Fibrin Sealant Reduces Suture Line Bleeding During Carotid Endarterectomy: A Randomised Trial

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Objectives: To determine whether topical fibrin sealant reduced suture line bleeding during carotid endarterectomy with polytetrafluoroethylene (PTFE) patch closure.
Design: Prospective randomised non-blinded control trial.
Setting: Regional vascular surgery unit.
Materials: Seventeen patients undergoing carotid endarterectomy were randomised either to receive fibrin sealant as a topical haemostatic agent at the arteriotomy suture line or to act as control.
Outcome measures: Time taken to achieve haemostasis at the suture line. Intraoperative blood loss. Total operative time.

Results: The median time to achieve haemostasis was 5.5 min (range 4–31 min) in the treatment group and 19 min (range 10–47 min) in the control group. This difference was statistically significant p < 0.005 by Mann-Whitney test. There was no statistical difference in total operative time. Operative blood loss was lower in the treatment group (median 420ml, range 300–500ml) than in the control group (median 550ml, range 350–1200ml) but this difference was not statistically significant. One patient in the control group suffered a perioperative thrombo-embolic event.

Conclusion: Fibrin sealant is an effective topical haemostatic agent for arteriotomy suture lines involving PTFE material.

Key Words: Randomised controlled trial; Polytetrafluoroethylene; Carotid surgery; Fibrin sealant; Haemostasis.

Introduction

Suture line bleeding at vascular anastomoses is a problem which can increase operative blood loss and lengthen operating time. This is especially a problem in anastomoses involving polytetrafluoroethylene (PTFE) grafts and patches and may be exacerbated by the use of intraoperative heparin.

Fibrin sealant is a topical haemostatic agent which consists of two principal components, fibrinogen and thrombin, which are mixed, in the presence of Factors VIII and XIII, fibronectin and calcium to produce insoluble fibrin. Thus the main components of the final stage in the physiological pathway of coagulation are present.

Fibrin sealant of this form was first described in 1972 as a tissue adhesive for nerve repair.1 Since then it has been used in a wide variety of clinical settings: otolaryngology,2 plastic surgery,3,4 neurosurgery,5–7 thoracic surgery,8–12 hepatobiliary surgery,13,14 pancreatic surgery,15,16 colorectal surgery,17 gynaecology18,19 and cardiac surgery.20–26

The possibilities for using fibrin sealant in cardiovascular surgery were recognised by Spangler early on during its development.27 Borst and Haverich (1982) further developed and promoted the use of fibrin sealant in this field describing its use for sealing knitted Dacron aortic grafts, puncture holes and suture lines in vascular anastomoses.20,21

The success of fibrin sealant in cardiac surgery would suggest that it may also be useful in peripheral vascular surgery. However there have been few studies of fibrin sealant in this setting. In randomised trials using an animal model of peripheral vascular surgery with PTFE grafts, fibrin sealant was shown to be more effective than oxidised regenerated cellulose in controlling anastomotic bleeding.28,29 However there are no reports of the clinical use of fibrin sealant...
in peripheral vascular surgery. Carotid endarterectomy using a PTFE patch is associated with prolonged anastomotic bleeding and the aim of this study was to determine whether fibrin sealant could significantly reduce suture line bleeding in these patients.

**Material and Methods**

The study was a prospective, randomised non-blinded trial. An initial pilot study involving eight patients was carried out in order to familiarise surgeons and theatre staff with the use of fibrin sealant prior to the commencement of the trial.

**Patients and operative details**

Patients were recruited from the vascular surgery unit of the Royal Infirmary of Edinburgh. All patients gave informed written consent and the trial was approved by the local ethical committee. Past medical history and drug use within the previous 14 days was recorded. To allow assessment of the viral safety of the sealant (as part of a larger safety study) patients who were known to be seropositive for anti-HIV, who had a history of hepatitis or whose liver function tests were outside the normal range were excluded. In addition, patients with a history of severe reactions to blood products or concurrent disease which might compromise their ability to be retained within the study were also excluded. A venous blood sample was taken for haemoglobin, haematocrit, platelet and white cell count, prothrombin time, activated partial thromboplastin time and liver function tests. A serum sample was stored at -40°C for later viral studies if required.

The mean age of patients was 64.5 years (range 48–75 years) and there was no difference in mean age between the patients in the treatment and control groups. Fifteen patients were taking regular aspirin; both the patients not taking aspirin were in the control group. No patient had any abnormality on preoperative coagulation screen.

Following entry into the trial the patients were randomised in a computer-generated sequence to treatment or control groups. In the treatment group, following completion of the vascular anastomosis, fibrin sealant was applied to the suture line using a dual syringe technique. In the control group nothing was applied to the suture line. The clamps were released 2 min after application was complete. Pressure was applied with surgical swabs if there was significant bleeding. The surgeon was allowed to use haemostatic gauze at any time. The arteriotomy was inspected frequently and the time taken to achieve haemostasis from release of the clamps was recorded.

