

**Long title:**

A systematic review and meta-analysis of systemic intraoperative anticoagulation during arteriovenous access formation for dialysis

**Short title:**

**Systemic anticoagulation in access surgery**

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## **Abstract**

**Purpose:** Surgical arteriovenous fistula (AVF) or graft (AVG) is preferred to a central venous catheter for dialysis access. Surgical access may suffer thrombosis early after placement and systemic anticoagulation during surgical access formation may increase patency rates but would be expected to increase bleeding related complications. A systematic review and meta-analysis of randomised controlled trials was conducted to examine the impact of systemic anticoagulation on access surgery perioperative bleeding and patency rates.

**Methods:** We included randomised controlled trials testing systemic anticoagulation during access formation versus a control group without systemic anticoagulation reporting bleeding complications and access patency. Medline, Embase, CENTRAL and CINAHL were searched up to March 2015. Risk of bias was assessed using the Cochrane risk of bias tool and the JADAD score. Meta-analysis was performed using Cochrane Revman software.

**Results:** Searches identified 445 reports of which four randomised studies involving 411 participants were included. Three studies pertained to AVF only and one included both AVF and AVG. Systemic anticoagulation led to increased bleeding events in all access (4 trials; RR 7.18; CI, 2.41 to 21.38;  $p < 0.001$ ). Patency was not improved for all access (4 trials; RR, 0.64; CI, 0.37 to 1.09;  $P = 0.10$ ) but was improved when AVF analysed alone (3 trials; RR, 0.57; CI, 0.33 to 0.97;  $p = 0.04$ ).

**Conclusions:** The use of intraoperative systemic anticoagulation during access formation is associated with a highly significant increased risk of bleeding related complications. A significant improvement in AVF patency was seen though not when AVF and AVG were analysed together.

**Keywords:** Anticoagulants, Arteriovenous fistula, graft occlusion (vascular), Heparin, Vascular Surgical Procedures

## **Introduction**

The use of autologous arteriovenous fistulae for the purpose of haemodialysis was first described in 1966 by Brescia *et al*(1) and the arteriovenous fistula (AVF) is now recognised as the gold standard for maintenance haemodialysis due to superior long term patency, reduced rates of complications and superior cost effectiveness in comparison to grafts or central lines(2). An alternative surgical access may be formed with interposition prosthetic arteriovenous graft AVG where autologous vein is not available as a conduit. Least preferable access is via a tunnelled central venous catheter due to high rates of infective complications(3)

Surgical access formation results in a number of failures due to thrombosis and many strategies have been researched in an attempt to minimise the loss of access and the lifesaving dialysis they provide (4, 5). The use of systemic anticoagulation during access formation surgery has been suggested as one such strategy to improve patency rates(6), however there is the potential of an increased risk of peri-operative bleeding and/or haematoma formation. The aim of this report is to review the evidence regarding outcomes of access surgery with and without use of systemic anticoagulation with specific reference to rates of bleeding related complications and access patency.

## **Methods**

A systematic review of randomised clinical trials (RCTs) comparing access procedures with and without intraoperative systemic anticoagulation was performed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for reporting of search results(7). The methodological quality of the studies was determined using both the Cochrane Collaboration bias tool(8) and the Jadad scoring system(9).

### *Search Strategy*

Systematic review was performed using MEDLINE and EMBASE, CENTRAL and CINAHL.

The search strategy aimed to include any RCT which compared access formed with and without intraoperative systemic anticoagulation therapy. Search terms used were:

(dialysis or haemodialysis or hemodialysis or hemofiltration or haemofiltration or (hemodiafiltration or haemodiafiltration)AND (Arteriovenous Fistula or Arteriovenous Shunt or vascular access or venous access or (fistula\* or avf\* or graft or shunt)) AND systemic (heparin or anticoagulant or anti-coagula\* or anticoagula\*) AND Surgery.

Search methods included all indexed citations of any language from the databases beginning to March 2015. Results were limited to human subjects only. In addition, references within identified or related publications were hand searched to identify any additional studies.

