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Randomized controlled trial of patient-controlled sedation for colonoscopy: Entonox *vs* modified patient-maintained target-controlled propofol

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Abstract

Aim Propofol sedation is often associated with deep sedation and decreased manoeuvrability. Patient-maintained sedation has been used in such patients with minimal side-effects. We aimed to compare novel modified patient-maintained target-controlled infusion (TCI) of propofol with patient-controlled Entonox inhalation for colonoscopy in terms of analgesic efficacy (primary outcome), depth of sedation, manoeuvrability and patient and endoscopist satisfaction (secondary outcomes).

Method One hundred patients undergoing elective colonoscopy were randomized to receive either TCI propofol or Entonox. Patients in the propofol group were administered propofol initially to achieve a target concentration of 1.2 μg/ml and then allowed to self-administer a bolus of propofol (200 μg/kg/ml) using a patient-controlled analgesia pump with a handset. Entonox group patients inhaled the gas through a mouthpiece until caecum was reached and then as required. Sedation was initially given by an anaesthetist to achieve a score of 4 (Modified Observer's Assessment of Alertness and Sedation Scale), and colonoscopy was then started. Patients completed an anxiety score (Hospital Anxiety and Depression questionnaire), a baseline letter cancellation test and a pain score on a 100-mm visual analogue scale before and after the procedure. All patients completed a satisfaction survey at discharge and 24 h postprocedure.

Results The median dose of propofol was 174 mg, and the median number of propofol boluses was four. There was no difference between the two groups in terms of pain recorded (95% confidence interval of the difference −0.809, 5.02) and patient/endoscopist satisfaction. There was no difference between the two groups in either depth of sedation or manoeuvrability.

Conclusion Both Entonox and the modified TCI propofol provide equally effective sedation and pain relief, simultaneously allowing patients to be easily manoeuvred during the procedures.

Keywords Propofol, Entonox, sedation, colonoscopy

Introduction

Colonoscopy is generally performed with the patient sedated using a combination of benzodiazepines and an opioid [1–5], mostly midazolam and fentanyl or pethidine (meperidine), which is the standard practice in many countries. This kind of intravenous sedation is associated with cardiorespiratory complications in up to 20% of patients [6], delayed recovery of psychomotor function and delayed discharge. The oxygen desaturation associated with these complications seems in part to be caused by medication, even when titration of the dose is attempted [3,7–9].

Therefore, an agent with a shorter duration of action would be desirable; one that permits more rapid recovery of function, while providing comparative patient comfort during the procedure and that has a safety profile better than the medications currently in use. Two such candidates we studied are Entonox (nitrous oxide in air) and propofol.

We have previously shown that patient-controlled Entonox analgesia is superior to routine intravenous sedation (midazolam and fentanyl) for colonoscopy [10]. Entonox is a weak inhalation anaesthetic agent with anaesthetic, sedative and anxiolytic properties. At 50% concentrations, it is an effective analgesic agent without respiratory

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depressant effects. It has a low blood/gas solubility ratio and hence allows fast onset and clearance time.

Propofol is a sedative agent that has been shown to be superior to benzodiazepines and narcotics with regard to rapid induction of sedation [11], faster recovery [12,13] and equivalent levels of amnesia [14,15]. Among gastroenterologists, there is increasing interest in the use of propofol for endoscopic sedation, and the number of reports of endoscopist-administered propofol efficacy is growing [16–22]. However, propofol has a narrow therapeutic index and can produce deep sedation, resulting in respiratory depression and even apnoea. As the depth of sedation is a continuum, the doses required for conscious sedation as used in colonoscopy are markedly lower than those used for induction of anaesthesia [23]. Moreover, deeper sedation makes it difficult to manoeuvre a patient during colonoscopy. Thus, the two problems with propofol sedation are greater depths of sedation and difficulty in manoeuvring the patients.