Surgical treatment was otherwise identical in the two groups. All operations were performed under general anaesthetic with subcutaneous local anaesthetic infiltration. The operations were all performed (6/9 control; 5/8 treatment) or supervised by one surgeon (C.V.R.). All patients received intraoperative heparin, 5000 I.U. before the artery was clamped. The heparin was not reversed. Arteriotomy closure was performed using a 0.5 mm PTFE patch (WL Gore) and 7.0 Goretex suture. In both groups any further manoeuvres, such as application of pressure or haemostatic gauze, required to achieve haemostasis were recorded. The length of operation, blood product usage were recorded and a personal assessment by the surgeon of effectiveness and ease of use was also recorded.

Patients were followed-up for 26 weeks. Blood was taken at 24 h and 5 days for haemoglobin, haematocrit, platelet count and white cell count; at 6 weeks and 12 weeks for liver function tests and at 26 weeks for virology testing. Virology testing consisted of determining the presence of hepatitis B surface antigen and enzyme immunoassay for antibodies to hepatitis A and hepatitis C, bioluminescence assay for antibodies to hepatitis B surface antigen, and radioimmunoassay for antibodies to hepatitis B core antigen.

Fibrin sealant kit was provided for the study by the Scottish National Blood Transfusion Service (SNBTS). Heat-treated human fibrinogen was manufactured at the SNBTS Protein Fractionation Centre from pooled donor plasma cryosupernatant. Solvent detergent treated human thrombin preparation was supplied by the Centre Regional de Transfusion Sanguine (CRTS) (Lille, France). The fibrin sealant supplied by SNBTS uses concentrations of thrombin between 200–500 I.U./ml and fibrinogen 29–39g/l.

After 17 patients had been randomised it appeared to the surgeon and anaesthetist that there was a clinical benefit in patients treated with fibrin sealant and an interim analysis of the data was requested. This confirmed that there was a statistically significant benefit and the trial was stopped. Statistical analysis was carried out using a Mann-Whitney U test.

**Results**

The median time to achieve haemostasis was 5.5 min.
Fibrin sealant in carotid endarterectomy

(range 4–31 min) in the treatment group and 19 min (range 10–47 min) in the control group (Fig. 1). This difference was statistically significant \( p < 0.005 \) by Mann-Whitney test. There was no statistical difference in total operative time. Operative blood loss was lower in the treatment group (median: 420 ml, range: 300–500 ml) than in the control group (median 550 ml, range 350–1200 ml) but this difference was not statistically significant. All patients (9/9) in the control group and one patient (1/8) in the fibrin sealant group required the use of oxidised cellulose gauze to aid haemostasis. In no cases were further sutures required to achieve haemostasis. There were no significant differences in the drop in haemoglobin following operation. There was no evidence of arterial embolism or thrombosis in the treatment group. No patients required reoperation for control of haemorrhage or evacuation of haematoma. There were no wound complications in any patient in either group.

![Time to achieve haemostasis in carotid endarterectomy](image)

**Fig. 1.** Time to achieve haemostasis in carotid endarterectomy.

**Discussion**

This study has shown that fibrin sealant is an effective topical haemostatic agent in vascular surgery. The only statistically significant benefit was a shorter time to achieve haemostasis. Blood loss was lower in the treatment group but this did not attain statistical benefit. This may be a type II statistical error: the trial was terminated after interim analysis was requested by the surgical team to confirm a clinical impression of haemostatic effectiveness.

It may be expected that fibrin-based adhesives and sealants are likely to be useful agents for surgical haemostasis and tissue adhesion since fibrin plays a central role in the physiological process of wound healing. Thus problems of foreign body reaction, delayed healing and fibrosis, which are associated with other haemostatic agents, might be avoided. The major advantages of fibrin-based glues over other tissue adhesives are tissue compatibility, biodegradability and the ability to adhere to wet surfaces. It may even promote healing since the first stage in normal wound healing is the production of a fibrin network into which fibroblasts and capillaries migrate. Evidence in support of this has been derived from several animal studies.

Concern has been expressed that viral transmission could occur as a result of fibrin sealant use. Theoretically virus remaining in the preparation could be adsorbed and retained by the patient and there are reports in the literature which implicate cryoprecipitated fibrinogen as a mechanism for the transmission of HIV-1 and hepatitis. Therefore the method of production has been designed to minimise the risk of viral transmission. The safety of fibrin sealant is further supported by this study in which no evidence of viral transmission could be found. The study of viral safety of this product is continuing, involving approximately 100 patients in detailed follow-up.

A further concern over the use of fibrin sealant on arterial suture lines is that it may promote intravascular thrombosis or embolism. No evidence to support such concerns was found in this study or has been reported elsewhere. There was only one embolic event and that was in a patient in the control group.

This study demonstrates that fibrin sealant is an effective and safe haemostatic agent for vascular suture lines involving PTFE.

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