest predictor of increased lengths of stay post-operatively (245).

The overall mean length of stay was 2.6 days (SD 2.6, median 2); a decrease on the figures previously published from the trust (246). This highlights the effectiveness of the overall care received and the systems currently in place to enable an efficient discharge. Indeed, it is a significant improvement on the figures quoted elsewhere such as the English NHS average in 2014 of 5.6 days (15). Our findings are comparable to the average length of stay

reported in the United States of America, where in 2014-2015, Courtney et al. reported an average length of stay of 2.95 days (247). This continued reduction in length of stay has a significant financial impact and can be used as a surrogate marker of improved clinical effectiveness (248).

Following analysis with a negative binominal model, neither bandage allocation nor tourniquet use were significant predictors of overall length of stay. With the sample size employed within this study, and the length of stay being low already due to the overall effectiveness of the ERAS system currently in place, it is not surprising that the use of a compression bandage did not alter this outcome significantly. The only statistically significant predictor for length of stay was age with younger patients predicted to have shorter stays. This is likely due to a combination of better overall health status, increased muscular strength and therefore an ability to advance with post-operative rehabilitation more efficiently. Logistical barriers such as the need for additional care at home may also be a contributing factor for older patients. ASA grade, however, was not deemed to be a statistically significant predictor although lower grades tended to have lower lengths of stay. This is similar to Smith et al's. findings, where increasing age and inferior pre-operative mobility levels were significant predictors for increased length of stay (249). In Piuzzi et al's. much larger cohort of 4,509 patients, in addition to increasing age, both gender and co-morbidities were also predictors of length of stay (250).

An improvement in overall length of stay would be seen as detrimental if other outcomes, such as complications and re-admissions were subsequently increased. Multiple studies have looked at the correlation between a reduction in length of stay and a potential increase in re-admission rates. Bini et al. analysed 23,655 consecutive primary, unilateral TKAs and did not find a difference in re-admission rates between two and three day discharges (251). Similarly, a 35% reduction in length of stay was not linked to a change in re-admission rates by Barad et al. and as such, significant cost savings were portrayed (252). From this study, re-admission and complication rates have remained low with 4 (2.6%) thirty day re-admissions recorded and no recorded myocardial infarctions, deep vein thromboses or pulmonary emboli. This is also evident in the low mortality rate of 0.7% (one participant) which is also consistent with contemporary study results (22, 246). The re-admission and mortality rates presented here are consistent to those presented elsewhere and again back-

up the current evidence that decreased lengths of stay are not linked to a subsequent increase in re-admission and complication rates.

Following on from the similar findings in the systematic review between compression and non-compression groups, and within an ERAS setting, any potential benefit from utilising compression bandaging was predicted to be modest; as such the study was set up to detect a difference in Hb drop of 0.35g/dl. Although there was a statistically significant difference between the two groups for Hb drop, HCT drop and estimated blood volume loss, this did not correspond to a difference in the other clinically relevant outcomes such as post-operative complications, transfusion rates and length of stay. This is likely due to the modest overall difference in blood loss that the study was designed to detect and it not having sufficient impact to alter those outcomes. Indeed, within a successful ERAS system the sample size necessary to detect a meaningful difference in these outcomes would be substantially larger than included in this study. KReBS, with a much larger sample size could have the power to detect relevant differences within these outcomes.

This study also reinforces the success of an ERAS system when used for TKA patients. An ERAS system was introduced in Northumbria NHS trust in 2008; both Malviya et al. and Khan et al. have displayed the improvements seen over the 'standard system' previously utilised (22, 246). The length of stay decreased from a mean of 8.5 to 4.8 days and from a median of 6 to 3 days ($p< 0.001$) and transfusion requirements also saw a significant reduction from 23% to 9.8% ($p<0.001$).

With the transfusion rates, length of stay, re-admission rates and overall mortality and complications rates all being low, the use of the current ERAS system following TKA is triumphed with this current study, irrespective of bandage use.

As an exploratory study which can be used to explain any findings observed in KReBS, basic predictions can be made by utilising the results observed in this trial. With a much smaller population sample, blood loss was the only statistically significant difference between the two groups and important indicators of overall care, such as length of stay and complications were comparable between groups. The blood loss was also modest and the very low transfusion rate reflects this. Therefore, I would expect that KReBS will not show a significant difference in its outcome measures

following analysis or indeed, if a negative outcome is in fact observed with compression bandage use, the significant increase in blood loss and trend towards higher pain scores observed within this trial could be used to explain the outcomes in KReBS. With the findings observed, the overall safety with bandage use and therefore the ability for KReBS to continue was not affected.

6.2 Correlation of post-operative blood loss and predictors of acute pain

No correlation was highlighted between post-operative pain scores and post-operative Hb or HCT drop or estimated blood volume loss within this study. This backs up the findings presented from the previous retrospective study by Hegarty et al. (230). Guay et al. presented a difference in post-operative morphine usage between 12 to 18 hours correlating with blood loss (227). Neither Hb drop, HCT drop or blood volume lost correlated with pain scores or breakthrough analgesia requirement. As expected, breakthrough analgesia requirement showed a strong correlation with both mean pain score (Pearson's correlation 0.544, p= 0.001) and highest recorded pain score (Pearson's correlation 0.473, p= 0.001).

As such, there was no notable threshold for the volume of blood lost beyond which particularly high pain scores were associated.

There was also no statistically significant difference in blood loss volume between those participants requiring breakthrough analgesia and those not (mean difference 79.4mls, 95% CI -43.8 to 202.7, p= 0.21). This is in keeping with the results from the multiple linear regression models which stated BMI and depression as being significant predictors of increased breakthrough analgesia requirement and female gender as predicting increased mean and highest pain scores, whereas estimated blood volume loss was not statistically significant. These findings are evident in work by Liu et al but interestingly, in our model, anxiety was a predictor of decreased pain scores post-operatively (225). This finding, from three participants, is unlikely to have significant clinical significance but further work should be initiated to explore it further. The level of anxiety or medications prescribed was not known and the three participants who stated 'anxiety' as part of their past medical history

may only have mild symptoms present. Interactions from medications cannot be dismissed, and may benefit post-operative, especially neuropathic pain (253).

Following this analysis, the amount of blood lost following TKA does not significantly influence post-operative pain or analgesic requirements.

6.3 Tourniquet use

With respect to post-operative blood loss and pain, there remains controversy surrounding the use of tourniquets in TKA. Although this study was not set up to explicitly analyse tourniquet use and its post-operative effects, as two of the twelve surgeons participating in the study routinely do not use tourniquets we were able to compare tourniquet and non-tourniquet use outcomes. The significant drawback with any conclusions drawn from these results is that tourniquet use was not randomised, and therefore we are analysing two surgeons' outcomes (who did not use tourniquet) against the outcomes of the remaining surgeon cohort (who did use tourniquets).

Importantly, this is the first study to analyse the effect of tourniquet use along with the effect of compression bandaging. Yu et al. is currently the only other study to analyse the effects of compression bandaging without tourniquet use, stating that their use 'is not necessary in routine clinical practice' (137). Their study design did not allow the use of tourniquets throughout and found no statistically significant differences in either post-operative pain or blood loss. In contrast, the remaining eight studies included in the systematic review used tourniquets for all participants with the resulting meta-analysis showing no significant difference in blood loss or acute pain scores.

Following analysis of the overall cohort in this trial, regardless of bandage application, a significant difference in post-operative Hb was highlighted (-0.52g/dl, p=0.001), favouring tourniquet use. This is in keeping with a meta-analysis of eleven RCTs involving 541 patients by Cai et al. (254). They report a significant reduction in overall and intra-operative blood loss with the use of tourniquet without an increase in transfusion rates, as also seen in this study.

There were no statistically significant differences in post-operative pain or breakthrough analgesia requirement when tourniquet use was assessed. Similar findings have been highlighted in a recent systematic review and meta-analysis but there are several other studies that have also reported increased pain with tourniquet use and there is no general consensus at present, highlighted by the difference in practice of surgeons within this trial (255, 256).

In keeping with the findings observed within the systematic review and meta-analysis by McCarthy et al. which included fourteen eligible studies and 440 participants, where no statistically important differences in mean pain scores, or indeed in post-operative function or lengths of stay were observed. These findings mirror those observed in the main outcomes from this study where tourniquet use was likewise, not a predictor of length of stay. This would suggest that any potential quadriceps AMI, as a result of tourniquet use, is not the limiting factor for post-operative rehabilitation and thus a delay to discharge (150, 257).

The new findings presented from this trial, following comparisons of the groups, provide additional information to that previously offered, by demonstrating that compression bandaging following TKA with and without a tourniquet exacerbates blood loss whilst not significantly affecting post-operative pain, complications or length of stay. This is the first study to attempt observation of these findings but they are limited. Tourniquet use was not randomised and the findings could therefore come from other aspects of individual surgeons' practice. This drawback was, however, limited by the same cemented knee prosthesis, ERAS pathway, anaesthetic and post-operative care being used throughout.

6.4 Theory for increased blood loss with compression bandaging

The key finding from the trial was a statistically significant increase in blood loss among patients allocated to compression bandaging, relative to those allocated to the non-compression bandage. There is some evidence in the literature to help explain this unexpected finding.

A potential theory is that this is due to increased hidden blood loss from enhanced haemolysis post-operatively. As post-operative swelling increases, the additional compression caused by the bandages reduces overall blood flow to the subcutaneous tissues and promotes hypoperfusion of surrounding tissues. This results in increased accumulation of reactive oxygen species and free fatty acids, released during and in response to surgery. The reduced blood flow and subsequent build-up of free fatty acids and reactive oxygen species with a resultant increased oxidative stress then potentiates their haemolytic effect.

6.4.1 Mechanism of action

As highlighted in previous studies and indeed in the systematic review and meta-analysis, the degree of swelling observed between compression and non-compression bandage groups is comparable; MD 0.11cm (95% CI -0.66 to 0.88) (137, 147, 158). This lends further credence to another mechanism affecting overall blood loss rather than just tamponade. If tamponade were to have a significant effect, we would expect to record a difference in size of swelling between groups post-operatively in correlation with blood loss.

Concerns have previously been raised regarding the use of external compression devices and the effects that excessive pressure may have on local blood flow. Ogata et al. state that too high of an external pressure could result in tissue ischaemia due to the reduction in blood flow to subcutaneous tissues (145). An increased pressure, due to compression bandaging was initially envisaged to confer a beneficial effect in terms of post-operative blood loss due to tamponade.

From this and previous trials, the complication rates, including deep vein thrombosis and peripheral nerve injuries, as well as overall knee function and pain scores are comparable between compression and non-compression groups. This suggests that excessive, or overtly damaging pressure is not a concern. However, the raised pressure may be of sufficient magnitude to effect localised blood flow and thus, be a causal factor in the results observed.

Little data currently exists for sub-bandage pressures following TKA. Currently, only one study, by Charalambides et al. has assessed this and then, only for 60 minutes post-operatively with intra-articular rather than cutaneous pressures (138). Most other data come from lymphoedema and chronic venous leg ulcer applications (192).

The swelling associated with lymphoedema and chronic venous leg ulcers occurs over a long period of time, in contrast to the acute swelling observed following TKA. Due to extensive tissue damage, bleeding and inflammatory reactions occur, resulting in a rapid increase in limb girth and size. Increases in limb girth of 8 to 10 cms equating to around a 25% increase in size, have been observed within the first 24 hours post-operatively (147, 258). As such, the two clinical applications for compression bandaging behave differently and can be termed dynamic, as with TKA, and static, as with lymphoedema and chronic venous leg ulcers.

It is hypothesized that this dynamic and rapid swelling in combination with the compression bandage results in the increased blood loss observed. Previous work by Yamaguchi et al. highlighted a reduction in peripheral temperature and peak pulsatile blood flow when external compression was applied to healthy individuals' limbs. This reduction occurred between 30mmHg and 50mmHg of external compression and significantly deteriorated above this (143). Similarly, Nielsen et al. observed that at 60mmHg of external pressure, local vascular resistance increased 91% above the reference value ($P > 0.01$) whilst subcutaneous blood flow was reduced to 21% ($P > 0.01$) (259).

These results are also in keeping with earlier work conducted by Landis et al. where the average capillary pressure in the arteriolar limb of a human fingernail was found to be 32mmHg and later by Ogata et al. who stated that excessive external pressure could lead to tissue ischemia by obliterating the blood flow to subcutaneous tissue (144, 145).

The significant degree of swelling following TKA could hence increase sub-bandage pressures upwards of 50mmHg, resulting in decreased blood flow and tissue perfusion. This reduced perfusion can lead to muscle protein oxidization, as demonstrated in limb muscles where a tourniquet has been used, with the muscle injury sustained during prolonged ischemia linked to altered microvascular function (260). Indeed, this oxidisation of muscle

proteins was demonstrated after only 15 minutes of tourniquet use by Appell et al. (261). The resting pressures achieved by Coban 2 are stated as being 35mmHg to 40mmHg, as observed in patients with lymphoedema and chronic venous leg ulcers. Due to the inelastic properties of the compression bandage, the post-operative swelling may cause the resultant pressure to be much higher.

In conjunction with muscle protein oxidization, decreased vascular function could also potentiate the action of locally released inflammatory mediators and free fatty acids. A significant proportion of overall blood loss is attributed to hidden losses following lower limb arthroplasty and surgery for hip fractures (187). These operations all result in the release of substantial amounts of free fatty acids into the circulation as a result of instrumentation of the medullary canals and the subsequent increase in pressure. This release of fat and resultant fatty emboli has been observed on transoesophageal echocardiograms (262). Increased hidden blood loss occurs during intramedullary nailing of the femur when compared to using plate and screws for fracture fixation; 1473 ml compared to 547 ml, an operation with significantly more disruption of the medullary cavity and subsequent release of fatty acids.