### *Inclusion criteria*

Studies were eligible for inclusion if they fulfilled the following criteria.

- Studies including adults requiring formation of arteriovenous graft or autologous fistulae as vascular access for haemodialysis.
- Randomised controlled trials and quasi-RCTs comparing intraoperative systemic anticoagulation with control group not receiving systemic anticoagulation
- No limits were placed on time, location or language of the study.

### *Outcomes*

The primary outcome was the rate of bleeding related complications of surgery (either visible postoperative bleeding or haematoma formation) following access formation. The secondary outcomes were the rate of early failure in access formed and rates of ongoing patency (as primary, secondary and functional patency).

### *Data extraction*

Assessment for inclusion and data extraction were carried out by two independent reviewers (PS, TC) and any disagreements were resolved by consensus and a third author (GS). For Meta-analysis, data were entered into and analysed using Cochrane RevMan software (RevMan 5.3. The Cochrane Collaboration, Copenhagen) and dichotomous outcomes presented as risk ratios (RR) with 95% confidence intervals (CI).

## **Results**

### *Literature search*

Systematic review of the literature identified 445 potential studies, of which 442 were discounted as ineligible after title and abstract review. After full text review of the remaining 3 papers, 3 were eligible for systematic inclusion (10-12). In addition, 1 paper was included following manual search of references of included reports (13).

### *Included studies*

Our analysis included four trials (10-13), all of which utilised anticoagulation with systemic heparin during access formation. A total of 411 patients were included across four trials. Three trials included only autologous AVF(11-13) with one trial incorporating both AVF and AVG(10). Summary data including anticoagulation employed, control regime and outcomes in included studies are reported in *table 1*. No study reported any measurement of anticoagulation effects using laboratory studies.

### *Risk of Bias*

No study protocols were available for the included trials. On the basis of information published within reports the methodological quality of the trials, as shown in *table 2*, was generally low with Jadad scores of one or two.

### *Bleeding related complications*

All papers reported on rates of perioperative bleeding or postoperative haematoma formation. Meta-analysis of data for AVF and AVG together(10-13) showed a significant effect towards higher incidence of bleeding related complications with the use of systemic heparin ( $p < 0.001$ ; RR 7.18; CI, 2.41 to 21.38). Data included is shown in *figure 1*.

Separate analysis of the three trials including only autologous AVF(11-13) still indicated a higher rate of bleeding related complications though this was less marked than for all access ( $p = 0.02$ ; RR 4.83; CI, 1.28 to 18.19).

Insufficient detail was present in the report which included AVG to allow analysis of AVGs as a separate sub group.

### *Patency*

Primary patency was assessed at different time points between included studies. Two papers reported 30 day primary patency (10, 12); one reported 14 day (13) and one 44 day follow up (11). One paper also reported three month functional patency (10).

No detailed survival meta-analysis was feasible due to heterogeneous follow up regimes reported and lack of reported data. A simple dichotomous meta-analysis of the rate of failure events prior to first follow up suggests that effects of systemic heparin on early patency favoured heparin but the result was not statistically significant when all access types (AVF and AVG) were analysed ( $P = 0.10$ ; RR, 0.64; CI, 0.37 to 1.09). Data included is shown in *figure 2*.

Separate analysis of the three trials including only autologous AVF(11-13) did reach statistical significance for improved patency at first follow up ( $p = 0.04$ ; RR, 0.57; CI, 0.33 to 0.97).

Insufficient detail was present in the report which included AVG to allow analysis of AVGs as a separate sub group.

## Discussion

This systematic review demonstrates that there is randomised controlled evidence in the current literature regarding the use of systemic anticoagulation during AVF surgery. Although the outcomes reported in all included studies were related to bleeding complications of surgery and early primary patency of AVF formed, the conclusions were contradictory between reports.

