TachoSil surgical patch versus conventional haemostatic fleece material for control of bleeding in cardiovascular surgery: a randomised controlled trial

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Methods: Patients scheduled for elective surgery on the heart, ascending aorta or aortic arch requiring cardiopulmonary bypass were eligible for this open-label multicentre trial. After primary haemostatic measures, patients were randomised to TachoSil or conventional haemostatic fleece if an area of persisting haemorrhage was identified (target area). After the application of trial treatment, haemostasis was evaluated at 3 min (primary endpoint). If haemostasis was not achieved, trial treatment was re-applied and haemostasis assessed at 6 min (secondary endpoint). Results: A total of 120 patients were randomised and 119 received trial treatment (TachoSil, n = 59; standard treatment, n = 60). Twenty-six percent of patients were female and the mean age was 67 years (range: 23—86 years). Baseline characteristics were similar in both groups. Bleeding occurred mainly from the aorta (56%), right ventricle (16%) or right atrium (13%), more often from a vessel (68%) than tissue (32%), and was assessed to be arterial in 74% of cases. TachoSil was significantly superior to standard haemostatic fleece for the control of bleeding in patients undergoing cardiovascular surgery.

Keywords: Cardiovascular surgical procedures; Haemostasis; TachoSil

1. Introduction

Prolonged bleeding is a serious complication of cardiovascular surgery and is associated with significant morbidity and mortality, increased duration and costs of surgery and prolonged postoperative hospital stay [1,2]. Haemostatic changes associated with extracorporeal circulation, heparinisation and high arterial pressures all predispose to bleeding and mean that cardiovascular surgery is a challenging environment in which to achieve haemostasis. Re-operation due to bleeding is performed in 2—6% of patients undergoing cardiac surgery and is generally associated with a worse prognosis [3,4].

Topical haemostatic agents are used for the control of bleeding during surgery when conventional surgical methods such as compression, ligation, clipping and electrocautery are impractical or inadequate. Liquid fibrin sealants, synthetic glues, oxidised cellulose fleece and cotton gauze are all widely used to help achieve haemostasis [5—8]. However, there have been very few controlled clinical studies
to assess the efficacy and safety of topical haemostatic agents in cardiovascular surgery.

TachoSil® (Nycomed, Linz, Austria) is a sterile, ready-to-use haemostatic agent and tissue sealant that consists of an equine collagen patch coated with human fibrinogen and human thrombin. TachoSil is a further development of TachoComb® that does not contain aprotinin or any other component of bovine origin. Unlike other prepare-to-use fibrin sealants, which require the coating of fibrin glue onto a fleece or patch immediately before or during surgery, TachoSil is a ready-to-use fixed combination that is activated by moisture on application, providing adherence to the resection surface. Haemostasis is generally achieved after 3—5 min of compression.

The efficacy and safety of TachoSil has previously been shown in studies in patients undergoing lung surgery [9,10], kidney resection [11] and liver resection [12]. However, there are no previous controlled trials of TachoSil in cardiovascular surgery. The current study was conducted to assess the efficacy and safety (for up to 30 days after surgery) of TachoSil compared with standard haemostatic fleece for the control of bleeding in patients undergoing cardiovascular surgical procedures.

2. Materials and methods

This was a randomised, parallel-group trial conducted at 10 centres in Europe (Denmark, France, Germany, Italy and Spain). The trial was open-label because the appearance of TachoSil makes blinding of treatments during surgery impossible. Relevant Ethics Committees approved the protocol and the trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and any applicable local regulations. All patients provided written informed consent. The trial is reported in accordance with the CONSORT Statement for reporting of randomised controlled trials [13].

Adult patients (aged ≥18 years) with planned elective surgery on the heart, ascending aorta or arch requiring a cardiopulmonary bypass procedure were eligible if bleeding from the heart muscle, pericardium, a major vessel (including the aorta) or a vascular bed was present after primary haemostatic treatment. The area of most prominent haemorrhage had to be identifiable, and it had to be possible to apply the trial treatment by compression for a minimum of 3 min. Patients were excluded if they had known coagulopathy or experienced microvascular bleeding (disseminated intravascular coagulation syndrome) during surgery. Other exclusion criteria included a history of allergic reactions after application of human fibrinogen, human thrombin or collagen of any origin, emergency surgery or treatment with any fibrin glue during surgery within 6 min after the trial treatment was applied.