These free fatty acids have been shown to compromise the stability of the membrane on red blood cells and increase their osmotic fragility, leading to haemolysis. They are also responsible for increased oxidative stress and reactive oxygen species, resulting in increased hidden blood loss (46, 263).

To support this, Qian et al. provide evidence that oxidative stress, as associated with free fatty acids, results in increased hidden blood loss and highlight the protective nature of anti-oxidants, such as Proanthocyanidin (264). The introduction of Arachidonic acid also resulted in a significant increase in red blood cell damage and hidden blood loss in later work by Yuan et al. (265).

The release of free fatty acids and oxidative stress reactions can also be used to explain some of the findings, highlighted in research comparing computer assisted surgery to standard surgery for TKA, where less blood loss has been cited (266, 267). By not instrumenting the femur and tibia, decreased volume of free fatty acids and oxidative stress would occur, thus reducing hidden blood loss. It is, however, difficult to delineate the exact

causality for the difference in blood loss as standard TKA is reported as having more significant soft tissue releases in addition to larger bone surfaces such as from the breached medullary canals, for potential bleeding (166).

The known release of free fatty acids and their effect on hidden blood loss could be magnified by the reduction in localised blood flow as a result of increased sub-bandage pressures due to the dynamic and evolving post-operative swelling. Free fatty acids and reactive oxygen species could accumulate following TKA due to compression bandage use, emphasizing their effect on red blood cells.

As increased sub-bandage pressure reduces the local blood flow, the body's ability to absorb or excrete substances would also decrease. Andersen et al. previously raised the idea of a decreased absorption rate, as a mechanism of action for the improved efficacy of local anaesthetic infiltration following TKA along with compression bandaging, although no excretion or absorption rates of local anaesthetic were able to be performed (156). As a result of decreased substance absorption, the effects from the reactive oxygen species could be propagated. In turn, potentially causing further swelling, damage and haemolysis and subsequently resulting in an increased hidden blood loss.

This effect may only be observed post-operatively due to the release of free fatty acids and inflammatory mediators due to surgery and tissue trauma, in conjunction with the dynamic swelling. As such, compression bandage use in other static applications would likely not be affected, as pressures also remain lower.

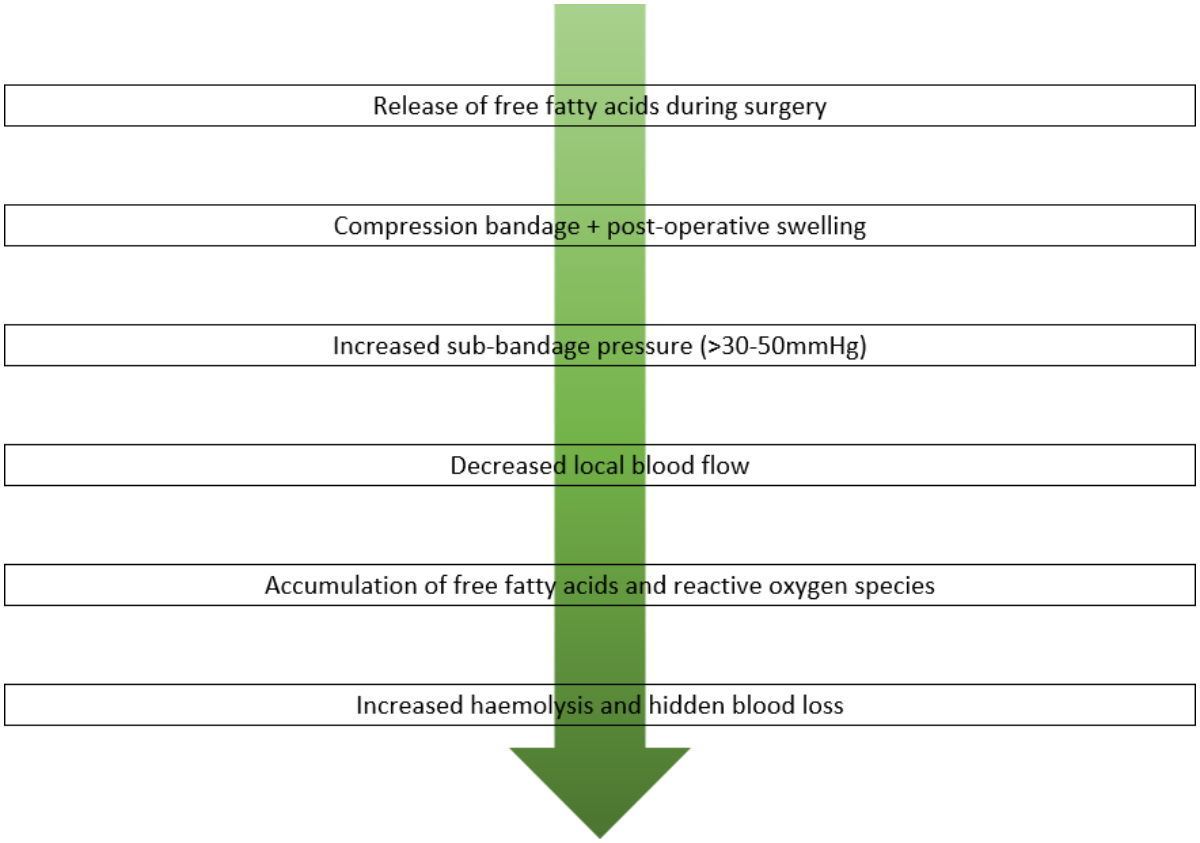

Figure 31: Proposed mechanism of action for increased hidden blood loss due to compression bandaging

6.4.2 Evidence from the trial for proposed theory

In this trial, compression bandaging not only surprisingly resulted in an increased amount of blood loss, there were also no differences in pain scores or analgesic requirements. In both compression and non-compression groups, high volume local anaesthetic infiltration was used, as with the study by Andersen et al. (156)**.** In contrast to the findings within Andersen et al. there were no beneficial analgesic effects experienced with the compression bandaging. Increased sub-bandage pressure, enough to alter local blood flow and increase levels of oxidative stress, has potentially negated any positive analgesic effect elicited from the local anaesthetic.

Although the pressures exerted from the compression bandages are considerably less than a

tourniquet, usually 250mmHg to 300mmHg during TKA, the mode of action is similar. Ischaemic type pain can thus be experienced and is often described as a dull ache which can continue to occur even with local anaesthetic infiltration (105). As a result, the effect of the local anaesthetic as an analgesic is likely to be negated by the discomfort experienced due to the compression bandage. If local anaesthetic was not used in either group, more pain may have been proportionally experienced in the compression bandage group due to the excess increase in pressure.

An important observation from our study was the reporting of 'discomfort' by several participants within the compression bandage group, often asking for its early removal (table 14). Of the seventy-four participants to receive a compression bandage, seventeen participants had the bandage removed early (less than 20 hours) with twelve participants citing either significant discomfort or by patient request specifically due to pain. Indeed, one patient anecdotally described 'tourniquet like pain'. This suggests that sub-bandage pressures were higher than intended and indeed may have continued to rise within the post-operative period. Of note, in the study by Andersen et al., an inner double layer of soft padding (Soffban;BSN Medical Ltd., Brierfield, UK) surrounded by an overlapping layer of elastic adhesive bandage (Acrylastic; BSN Medical SAS, Vibraye, France) was used for the compression bandage group. The double inner layer and use of an elastic bandage may have resulted in a lower sub-bandage pressure than those achieved in our study with the complete Coban 2 system and therefore was better tolerated overall, enabling the local anaesthetic infiltrate to provide the reported improved analgesic effect. In order to quantify the discomfort and to analyse with greater accuracy the reasons behind early compression bandage removal, a formal qualitative patient study could be performed in the future and may help explain subtle differences in pain scores.

This level of increased discomfort with compression bandaging was also described by Yu et al. The non-compression group reported significantly higher comfort ratings than the compression group during the first 24 hours post-operative ($p>0.03$) (137). From the effects noted in the current study and that by Yu et al., compression bandaging within an ERAS setting, may be detrimental to a patient's post-operative pain relief, although with local anaesthetic use, no statistically significant differences in pain scores were identified.

Following TKA, between 80% to 86% of total blood loss occurs within the first day post-

operative, with approximately 50% happening in the first 3 hours (169, 227). This is a contributing factor to post-operative swelling and would also correspond to the peak levels of free fatty acids and resultant oxidative stress due to instrumentation of the medullary canals during surgery. As such, this time frame fits for the proposed mechanism of action for increased hidden blood loss with compression. Over time the body redresses the balance between oxidative and non-oxidative species and the damaging effect on red blood cells diminishes (264). With compression bandaging, the ability of the body to re-dress the oxidative balance is likely reduced, taking longer to rectify and thus increasing haemolysis.

There were no statistically significant interactions between tourniquet use and bandage allocation with regards post-operative blood loss and pain. However, when analysed in the main regression model, both were independent predictors of blood loss. As such, the mechanism for this loss is not affected by an interaction between the two. A common theme for all TKAs within this study is the instrumentation of the medullary canal and subsequent release of free fatty acids. The use of compression bandaging, irrespective of tourniquet use has been shown to increase post-operative blood loss, occurring as 'hidden loss' or following skin closure. From previous studies, similar levels of post-operative swelling are observed in both compression and non-compression groups, therefore extravasation of blood into the surrounding tissues, as is often cited, is unlikely to be the cause of this observed difference. Therefore, an increase in haemolysis is more likely to be the causal mechanism, which is also, unlikely to result in a clinically relevant increase in pain.

6.5 Clinical implications and further work

This trial and the systematic review and meta-analysis have shown no clear benefit, for short- term outcomes, of compression bandage use. The use of Coban 2 compression bandage system within an ERAS setting cannot currently be endorsed due to the increased blood loss observed within this RCT without other clinical benefits. The findings presented here, along with those observed in the meta-analysis, suggest that the use of compression

bandaging does not confer significant clinical benefits for patients undergoing TKA. As such, a more widespread uptake of compression bandage use following TKA, and therefore a change to current 'standard' post-operative care is not suggested on this evidence. The outcomes from the main study, KReBS, will broaden the clinical implications and potential ramifications once long-term outcomes are known. However, with the short-term outcomes observed, the likelihood of KReBS observing an outcome in favour of compression bandaging is low.

One weakness of the current trial is it is based in a single site and it is possible that site specific characteristics, such as factors with the post-operative care, implants and surgical technique or bandage application itself, may have influenced the results.

Consequently, a further study could be performed at different sites. Indeed, such a study taking other subsamples of KReBS could be performed at relatively little cost. Whether or not this would be useful would, in part, depend upon the findings of KReBS. If KReBS finds no difference overall between the groups in the longer-term outcomes, or a difference favouring the non-compression group as observed in the trial in this thesis, then there may be no need to replicate the sub-study analysis. On the other hand, if KReBS were to show a positive effect or if there was a site interaction with the Northumbria NHS Trust having different results to other centres then it might be sensible to replicate the trial in other collaborating centres.

The findings from KReBS will add further knowledge and information around the use and effectiveness of compression bandaging, specifically, long-term outcomes and PROMs. Although this trial has highlighted a surprising increase in blood loss due to the intervention, there was not an associated significant increase in blood transfusions, complications or length of stay, markers of overall care and safety. As such, KReBS should continue to completion, as the blood loss observed due to the compression bandage is not of the magnitude to cause significant clinical harm and the findings from KReBS will carry specific clinical implications regarding compression bandage use and potential uptake, dependent on outcomes.

Further research might also be undertaken to help understand the pressures achieved with compression bandaging following TKA, the use of pressure sensors or inducers could be

used. There are multiple techniques available to facilitate this including optical fibre tape and oximeters (268-270). By analysing the sub-bandage pressures for the duration of their use, the effect of the dynamic swelling occurring following TKA on the compression achieved can be quantified. Previously only Charalambides et al. have measured pressures post-TKA (138). However, these were intra-articular, and not sub-bandage pressures and were only analysed for the first hour post-operative. Therefore, they do not portray the full clinical picture which occurs. With this additional information the proposed dynamic theory of the compression achieved following TKA being excessive and increasing with swelling, thus resulting in decreased blood flow would be enhanced. In order to analyse this, relatively small numbers of participants would be required and the findings then correlated with those from this RCT and those from KReBS.

Other important avenues to explore revolve around the analysis of substrate re-absorption rates and kinetics under compression bandages. As first highlighted by Andersen et al, compression bandage use appears to prolong the effects of local anaesthetic, with the theory of slower absorption and alteration of re-absorption kinetics. This effect has not since been confirmed. If proven, it would also lend credence to the theory of reduced blood flow under compression bandages and the potential increased accumulation and therefore effect of reactive oxygen species and free fatty acids on red blood cells. As an additional part of this, accumulation of free fatty acids post-operatively could similarly be assessed, potentially with blood assays.

Proanthocyanidin and other anti-oxidants also have some interesting but un-confirmed benefits on reducing hidden blood loss (46, 264). This could be more beneficial for those patients where long bones such as the femur are instrumented including, primary and revision hip and knee arthroplasty and intramedullary nailing for fracture fixation, broadening the potential clinical benefits for this research. At present the reduction in hidden blood loss and protective nature of antioxidants has only be highlighted in rat models and further studies in human cohorts is needed but it remains a significant prospect (264, 265).

If the findings from KReBS corroborate with the systematic review and this sub-study, further research should be directed in ways in which to help decrease hidden blood loss following surgery and to develop standardised and accurate ways of measuring overall

and hidden blood loss. This will have wider clinical implications, not only within orthopaedics but in other specialities too. Within current ERAS settings, with the evidence presented, further research into clinical outcomes with compression bandage use following TKA will have limited benefit. A more comprehensive understanding of the basic sciences and mechanisms in play, could however bring further reward.

