Randomized clinical trial

Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures

R. T. A. Chalmers[1], R. C. Darling III[3], J. T. Wingard[4], I. Chetter[2], B. Cutler[5], J. A. Kern[6] and J. C. Hart[7]

[1]Royal Infirmary of Edinburgh, Edinburgh and [2]Hull Royal Infirmary, Hull, UK, [3]Albany Medical Center Hospital, Albany, New York, [4]Memorial Hospital, Jacksonville, Florida, [5]University of Massachusetts Medical Center, Worcester, Massachusetts, [6]UVA Health System, Charlottesville, Virginia, and [7]Ethicon, Somerville, New Jersey, USA

Correspondence to: Mr R. T. A. Chalmers, Vascular Surgical Service, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK (e-mail: rod.chalmers@luht.scot.nhs.uk)

Background: This study evaluated the safety and haemostatic effectiveness of a fibrin sealant (EVICEL™ Fibrin Sealant (Human)) during vascular surgery.

Methods: This prospective randomized controlled trial compared the haemostatic effectiveness of fibrin sealant (75 patients) or manual compression (72) in polytetrafluoroethylene (PTFE) arterial anastomoses. The primary endpoint was the absence of bleeding at the anastomosis at 4 min after randomization. Secondary endpoints included haemostasis at 7 and 10 min, treatment failures and the incidence of complications potentially related to bleeding. Adverse events were recorded.

Results: A higher percentage of patients who received fibrin sealant *versus* manual compression achieved haemostasis at 4 min (85 *versus* 39 per cent respectively; odds ratio 11·34, 95 per cent confidence interval 4·67 to 27·52; $P < 0·001$). Similarly, a higher percentage of patients who received fibrin sealant achieved haemostasis at 7 and 10 min (both $P < 0·001$). The incidence of treatment failure was lower in the fibrin sealant group ($P < 0·001$). The rate of complications potentially related to bleeding was similar ($P = 0·426$). Some 64 per cent of patients who received fibrin sealant experienced at least one adverse event, compared with 71 per cent who received manual compression.

Conclusion: This fibrin sealant was safe, and significantly shortened the time to haemostasis in vascular procedures using PTFE. Registration number: NCT00154141 (http://www.clinicaltrials.gov).

Paper accepted 7 July 2010

Published online 20 August 2010 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.7235

Introduction

Commercially available fibrin sealants typically consist of human plasma-derived thrombin and fibrinogen, which are combined at a target bleeding site to achieve haemostasis. The effectiveness and safety of fibrin sealants used as haemostatic agents have been described for a variety of surgical procedures[1–4].

Fibrin sealants have traditionally been manufactured with antifibrinolytic agents (such as tranexamic acid and aprotinin); however, tranexamic acid and aprotinin may be associated with adverse outcomes or risks during surgery[5]. Tranexamic acid has been associated with neurological adverse events when exposed to cerebrospinal fluid. Previous-generation fibrin sealants containing tranexamic acid are contraindicated for use during surgery where contact with cerebrospinal fluid may occur[6]. Aprotinin has been associated with hypersensitivity reactions, and aprotinin-containing fibrin sealants have been implicated in these adverse events as a possible source of initial sensitivity to the molecule[7]. It was therefore desirable to develop a fibrin sealant that did not require an antifibrinolytic agent.

EVICEL™ Fibrin Sealant (Human) (Johnson & Johnson Wound Management, a division of Ethicon, Somerville, New Jersey, USA) is a second-generation fibrin sealant that contains only human components, no aprotinin or tranexamic acid, and is indicated as an adjunct for haemostasis in patients undergoing surgery. The manufacturing process includes a plasminogen removal step, thus negating the need for aprotinin or tranexamic

acid. It is a modification of CROSSEAL™ Fibrin Sealant (Human) (Johnson & Johnson Wound Management), from which the plasminogen component has been removed. Preclinical studies have demonstrated that the efficacy of haemostasis, the volume of fibrin sealant required to achieve haemostasis, and clot stability for EVICEL™ Fibrin Sealant (Human) and CROSSEAL™ Fibrin Sealant (Human) are comparable[8].