Target-controlled infusion (TCI) of propofol enables an exact amount of the drug to be delivered, maintaining a preset concentration of propofol in the blood or brain. This technique, routinely used in anaesthetic practice, has previously been used in colonoscopy, and Campbell *et al.* [24] modified a TCI pump to achieve patient-maintained sedation. However, this modification is not available from the manufacturers and is only experimental, and its efficacy has not been proved in large studies. We developed a target-controlled patient-maintained (TCI-PCA) propofol sedation protocol in our unit. In this protocol, propofol sedation was initiated with a TCI pump to achieve a preset effect-site concentration, and subsequently sedation was maintained by the patients using a simple patient-controlled analgesia pump (PCA) delivering propofol on demand.

Moreover, though there have been studies [23,25,26] comparing propofol with routine intravenous sedation, there is no comparison between PCA-TCI propofol and Entonox.

Based on this background, we performed the study with the aim of primarily comparing TCI-PCA propofol with Entonox in terms of analgesic efficacy (primary outcome), and also depth of sedation, manoeuvrability, rate of complications, recovery of psychomotor function and time to discharge. We also aimed to establish the safety and feasibility of using patient-maintained target-controlled propofol as sedation for colonoscopy.

Method

Study design

This is a randomized controlled trial comparing Entonox with TCI-PCA propofol for colonoscopy and was performed in the endoscopy unit at Castle Hill Hospital, Cottingham, UK from January 2005 to June 2006. This is a tertiary hospital, and is one of the national endoscopy training centres in the UK.

The study was approved by the South Humber Research Ethics Committee, UK and the Clinical Trials Unit, Medicines and Health Regulatory Authority, London, UK and registered with the European Clinical Trials Database. The study was preregistered with the International Standardised Randomised Controlled Trials Database (available at http://www.controlled-trials.com/isrctn; trial registration number ISRCTN65879800).

It was undertaken according to International Conference on Harmonisation good clinical practice standards, including independent on-site monitoring and source data verification.

Inclusion and exclusion criteria

All patients undergoing elective colonoscopy, including males and females, were invited to participate in the trial by sending letters and patient information leaflets (approved by Ethics Committee) 2 weeks before the intended procedure. Patients were given both oral and written information regarding the trial and the drugs involved once again when they reported for their colonoscopy. Subsequently, informed written consent was obtained from all patients 15 min before they were randomized to either group. The exclusion criteria are shown in Table 1.

Randomization and allocation concealment

The participants were randomized by using block randomization, with a block size of five used to make less predictable what might be the next treatment allocation. The assignments were held centrally in sequentially numbered, opaque, sealed envelopes, and the envelopes were opened sequentially and only after the participant's name, address, date of birth and other details were written on the appropriate envelope. The randomization sequence was generated by a person not involved in this study, and he opened the envelope for allocation after a telephone call.

None of the endoscopists was aware of the location of these envelopes. Neither the patients nor the colonoscopists were blinded to the treatment modality after the allocation.

Interventions

After informed written consent was obtained, patients were randomly assigned to one of the two treatment

Table 1 Monitoring of patients, discharge criteria, sedation scoring and exclusion criteria.

Monitoring
1. 2–3 l oxygen given to all patients
2. Intravenous cannulae *in situ* before procedure in all patients
3. Pulse oximetry
4. Clinical monitoring, including heart rate and blood pressure. This is continued into the recovery area, and it is the responsibility of both the endoscopists as well as the nurse to monitor these physiological variables
5. Chest excursion and respiratory effort monitored by the recovery nurse
6. Full resuscitation equipment available within easy reach in endoscopy suite
Discharge criteria
1. Patient responds appropriately to questions and is able to communicate clearly
2. Patient is able to sit upright for at least 5 min and is able to tolerate liquids/solids
3. Patient is able to dress independently and use the toilet
Sedation scoring (ASA/MOAAS)
5 responds readily to name spoken in normal tone
4 lethargic response to name spoken in normal tone
3 responds only after name is called loudly and/or repeatedly
2 responds only after mild prodding or shaking
1 responds only after painful trapezius squeeze
0 no response after painful trapezius squeeze
Exclusion criteria
1. Patients with chronic pulmonary disease
2. History of colonic resection
3. Intolerance to any of the drugs
4. Unwilling to enter the trial
5. ASA class IV
6. Allergy to soybeans, eggs
7. History of seizure disorder, sleep apnoea or difficult intubation, a short thick neck and inability to open mouth widely
Degree of manoeuvrability (manoeuvrability scoring)
1. Patient was awake and responded to all verbal commands
2. Drowsy and responded to most of the commands to move (>50%)
3. Patient was able to move to some commands (<50%)
4. Quite difficult to manoeuvre and/or no response to verbal commands to move (<10%)