6.6 Strengths and weaknesses

This study has several strengths.

With 156 participants randomised this is currently the largest study investigating the short-term effects of compression bandaging following TKA. KReBS, with a target of 2,600 participants will become the largest study looking at the overall quality of life effects of compression bandaging following TKA, although it is not specifically collecting blood loss data on the other participants. The next largest studies, by Yu et al. and Munk et al. included 88 participants in each of their respective cohorts. This enables the findings included here to be relatively precise and have sufficient statistical power to identify modest, but important, differences between the groups in terms of blood loss outcomes. The attrition rate within the study is relatively modest, therefore, limiting the potential for that as a possible source of bias.

The findings are also highly clinically applicable and generalisable to a wide population. Although conducted in one NHS trust and within an ERAS setting, multiple surgeons participated, and the use of tourniquets was not dictated. The inclusion and exclusion criteria also allow for an accurate representation of the patient population. This expands on previous work, such as by Yu et al. where an upper limit of 35 was placed on BMI, thus limiting its generalisability. This pragmatic approach to those patients likely to undergo TKA enables the findings to be applied across a broad range of patients and clinical settings.

Although both groups had comparable BMIs, the amount of compression achieved underneath the bandage is not known. As such, BMI, through differences in limb girth may give rise to different sub-bandage pressures and therefore in overall blood loss. By measuring sub-bandage pressure, as well as limb girth pre-operatively, this could be

correlated. With higher BMIs however, it is unlikely that a significant enough pressure to achieve intra-articular tamponade would be achieved, as previously described by Charalambides et al. (138).

In addition, the surface area underneath the compression bandage is also likely to be larger in those participants with higher BMIs, raising the possibility of increased microvascular compromise and therefore, increased haemolysis dur to the afore mentioned mechanism.

Importantly this study not only expands on previous knowledge by highlighting a modest but statistically significant difference in blood loss due to a larger sample size than previously designed studies, it has also added completely new information. It is the first study to compare the use of compression banding following TKA with and without the use of tourniquets. Previously, studies exclusively used tourniquets throughout, whereas the most modern included study, by Yu et al. performed TKAs exclusively without tourniquets. The findings presented do however have limitations, as tourniquet use was not randomised, being used routinely by two surgeons. The findings are therefore open to a degree of selection bias and variability as a result of individual surgeon's practice, rather than solely due to tourniquet use itself.

By using the same cemented cruciate retaining knee prosthesis, ERAS pathway, anaesthetic and post-operative care, this limitation has, however been reduced. Previously, the use of a posterior stabilised knee prosthesis has been observed to increase blood loss, when compared to a cruciate-retaining design, likely due to the vascular posterior cruciate ligament being sacrificed and removed (49, 271). Similarly, the use of cemented prostheses has some evidence highlighting reduced operative blood loss, however, this remains an area of controversy (49). Within Northumbria NHS trust, the use of a cruciate retaining, cemented prosthesis is the standard primary knee replacement and was used throughout this trial for all participants.

To strengthen the findings further and reduce potential bias and variation, another trial, comparing tourniquet use when compression bandaging alone is used could be performed.

There are also some limitations associated with this trial stemming from its pragmatic design and position as a sub-study within KReBS.

By using multiple surgeons and allowing a pragmatic surgical approach, this trial's

generalisability has been increased but also too, the potential variability of results. This is also true for the application of the compression bandage. This potential variability has been combated by the large sample size and as such, any heterogeneity in technique, should not lead to a large bias as bandages were applied by multiple clinicians. Variability due to application technique was minimised with adequate training, supervision and on-going support was also given to those surgeons applying the compression bandage to help reduce any possible inconsistencies.

Due to the application of visually different bandages in the two comparisons groups, it was impossible to blind participants and surgeons following treatment allocation. Participating surgeons, however, were blinded to proposed treatment allocation during surgery and only informed of which bandage to apply during wound closure. Randomisation and subsequent treatment allocation were all performed via a remote electronic system further reducing the risk of bias. Additionally, no surgeons were involved in the collection or analysis of data. Therefore, it would seem unlikely that knowledge of the allocation could have influenced blood loss by patients.

To aid collection of data, a pragmatic approach was applied. Routinely taken blood results at participants pre-assessment consultation were used as baseline levels. This had the added benefits of reducing cost and limiting interventions for participants, likely increasing study participation and rationalising study time. As a result, the levels measured at this time may differ from the levels present on the day of surgery. This is true for both treatment groups and due to the large sample size, the outcomes remain valid. Although there will be a degree of variability in the individual levels measured, overall, the result should be applicable as Hb levels do not fluctuate significantly in this time frame, hence the safe use of pre-assessment clinics and the rise of pre-operative anaemia screening.

Anxiety and depression data were collected as dichotomous variables. Anxiety, surprisingly, had a negative predictive value for post-operative pain but the sample size was small (n= 3). Further detail surrounding specific psychotropic medication used and the use of a severity scale could have aided more detailed analysis, increasing applicability and would be worthy of further investigations in future work.

Post-operative pain scores were also recorded in a pragmatic manner as part of routine care

by ward nurses. As such, specified time points were not dictated by the study.

The results from the trial are also specific to the Coban 2 compression bandage system utilised within an ERAS setting, with the use of adjuncts such as Tranexamic acid. As such, it can be argued that other compression bandages in different clinical settings may not result in the same outcomes. The findings in the systematic review and meta-analysis and their relationship to the similar results observed in this trial would suggest that the findings are transferable. However, the amount of compression achieved by different bandages might be different and therefore may impact on results. It is unlikely though, that this impact will result in a positive outcome for compression as many bandages intend to achieve a similar amount of compression as Coban 2, around 30 -40mmHg.

This study was powered to highlight differences in acute post-operative outcomes such as blood loss and not long-term outcomes such as quality of life. KReBS will address these important long-term outcomes with use of the OKS and EQ-5D as well as analysing overall complication rates. With the information from this study combined with the outcomes from KReBS, the short- and long-term effects of using compression bandaging following TKA will be known.

6.7 Systematic review

When registering and performing the systematic review and meta-analysis in chapter two, there were no other published or registered systematic reviews on compression bandaging use following TKA.

On completion of this review, a further search of the electronic literature has identified a systematic review on the subject, by Feng et al. published in March 2019 (272). Their systematic review, however, has no stated protocol and is not registered on PROSPERO and is not stated as being registered elsewhere.

Following the electronic searches, Feng et al. identified five eligible studies with 402 participants, compared to the nine included here. The studies not included were; Munk et al. Andersen et al. Brock et al. Stocker et al. It is not stated why these were not included or if

indeed they were identified at all, although publication bias is present by limiting the search to English language only.

For the five studies included in both reviews (Gibbons et al. Smith et al. Pinsornsak et al. Pornrattanamaneewong et al. Yu et al.) there is a clear difference in the interpretation in risk of bias (tables 31 and 32). As discussed previously in section 2.1.3.2, a simple coin toss is not considered an adequate random sequence generator and the use of opaque sealed envelopes is not a robust method of concealment (164, 165). In addition, there is no clear statement from Gibbons et al. and Smith et al. regarding a conflict of interest so this bias is unclear and the stated blinding of participants could not have been done due to the overt intervention used. The latest review shows a much more robust criteria for analysing the risk of bias inherent within the included studies and guides the interpretation of results.

The specific outcomes assessed were indistinctly described and narrow. It is not clear which pooled data was used for outcomes such as blood loss, Hb decline and pain scores, which are known to have different time points and measures. Indeed, they state, four studies have data on length of stay but include Pinsornsak et al. twice in the analysis. As such no sub-group analysis was done at different time points. Importantly there was no inclusion of analgesia use as an outcome, the only statistically significant difference in this meta-analysis. The findings presented by Feng et al. do corroborate with the findings in this systematic review. Namely that there are no statistically significant differences in blood loss, Hb decline, transfusion rates, pain scores, length of stay or adverse effects between groups.

With the areas of significant concern regarding potential bias, superficial and incomplete outcome analysis along with a much smaller participant cohort and included studies, the latest systematic review is however a more robust and complete study and therefore supersedes and sets the standard for analysis of compression bandaging following TKA.

Study	Year	Random sequence generation (Selection bias)	Allocation concealment (Selection Bias)	Blinding (Performance bias and detection bias)	Incomplete outcome data (Attrition data)	Selection reporting (Reporting bias)	Free of conflict of interest (other bias)
Gibbons	2001						
Smith	2002						
Pinsornsak	2013						
Pornrattanamaneewong	2018						
Yu	2018						

Table 31: Current systematic review risk of bias table for studies also included in Feng et al.

Low risk of bias		Unclear risk of bias		High risk of bias	

Study	Year	Random sequence generation (Selection bias)	Allocation concealment (Selection Bias)	Blinding (Performance bias and detection bias)	Incomplete outcome data (Attrition data)	Selection reporting (Reporting bias)	Free of conflict of interest (other bias)
Gibbons	2001						
Smith	2002						
Pinsornsak	2013						
Pornrattanamaneewong	2018						
Yu	2018						

Table 32: Risk of bias table as included in Feng et al.

6.8 Conclusion

This pragmatically designed and conducted study has improved our overall understanding about the effects of compression bandaging following TKA. The findings have also led to a

new hypothesis being generated, due to the surprising results seen, which is a significant extension from those initially hypothesised and proposed in previous studies. As such, further work and studies have been suggested to confirm or refute the new theory.

As the largest current study investigating compression bandaging following TKA and the first to compare their use with and without tourniquet, in combination with the comprehensive systematic review and meta-analysis the findings are wide reaching. Within an effective and evidence-based ERAS setting, the use of Coban 2 compression bandaging following TKA is not recommended. This is due to a higher amount of post-operative blood loss, with no significant improvements in pain scores, analgesia use or length of stay. Coupled with the findings from the systematic review and meta-analysis, there does not appear to be any significant clinical benefit conferred to patients following TKA. Long term outcomes from the use of Coban 2 in KReBS will inform us further and help guide and validate the findings presented here.

The proposed mechanism for this increased blood loss is one of dynamic swelling, increased sub-bandage pressures and a resultant increased hidden blood loss due to haemolysis. The release and subsequent accumulation of free fatty acids and reactive oxygen species along with localised decreased blood flow are a potential mechanism for this occurrence.

The findings within this study have important clinical impacts and will help guide future clinical care and will potentially give a foundation for explaining final observations from KReBS once presented.

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Appendix

A 1 Systematic review and meta-analysis

A 1.1 Electronic database search strategies

A 1.1.1 Cochrane Central Register of Controlled Trials (CENTRAL)

(compression bandage or compression or inelastic or elastic or short stretch or stocking or bandage or wrap or hosiery or bandaging technique or compression technique or compression bandaging technique or compression bandaging therapy or Robert jones) and (((knee or knee joint) and (new or arthroplasty or replacement or surgery or implant or prosthesis or artificial)) or total knee replacement or total knee arthroplasty or total knee prosthesis or TKA or TKR) and (randomised or randomized or RCT)

A 1.1.2 Medline via OVID 1946 to 12th December 2018

1. exp Compression Bandages/
2. compressi$.mp.
3. inelastic.mp.
4. elastic.mp.
5. short stretch.mp.
6. stocking$.mp.

7. bandag$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8. wrap$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9. hosier$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. garment$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11. bandaging technique.mp.

12. compress$ technique.mp.

13. compress$ bandaging technique.mp.

14. compress$ bandaging therapy.mp.

15. compress$ therapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. robert jones.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17. multi$layered compression.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. coban.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

19. Elastocrepe.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. Leukocrepe.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. lenkelast.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

22. Comprilan.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

23. Parema.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

24. tensolastic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

25. tensopress.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

26. Setopress.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

27. surepress.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

28. varico.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

29. actico.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

30. proguide.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31. elset.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

32. 2 or 3 or 4 or 5

33. 6 or 7 or 8 or 9 or 10

34. 32 and 33

35. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

36. 1 or 34 or 35

37. exp Knee Joint/

38. knee.mp.

39. knee joint.mp.

40. new.mp.

41. arthroplast$.mp.

42. replacement$.mp.

43. surger$.mp.

44. prosthe$.mp.

45. implant$.mp.

46. artificial.mp.

47. orthop$edic prosthe$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

48. exp Joint Prosthesis/

49. endoprosthetic joint$.mp.

50. joint replacement$.mp.

51. (artificial adj3 arthroplast$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

52. (replacement adj3 arthroplast$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

53. endoprosthe$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

54. total knee replacement$.mp.

55. total joint replacement.mp.

56. total knee arthroplast$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

57. tkr.mp.

58. tka.mp.

59. Arthroplasty, Replacement, Knee/

60. Knee Prosthesis/

61. 37 or 38 or 39

62. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53

63. 54 or 55 or 56 or 57 or 58 or 59 or 60

64. 61 and 62

65. 63 or 64

66. "randomized controlled trial".pt.

67. (random$ or placebo$ or single blind% or double blind$ or triple blind$).ti,ab.

68. (retraction of publication or retracted publication).pt.

69. 66 or 67 or 68

70. (animals not humans).sh.

71. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.

72. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.

73. 69 not (70 or 71 or 72)

74. 36 and 65 and 73

A 1.1.3 EMBASE via OVID 1974 to 12th December 2018

1. exp Compression Bandages/

2. compressi$.mp.

3. inelastic.mp.

4. elastic.mp.

5. short stretch.mp.

6. stocking$.mp.

7. bandag$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

8. wrap$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

9. hosier$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10. garment$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

11. bandaging technique.mp.

12. compress$ technique.mp.

13. compress$ bandaging technique.mp.

14. compress$ bandaging therapy.mp.