The haemostatic effectiveness of CROSSEAL™ was proved in a phase III randomized parallel-group multicentre study, which demonstrated a significantly reduced time to haemostasis during liver resection surgery compared with standard topical haemostatic agents (282 *versus* 468 s respectively; $P = 0{\cdot}006$)[3]. The present study compared the haemostatic effectiveness and safety of human fibrin sealant (EVICEL™ Fibrin Sealant (Human)) *versus* manual compression during vascular surgical procedures using polytetrafluoroethylene (PTFE) on an end-to-side femoral or upper extremity arterial anastomosis.

Methods

This randomized controlled parallel-group multicentre study was conducted at 16 centres in the USA and the UK. Men and women aged 18 years or older, who were expected to undergo a vascular procedure using uncoated or heparin-coated PTFE prosthetic graft material with at least one end-to-side anastomosis to a femoral or upper extremity artery, were eligible for the study. Patients were screened within 21 days of surgery to determine their eligibility for study enrolment. Patients were excluded from the study if they were undergoing revascularization with prosthetic material other than PTFE, if they were having emergency surgery, or if they had any intraoperative findings (such as no anastomotic bleeding) that precluded conduct of the study procedures. Patients who were allergic to heparin, blood products (or were unwilling to receive these) or any component of the fibrin sealant were excluded from the study, as were those with autoimmune immunodeficiency diseases, including human immunodeficiency virus infection, or current drug or alcohol abuse. Patients were prohibited from study entry if they had participated in another investigational drug or device study within 30 days of enrolment. Women who were pregnant or nursing were also excluded. In accordance with the International Conference for Harmonisation Tripartite Guideline for Good Clinical Practice[9] and the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects as amended in Tokyo, Venice, South Africa and Hong Kong[10], all patients provided written informed consent, and appropriate institutional review board approvals were obtained.

All patients received heparin before arterial clamping; the exact dose administered was based on the surgeon's standard practice. Fibrin sealant was prepared before randomization for potential use in the operating theatre by thawing it in a refrigerator (2–8°C) for 24 h before surgery, at room temperature (20–25°C) for 1 h before operation or by using a warm water bath for no more than 10 min before surgery. The study anastomotic sites were constructed with uncoated or heparin-coated PTFE and polypropylene sutures (needle to suture diameter ratio 1 : 1). In patients having bilateral groin procedures, the study anastomosis was the final anastomosis to the femoral or upper extremity artery, with the exception of a femoral crossover graft, when the study anastomosis was the proximal anastomosis, performed as the last one in the procedure. Arterial clamps were then removed, and additional sutures were placed, if necessary, to ensure that the suture line was secure. If bleeding at the anastomosis persisted and the surgeon determined that adjunctive haemostatic measures were required, arterial clamps were reapplied, and the patient was considered to be eligible for randomization in a 1 : 1 ratio to receive either the fibrin sealant or manual compression. The computer randomization schedule was balanced within each study site, as well as for femoral *versus* upper extremity procedures. The time at which the patient was randomized to a treatment group was considered 0 min.

Fibrin sealant was dripped on to the anastomosis of patients randomized to the fibrin sealant group, and arterial clamps were removed 1 min after the end of application. For patients who were randomized to receive manual compression, arterial clamps were removed at the time of randomization, and light manual pressure with gauze sponges was applied to the anastomosis. Reversal of heparin (with protamine), if applicable, was recorded. Bleeding at the anastomosis was then assessed at 4, 7 and 10 min, or until haemostasis was achieved.

Patients returned for a follow-up visit 5 weeks after the surgical procedure for the assessment of adverse events and complications that were potentially related to bleeding.

The primary effectiveness endpoint was the absence of bleeding at the anastomosis at 4 min after randomization. Secondary endpoints included the absence of bleeding at the anastomosis at 7 and 10 min, the incidence of treatment failure (defined as the presence of bleeding at the anastomosis at 10 min after randomization, or the requirement for additional haemostatic measures during the initial 10-min observation), and the incidence of complications that were potentially related to bleeding

up to 5 weeks after surgery. Adverse events that occurred up to 5 weeks after surgery were recorded using *Medical Dictionary for Regulatory Activities* (MedDRA®) codes (http://www.meddramsso.com/index.asp).