After grouping, patients underwent surgery according to the routine of the centre. Primary haemostatic treatment could include compression, suturing, clipping, electrocoagulation or no treatment based on the surgeon’s discretion. Patients requiring further haemostatic treatment who met the intra-operative eligibility criteria were randomised to TachoSil or a standard haemostatic fleece material that did not contain additional active coagulation-stimulating compounds. Centralised randomisation was by an Interactive Voice Response System (IVRS) and was stratified by the centre. The bleeding target area was identified (aorta, left or right ventricle, left or right atrium, or other), and the site (vessels or heart tissue), type (arterial or venous) and severity of bleeding (mild oozing, moderate or severe) were assessed. In patients with more than one area of bleeding after primary haemostatic treatment, the most prominent haemorrhage was considered the target area. TachoSil was provided as 9.5 cm × 4.8 cm × 0.5 cm patches and was applied after the target area had been cleaned of surgical debris. Patches had to extend 1—2 cm beyond the wound margins. If more than one patch was needed, an overlap of 1—2 cm was required. TachoSil could be applied before or after protamine infusion.

The trial treatments were applied with pressure to the target area for 3 min. If haemostasis was achieved within this time, the time to haemostasis was recorded as 3 min. If haemostasis was not achieved, new trial treatment was reapplied for a further 3 min. If haemostasis was then achieved, time to haemostasis was recorded as 6 min. If haemostasis was not achieved after 6 min, rescue treatment could be applied. Rescue treatment could include any conventional surgical method, liquid fibrin sealant or other haemostatic material, except for TachoSil in patients randomised to standard treatment.

The primary efficacy endpoint was the proportion of patients achieving haemostasis after 3 min. The secondary efficacy endpoint was the proportion of patients achieving haemostasis after 6 min. The duration of surgery (incision to skin-to-skin closure), duration of extracorporeal circulation, time of protamine infusion, use of aprotinin or other inhibitors of fibrinolysis and the need for intra-operative transfusions were all recorded. Transfusion was based on routine practice at each centre rather than a standardised study transfusion protocol.

Postoperative assessments included duration of drainage (from the end of surgery to removal of drains), postoperative drainage volume, incidence of re-operation due to bleeding complications, postoperative transfusion (type and number of units) and other postoperative complications. Safety was assessed by adverse events (AEs) from screening to follow-up 30 days after surgery, vital signs and clinical laboratory measurements. Body temperature was measured in the ear in the evening of the day of surgery and in the morning and evening on days 1—5 after surgery. Any patients with a body temperature >38.5 °C were evaluated in order to identify the possible cause.

2.1. Statistical analysis

Based on the previous studies of haemostatic agents [6,7], it was estimated that 75% of patients treated with TachoSil and 45% of patients receiving standard treatment would achieve haemostasis after 3 min. To show a difference between the treatments at a power of 90% (two-sided continuity corrected chi-square test) with a significance level of 5%, 120 patients were required (60 per treatment group). The primary and secondary efficacy endpoints (proportion of patients with haemostasis at 3 and 6 min) were analysed using the Cochran—Mantel—Haenszel test controlling for the centre and by the
Breslow–Day test to assess homogeneity of odds ratios (i.e., treatment effect) across the centres. Wilcoxon rank-sum tests were performed for duration and volume of postoperative drainage. The primary analysis was performed on the intent-to-treat (ITT) population, which included all patients who were randomised and received trial treatment.

3. Results

3.1. Patients

A total of 326 patients were screened, 120 were randomised and 119 received trial treatment (ITT population: TachoSil, n = 59; standard treatment, n = 60) between March 2007 and September 2007. Two of the 10 participating centres screened but did not randomise any patients. Three patients randomised to standard treatment were mistakenly treated with TachoSil and were included in the TachoSil group for safety analyses (safety population: TachoSil, n = 62; standard treatment, n = 57). Five patients in the standard treatment group were treated with sutures (n = 4) or liquid fibrin glue (n = 1) for further haemostasis rather than haemostatic fleece but were included in the ITT analysis.

Of the 119 patients who received trial treatment, 31 (26%) were female, the mean age was 67 years (range: 23–86 years) and the mean body mass index was 27.1 kg m$^{-2}$ (range: 16.5–50.2 kg m$^{-2}$). The baseline characteristics were similar in the two groups (Table 1).