15. compress$ therapy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

16. robert jones.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

17. multi$layered compression.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18. coban.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

19. Elastocrepe.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

20. Leukocrepe.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. lenkelast.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

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23. Parema.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

24. tensolastic.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

25. tensopress.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

26. Setopress.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

27. surepress.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

28. varico.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

29. actico.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

30. proguide.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

31. elset.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

32. 2 or 3 or 4 or 5

33. 6 or 7 or 8 or 9 or 10

34. 32 and 33

35. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

36. 1 or 34 or 35

37. exp Knee Joint/

38. knee.mp.

39. knee joint.mp.

40. new.mp.

41. arthroplast$.mp.

42. replacement$.mp.

43. surger$.mp.

44. prosthe$.mp.

45. implant$.mp.

46. artificial.mp.

47. orthop$edic prosthe$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

48. exp Joint Prosthesis/

49. endoprosthetic joint$.mp.

50. joint replacement$.mp.

51. (artificial adj3 arthroplast$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

52. (replacement adj3 arthroplast$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

53. endoprosthe$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

54. total knee replacement$.mp.

55. total joint replacement.mp.

56. total knee arthroplast$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

57. tkr.mp.

58. tka.mp.

59. Arthroplasty, Replacement, Knee/

60. Knee Prosthesis/

61. 37 or 38 or 39

62. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53

63. 54 or 55 or 56 or 57 or 58 or 59 or 60

64. 61 and 62

65. 63 or 64

66. Clinical Trial/

67. Randomized Controlled Trial/

68. controlled clinical trial/

69. multicentre study/

70. Phase 3 clinical trial/

71. Phase 4 clinical trial/

72. exp RANDOMIZATION/

73. Single Blind Procedure/

74. Double Blind Procedure/

75. Crossover Procedure/

76. PLACEBO/

77. randomi?ed controlled trial$.tw.

78. rct.tw.

79. (random$ adj2 allocat$).tw.

80. single blind$.tw.

81. double blind$.tw.

82. ((treble or triple) adj blind$).tw.

83. placebo$.tw.

84. Prospective Study/

85. 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84

86. Case Study/

87. case report.tw.

88. abstract report/ or letter/

89. Conference proceeding.pt.

90. Conference abstract.pt.

91. Editorial.pt.

92. Letter.pt.

93. Note.pt.

94. 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93

95. 85 not 94

96. 36 and 65 and 95

97. from 96 keep 2,6,11,26,40,59,63,123,134,141,145,148,167,172,178

A 1.1.4 PedRO

Abstract and Title: compression bandage

AND

Body part: lower leg or knee

AND

Method: clinical trial

A 1.2 Eligible study characteristics and judgement of risk of bias

A 1.2.1 Andersen et al.

Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage improves local infiltration analgesia in total knee arthroplasty. Acta Orthop. 2008;79(6):806-11.

Methods	Randomised parallel group trial.
Participants	48 consecutive patients undergoing unilateral primary TKA. Cemented knee prosthesis. Fast track setting. Intervention group: 24. 15 women, 9 men (median age 75 years, (IQR 65 to 79)); ASA 1: 3, ASA 2: 17, ASA 3: 4 control group: 24. 15 women, 9 men (median age 67 years, (IQR 61 to 75)); ASA 1: 3, ASA 2; 19, ASA 3:2 Inclusion criteria: (1) being scheduled for unilateral total knee arthroplasty, (2) being able to understand and speak Danish, (3) being able to give informed oral and written consent to participate. Exclusion criteria: (1) being under treatment with opioids or steroids, (2) having rheumatoid arthritis or other immunological diseases, (3) having a history of stroke, or any neurological or psychiatric condition capable of influencing pain perception (e.g. depression, diabetic neuropathy etc.), (4) being allergic to any of the drugs administered Location: Denmark

Interventions	Following skin closure and dressing application at the time of surgery; Intervention group (n= 24) a compression bandage was then applied firmly from the toes to the mid-thigh consisting of an inner double layer of soft padding (Soffban; BSN Medical Ltd., Brierfield, UK) surrounded by an overlapping layer of elastic adhesive bandage (Acrylastic; BSN Medical SAS, Vibraye, France). Fast Track analgesia. Control group (n= 24) a non-compression bandage applied from the mid-calf to the mid-thigh and consisted of an inner double layer of soft padding and an outer layer of standard wrapping. Fast track analgesia. Both bandages stayed in-situ for 24 hours post-operative.
Outcomes	1. Pain: NRS. Assessed every hour for 8 hours and again at 24 hours at rest, 90^{o} knee flexion and at 45^{o}. 2. Additional doses of Oxycodone (mg), in addition to regular analgesia, during first 24 hours post-operative. 3. Duration of inpatient hospital stay following surgery.

Judgement of risk of bias Andersen et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	High risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and non-compression bandage use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for, no drop-outs
Selective reporting (reporting bias)	Low risk	All pain scores recorded at designated time points, length of stay and additional opioid use stated.
Other bias	Low risk	"No benefits or funds were received in support of the study".

A 1.2.2 Brock et al.

Brock TM, Sprowson AP, Muller S, Reed MR. STICKS study - Short-sTretch Inelastic Compression bandage in Knee Swelling following total knee arthroplasty - a feasibility study. Trials. 2017;18(1):6.

Methods	Randomised parallel group trial.
Participants	50 patients undergoing unilateral primary TKA. Cemented knee prosthesis. Fast track setting. Intervention group: 25. 16 women, 9 men (mean age 69.5 years (SD 6.8)); BMI 28.8 (SD 4.4) Control group: 25. 16 women, 9 men (mean age 67.3 years (SD 8.2)); BMI 29.7 (SD 5.5) Inclusion criteria: (1) primary TKA for osteoarthritis, (2) age over 18 years and (3) being able to provide written, informed consent Exclusion criteria: (1) peripheral vascular disease characterised by an ABPI <0.8, (2) peripheral neuropathy and (3) BMI >40. Location: Northumbria NHS Foundation trust, England
Interventions	Following skin closure and hydrocolloid dressing application at the time of surgery; Intervention group (n = 24) a soft inner layer (Soffban, BSN Medical Ltd., Brierfield, UK) was applied from the toes to the groin with a 50% overlap of bandage. Following this the outer compressive layer bandage (Actico bandage, Activa Healthcare Ltd., UK) was applied firmly over the top,

again, with a 50% overlap of bandage. It was applied after release of the tourniquet by necessity due to its length up the thigh.

Control group (n=25) consists of a soft inner layer (Soffban, BSN Medical Ltd., Brierfield, UK) applied from 10 cm below to 10 cm above the patella with a 50% overlap of bandage, followed by a similar outer layer of crepe bandage (BSN Medical Ltd., Brierfield, UK) prior to deflation of the tourniquet.

Both bandages were removed at 24 hours post-operatively and a cryo-cuff utilised.

Outcomes

1. OKS: Scored pre-operatively and 6 months post-operative.
2. EQ-5D-3L: Scored pre-operatively and 6 months post-operative.
3. Knee swelling: Circumference of knee in cm. Measured pre-operatively, daily until discharge and at 6 weeks.
4. Knee Range of Movement: Measured pre-operatively, daily until discharge and at 6 weeks.
5. Pain scores: VAS. Recorded preoperatively, daily until discharge (pre- and post-physiotherapy) and at 6 weeks.
6. Length of stay.
7. Complications: Thromboembolic events, post-operative infections or skin complaints.

Judgement of risk of bias Brock et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Distance computer-generated random sequence, random permuted blocks
Allocation concealment (selection bias)	Low risk	Day of surgery, www.sealedenvelope.com, does not state who had access
Blinding (performance bias and detection bias) All outcomes	High risk	Compression and non-compression bandage use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete CONSORT diagram. All patients accounted for including dropouts and reasons given. Intervention n: 3 Control n: 4
Selective reporting (reporting bias)	Low risk	Results match outcomes proposed in methodology
Other bias	Low risk	"No benefits or funds were received in support of the study". Funded by Northumbria NHS trust

A 1.2.3 Gibbons et al.

Gibbons CE, Solan MC, Ricketts DM, Patterson M. Cryotherapy compared with Robert Jones bandage after total knee replacement: a prospective randomized trial. Int Orthop. 2001;25(4):250-2.

Methods	Parallel group prospective randomised trial. No time period specified.
Participants	60 patients undergoing unilateral primary TKA. Non fast track setting. Intervention group: 30. 19 women, 11 men (70 years, no mention of variance) Control group: 30. 16 women, 14 men (71 years, no mention of variance) Inclusion criteria: Not stated Exclusion criteria: Not stated Location: Princess Royal Hospital, West Sussex, UK
Interventions	Following skin closure at the time of surgery; Intervention group (n = 30) a single layer of velband and crepe followed by a Cryo-cuff (cold water compression device). The velband and crepe was removed by the physiotherapist on the ward. The Cryo-cuff was used for a minimum of 6 hours daily during the patients stay. Control group (n=30) three layers of velband and crepe applied firmly for compression. This was removed at 48 hours. Both groups had PCAs.
Outcomes	1. Blood loss. Volume in suction drainage (mls) at 48 hours post-operative.

2. Pain: VAS. Measured at days one, three, five, seven and nine post-operatively.

3. Adverse effects

4. Transfusion rate

5. Analgesia use (mg/kg of morphine received via PCA at 48 hours; doses of co-dydramol oral analgesia in mg at ten days)

6. Knee range of motion (degrees of flexion at day ten post-operative, measured with goniometer)

7. Length of hospital stay (days)

Judgement of risk of bias Gibbons et al.

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further detail given other than 'randomisation'
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	Cryo-cuff and RJB apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for, no drop-outs
Selective reporting (reporting bias)	High risk	Length of stay and post-operative complications are not stated in the design and methods section
Other bias	Unclear	No statement regarding funding or conflicts of interest

A 1.2.4 Munk et al.

Munk S, Jensen NJ, Andersen I, Kehlet H, Hansen TB. Effect of compression therapy on knee swelling and pain after total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013;21(2):388-92.

Methods	Parallel group prospective randomised trial. September 2009 until December 2010.
Participants	88 patients undergoing unilateral primary TKA were randomised. Fast track setting. Intervention group: 43. 26 women, 17 men (65 years, SD 8) Control group: 42. 22 women, 20 men (63 years, SD 7) Inclusion criteria: Unilateral TKA Exclusion criteria: 1) Alcohol and medical misuse, 2) age<18, 3) Rheumatoid arthritis, 4) Clinical signs of venous insufficiency or previous DVT, 5) indication of severe arterial insufficiency, 6) BMI >40, 7) Unable to provide consent. Location: The Lundbeck Centre for Fast-track Hip and Knee Arthroplasty, Copenhagen, Denmark.
Interventions	Both groups had a compression bandage (Coban 2) applied at the time of surgery. This was removed the morning after the day of surgery. Cooling packs were also used in both groups. Intervention group (n = 43) a medical elastic compression stocking (class 2) following bandage removal, before patient ambulation. Control group (n=42), no further bandages or stockings.

Outcomes	1. Mean knee, ankle and calf circumference (cm); pre-operatively and days 1,2 ,7 and 14 and 1 month post-operatively 2. Complications including DVT, infections, wound problems 3. Pain at rest and mobilising using VAS (0-100mm). Measured pre-operatively and days 1,2 ,7 and 14, and 1 month post-operatively 4. Knee flexion- pre-operatively and days 1,2 ,7 and 14 and 1 month post-operatively 5. Knee function- OKS. Measured at 14 days and 1 month post-operative. 6. Qualitative questionnaire on stability, pain and knee swelling after 1 month.

Judgement of risk of bias Munk et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence, randomised after surgery
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and cryo pad use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs (n=2) and excluded patients (n=1) accounted for. 10 extra patients included as part of sample calculation to account for possible attrition rate.
Selective reporting (reporting bias)	Low risk	Results reflect the domains stated in methods
Other bias	Low risk	No conflicts of interest stated. Funding acknowledged and not industry based

A 1.2.5 Pinsornsak et al.

Pinsornsak P, Chumchuen S. Can a modified Robert Jones bandage after knee arthroplasty reduce blood loss? A prospective randomized controlled trial. Clinical orthopaedics and related research. 2013;471(5):1677-81.

Methods	Randomised parallel group trial.
Participants	60 patients undergoing unilateral TKA under one surgeon. November 2010 until July 2011. Intervention group: 30. 25 women, 5 men (mean age 69.2 years, SD 10.7) control group: 30. 25 women, 5 men (mean age 70.2 years, SD 8.6) Inclusion criteria: Not fully stated Exclusion criteria: Not fully stated Location: Thailand
Interventions	Following skin closure and tourniquet deflation Intervention group (n = 30). Sterile wound dressing and a modified RJB using webril padding and cotton wool roll and a final elastic bandage layer. Left in place for 24 hours. Control group (n=24) sterile wound dressing. Surgical drains used in both groups.
Outcomes	1. Blood loss; volume in drains (ml), HCT drop (%). Measured at 24 and 48 hours post-operative. 2. Transfusion rates. 3. Pain; VAS (0 to 10) measured at 24 and 48 hours post-operative.

4. Knee swelling; Thigh and leg circumference (cm). Measured at 24 and 48 hours post-operative.
5. Length of stay.
6. Post-operative complications.
7. Knee range of movement at discharge (degrees).

Judgement of risk of bias Pinsornsak et al.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised by computer
Allocation concealment (selection bias)	High risk	sequentially numbered, sealed envelopes in two strata
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and non-compression bandage use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for, no drop-outs
Selective reporting (reporting bias)	Low risk	Primary and secondary outcome measurements recorded as stated in method
Other bias	Low risk	No conflicts of interest stated

A 1.2.6 Pornrattanamaneewong et al.

Pornrattanamaneewong C, Ruangsomboon P, Chareancholvanich K, Wilairatana V, Narkbunnam R. Modified Robert Jones bandage can not reduce invisible blood loss after total knee arthroplasty: a randomized-controlled trial. Arch Orthop Trauma Surg. 2018;138(8):1151-7.