Statistical analysis

Effectiveness analyses were performed using the intention-to-treat (ITT) population, which included all randomized patients; effectiveness analyses were confirmed using patients in the per-protocol population (patients in the ITT population who had no major protocol violations). Safety analyses were performed using the ITT population.

The null hypothesis of the study was that the proportion of patients with bleeding at 4 min would be the same in both treatment groups, whereas the alternative hypothesis was that the proportion of patients with bleeding at 4 min would differ between the treatment groups. The sample size of the study was based on the assumption that the proportion of patients with successful haemostasis at 4 min would be 63 per cent for those who received fibrin sealant compared with 35 per cent for those who received manual compression; these values were selected based on the results of a similar study[11]. Using a 5 per cent significance level, it was calculated that 144 patients (72 per treatment group) were required to achieve 90 per cent power to detect a difference of 28 per cent between the null and alternative hypotheses. The sample size was increased to 150 (75 per treatment group) to account for early study discontinuations.

Between-group differences in the absence of bleeding at the anastomosis at 4, 7 and 10 min, the incidence of treatment failures, and the rate of complications that were potentially related to bleeding were analysed using a logistic model (with treatment, site and artery type as variables). Odds ratios (ORs) with two-sided 95 per cent confidence intervals (c.i.) were calculated to evaluate between-group differences in effectiveness endpoints, and a significant ($P < 0{\cdot}050$) between-group difference in the percentages of patients with no bleeding at the anastomosis at 4 min allowed acceptance of the alternative hypothesis. Between-group differences in the incidence of adverse events were evaluated using a two-sided Fisher exact test.

Results

A total of 147 patients were enrolled and randomized to receive treatment with either fibrin sealant (75) or manual compression (72) (*Fig. 1*). The 147 patients comprised the ITT population, of whom 142 were included in the per-protocol population; five patients were excluded as a result

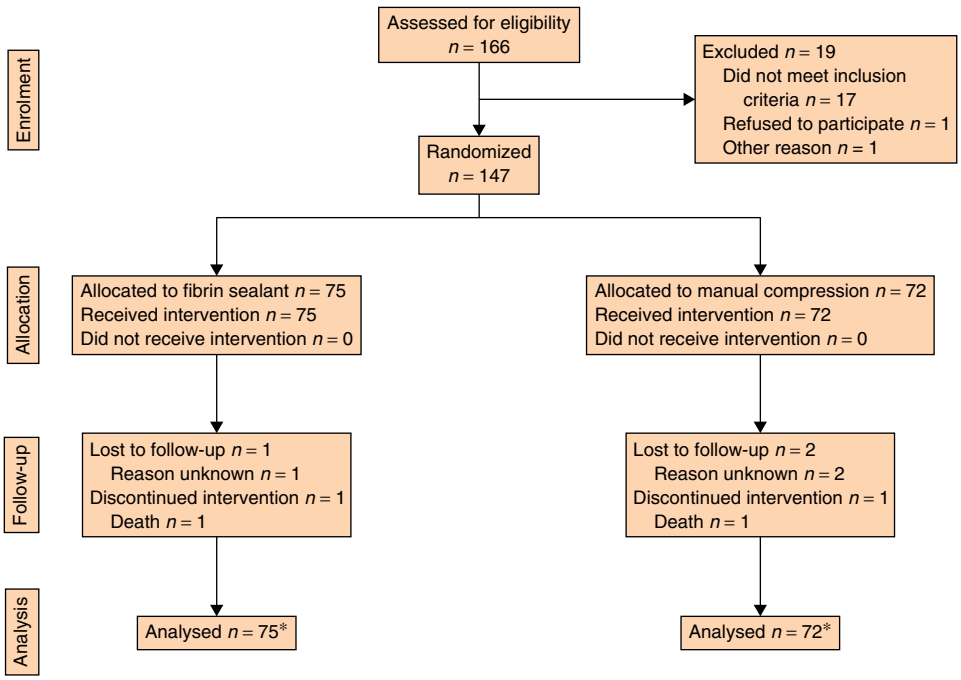

Fig. 1 CONSORT diagram showing the treatment groups that resulted from screening and randomization. *Five patients who withdrew from the study had a time to haemostasis measured and were therefore included in the analyses