groups: (1) propofol group or (2) inhaled Entonox® (BOC gases; UK) group.

Those patients who refused to participate were asked about the reasons for doing so, including past experiences with any of the drugs, whether they were frightened by the idea of deciding their own sedation or any other reason. All such patients completed pre- and postprocedure questionnaires, similar to the participants.

All participants completed a Hospital Anxiety and Depression questionnaire and a baseline letter cancellation test and marked their pain on a 100-mm visual analogue scale (VAS) before randomization, but after giving consent for the trial (Table 2).

Table 2 Administration of questionnaires to participants.

A. Precolonoscopy (after consent and before randomization)
1. Hospital Anxiety and Depression Scale
2. Letter cancellation test
3. 100 mm visual analogue scale
B. Postcolonoscopy
1. Visual analogue scale – immediately after procedure and at 15-min intervals up to and including at discharge; repeated at 24 h postcolonoscopy
2. Letter cancellation test – immediately after procedure and at 15-min intervals up to and including at discharge
3 Patient satisfaction questionnaire – at discharge and at 24 h postcolonoscopy

Protocol for propofol

Patients randomized to the propofol group were informed about the procedure and the reasons for sedation as well the technique. Subsequently, propofol was administered through an intravenous cannula using our modified target-controlled infusion system. The system consisted of a Graseby® (Watford, Herts, UK) 3400 infusion pump, controlled by a microprocessor system. The microprocessor in this pump is preprogrammed with the pharmacokinetic data describing the distribution and elimination of propofol. The anaesthetist entered the patient's age and weight into the microprocessor, and the system displayed the target blood concentration and calculated effect-site (brain) concentration. In addition, the anaesthetist was able to manually override the system to alter the concentration in the event of over-sedation.

Patients were given propofol through the pump to achieve a target concentration of 1.2 μg/ml/h. However, colonoscopy was started as soon as the depth of sedation [as scored by the Modified Observer's Assessment of Alertness and Sedation Scale (MOAAS)] reached a score of 4. Subsequently, patients were connected via a Y-connector to another PCA (PCA-Graseby) pump containing propofol, and were also given a handset. Pressing the handset delivered a bolus of 200 μg/kg/ml, with a lockout period of 2 min. They were encouraged to press the button during the procedure if they wanted to feel sleepier. The anaesthetist was allowed to give intravenous fentanyl if patients had pain or were uncomfortable during the procedure.

Protocol for Entonox

Patients randomized to Entonox were first told what the gas was for and what was required of them. Entonox

was administered through a mouthpiece connected to an Entonox cylinder. This mouthpiece has a one-way demand valve system, which is operated by the act of inhalation of the patient and closes down when the patient ceases to inhale. The Entonox group patients then inhaled the gas initially until a MOAAS score of 4 was reached, and then colonoscopy was started. Patients continued to inhale Entonox until the caecum was reached, and subsequently as and when required while the endoscope was being withdrawn. If the patient or the colonoscopist found the procedure too uncomfortable, then they were able to administer additional propofol intravenous sedation; this was given after a washout of 5 min.

Monitoring

All patients were continually assessed throughout the entire procedure, according to the guidelines of the British Society of Gastroenterology [27] (see Table 1). The aim of conscious sedation was that at all times the patient should be able to obey commands, and hence an MOAAS score of 4 was the target. The anaesthetist marked the level of sedation every 3 min for both the propofol and Entonox groups (Table 1). Postprocedure, all patients were allowed to recover and be discharged according to the existing protocols as mentioned in Table 1.