Method	Randomised parallel group trial.
Participants	80 consecutive patients undergoing unilateral primary TKA for osteoarthritis. 5 from each group excluded from analysis. March 2016-January 2017 Intervention group: 35. 28 women, 7 men (mean age 69.3, SD 8.2) control group: 35. 33 women, 2 men (mean age 71.0, SD 8.3) Inclusion criteria: (1) being scheduled for unilateral TKA, 2) Primary Osteoarthritis Exclusion criteria: (1) coagulation disorders, (2) received antiplatelet drug within the previous week, (3) a previous history of thromboembolic events, (4) vascular compromise of operated limb, (5) chronic kidney disease, (6) liver cirrhosis, (7) allergic to tranexamic acid, sulfa, or morphine, (8) inability to follow the anaesthetic protocol, (9) refused to participate Location: Thailand
Interventions	Following skin closure at the time of surgery; Intervention group (n = 35); a modified RJB defined as three layers of thick cotton wool and two layers of elastic bandages. This extended above the

	ankle joint to 6 inches above the knee joint. Before applying this bandage, sterile gauze pads were placed over the wound and followed by Webril™ padding (Covidien, Mansfield, MA, USA) Control group (n=35); a non-compressive dressing was made by placing sterile gauze pads over the wound and covering with a hypoallergenic self-adhesive, non-woven fabric tape. The modified RJB stayed in-situ for 24 hours post-operative. Wound drains were used in both groups.
Outcomes	Primary 1. Invisible blood loss. Calculated at 48 hours using HCT levels. Secondary 1. Maximal pain score. VAS (0 to 10). First and second days post-operative, at rest and during ambulation. 2. Morphine usage 3. Range of movement 4. Complications

Judgement of risk of bias Pornrattanamaneewong et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence, blocks of ten
Allocation concealment (selection bias)	High risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and non-compression bandage use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for- no dropouts, flow chart included
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes measured and recorded
Other bias	Low risk	"No benefits or funds were received in support of the study".

A 1.2.7 Smith et al.

Smith J, Stevens J, Taylor M, Tibbey J. A randomized, controlled trial comparing compression bandaging and cold therapy in postoperative total knee replacement surgery. Orthop Nurs. 2002;21(2):61-6.

Method	Randomised parallel group trial.
Participants	84 patients undergoing unilateral primary TKA. Non-fast track setting. Compression bandage group: 40 patients and knees, 19 Female: 21 Male, 72 years (SD 7.1) Cold therapy group: 44 patients and knees, 23 Female: 21 male, 72.1 years (SD 7.8) Inclusion criteria: Unilateral TKA Exclusion criteria: Haematological or coagulation disorders Location: Lismore, Australia
Interventions	Following skin closure and dressing application at the time of surgery; Compression bandage group (n = 40) RJB applied immediately after surgery and removed after 24 hours. Ice bags were then applied for 15 minutes three time a day for the next 48 hours. Cold therapy group (n = 44) RJB applied immediately after surgery as per control group. RJB removed after 6 hours and cryotherapy delivered via cryo-pad machine with the pad placed directly over but not completely covering incision site. Cryo-pad infused with water between 2°C and 5°C for 15 minutes, then deflate for 15 minutes. The cryopad was removed after 24 hours.

	Both bandages stayed in-situ for 24 hours post-operatively.
Outcomes	1. Blood loss - wound drainage in 48 hours (ml); Hb (g/L); 2. Pain - VAS (0 to 10). Measured on days 1,2 and 3 post-operatively 3. Analgesic use - total opiate use (morphine) in 48 hours post-surgery (mg/kg) 4. Knee range of motion - degrees (pre-operative flexion; flexion at 24hours; flexion at 48hours) 5. Knee swelling - mm (pre-operative; 24hours; 48hours). Specific measurement site not stated. 6. Length of hospital stay (days) 7. Transfusion volume (ml) A simple, descriptive cost comparison is also stated.

Judgement of risk of bias Smith et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Coin toss at pre-assessment clinic
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and cryo pad use apparent to patient and data collector
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for- no dropouts
Selective reporting (reporting bias)	Low risk	Results reflect those domains stated in methods
Other bias	Unclear risk	No statement regarding funding or conflicts of interest

A 1.2.8 Stocker et al.

Stocker B, Babendererde C, Rohner-Spengler M, Muller UW, Meichtry A, Luomajoki H. Effective therapy to reduce edema after total knee arthroplasty Multi-layer compression therapy or standard therapy with cool pack - a randomized controlled pilot trial. Pflege. 2018;31(1):19-29.

Methods	Randomised controlled pilot study.
Participants	16 patients undergoing unilateral primary TKA between September 2014 and March 2015. Enhanced recovery setting. Intervention group: 8. 4 women, 4 men (Mean age 68, SD 8.6) control group: 8. 3 women, 5 men (Mean age 73.1, SD 6.3) Inclusion criteria: (1) Age 45 to 90 years, (2) Consentable patient (3) walking ability 10 minutes without walking aids or with one or two walking sticks (4) Unilateral TKA in degenerative or post-traumatic knee osteoarthritis (5) planned anaesthesia: Femoral nerve catheter (6) good knowledge of German Exclusion criteria: (1) knee joint arthritis with additional tuberosity osteotomy (2) BMI over 40 (3) relevant cardiac or neurological deficits (4) Uncontrolled Diabetes Mellitus (5) CKD stage 3 or above (6) pre-existing lymphoedema, (7) Significant known osteoporosis (8) Tumour (9) Clinically relevant post-thrombotic syndrome, (10) Alcohol abuse, (11) Mental illness such as depression, (12) Peripheral vascular disease Location: Switzerland
Interventions	Intervention group (n = 44); a bandage consisting of several layers (tube gauze Tricofix®, padding wadding Artiflex® 10 cm, short-stretch bandage

	[Comprilan®, Beiersdorf] 8 to 12 cm) was applied. The short-stretch bandage was applied with enough pressure to be well tolerated by the patient (about 30 mmHg). This was worn from first to the fifth post-operative day, for 22 hours per day and only removed for measurements, visits and wound control. It was re-applied by trained physiotherapists. Control group (n=24); from the first to the fifth postoperative day received a cold pack (Physiopack® 13 × 30 cm, stored at -19 ° C.) for ten minutes ten times a day. Continuous passive motion devices were used for both groups.
Outcomes	Primary 1. Swelling. Circumferential measurements at the knee joint space, 5 cm, 10 cm and 15 cm proximal and 15 cm distal to the joint space on the operated leg. Secondary 1. Range of motion. First, third and sixth post-operative days and at six weeks. 2. Pain. NRS (0 to 10). First, second and third days post-operative. 3. Fast self-paced walking test- patient walked as fast as possible a distance of 20 metres then, turned around and walked back the 20 metres as fast as possible. 4. Length of hospital stay (days). 5. Complications.

Judgement of risk of bias Stocker et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly stated
Allocation concealment (selection bias)	High risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and non-compression bandage use apparent to patient and surgeon. Data collector blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients received the treatment as allocated, completed the study as foreseen in the protocol, and were included in the data analysis as planned
Selective reporting (reporting bias)	Low risk	All outcomes were recorded and measured at the set time points.
Other bias	Low risk	"No benefits or funds were received in support of the study".

A 1.2.9 Yu et al.

Yu H, Wang H, Zhou K, Rong X, Yao S, Pei F, et al. Modified Robert Jones bandage can not reduce postoperative swelling in enhanced-recovery after primary total knee arthroplasty without intraoperative tourniquet: a randomized controlled trial. BMC Musculoskelet Disord. 2018;19(1):357.

Methods	Randomised parallel group trial.
Participants	90 patients undergoing unilateral primary TKA between December 2016 and May 2018. Enhanced recovery setting. Intervention group: 44. 34 women, 10 men (Mean age 69.32, SD 8.29) control group: 44. 34 women, 10 men (Mean age 69.11, SD 8.66) Inclusion criteria: (1) being scheduled for unilateral TKA, (2) aged 18 and older (3) Osteoarthritis Exclusion criteria: (1) simultaneously bilateral total knee arthroplasty or revision case, (2) surgical history of the knee joint, (3) peripheral vascular disease, (4) ankle brachial pressure index, (5) ABPI< 0.8, (6) peripheral neuropathy, (7) blood coagulation disorders, (8) history of deep venous thrombosis, (9) BMI > 35, (10) knee stiffness characterized as flexion deformity of ≥30° **Location:** China
Interventions	Following skin closure and adhesive dressing application at the time of surgery; Intervention group (n = 44) a modified RJB consisting of a soft inner layer thick cotton padding Winner (Chengdu Wenjian Likang Medical Products Ltd., Sichuan, China) which was applied from toes to thigh and an outer

	layer composed of elastic bandage Coban™ (3 M Deutschland GmbH, Neuss, Germany) from toes to thigh. Control group (n=44) consisted of a sterile adhesive dressing over the wound only. The modified RJB stayed in-situ for 24 hours post-operatively.
Outcomes	Primary 1. Swelling. Measured as circumference of superior pole of patella, inferior pole of patella, mid-line of patella, thigh and calf on days one and three- and three-weeks post-operative. Secondary 1. Range of motion (degrees movement) 2. Knee function. HSSK (0 to 100). 3. Pain. VAS (0 to 10). Measured at rest and during motion higher score indicates more pain). Days one and three post-operatively. 4. Reduction in Hb level (g/dl). From pre to post-operative levels. Days one and three. 5. Patient satisfaction. Qualitative questionnaire. 6. Complications. 7. Post-operative calculated blood loss volume (mls).

Judgement of risk of bias Yu et al.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	High risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Compression bandage and non-compression bandage use apparent to patient and surgeon. Data collector blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for, one patient lost to follow up from each group
Selective reporting (reporting bias)	Low risk	All outcomes were recorded and measured at the set time points.
Other bias	Low risk	"No benefits or funds were received in support of the study".

A 1.3 Calculation of mean pain scores for Munk et al.

In Munk et al. individual post-operative pain scores were added to three groups: low (0 to 2), medium (3 to 5) and high (6 to 10) for analysis. For the systematic review and meta-analysis these 'groups' were converted to a mean pain score by the calculation below.

Assumption: everyone falling into the low category (VAS 0-2) scored 1, the moderate (VAS 3-5) as 4, and high (VAS 6-10) as 8.

Mean MECS group on day one post-operative: ((8*1) + (13*4) + (18*8))/43 = 4.7

Standard Deviation MECS group on day one post-operative estimated as (max-min)/4 = (10-0)/4=2.5

Mean non-MECS group on day one post-operative: ((5*1) + (15*4) + (15*8))/42 = 4.4

Standard deviation non-MECS group on day one post-operative estimated as (max-min)/4 = (10-0)/4=2.5

	MECs group	**Non-MECs group**
VAS day one **Mean (SD)**	4.7 (2.5)	4.4 (2.5)
VAS day two **Mean, (SD)**	3.6 (2.5)	3.0 (2.5)

Table 33: Calculated mean pain scores (points) from Munk et al.

A 1.4 Extrapolation of knee swelling measurements Brock et al.

Control group day one post-operatively: 43.5 cm

Compression group day one post-operatively: 44.0 cm

Control group day two post-operatively: 45.5 cm

Compression group day two post-operatively: 46.0 cm

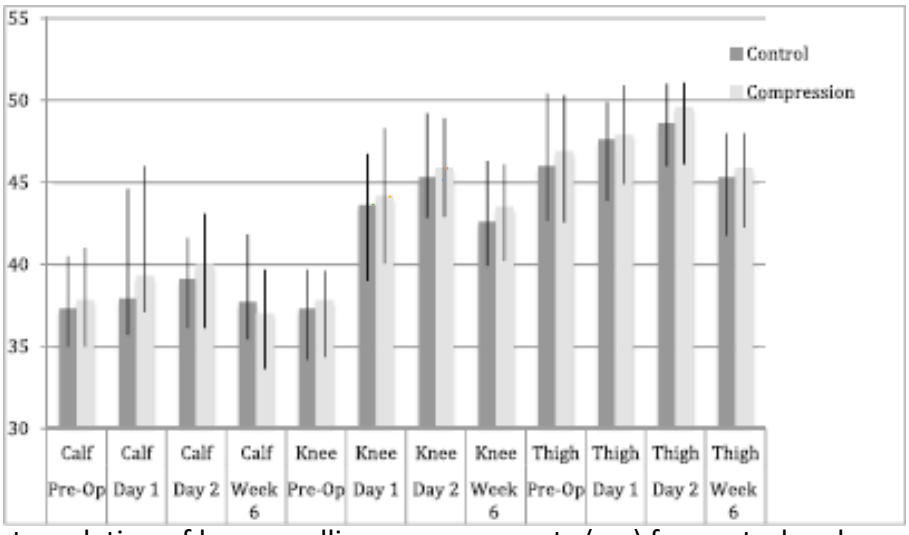

Figure 32: Extrapolation of knee swelling measurements (cm) for control and compression groups on day one and day two from Brock et al. data used for meta-analysis

A 2 Additional information from trial

A 2.1 Blood loss percentage calculation

Calculation to highlight the as a percentage of the overall amount of Hb lost from pre to post-operatively. Hb levels from Prasad et al. (120).

Pre-operative Hb, g/dl Mean, SD	11.9 (1.5)
Day one Hb, g/dl Mean, SD	10.0 (1.3)
Hb drop, g/dl Pre-operative Hb - day one Hb	1.9
Percentage of Hb drop (0.35/1.9) x 100	18.4%

Table 34: Calculation of proposed statistically significant Hb difference (0.35g/dl) Hb drop as a percentage of overall Hb drop.