Table 1 Baseline demographic and clinical characteristics

	Fibrin sealant ($n = 75$)	Manual compression ($n = 72$)
Age (years)		
Mean(s.d.)	66(11)	66(14)
Median (range)	67 (38–84)	70 (39–90)
Sex ratio (M : F)	41 : 34	36 : 36
Race		
Caucasian	54 (72)	61 (85)
Black of African descent	16 (21)	10 (14)
Other	5 (7)	1 (1)
Femoral procedures	48 (64)	51 (71)
Femoropopliteal bypass	13 (17)	13 (18)
Femorofemoral bypass	11 (15)	13 (18)
Aortobifemoral bypass	9 (12)	10 (14)
Axillofemoral bypass	8 (11)	5 (7)
Femoral arteriovenous access graft	1 (1)	3 (4)
Femoral aneurysm graft	3 (4)	0 (0)
Femorotibial bypass	3 (4)	2 (3)
Iliofemoral bypass	0 (0)	2 (3)
Ilioprofunda bypass	0 (0)	1 (1)
Femorofemoral and femoropopliteal bypass	0 (0)	1 (1)
Femoropedal bypass	0 (0)	1 (1)
Vascular access in upper extremity graft procedures	27 (36)	21 (29)
Radial	5 (7)	5 (7)
Brachial	22 (29)	16 (22)
Total heparin dose (units/kg)		
Mean(s.d.)	66·9(27·0)	67·9(25·2)
Median (range)	63·5 (22·0–150·3)	63·4 (7·7–156·7)

Values in parentheses are percentages unless indicated otherwise.

of major protocol violations that may have affected their time to haemostasis.

Baseline demographic and clinical characteristics for the individual treatment groups are shown in *Table 1*. The majority of patients (63·3 per cent, 93 of 147) were between 50 and 74 years of age. Overall, 78·2 per cent (115 of 147) were Caucasian and 17·7 per cent (26 of 147) were black of African descent. With the exception of one patient who received a heparin-coated PTFE graft, all patients received an uncoated PTFE graft. The mean doses of heparin used were similar between the two groups (*Table 1*).

Effectiveness

The proportion of patients who achieved haemostasis at 4, 7 and 10 min is shown in *Fig. 2*. A significantly higher percentage of patients who received fibrin sealant achieved haemostasis at 4 min compared with those who received manual compression: 85 per cent (64 of 75) *versus* 39 per cent (28 of 72) (OR 11·34, 4·67 to 27·52; $P < 0·001$).

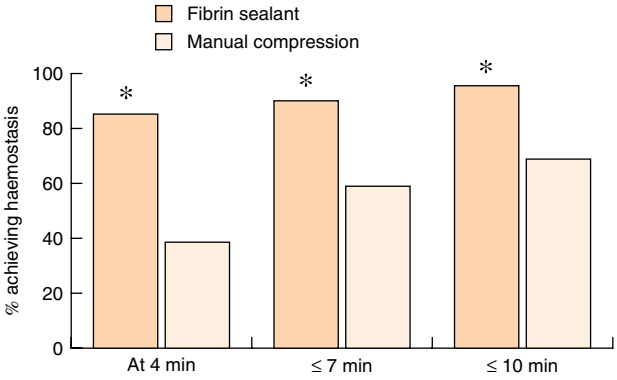

Fig. 2 Proportion of patients who achieved haemostasis at 4 min, and within 7 and 10 min after randomization. *$P < 0·001$ *versus* manual compression (logistic model with treatment, site and artery type as factors)

Exploratory analyses showed similar results regardless of artery type: of patients treated with fibrin sealant, 85 per cent (23 of 27) had haemostasis at 4 min after an upper extremity procedure and 85 per cent (41 of 48) after a femoral surgical procedure, compared with 43 per cent (9 of 21) and 37 per cent (19 of 51) respectively of those receiving manual compression.