An attending nurse was available throughout the procedures. This individual had the responsibility of assessing and recording medication administration, times and time intervals related to the procedure, patient's physiological parameters and level of sedation.

Times and intervals recorded for all patients were as follows: start of sedation, start of colonoscopy, time when caecum was reached, withdrawal time, total colonoscopy time, recovery time and time to discharge (time interval between removal of the endoscope and when patient is discharged).

Measurements

Primary outcomes

The primary end-point measured was the degree of pain experienced by the patient during the procedure and assessed on a validated 100-mm VAS. These measurements were taken immediately, and at 15-min intervals post procedure up to and including at discharge. Patients also marked a VAS at 24 h post procedure to overcome any persisting effects of sedation.

Secondary outcomes

The secondary end-points measured included satisfaction of the patient, the nurse and the endoscopist (on a 100-mm VAS), manoeuvrability, depth of sedation, rate of complications, time to reach caecum and total colonoscopy time, rate of completion, degree of psychomotor recovery (using the previously validated letter cancellation test) and time to discharge.

Patient satisfaction was measured using a modification of a validated satisfaction questionnaire developed for endoscopy [28]. Nurse and endoscopist satisfaction was measured using a 100-mm VAS, as part of a separate questionnaire.

Psychomotor recovery was assessed using a validated psychometric test called the letter cancellation test [29]. This test measures concentration and perception. The patient was presented with a sheet of paper containing a printed paragraph of 20 rows of 40 randomly arranged letters, and was then asked to read from left to right and top to bottom, simultaneously marking through all the occurrences of a predesignated letter. The number of lines completed in 120 s and the number of occurrences of the predesignated letter correctly identified were recorded for scoring. The postprocedure scores were then compared with their baseline scores to measure recovery. The results are presented in terms of the percentage recovery of psychomotor function (i.e. percentage recovery of the letter cancellation test score compared with the preprocedure score). This test has previously been shown to be an accurate, easy to administer and efficient means of measuring psychomotor recovery in the postendoscopy setting [29,30].

The endoscopists also marked a simple questionnaire concerning degree of sedation, degree of ease of colonoscopy and difficulty in manoeuvring the patient. The attending nurses also completed a questionnaire after the procedure concerning the perceived adequacy of sedation, ability of patients to assist with moving during the procedure and maximal depth of sedation.

Demographic and clinical features recorded from all patients included age, sex, weight, height, clinical indications, past and family history, results, procedural findings and complications. Intraprocedural and immediate postprocedure complications were noted by the anaesthetist. Patients were contacted at the end of 1 month postprocedure to identify delayed complications.

Sedation complications were defined as a prolonged drop in oxygen saturation below 90% for at least 30 s, with the need for positive pressure ventilation using a bag-valve system. Other complications recorded included a prolonged drop in blood pressure below 90 mmHg, heart rate below 60 or above 110 beats/min.

Colonoscopic procedure

All colonoscopies were performed according to the standard operating procedure with the use of Pentax

video colonoscopes (Pentax, Hamburg, Germany). Colonoscopy was carried out by JAG-certified, fully independent colonoscopists. Completion to caecum was documented using two out of the following three landmarks: ileocaecal valve, appendiceal orifice or the tri-radiate fold.

Statistical analysis and sample size calculation

This is an equivalence study. In this process, we start by prespecifying delta (δ), the absolute value of the difference that could be found between Entonox and propofol and still conclude that the two interventions are equivalent. This is called the equivalence margin, and $-\delta$ to $+\delta$ is the range within which the 95% confidence interval (CI) of the difference in the mean between the two groups can vary and still be of no clinical importance [31]. The aim, therefore, is to check whether the CI for the difference between the groups on various outcome measures is within this range.