A 2.2 Coban 2 application

Equipment:

1 x 3M Coban 2 Inner Comfort Layer 10cm x 3.5M (1 on packet)

Order ref number 1 box x 18 rolls: 3M code: 20014 NPC code: ECA210

1 x 3M Coban 2 Compression Layer 10cm x 4.5M (2 on packet)

Order ref number 1 box x 32 rolls: 3M code: 20024 NPC code: ECA214

Micropore Tape

Scissors

Technique:

Following application of an adhesive dressing over the surgical site the non-sterile Coban 2 Inner comfort layer (1) can be applied.

This can be started with or without the tourniquet being inflated and the foot should be in a slightly dorsi-flexed position to aid ankle articulation following application.

Start at the foot, just above toe line and wrap proximally. The foam layer (white) is positioned against the skin.

Avoid wrapping the plantar aspect of the heel. This reduces bulk and allows normal footwear to be worn.

This layer should be put on with minimal tension and approximately 10-20% overlap enabling minimal bulk. This layer often looks untidy.

When you reach the mid-thigh level trim the remaining bandage and secure the flap with tape.

Next, apply Coban 2 Compression Layer (2).

Start at the foot (metatarsal heads) ensuring there is a small amount of 'Comfort layer' left free.

Now wrap the foot including heel area. Stretch the Coban 2 from its resting state but not up to the 'locked out' tension.

To prevent dog ears and flaps utilise a further throw back around the foot before working proximally up the leg.

Ensure that the Compression layer is stretched and applied with a 50% overlap. This allows the bandage to compress. If you miss a bit, simply re-wrap and double over.

Be mindful not to over stretch, for this study we are preventing swelling post-op, rather than compressing excess fluid pathology such as lymphoedema. Aim to stretch this layer between its wrapped (i) and locked-out (ii) tension as highlighted in the accompanying videos.

Wrap the rest of leg leaving a small amount of 'Comfort layer' uncovered around the thigh. Trim the remaining bandage using scissors.

Finally, pat down and smooth the compression layer onto the leg to ensure good adhesion to the first layer.

The aim is to keep the bandage in-situ for 48 hours. It must be removed prior to discharge. Time of removal should be noted in the medical/nursing notes and if removed before 24 hours the reason why must also be stated.

Removal:

For removal, simply use a pair of blunt nosed scissors and cut the bandage on the front of the leg taking care of the underlying skin. This can be done both proximally and distally. Remove the bandage.

Instruction leaflet as used by surgeons and theatre staff as part of KReBS to guide bandage application and removal.

A 3 Trial results

A 3.1 Scatter plots of residuals and Q-Q plots for regression analysis of primary and secondary outcomes

A 3.1.1 Post-operative Hb as dependent variable

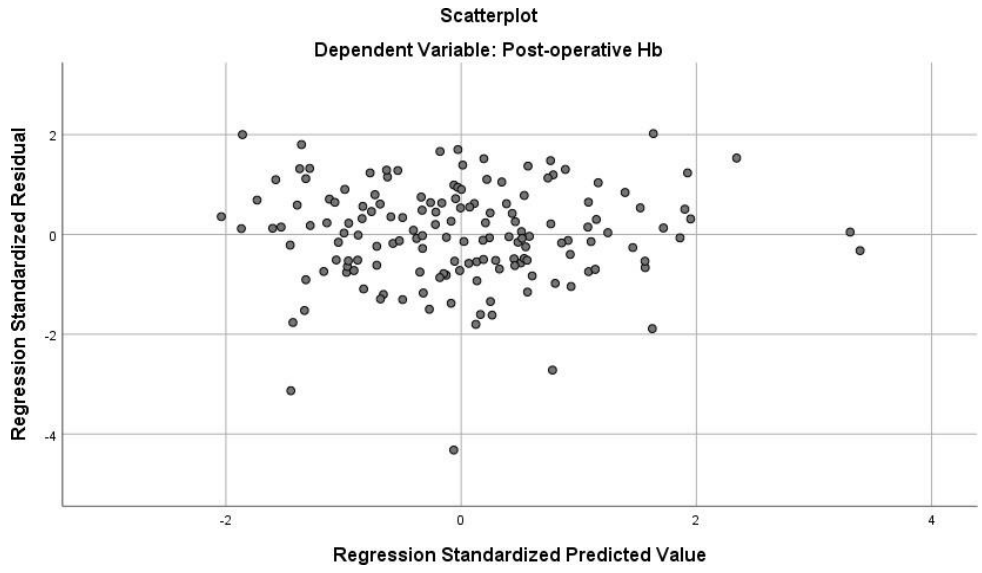

Figure 33: Scatter plot of residuals vs predictor values for post-operative Hb

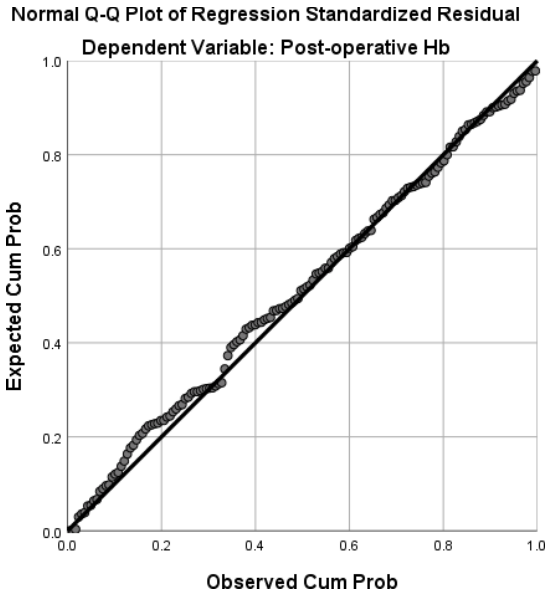

Figure 34: Q-Q plot of residuals for post-operative Hb

A 3.1.2 Post-operative HCT as dependent variable

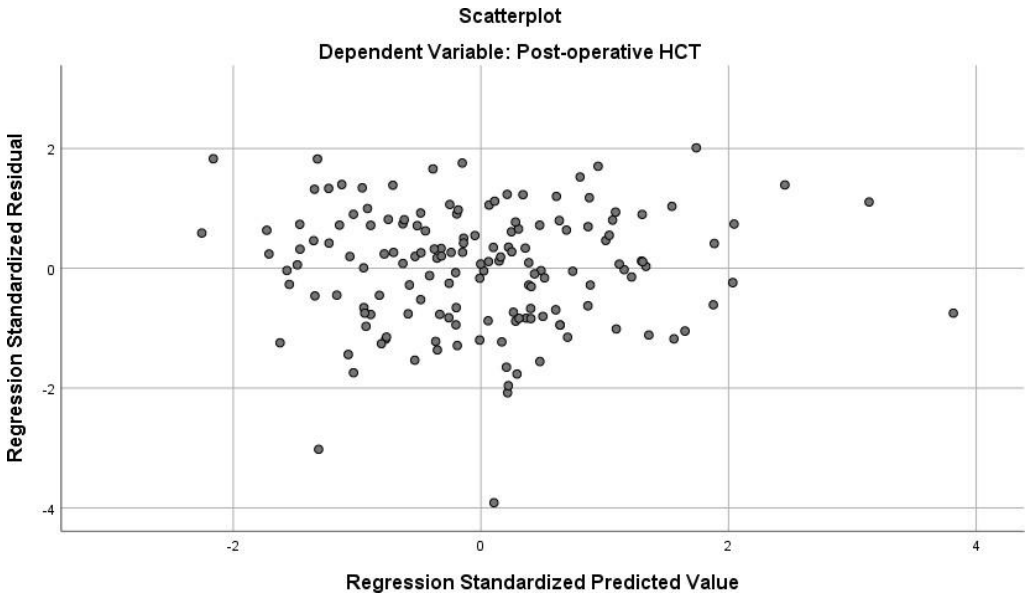

Figure 35: Scatter plot of residuals vs predictor values for post-operative HCT

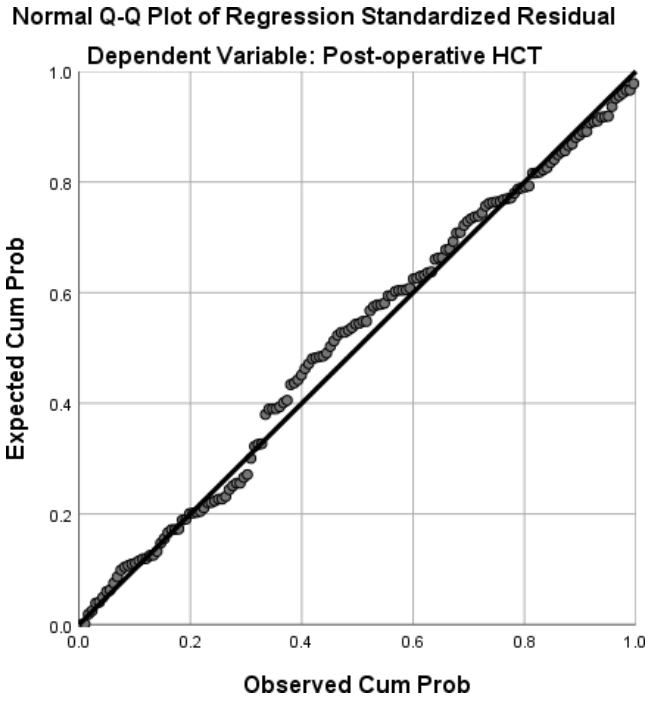

Figure 36: Q-Q plot of residuals for post-operative HCT

A 3.1.3 Estimated blood volume lost as dependent variable

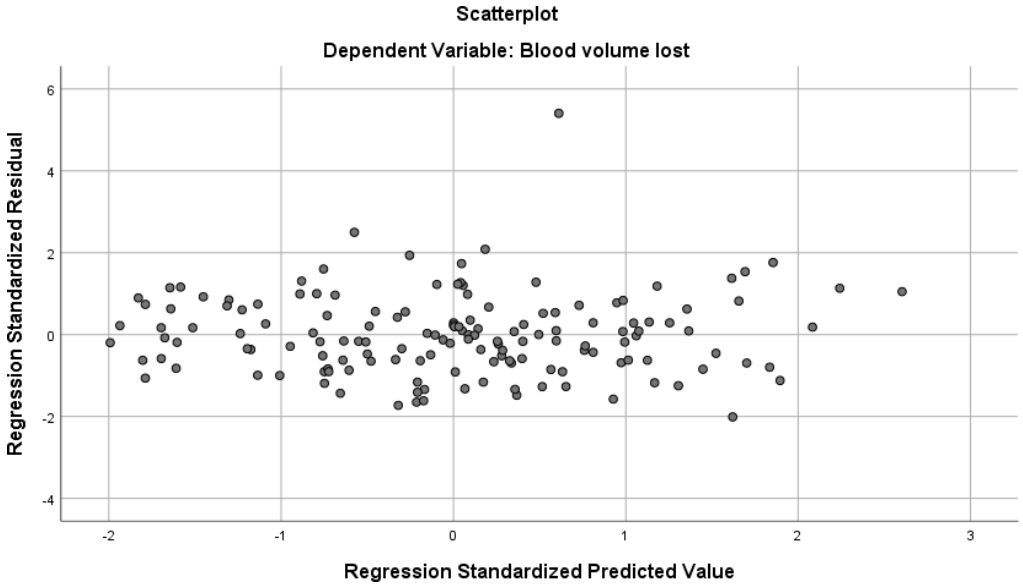

Figure 37: Scatter plot of residuals vs predictor values for estimated blood volume loss

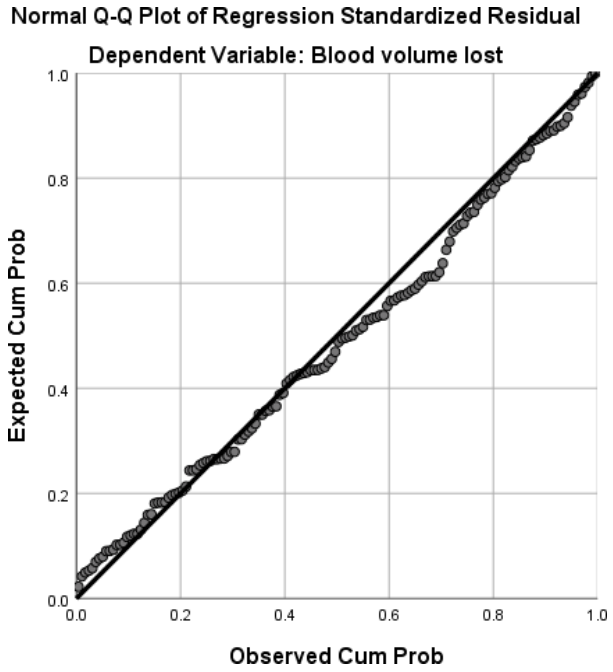

Figure 38: Q-Q plot of residuals for estimated blood volume loss

A 3.1.4 Post-operative 24 hour mean pain score as dependent variable

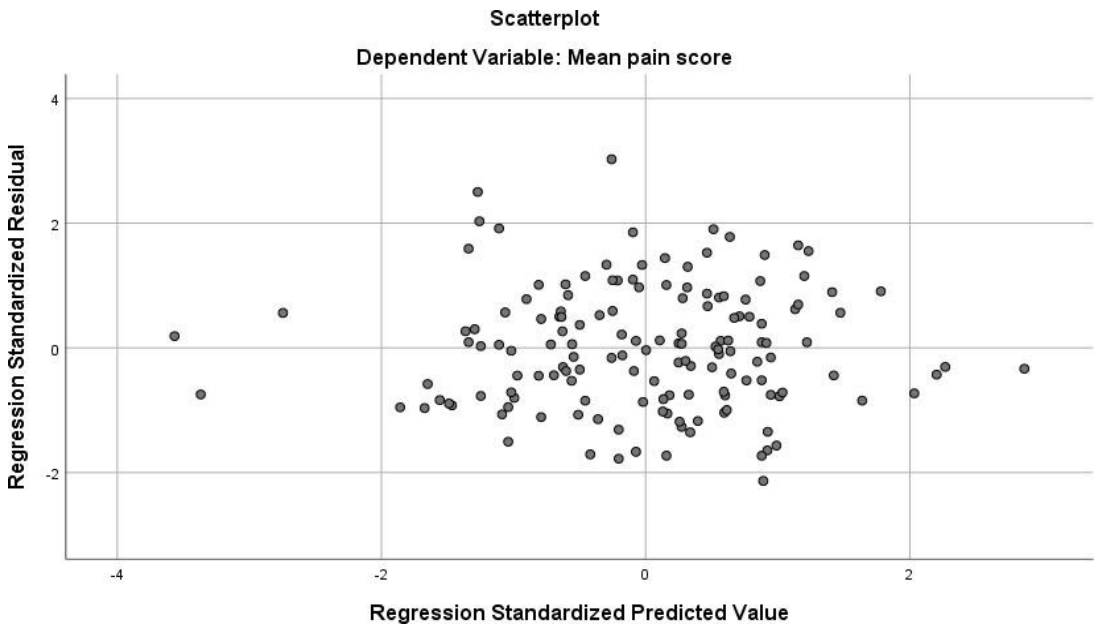

Figure 39: Scatter plot of residuals vs predictor values for post-operative 24 hour mean pain scores