Similarly, a significantly higher percentage of patients who received fibrin sealant achieved haemostasis within 7 min (OR 7·88, 2·84 to 21·86; $P < 0·001$) and 10 min (OR 18·53, 3·74 to 91·77; $P < 0·001$). Protamine was administered for heparin reversal in 5 per cent of patients (4 of 75) who received fibrin sealant and 7 per cent (5 of 72) who received manual compression.

Consistent with the proportion of patients achieving haemostasis, there was a significantly lower incidence of treatment failure for patients who received fibrin sealant compared with manual compression: 8 per cent (6 of 75) *versus* 32 per cent (23 of 72) (OR 0·14, 0·05 to 0·45; $P < 0·001$).

The rate of complications potentially related to bleeding was similar between the groups: 16 per cent (12 of 75) for fibrin sealant *versus* 21 per cent (15 of 72) for manual compression (OR 1·46, 0·58 to 3·69; $P = 0·426$). These complications included anaemia/low haemoglobin/low haematocrit, haematoma, bleeding, increased sanguinous drainage, seroma and bruising.

Safety

Some 64 per cent (48 of 75) of patients who received fibrin sealant experienced at least one adverse event compared with 71 per cent (51 of 72) who received manual compression. The adverse event profile was as

Table 2 Incidence of adverse events

	Total ($n = 147$)	Fibrin sealant ($n = 75$)	Manual compression ($n = 72$)	P*
Nausea	8 (5)	2 (3)	6 (8)	0·161
Anaemia	5 (3)	0 (0)	5 (7)	0·026
Cardiac failure	5 (3)	0 (0)	5 (7)	0·026
Hypotension	6 (4)	1 (1)	5 (7)	0·111
Constipation	7 (5)	2 (3)	5 (7)	0·269
Graft infection	9 (6)	4 (5)	5 (7)	0·742
Graft occlusion/thrombosis	12 (8)	7 (9)	5 (7)	0·269
Oedema, peripheral	7 (5)	5 (7)	2 (3)	0·442
Urinary tract infection	5 (3)	1 (1)	4 (6)	0·203

Values in parentheses are percentages. *Two-sided Fisher's exact test.

expected for this patient population (*Table 2*). Only nine (12 per cent) of the 75 patients in the fibrin sealant group experienced adverse events that were considered possibly related to treatment; none was considered probably or definitely related to treatment. As manual compression was considered to be a standard approach rather than an investigational agent, investigators did not ascribe a causal relationship between adverse events and the use of manual compression. The rate of vascular graft occlusion and graft thrombosis was 9 per cent (7 of 75) in the fibrin sealant group and 7 per cent (5 of 72) in the manual compression group ($P = 0·269$).

Discussion

In this study, the fibrin sealant (EVICEL™ Fibrin Sealant (Human)) effectively achieved haemostasis for the majority of patients (85 per cent) within 4 min after completion of the suture line of a PTFE graft to the femoral or upper extremity arteries. In addition, the rate of complications potentially related to bleeding and the incidence of adverse events were similar in both groups. No new safety concerns associated with the use of this fibrin sealant were identified during the study.

In a similar randomized multicentre clinical trial, the effectiveness of a fibrin sealant, Beriplast® P (Aventis-Behring, Strasbourg, France), was compared with topical application of thrombin-soaked gelatin sponge to the suture line for its ability to provide haemostasis in anastomoses of PTFE grafts to the femoral artery[11]. In that trial, 63 per cent of patients who received fibrin sealant achieved haemostasis after 4 min. Another study evaluated the haemostatic effectiveness and safety of a fibrin sealant (ZLB Bioplasma, Berne, Switzerland) compared with an oxidized regenerated cellulose haemostatic agent (SURGICEL® Original Absorbable Hemostat; Johnson & Johnson Wound Management) during vascular access surgery using PTFE grafts for dialysis[12]. The results demonstrated a significant decrease in the time to haemostasis for patients who received the fibrin sealant *versus* the absorbable haemostat, similarly demonstrating the haemostatic effectiveness of a fibrin sealant during a vascular procedure using PTFE.