All included studies reported increased rates of bleeding complications with the use of systemic heparin though this was reported to be statistically significant in only two studies (10, 11). Meta-analysis of this data suggested a highly significant increase in bleeding related complications with the use of intra-operative systemic anticoagulation with heparin for all access surgery ( $p=0.002$ ). This effect was also evident, though less significant when only autologous AVF were included in the analysis ( $p=0.02$ ).

An increase in bleeding related complications is to be expected in the presence of systemic heparin administration and studies reported mainly self-limiting or relatively minor bleeding events only. A minority of the participants receiving systemic heparin subsequently suffered more significant complications such as transfusion (4 transfusions in 3 participants(10)) or reoperation for evacuation of haematoma (1 reoperation (12)). Only one report stated whether the haematomas which occurred in the patients receiving systemic anticoagulation with heparin had any direct effect on early patency due to compression of AVF (three AVF lost patency with haematoma development(10)).

The above bleeding risks may be deemed acceptable if a clear benefit in terms of patency were to be apparent with systemic anticoagulation. Studies reported no significant difference in primary patency at 30 days (10, 12) and 6 weeks (11) and no difference in functional patency at

3 months (10). Only 1 of the 4 included studies reported a significant increase in patency with intraoperative systemic heparin administration as measured at 2 weeks post procedure (13).

Heparin administered intravenously during AVF formation would not be expected to remain present within a participant's blood stream much beyond a period of 2 hours(14). The potential action for improved patency with intraoperative systemic heparin may therefore be the prevention of thrombosis in the immediate post-operative period when flow may be reduced due to localised inflammatory swelling of tissues and spasm in the vessels. However, the only study that reported a significant improvement in patency with systemic heparin was also the only one to report patency within 24 hours of procedure, and found no significant difference in patency between groups at that time point ( $P=0.609$ )(13). The protective effects of heparin against loss of patency which this study reports would therefore appear to have occurred beyond 24 hours post procedure during a period in which the heparin was no longer active, further confusing the conclusions drawn by individual studies and interpretation of the trend demonstrated in this limited meta-analysis.

Meta-analysis of dichotomous outcomes for AVF patency at early follow up was performed due to the lack of detailed survival information in reports and accessible individual patient data. The analysis of access patency rates at early follow up shows a non-significant trend in favour of improved early primary patency with intraoperative systemic heparin administration when all access were included in the analysis (*Figure 3*). Analysis of data for autologous AVF only(11-13) did show a just significant improvement in patency at first follow up ( $p=0.04$ ) suggesting that systemic anticoagulation with heparin during AVF formation may be of some benefit to ongoing patency.

There are some clear limitations to this review and meta-analysis as the studies were generally small and most had methodological limitations suggesting a risk of bias. With the exception of

one study (10) follow up periods and outcomes included in reports were very limited. The doses of anticoagulation utilised were not consistent between trials included. Finally, no study reported monitoring of the baseline coagulation studies or the effects of administered anticoagulation in the intervention group with laboratory studies. This is important as uraemic patients are already at elevated risk of bleeding due to the so called “uremic thrombopathy” , a multifactorial condition brought about by platelet dysfunction, platelet-endothelial interaction defects, increased prostacyclin and nitric oxide levels and anaemia with a low haematocrit(15). Without monitoring it is difficult to ascribe all bleeding related complications to the use of heparin or to know if appropriate doses were utilised in already compromised patients.

The use of intraoperative systemic heparin during AVF formation is associated with a scarcely significant improvement in patency at early follow up. Though the very highly significant increased risk of bleeding related complications with intraoperative systemic heparin use, occasionally requiring transfusion or re-operation, would appear to outweigh the small potential benefit to patency. No benefit in patency was shown when AVG and AVF were analysed together though the bleeding risk remained significant. Accepting the limitations of this review, current evidence does not appear support the use of systemic anticoagulation during access surgery.