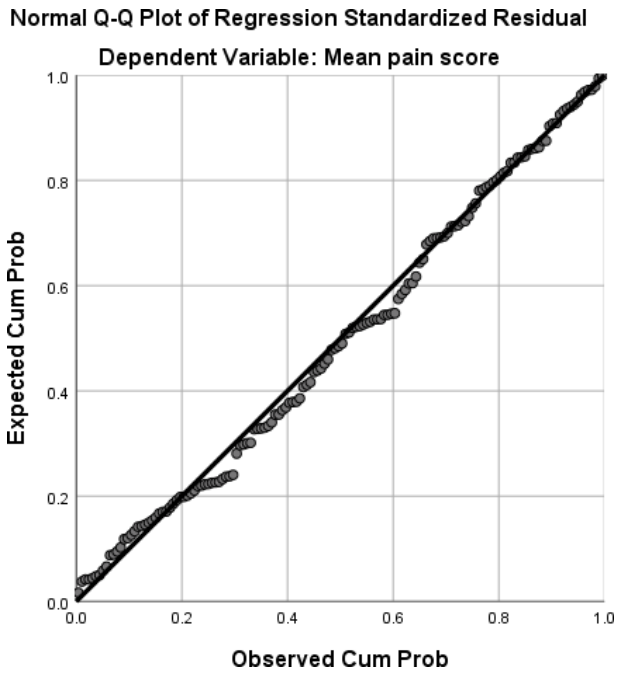

Figure 40: Q-Q plot of residuals for post-operative 24 hour mean pain scores

A 3.1.5 Post-operative highest 24 hour pain score as dependent variable

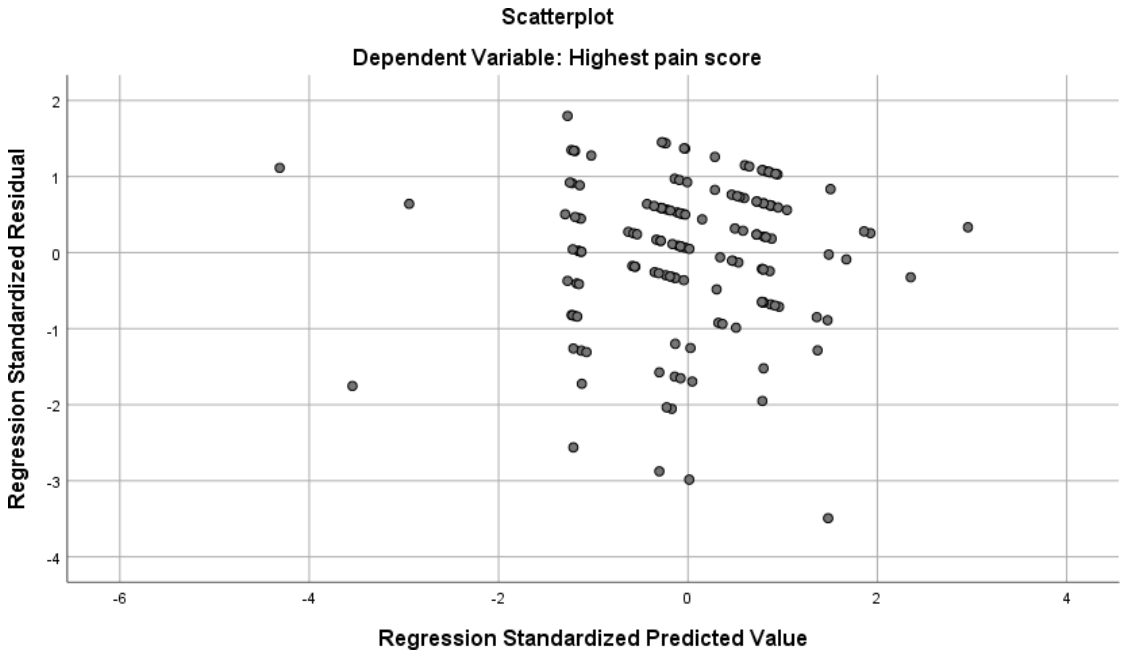

Figure 41: Scatter plot of residuals vs predictor values for highest 24 hour post-operative pain score

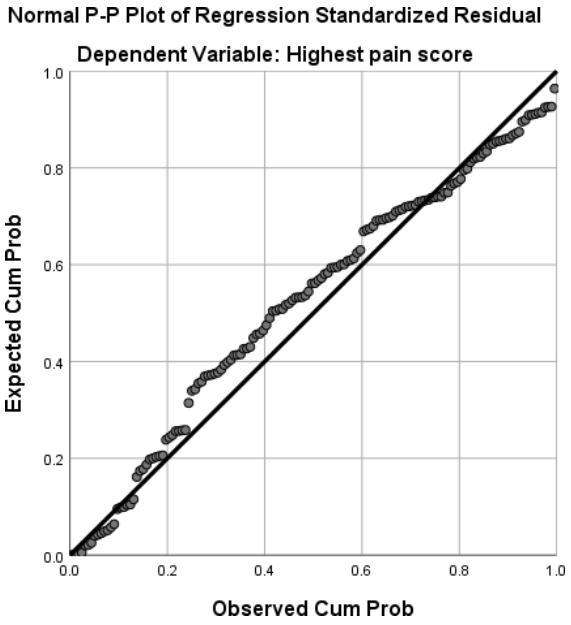

Figure 42: Q-Q plot of residuals for highest 24 hour post-operative pain score

A 3.1.6 Post-operative breakthrough analgesia requirement as dependent variable

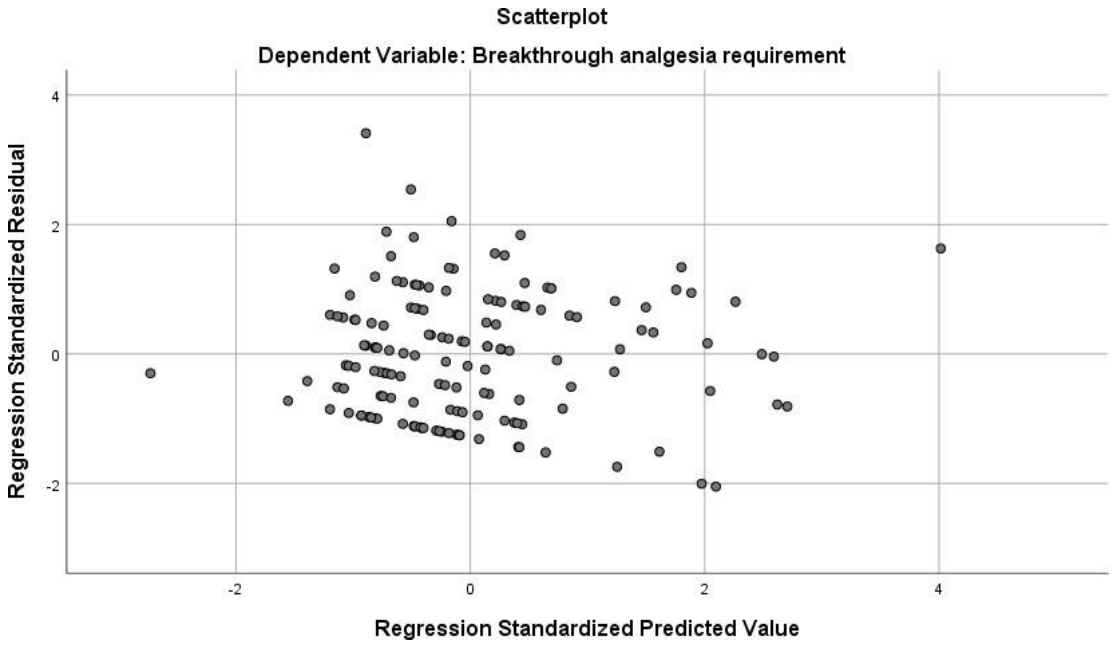

Figure 43: Scatter plot of residuals vs predictor values for breakthrough analgesia requirement

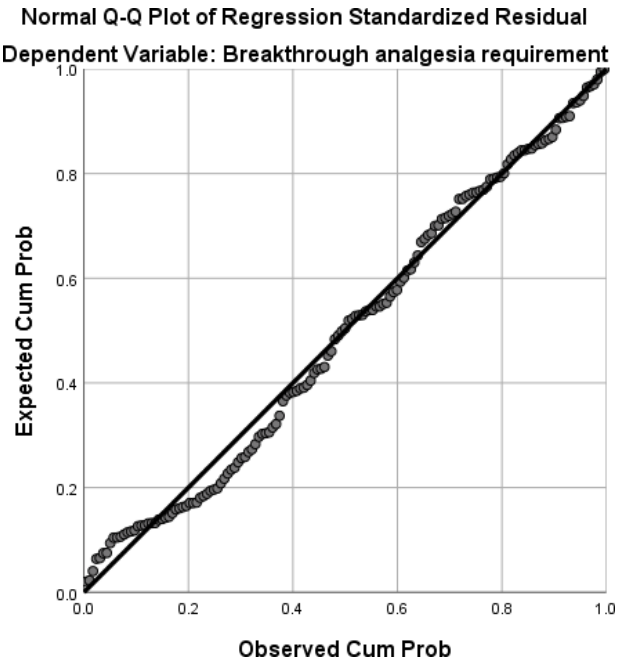

Figure 44: Q-Q plot of residuals for breakthrough analgesia requirement

A 3.2 Simple scatter plots for assessing post-operative Hb drop and mean pain scores with length of stay

A 3.2.1 Hb drop by length of stay

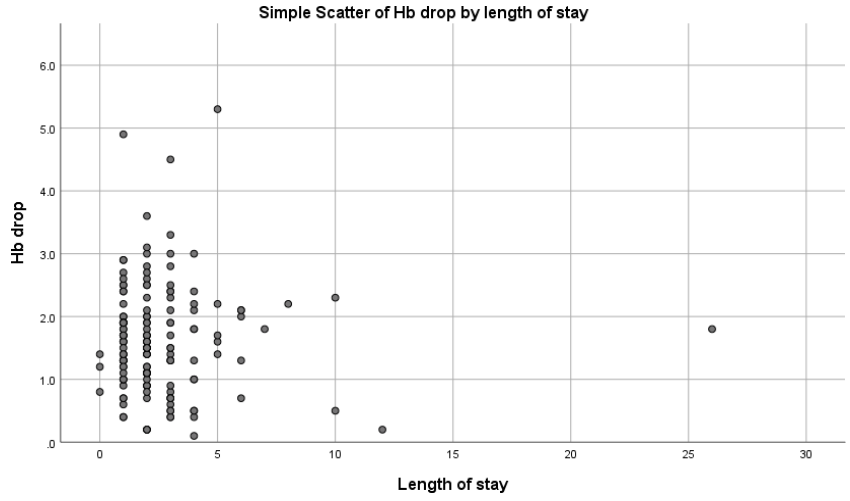

Figure 45: Simple scatter plot of Hb drop (g/dl) by length of stay (days)

A 3.2.2: Post-operative mean 24 hour pain score by length of stay

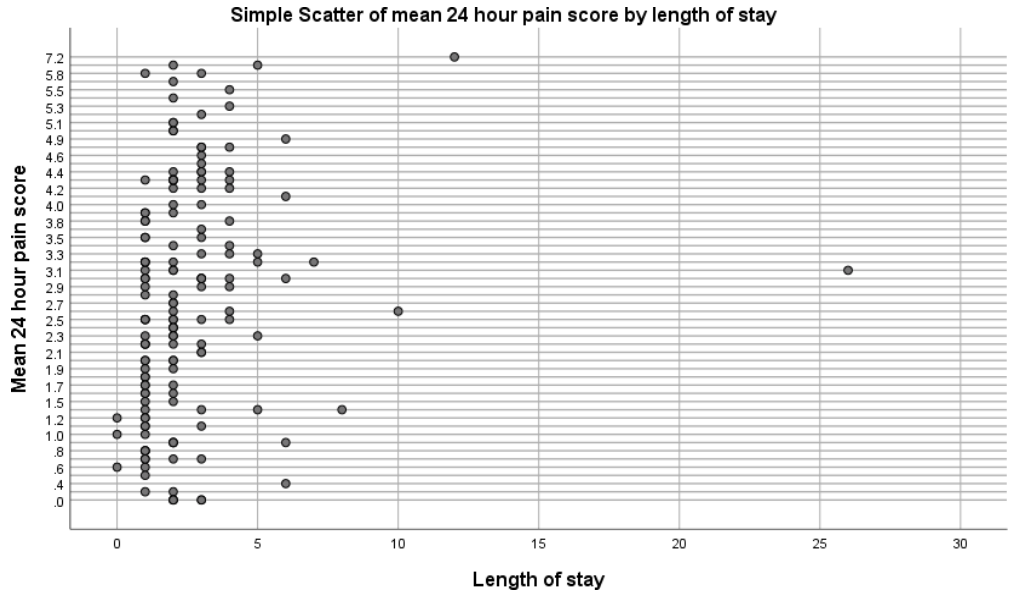

Figure 46: Simple scatter plot of mean 24-hour pain score (points) by length of stay (days)