3.2. Surgical procedures

Surgical procedures were combined or complex (involving two or more cardiovascular procedures) in 44% of patients in the TachoSil group and 59% of patients in the standard treatment group (Table 2). The mean duration of surgery (incision to skin-to-skin closure) was 249 ± 77 min in the TachoSil group (range: 120–453 min) and 235 ± 59 min in the standard treatment group (range: 127–415 min), while the duration of extracorporeal circulation was 98 ± 35 min (range: 40–195 min) compared with 109 ± 46 min (range: 48–309 min). The aorta was the target area in a high proportion of patients (59% in the TachoSil group and 53% in the standard treatment group). Bleeding was mainly vascular rather than from tissue, arterial and mild to moderate in severity. There were no major differences between bleedings in the two treatment groups. However, more bleedings were arterial (81% vs 67%) and more were classified as severe (9% vs 3%) in the TachoSil group compared with the standard treatment group.

Suturing was the primary haemostatic treatment in both treatment groups (73% in the TachoSil group and 72% in the standard treatment group). The use of systemic aprotinin was less frequent in the TachoSil group than the standard treatment group (46% vs 58% of patients), while use of other fibrinolysis inhibitors (primarily tranexamic acid) was similar (31% vs 33%). The characteristics of bleeding and haemostatic variables are summarised in Table 3.

3.3. Trial treatments

In the TachoSil group, 53 patients were treated with a single patch, seven patients received two patches, one patient received three patches and another received four patches. In the standard treatment group, 52 patients were

### Table 1

Baseline characteristics (ITT population).

<table>
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<tr>
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<th>TachoSil (n = 59)</th>
<th>Standard treatment (n = 60)</th>
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<tbody>
<tr>
<td>Male/Female (n)</td>
<td>45/14</td>
<td>43/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 59</td>
<td>65 ± 12 (23–82)</td>
<td>68 ± 10 (36–86)</td>
</tr>
<tr>
<td>Age &gt;65 years (%)</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>26.8 ± 5.4 (18.3–50.2)</td>
<td>27.4 ± 4.4 (16.5–37.2)</td>
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<tr>
<th>Blood pressure (mmHg)</th>
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<tr>
<td>Systolic</td>
<td>128 ± 17 (100–170)</td>
<td>128 ± 22 (90–183)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74 ± 13 (40–102)</td>
<td>73 ± 11 (50–93)</td>
</tr>
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Data are mean ± standard deviation (range). Blood pressure is presented for the safety population.
treated with compression and haemostatic fleece. Four patients were treated with sutures and one with liquid fibrin glue (Tissucol® W, Baxter AG, Vienna, Austria) rather than the intended haemostatic fleece.

3.4. Haemostasis at 3 and 6 min

Haemostasis at 3 min was achieved by 75% of patients in the TachoSil group (95% confidence interval (CI): 0.64—0.86) compared with 33% of patients in the standard treatment group (95% CI: 0.21—0.45). This difference was statistically significant (p < 0.0001) (Fig. 1). The proportion of patients achieving haemostasis at 6 min was also significantly higher in the TachoSil group (p = 0.0006) with 95% of the TachoSil-treated patients (95% CI: 0.89—1.0) achieving haemostasis compared with 72% of the standard treatment patients (95% CI: 0.60—0.83). There was no evidence of a centre effect at either 3 or 6 min.

Three (5%) TachoSil patients compared with 17 (28%) standard treatment patients failed to achieve haemostasis at 6 min and received rescue treatment. In the three TachoSil patients, rescue treatment was fibrin glue, suture alone or suture plus TachoSil. In the standard treatment patients, rescue treatment was suture alone (n = 11), fibrin glue (n = 4), suture and oxidised cellulose (n = 1) or electrocoagulation (n = 1).

In a post-hoc subgroup analysis, significantly more patients in the TachoSil group than the standard treatment group achieved haemostasis at 3 min when the site of bleeding was either the vessels or heart tissue (Fig. 2a). TachoSil was also significantly more effective in patients who received trial treatment during or after protamine infusion, with more patients in the TachoSil group compared with standard treatment achieving haemostasis at 3 and 6 min (Fig. 2b).

3.5. Postoperative assessments

The mean duration of drainage was 93 ± 177 h (median: 46 h, range: 18—1093 h) in the TachoSil group and 67 ± 106 h (median: 44 h, range: 15—687 h) in the standard treatment group (p = 0.11). The mean total volume of postoperative drainage was 1005 ± 1128 ml (median: 600 ml, range: 75—5240 ml) in the TachoSil group and 932 ± 1320 ml (median: 498 ml, range: 100—9100 ml) in the standard treatment group (p = 0.24).