Estimates of sample size were based on the primary outcome measure, which was the degree of pain experienced by the patient and assessed using the 100-mm VAS. The variance was assumed to be around 30 points, as determined by previous studies [18] as well as our own randomized controlled trial [32]. This variance was assumed to be similar in both groups. The two drugs would be considered equivalent if the 95% two-sided confidence interval for the treatment difference, measured using the 100-mm VAS, falls wholly within the interval ±15 mm. If the difference between the propofol and Entonox groups is less than this predetermined equivalence margin (−15 to +15 mm), then the treatments would be considered equally effective or equivalent, even though one can never definitively 'prove' equivalence.

With an alpha level of 0.05 (two-sided) and statistical power of 80%, we used the sample size formula from Jones *et al.* [31] for the two-sided case for comparison of means in equivalence trials, indicating a requirement of 48 patients per group, or 96 patients total.

Differences in proportion were tested using the χ^2 test, resorting to Fisher's exact test for smaller samples. The primary outcomes (visual analogue scores), postoperative time to discharge and results of the letter cancellation test were evaluated using the Mann–Whitney *U*-test. Demographic and baseline characteristics were compared with the use of a two-way analysis of variance for continuous data and Fisher's exact test for categorical data. All analyses followed the intention-to-treat principle. All reported *P*-values are two-tailed. No interim analyses were performed before the primary end-point was analysed.

Results

Patients

During the study period, a total of 112 patients were assessed for eligibility, of whom 100 patients participated in the trial and 50 each were randomized to receive Entonox or propofol (Fig. 1). Twelve patients were excluded after eligibility assessment, as follows: eight were ineligible (seven patients were postsurgical resection, one patient had severe chronic obstructive airways disease) and four patients refused to participate. Among those patients who refused to participate, two patients said that they did not want to participate in any trial as they were too anxious and the remainder said that they had inhaled Entonox in the past and were not happy to participate.

The baseline characteristics of patients were similar in both groups, as shown in Table 3. More significantly, there was no difference between the two groups in terms of preprocedure anxiety scores (7.5 *vs* 8.4; $P = 0.1$). There were no complications in either group.

Medication

Patients in the propofol group pressed the PCA handset a median of four times [interquartile range (IQR) 1–7)] during each procedure, with 96% of the attempts being successful. The median dose of PCA propofol was 37 mg and the median dose of TCI propofol was 137 mg. The median total dose of propofol was 174.8 mg (range 148, 190). None of the propofol patients required additional Fentanyl®.

In the Entonox group, patients inhaled the gas until the caecum was reached, and thereafter only 30%

Table 3 Baseline characteristics of patients in both groups.

	Entonox	Propofol
Gender (M:F)	29:21	24:26
Median age in years (range)	56.1 (42, 66)	60.4 (40, 71)
ASA class		
1	08 (16%)	10 (20%)
2	33 (66%)	29 (58%)
3	09 (18%)	11 (26%)
Preprocedure anxiety (median)	7.5	8.4
Diagnosis		
Colorectal cancer	6	4
Colorectal polyp	12	16
Diverticulitis	8	12
Colitis	7	3
Others/normal	21	16

(15/50) of the patients continued to need Entonox. None of the Entonox patients required additional sedation or conversion to the intravenous group.

Primary outcome: pain scores

The median pain score at discharge in the Entonox group was 15.38 (IQR 14, 20), compared with 17.31 in the Propofol group (IQR 10, 20). The 95% CI of the difference in means was −0.89, 5.02. This falls well within the preset interval of −15, 15, implying that the two drugs are equivalent in terms of pain relief. Likewise, no statistically significant differences were found between the two groups when assessed at 15 min or 24 h postprocedure (Table 4).

Secondary outcomes

Depth of sedation

The median depth of sedation in the Entonox group was 4 (IQR 5–4), compared with the propofol group (median 3, IQR 5–3). These differences were not statistically significant ($P = 0.091$), though the depth of sedation was higher in the propofol group.