A 3.3 Scatter plot of residuals and Q-Q plot for regression analysis of predictors of post-operative pain

A 3.3.1 Post-operative mean 24 hour pain score as dependent variable

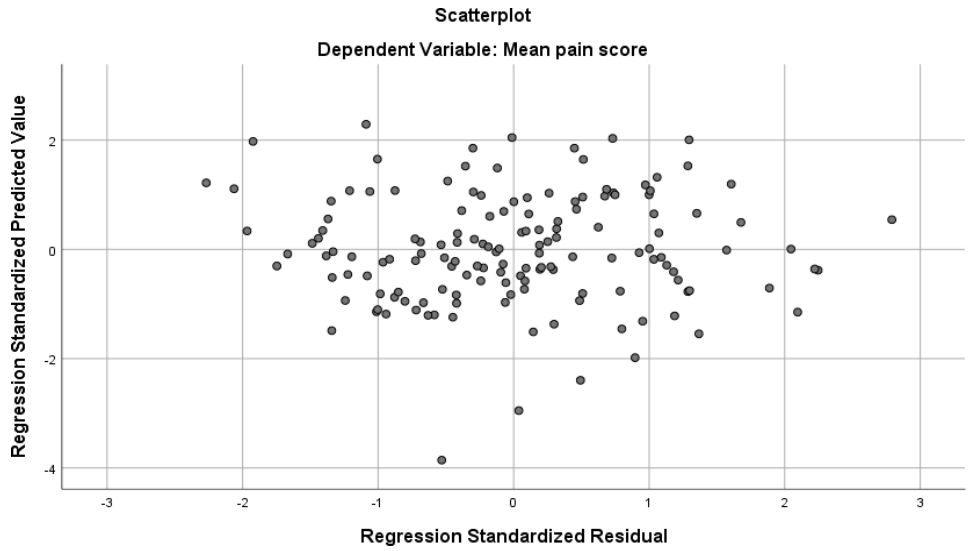

Figure 47: Scatter plot of residuals vs predictor values for post-operative mean pain scores

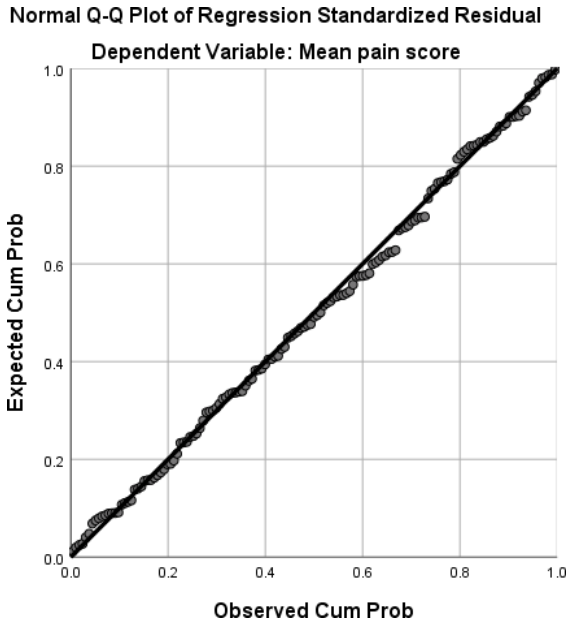

Figure 48: Q-Q plot of residuals for post-operative mean pain scores

A 3.3.2 Post-operative highest 24 hour pain score as dependent variable

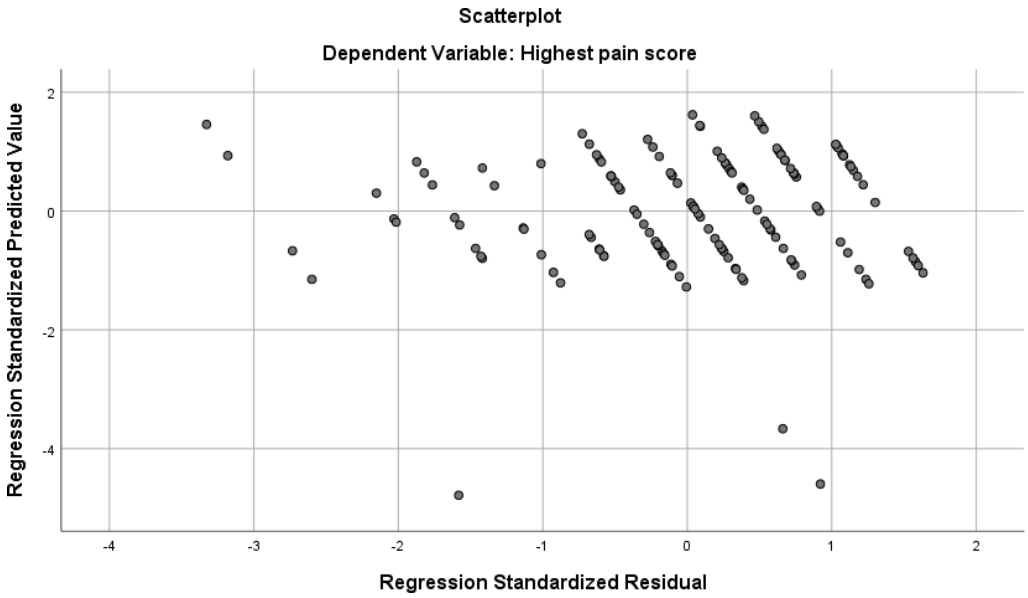

Figure 49: Scatter plot of residuals vs predictor values for post-operative highest pain scores

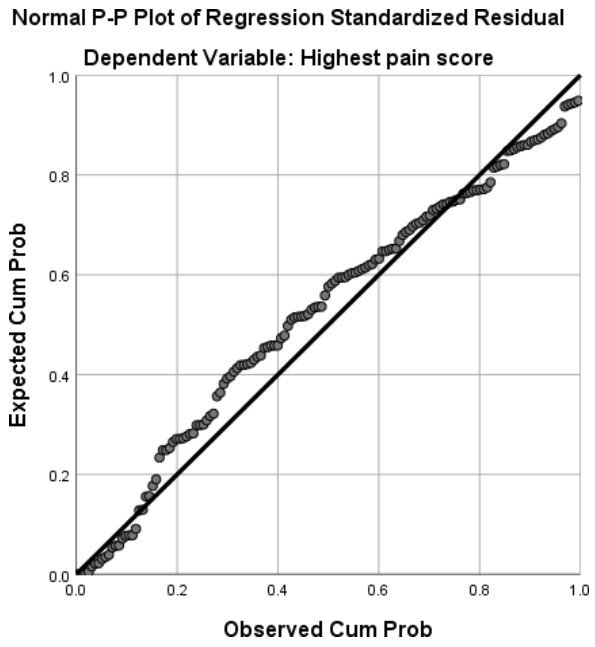

Figure 50: Q-Q plot of residuals for post-operative mean pain scores

A 3.3.3 Post-operative breakthrough analgesia requirement as dependent variable

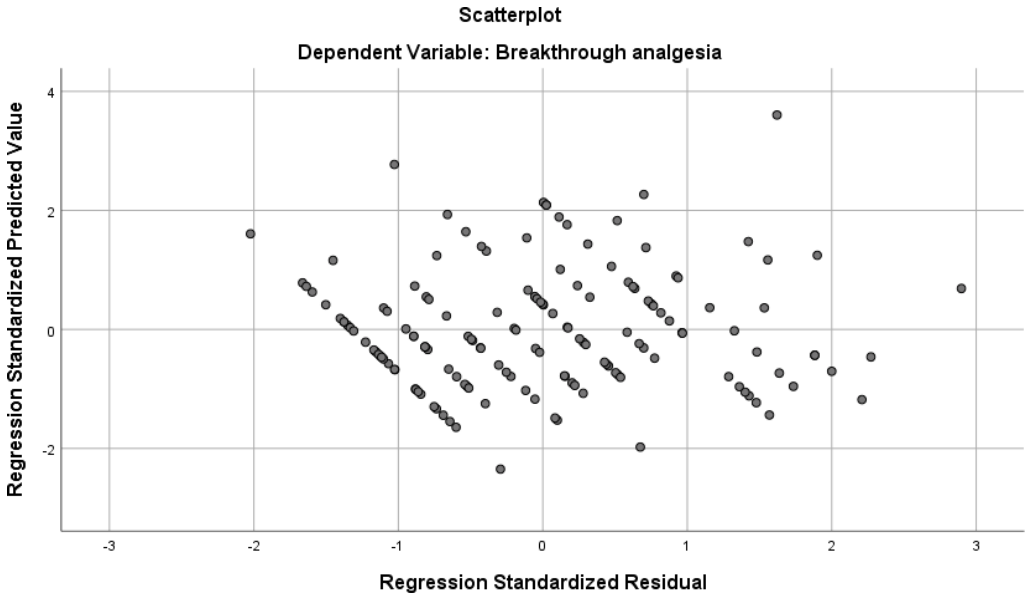

Figure 51: Scatter plot of residuals vs predictor values for breakthrough analgesia requirement

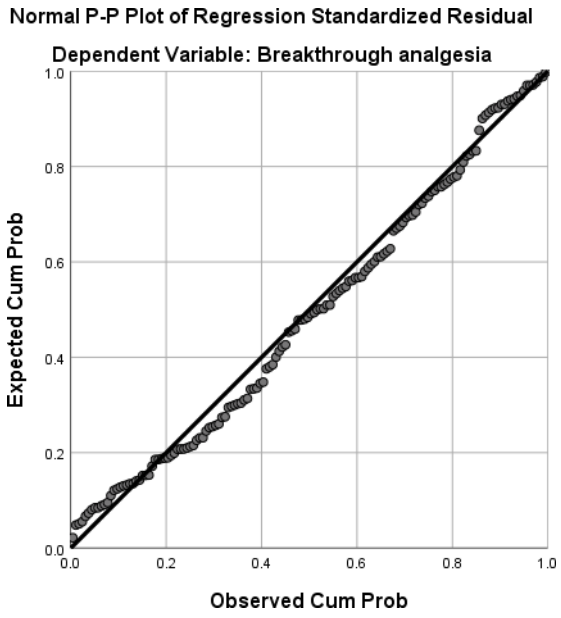

Figure 52: Q-Q plot of residuals for breakthrough analgesia requirement

List of abbreviations and glossary

ABPI	Ankle-brachial pressure index
AMI	Arthrogenic muscle inhibition
ASA	American Society of Anaesthesiologists
BMI	Body *mass* index, unit: kg/m2
CENTRAL	Cochrane central register of controlled trials
CFNB	Continuous femoral (three-in-one) nerve block
CI	Confidence interval
cm	Centimetre, unit of length
COPD	Chronic obstructive airways disease
CPNB	Continuous posterior lumbar plexus (psoas compartment) nerve block
DOAC	Direct oral anti-coagulants
DVT	Deep vein thrombosis
EBV	Estimated blood volume
EPO	Erythropoietin
EQ-5D-3l	EuroQol-5 dimensions-3 levels, 5 to 15 points
ERAS	Enhanced recovery after surgery
et al.	Et alii/ et aliae/ et alia
H	Height, unit: metres
Hb	Haemoglobin, unit: g/dl
$Hb_{loss\ total}$	Difference in haemogbloin levels from pre to post-operative, unit: g/dl
Hb_{post}	Post-operative haemoglobin levels, unit: g/dl
Hb_{pre}	Pre-operative haemoglobin levels, unit: g/dl
Hb_t	Blood transfusion total, unit: g/dl
HCT	Haematocrit, unit: litre of cells/litre of blood (l/l)
HEA	Hypotensive epidural anaesthesia

List of abbreviations and glossary

HES	Hospital episode statistics
ICC	Intra-cluster correlation
IRR	Incidence rate ratio
ISCRTN	International standard randomised controlled trial number
IV	Intravenous
kg	Kilogram, unit of weight
KReBS	Knee Replacement Bandaging Study
l	Litres, unit of volume
m	Metre, unit of length
MAP	Mean arterial pressure
MCID	Minimal clinically important difference
MD	Mean difference
mg	Milligram, unit of weight
MI	Myocardial infarction
ml	Millilitre, unit of volume
mmHg	Millimetres of Mercury, unit of pressure
n	Sample size
NHS	National Health Service
NRS	Numerical rating score, 0 to 10 points
o	Degrees, unit of measurement for angles
OKS	Oxford knee score, 0 to 48 points
PCA	Patient-controlled analgesia
PE	Pulmonary embolism
PROMs	Patient reported outcome measures
QALYs	Quality adjusted life years
RCT	Randomised controlled trial
RJB	Robert Jones bandage

List of abbreviations and glossary

ROM	Range of movement
RR	Relative risks
SD	Standard deviation
STICKS	Short-sTretch Inelastic Compression bandage in Knee Swelling following total knee arthroplasty study
TBV	Total blood volume lost, unit: ml
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VAS	Visual analogue score, 0 to 10 points
W	Weight, unit: Kilograms
YTU	York Trials Unit