Concerns have been raised regarding the use of fibrin sealants that contain tranexamic acid or aprotinin[13–16]. The fibrin sealant used in the present study contained no tranexamic acid or aprotinin, and no allergic or anaphylactic reactions were noted.

This study may have been limited because the surgical procedure was not standardized at each site. Each surgeon performed the procedure according to his or her standard practice, including the dose of heparin administered before arterial clamping. In addition, the percentage of patients who achieved haemostasis within each time point may have been affected by the amount of time that lapsed between randomization and the application of fibrin sealant or manual pressure. These factors may have contributed some variability to the study results. Finally, the method used to achieve haemostasis in the intervention arm included arterial clamping, to allow application of the sealant in a dry field. Although it is not possible to separate the haemostatic effect of the clamping from that of the fibrin sealant, when considered as a whole, the time to achieve haemostasis was shorter with fibrin sealant than with manual compression.

A reduced time to haemostasis in vascular surgery is widely accepted by the surgical community to be beneficial for patients. Findings from this study suggest that EVICEL™ Fibrin Sealant (Human) is useful in achieving rapid haemostasis following vascular anastomoses when using PTFE.

Contributors

This clinical trial was conducted under the guidance of the following principal investigators, who participated in data collection for this study at 16 sites: D. Adam (Birmingham Heartlands Hospital, Birmingham, UK), K. Cassar (Aberdeen Royal Infirmary, Aberdeen, UK), R. Chalmers (Royal Infirmary of Edinburgh, Edinburgh, UK), I. Chetter (Hull Royal Infirmary, Hull, UK), A. J. Comerota (Jobst Vascular Center, Toledo, Ohio, USA), C. T. Cousar (Baptist Medical Center, Jacksonville, Florida, USA), B. Cutler (University of Massachusetts Medical Center, Worcester, Massachusetts, USA), R. Clement Darling III (Albany Medical Center Hospital, Albany, New York, USA), M. L. Dryjski (Millard Fillmore Hospital, Buffalo, New York, USA), M. H. Glickman

(Vascular and Transplant Specialists, Norfolk, Virginia, USA), J. A. Kern (UVA Health System, Charlottesville, Virginia, USA), R. B. McLafferty (Southern Illinois University School of Medicine, Springfield, Illinois, USA), C. Moss (Hackensack Medical Center, Hackensack, New Jersey, USA), M. A. Passman (Vanderbilt University Medical Center, Nashville, Tennessee, USA), A. F. Schild (Jackson Memorial Hospital, Miami, Florida, USA) and T. Wingard (Memorial Hospital, Jacksonville, Florida, USA).

Acknowledgements

The authors acknowledge the contributions of Jessica Shen (Ethicon, Somerville, New Jersey, USA) and Judith Gauld and Peter Jones (Johnson & Johnson Medical, Livingston, UK). Editorial support for the writing of this manuscript was provided by Ashley O'Dunne of MedErgy (Yardley, Pennsylvania, USA) and was funded by Ethicon. The authors were not compensated and retained full editorial control over the content of the manuscript. J.C.H. is employed by Ethicon. This study was funded by Johnson & Johnson Wound Management, a division of Ethicon (Somerville, New Jersey, USA). The authors declare no other conflict of interest.

References

1 Atkinson JB, Gomperts ED, Kang R, Lee M, Arensman RM, Bartlett RH *et al*. Prospective, randomized evaluation of the efficacy of fibrin sealant as a topical hemostatic agent at the cannulation site in neonates undergoing extracorporeal membrane oxygenation. *Am J Surg* 1997; **173**: 479–484.

2 Frilling A, Stavrou GA, Mischinger HJ, de Hemptinne B, Rokkjaer M, Klempnauer J *et al*. Effectiveness of a new carrier-bound fibrin sealant *versus* argon beamer as haemostatic agent during liver resection: a randomised prospective trial. *Langenbecks Arch Surg* 2005; **390**: 114–120.

3 Schwartz M, Madariaga J, Hirose R, Shaver TR, Sher L, Chari R *et al*. Comparison of a new fibrin sealant with standard topical hemostatic agents. *Arch Surg* 2004; **139**: 1148–1154.