Manoeuvrability during the procedure

There was no difference in the manoeuvrability in patients in both groups. The score was similar in both groups (Entonox group, mean score 1, range 1–2 *vs* propofol group, mean score 2, range 1–3), but the differences did not reach statistical significance ($P = 0.2$). The 95% CI of the difference in means between the two groups (−1, 1) was well within the preset range (−2, 2).

Completion rates and procedure time

Total colonoscopy up to caecum or ileum was achieved in all patients except two patients in the Entonox group and one patient in the propofol group (Table 5). One patient in the Entonox group had an impassable stricture and another had poor bowel preparation leading to incomplete colonoscopy. In the propofol group, the single incomplete colonoscopy was because of an obstructing lesion in the hepatic flexure. The two groups were similar in terms of time to caecum and total procedure time (Table 5).

Table 4 Visual analogue scores (primary outcome measure).

Pain scores on VAS	Entonox (IQR)	Propofol (IQR)	95% CI	Predetermined equivalence margin
At discharge	15.38 (14, 20)	17.31 (10, 20)	−0.89, 5.02	−15, 15
15 min	15.78 (12, 20)	16.54 (10, 20)	−0.93, 5.06	−15, 15
At 24-h post procedure	16.14 (14, 21)	17.89 (10, 20)	−0.88, 5.03	−15, 15

CI, confidence interval; IQR, interquartile range; and VAS, visual analogue scale.

Table 5 Patient assessment.

Endoscopist assessment	Entonox (IQR)	Propofol (IQR)	Significance (*P*-value)	95% CI	Predetermined equivalence interval
Caecal intubation (%)	48/50 (96)	49/50 (98)	0.55	−0.56,	−5, 5
Mean time to caecum (min)	13 (10, 16.25)	14 (12, 23.25)	0.18	−1.82, 3.82	−5, 5
Mean completion time (min)	22.6 (18, 28)	20.8 (17, 23)	0.09	−0.83, 4.36	−5, 5
Median difficulty of colonoscopy	24	22	0.79	–	–
Satisfaction	96 (95, 98)	98 (96, 100)	0.26	−2.9, 0.26	−5, 5
Nurse's assessment					
Mian satisfaction score (out of 100)	95.8 (93.4, 98)	97.24 (95, 99)	0.34	−3.36, 0.49	−5, 5
Adequate sedo-analgesia	56	54	0.2	−5, 0.89	−5, 5
Manoeuvrability Score	1	2	0.2	–	–
Patient assessment					
Median satisfaction score	94	96 (94, 98)	0.10	−0.46, 3.6	−5, 5
Agree to repeat use of same sedation	46	48	0.56	–	–
Remember start of procedure	39/50	42/50	0.39	–	–
Remember end of procedure	41/50	45/50	0.35	–	–

Table 6 Recovery of psychomotor function and time to discharge.

Variables	Entonox (IQR)	Propofol (IQR)	95% CI	Significance (*P*-value)
Recovery of function				
Immediate	92% (89.5, 96)	90% (84, 92)	−0.56, 4.56	0.79
15 min	99% (98.5, 100)	96% (91, 99)	1.1, 4.9	0.08
Discharge	100%	97% (94, 100)	0.06, 5.94	0.07
Time to discharge (mean)	27.86 min (22, 30.5)	28.08 min (23, 32)	−2.28, 2.7	0.86

Psychomotor recovery and time to discharge

The psychometric tests were administered immediately upon the arrival of the patients in the recovery area and then at 15-min intervals until the patients were discharged. Inability of the patients to perform the tests immediately on return to the recovery room was also noted. All patients were discharged by the recovery room nursing staff based on preexisting discharge criteria (Table 1).

Patients in both groups demonstrated rapid recovery of psychomotor function after the procedure (Table 6). However, patients in the Entonox group had complete recovery of psychomotor function at discharge compared with the propofol group, where the median recovery was 96% (IQR, 94,100; $P = 0.04$). It follows that the time to discharge was also similar in both groups (Table 6).