## References

1. Brescia MJ, Cimino JE, Appel K, Hurwicz BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med.* 1966 Nov 17;275(20):1089-92.
2. Lew SQ, Nguyen BN, Ing TS. Hemodialysis vascular access construction in the upper extremity: a review. *J Vasc Access.* 2015 Mar-Apr;16(2):87-92.
3. Berardinelli L. The endless history of vascular access: A surgeon's perspective. *J Vasc Access.* 2006;7(3):103-11.
4. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int.* 2002 Oct;62(4):1109-24.
5. Ravani P, Spengel LM, Asif A, Roy-Chaudhury P, Besarab A. Clinical epidemiology of arteriovenous fistula in 2007. *J Neph.* 2007;20(2):141-9.
6. Smith GE, Gohil R, Chetter IC. Factors affecting the patency of arteriovenous fistulas for dialysis access. *J Vasc Surg.* 2012 Mar;55(3):849-55.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.
8. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Cont clin trials.* 1996 Feb;17(1):1-12.
10. D'Ayala M, Smith RM, Martone C, Briggs W, Deitch JS, Wise L. The effect of systemic anticoagulation in patients undergoing angioaccess surgery. *Ann Vasc Surg.* 2008; (1): 11-5
11. Bhomi KK, Shrestha S, Bhattachan CL. Role of systemic anticoagulation in patients undergoing vascular access surgery. *Nepal Med Coll J.* 2008 Dec;10(4):222-4.
12. Wang BR, Rowe VL, Ham SW, Han S, Patel K, Weaver FA, et al. A prospective clinical evaluation of the effects of intraoperative systemic anticoagulation in patients undergoing arteriovenous fistula surgery. *Am Surg.* 2010 Oct;76(10):1112-4.
13. Ravari H, Kazemzade GH, Sarookhani A, Khashayar P. Effect of heparin on the patency of arteriovenous fistula. *Acta Medica Iranica.* 2008;46(5):379-82.
14. Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to Anticoagulant Therapy: Heparin: A Statement for Healthcare Professionals From the American Heart Association. *Circulation.* 2001 June 19, 2001;103(24):2994-3018.

15. Pavord S, Myers B. Bleeding and thrombotic complications of kidney disease. *Blood Rev.* 2011 Nov;25(6):271-8.

Table 1 Summary of included studies and results (ND = Not described, LA = Local anaesthetic)

Study	Sample size	Intervention	N=	Autologous or prosthetic access	Anaesthesia	Mean age	Male Gender (%)	Bleeding events	Failure within 30 days (%)
D'Ayala et al (2008)	115	5000U Systemic Heparin	57	Mixed	LA with sedation	60	57	13 (23%)	9 (16%) at 30 days
		Heparinised Saline	58			62	53	1(1.8%)	8 (14%) at 30 days
Bhomi et al (2008)	50	5000U Systemic Heparin	25	Autologous	LA	48	56	6 (24%)	1 (4%) at 6 weeks
		Heparinised Saline	25			50	52	0 (0%)	2 (8%) at 6 weeks
Ravari et al (2008)	198	5000U Systemic Heparin	96	Autologous	ND	48	62	3(3%)	14 (15%) at 2 weeks
		ND	10			49	62	1 (1%)	26

			2						(26%) at 2 weeks
Wang et al (2010)	48	75units/K G Heparin	26	Autologo us	ND	52	54	3 (12%)	2 (8%) at 30 days
		ND	22			50	45	1 (5%)	3 (14%) at 30 days

Table 2 Summary assessment of risk of bias in the studies identified

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other Bias	Jadad score
D' Ayala (2008)	Unclear	Unclear	Unclear	Low	Unclear	Low	2
Bhomi (2008)	Unclear	Unclear	Unclear	Low	Unclear	Low	2
Ravari (2008)	Low	High	Unclear	Unclear	Unclear	Low	1
Wang (2010)	Unclear	Unclear	Unclear	Low	Unclear	Low	2

Figure 1. Forrest plot demonstrating significantly increased risk of bleeding related complications with systemic anticoagulation use in all access types

Figure 2. Forrest plot demonstrating no significant difference in risk of loss of patency at first follow up in all access types