4 Wang GJ, Hungerford DS, Savory CG, Rosenberg AG, Mont MA, Burks SG *et al*. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty: a brief note on a randomized prospective trial. *J Bone Joint Surg Am* 2001; **83-A**: 1503–1505.

5 Martin K, Wiesner G, Breuer T, Lange R, Tassani P. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. *Anesth Analg* 2008; **107**: 1783–1790.

6 Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010; **110**: 350–353.

7 Scheule AM, Beierlein W, Wendel HP, Eckstein FS, Heinemann MK, Ziemer G. Fibrin sealant, aprotinin, and immune response in children undergoing operations for congenital heart disease. *J Thorac Cardiovasc Surg* 1998; **115**: 883–889.

8 Nur I, Bar L, Meidler R, Gorman A. Plasminogen free fibrin sealant. *Transactions of the Society For Biomaterials*, Pittsburgh, 2006.

9 ICH Expert Working Group. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1)*. Current Step 4 version. 10 June1996. http://www.who.int/vaccine_research/ICH_GCP.pdf [accessed 27 July 2010].

10 World Medical Association. *Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects*. http://www.wma.net/en/30publications/10policies/b3/index.html [accessed 27 July 2010].

11 Taylor LM Jr, Mueller-Velten G, Koslow A, Hunter G, Naslund T, Kline R *et al*. Prospective randomized multicenter trial of fibrin sealant *versus* thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from polytetrafluoroethylene femoral artery grafts. *J Vasc Surg* 2003; **38**: 766–771.

12 Schenk WG III, Burks SG, Gagne PJ, Kagan SA, Lawson JH, Spotnitz WD. Fibrin sealant improves hemostasis in peripheral vascular surgery: a randomized prospective trial. *Ann Surg* 2003; **237**: 871–876.

13 Schlag MG, Hopf R, Redl H. Convulsive seizures following subdural application of fibrin sealant containing tranexamic acid in a rat model. *Neurosurgery* 2000; **47**: 1463–1467.

14 Beierlein W, Scheule AM, Antoniadis G, Braun C, Schosser R. An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; **40**: 302–305.

15 Scheule AM, Beierlein W, Lorenz H, Ziemer G. Repeated anaphylactic reactions to aprotinin in fibrin sealant. *Gastrointest Endosc* 1998; **48**: 83–85.

16 Oswald AM, Joly LM, Gury C, Disdet M, Leduc V, Kanny G. Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99**: 762–763.

Commentary

Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures (*Br J Surg* 2010; 97: 1784–1789)

There is a growing number of commercially available products that help surgeons achieve haemostasis when conventional means prove unsuccessful. Fibrin sealants are well established, effective and occasionally life saving but may cause adverse reactions. A sealant that lacks aprotinin and tranexamic acid is therefore welcome.

This study demonstrates that this new sealant works. We are not told, however, how much heparin was usually given and whether the total heparin dose varied between the treatment and control groups. The fibrin sealant significantly reduced the time taken for arterial polytetrafluoroethylene anastomoses to stop bleeding. The authors claim that this time (measured in minutes) is valuable and may justify the (not inconsiderable) expense of the sealant.

In my experience, bleeding from anastomoses is rarely serious, more of a nuisance than a major adverse event. I would find it difficult to justify the routine use of a sealant therefore. The value of the study is that it has provided evidence that this new (potentially safer) fibrin sealant is effective so that we might have it on the shelf for the odd occasion when it is really useful, such as the splitting, calcified neck of an aortic aneurysm. The relative effectiveness of fibrin sealants and other haemostatic products remains unclear.

N. C. Hickey
Department of Vascular Surgery, Worcestershire Royal Hospital, Worcester WR5 1DD, UK (e-mail: nick.hickey@worcsacute.nhs.uk)
DOI: 10.1002/bjs.7250

If you wish to comment on this, or any other article published in the *BJS*, please visit the on-line correspondence section of the website (www.bjs.co.uk). Electronic communications will be reviewed by the Correspondence Editor and a selection will appear in the correspondence section of the Journal. Time taken to produce a thoughtful and well written letter will improve the chances of publication in the Journal.