Re-operation was required in three patients (5%) in the TachoSil group and eight patients (13%) in the standard treatment group. The need for re-operation was not related to the trial treatment or target area in any patient. Twenty-six patients (42%) in the TachoSil group had 31 postoperative blood transfusions while 22 patients (39%) in the standard treatment group had 44 transfusions. Most transfusions consisted of packed red blood cell (RBC) transfusions (38 in the TachoSil group and 35 in the standard treatment group). Other postoperative complications were reported in 13 TachoSil-treated patients (22%) and 16 standard treatment patients (27%).

3.6. Safety

A total of 328 AEs were reported, 149 events in 46 (74%) TachoSil-treated patients and 179 events in 44 (77%)
standard-treated patients. The most frequently reported AEs were supraventricular arrhythmias (including atrial fibrillation, atrial flutter and supraventricular tachycardia; TachoSil, \( n = 20 \); standard treatment, \( n = 16 \)), pleural effusion (\( n = 14/14 \)), nausea (\( n = 8/5 \)), hyperglycaemia (\( n = 6/7 \)) and haemorrhagic anaemia (\( n = 5/6 \)), all of which are known complications of the surgical procedure and underlying disease. One AE in the TachoSil group (mild pyrexia) was considered possibly related to trial medication. There were no major differences in the occurrence of AEs between the trial treatments. Fifty-eight serious AEs were reported, 15 events in eight (13%) TachoSil patients and 43 events in 18 (32%) standard treatment patients. No serious AEs were considered to be related to trial treatment. Four deaths occurred, three as a result of sepsis with multi-organ failure (two TachoSil patients and one standard treatment patient) and one as a result of ventricular tachycardia, myocardial infarction and respiratory failure (standard treatment patient).

There were no differences between the groups in mean body temperature in the evening after surgery and from days 1 to 5. A body temperature \( >38.5^\circ C \) was reported in two TachoSil patients and three standard treatment patients. Pyrexia (including postoperative fever) was reported as an AE in four patients in each group. One case of mild pyrexia in the TachoSil group was considered possibly related to trial treatment by the investigator. There were no significant differences between the groups with regard to vital signs or clinical laboratory measurements.

4. Discussion

Patients undergoing cardiovascular surgery represent a challenging group with regard to achieving haemostasis during surgery. Heparinisation and extracorporeal circulation compromise the coagulation capacity of the blood, while high arterial pressures predispose to bleeding [3,14]. As such, the coagulation system of patients during cardiopulmonary bypass is significantly impaired.

TachoSil has previously been shown to be an effective and safe haemostatic and sealing agent in patients undergoing lung surgery [9,10], kidney resection [11] and liver resection [12]. However, this is the first controlled study of TachoSil in patients undergoing cardiovascular surgery.

In this study, TachoSil was significantly superior to conventional haemostatic fleece material in achieving effective and fast intra-operative local haemostasis. Three-quarters of patients achieved haemostasis after 3 min with TachoSil, compared with only a third of the patients treated with compression or standard haemostatic fleece (\( p < 0.0001 \)). This difference between treatments remained after 6 min (\( p = 0.0006 \)). Compared with TachoSil, almost 6 times as many patients treated with the standard haemostatic fleece failed to achieve haemostasis and required rescue treatment (28% vs 5%). The limited haemostatic efficacy of standard treatment observed in this study is clinically significant, given that standard haemostatic fleeces are widely regarded as effective and are routinely used in cardiovascular surgery.

The results of the present trial are comparable with the previous randomised studies assessing topical haemostatic agents in cardiovascular surgery [6—8,15—17]. In a randomised controlled trial of 93 patients undergoing cardiac surgery, significantly more patients achieved haemostasis after 3 min (72% vs 23%) and 10 min (94% vs 60%) with a gelatine-based haemostatic sealant (Floseal Matrix™) than with thrombin-soaked Gelfoam [6]. Similarly, 88—90% of patients undergoing cardiac operations who received fibrin sealant (TISSEEL® VH or TISSEEL VH S/D) as an adjunct to standard haemostatic techniques achieved haemostasis at 5 min [8]. In another randomised trial, a 93% success rate for fibrin sealant in controlling bleeding within 5 min was reported in patients undergoing either re-operative cardiac surgery or emergency re-sternotomy, compared with only 12% with conventional topical agents [16].

The adhesive strength of TachoSil has been shown to be approximately twice that of other prepare-to-use treatments (fibrin glue coated onto fleece) and significantly higher than fibrin glue alone [18—20]. Strong adhesion of the fibrin clot to
the application site combined with the mechanical support of the collagen patch and fibrin network result in a physically stable barrier capable of preventing bleeding. Fixation of the local haemostatic effect may help prevent haemorrhage caused by post-surgical hyperfibrinolytic activity of cut or severed cardiac parenchymal tissue.