Patient, nurse and endoscopist satisfaction

Patients marked their satisfaction questionnaire at discharge, but before they were given the results of the colonoscopy to ensure that any bias was eliminated. Patient satisfaction was similar in both Entonox and propofol groups (Table 5). Also, a similar proportion of patients agreed to repeat their procedure under same sedation if required.

The attending nurses and endoscopists found no differences in their assessment of satisfaction with either Entonox or propofol sedation (Table 5).

Amnesia and additional sleep and return to normal activities

At 24 h postprocedure, patients filled out a questionnaire regarding the number of additional hours of sleep required and also the time taken to get back to routine work. In the Entonox group, the resumption of normal activities was at a median of 2–4 h, whereas in the propofol group, the resumption was at a median of more than 6 h ($P = 0.02$). As many as 54% of the patients in the Entonox group reported requiring additional sleep compared with 96% of patients in the propofol group ($P = 0.03$).

Discussion

We have shown in this randomized controlled trial that patient-controlled sedation for colonoscopy using either our modified TCI-PCA infusion of propofol or Entonox inhalation is equally effective (and safe). The modified protocol for propofol provides adequate sedation and analgesia, with equivalent patient satisfaction.

Propofol is a rapidly acting sedative drug with a short duration of action and has attracted increasing attention as it is well tolerated by patients and dramatically reduces recovery time after successful sedation, in comparison with routine intravenous sedation [33,34].

However, three primary concerns have been expressed, and probably this has led to a relatively lesser uptake of propofol for sedation during colonoscopy in the UK. These relate to its narrow therapeutic range and the lack of an antidote in cases of oversedation and ensuing apnoea. The sedation provided by propofol is a continuum, extending from mild sedation to general anaesthesia. The third important concern is the difficulty in manoeuvring patients during colonoscopy when sedated with propofol.

To overcome these problems, we modified the technique of propofol administration to make it a patient-maintained seation regime. The aim was to ensure that a low dose of propofol was used while providing effective pain relief, simultaneously maintaining the target level of sedation (conscious sedation) and ensuring that the patient was awake enough to move as required during the procedure. In our study, patients in the propofol group were initially given propofol to reach a target (effect-site brain) concentration of 1.2 μg/kg/ml. Once this concentration was reached, patients were connected to a PCA pump (containing propofol), and patients were encouraged to press the PCA button if necessary throughout the procedure, while a background infusion of propofol was continued to maintain the preset target concentration. Colonoscopy was started when the sedation score reached 4 (on MOAAS), which is the definition of conscious sedation. With this arrangement, we have successfully sedated patients for colonoscopy,

achieving the target depth of sedation (conscious) and allowing patients to be manoeuvred as necessary during the procedure. The median depth of sedation in the propofol group was 3, which was slightly higher than in the Entonox group (median 4), but the difference did not reach any statistical or clinical significance (in terms of complications, difficulty in manoeuvring, recovery from sedation, completion rates or time to completion). We believe that this modified technique of propofol sedation is very effective for colonoscopy. There were no complications with the use of propofol; verbal communication was not lost in any of the patients, and haemodynamic stability was maintained, even in the elderly patients.

The primary outcome measure was the degree of pain relief. We have shown that both propofol and Entonox provide equivalent pain relief. The difference in means (of VAS scores) between the two groups was within the preset interval. We believe that good pain relief has a significant bearing on patient satisfaction and other outcome measures. Moreover, propofol is basically a hypnotic with minimal analgesic effect. In the absence of significant analgesic effect, it is notable that none of the patients needed additional analgesia and at the same time, they were highly satisfied with propofol. We believe that such an effect is because of its amnesic and sedative properties. On the other hand, we found that Entonox provides effective sedation and analgesia for colonoscopy and is very safe. We chose to compare propofol with Entonox because we have previously demonstrated that the latter is more effective than routine intravenous sedation, including opiates and benzodiazepines [32]. Entonox was delivered through a mouth piece with a one-way valve demand system, which is activated by the patient's inspired breath. Longer and deeper breaths allow greater volumes of gas to be taken into the lungs if necessary. We believe that this not only helps in relieving discomfort/pain, but also alleviates patients' anxiety, as they realize that a few deep breaths can relieve pain, thus putting pain control in their hands as well. There are no complications with the short-term use of Entonox; however, continuous inhalation at analgesic doses for a number of days has been associated with depression of the bone marrow, megaloblastic anaemia and neurological dysfunction.