Patients who were screened for this trial tended to be high-risk patients who were expected to bleed, such as those undergoing aortic surgery or re-operation. It is probable that the EuroSCOREs of patients tended to be high, although data to determine these were not routinely collected. Over half of the surgical procedures in randomised patients were combined or considered to be complex procedures necessitating prolonged extracorporeal circulation. These procedures were more frequent among patients who were randomised compared with screening failures (52% vs 39%). This suggests that patients randomised in this trial may represent a higher-risk group than a general cardiovascular surgery population. This is also suggested by the high occurrence of postoperative transfusions (approximately 40%).

Two-thirds of bleedings occurred from a vessel, with one-third from the surrounding tissue. In a post-hoc analysis of patients with vessel bleeding, significantly more patients in the TachoSil group achieved haemostasis at 3 and 6 min compared with those in the standard treatment group (69% vs 31%; \( p = 0.003 \), and 94% vs 67%; \( p = 0.004 \), respectively). Although suture support was not specifically assessed, this indicates that TachoSil is effective as a suture support in vascular surgery. Previous studies with TachoSil or TachoComb have also demonstrated efficacy for the control of suture hole bleeding in vascular reconstruction and aortic arch aneurysm repair [21–23]. Other haemostatic agents have also been shown to be effective in the prevention of suture hole bleeding [24].

Nearly three-quarters of bleedings were arterial with a slightly higher occurrence in the TachoSil group than the standard treatment group (81% vs 67%), and more than half of bleedings were from the aorta. Arterial bleedings are haemostatically demanding because of the high arterial blood pressure, especially in anti-coagulated patients. In this study, the ability of TachoSil to withstand high-pressure suture hole bleeding was shown by its effective application to the aorta and left ventricle. Venous bleedings are also a challenge because of the vulnerability of the venous tissue, which can be delicate and difficult to suture. TachoSil was shown to be effective when applied to venous vessels, the right atrium and right ventricle. The ability of TachoSil to achieve haemostasis after application to a variety of vascular structures suggests that it may also be useful in more peripheral vascular surgery.

TachoSil was also effective when given before protamine reversion of heparinisation, indicating haemostatic and sealing properties independent of blood coagulability. In a small subgroup of 19 patients (TachoSil, \( n = 10 \); standard treatment, \( n = 9 \)) who received trial treatment before protamine infusion, 70% of the TachoSil patients compared with 56% of the standard treatment patients had haemostasis at 3 min. Although the trial was not powered to detect a difference between treatments in this subgroup, and the difference was not statistically significant, these results suggest that TachoSil may be effective in a very challenging environment.

The centralised randomisation procedure helped minimise the risk of potential bias that can occur in a trial with an open-label design. However, use of the intra-operative IVRS procedure had the disadvantage of introducing a delay of 2—3 min before the application of trial treatment, during which time compression of the target area may have been required. During these 2—3 min of compression, the severity of the bleeding was to some extent reduced. This reduction in bleeding before the application of trial treatment may have potentially reduced the observed difference between the treatments.

Combined or complex procedures that would be expected to be associated with a higher risk of bleeding were more frequent in the standard group than the TachoSil group (59% vs 44%). Despite this, there was a tendency towards greater severity of bleeding in the target area in the TachoSil group, indicating that the difference in the proportion of combined or complex procedures did not affect the validity of the trial results. There was no significant centre effect on the primary efficacy endpoint. It is conceivable that this observation is due to uniform basic standard procedures used in cardiac surgery irrespective of centre.

TachoSil was safe and well tolerated, with AEs generally similar in the two treatment groups. Most AEs were related to the surgical procedure or the underlying disease. There was a slight tendency towards a higher occurrence of AEs in the standard treatment group, although this was most likely a random finding.

Raised body temperature has previously been reported to be more frequent with TachoSil than standard treatment [11]. However, no differences were observed between treatments in mean body temperature or in the number of patients with body temperature \( >38.5 \) °C. A single patient in the TachoSil group had pyrexia that was considered possibly related to treatment. However, this patient had postoperative inflammatory syndrome which may have accounted for the pyrexia. There was no evidence to suggest that pyrexia or postoperative fever increased with TachoSil treatment.

In conclusion, the results of the trial indicate that TachoSil is safe and significantly more effective than conventional standard haemostatic fleece material for the control of local bleeding during cardiovascular surgical procedures.

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