However, the propofol delivery technique necessitated the use of two pumps, the TCI pump and the PCA pump; both were connected to the same intravenous line. Campbell *et al.* [24] have previously modified the TCI system to include PCA functionality. However, there were a number of complications in their study, and the authors concluded that the technique is feasible but needs further trials. Moreover, this pump is not commercially available, and the manufacturer was unable to modify the same because of patent problems with their own pumps (personal communication with manufacturer representative).

The onset of action was rapid in both groups, and the effects could be seen within 1–2 min. In order to ensure comparability between both groups, colonoscopy was started when a MOAAS score of 4 was reached. The time to caecum, total colonoscopy time and completion rates were similar in both groups.

We found in our study that recovery of psychomotor function was initially similar with both Entonox and modified TCI propofol. However, at discharge, only Entonox patients had complete recovery of psychomotor function. As both the sedative regimes were associated with early enhanced recovery and early discharge, there is a potential for higher patient turnover and possibly increased number of colonoscopies. It has been shown that prolonged recovery from sedation is the major factor that keeps the patient waiting in the recovery area after the completion of colonoscopy. Vargo *et al.* [35] have shown that if the recovery from sedation is faster than achieved with conventional intravenous sedation, the practice efficiency for colonoscopy can be improved, both in terms of performing more procedures, as well as cost effectiveness. We have shown that such improvement in colonoscopy practice is achievable with both Entonox and propofol because of reasons mentioned above.

Patient satisfaction is another area where current practice is suboptimal. We have shown in our study that patient satisfaction was high with both Entonox and propofol. It is also important to note that more patients in both groups agreed to use the same sedation for a repeat procedure. Higher patient satisfaction has huge implications; it is already known that uptake of screening for colorectal cancer is still unsatisfactory. Any improvement in patient experience with colonoscopy will help to increase the number of patients willing to undergo the procedure for screening. It is possible that high patient satisfaction with both these agents could have been related to the patients' control of their own pain relief.

There are some limitations to our study. First, neither patients nor endoscopists were blinded. We deliberately chose not to blind because our aim was to establish the safety and effectiveness of a new regime of propofol. Moreover, it is difficult to blind patients and endoscopists to Entonox as it makes a typical noise when inhaled, though blinding has been achieved in previous studies. Second, we started colonoscopy when the MOAAS score of 4 was reached, rather than waiting for the target concentration of propofol to be achieved. We adopted this methodology to enable comparability in both groups and also because the aim of all sedation in colonoscopy is to provide conscious sedation. Third, this trial was performed in a tertiary hospital; however, there is no

reason to believe that the results cannot be extrapolated to most hospitals and most endoscopists. Moreover, it must be emphasized that the study was powered to detect any differences in analgesic ability of the two drugs. In other words, it was not powered to detect differences in secondary measures. Finally, the propofol delivered was controlled by the anaesthetist. This need for an additional doctor to provide propofol seems nonfeasible given the current budgetary constraints of most hospitals in UK as well as all over the western world. However, several studies have shown that nurses can be trained to provide and monitor the administration of propofol for colonoscopy. There is no reason why this technique cannot be easily adopted by trained and qualified nurses to provide sedation.

In summary, both our novel method of administering propofol as well as Entonox inhalation provide effective (and safe) sedation, and are associated with a high degree of patient and endoscopist satisfaction. The depth of sedation seems appropriate, allowing patients to be easily manoeuvred during the procedures. We believe that either Entonox or modified TCI-PCA propofol sedation can be used to provide routine sedation for all patients undergoing colonoscopy. However, there is a need for further randomized controlled trials to compare different methods of delivering propofol and a direct comparison with different agents for sedation.

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