Comparison Between TachoComb and TachoSil for Surgical Hemostasis in Arterial Bleeding: An Animal Experimental Study

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Background: TachoComb has frequently been used for the treatment of both venous and arterial bleeding. However, anaphylactic reactions have been reported after repeated use of hemostatic agents containing aprotinin such as TachoComb. Because aprotinin is also associated with risk of renal failure, manufacturing of a new product—TachoSil—which lacks aprotinin seems a logic evolvement. Furthermore, thrombin on the TachoSil material has been changed from bovine in TachoComb to human origin. These changes in the biochemical composition could lead to changes in the hemostatic performance. Therefore, we aimed to disclose any difference in hemostatic efficacy of the two products.

Methods: Twelve 70-kg pigs had controlled insults to the thoracic aorta with and without heparin administration. The iatrogenic lesion was randomly covered with either TachoComb or TachoSil and the time to hemostasis was measured.

Results: Time to hemostasis when using TachoSil compared with TachoComb was increased 14% (–13% to 48%) with heparin and 10% (–26% to 66%) without heparin (mean ± 95% confidence interval; p > 0.05 in both). Time to hemostasis with heparin administration increased significantly in both treatments: TachoComb 80% (26%–156%) (p = 0.001) and TachoSil 75% (18%–158%) (p = 0.005).

Conclusion: We found neither statistical nor clinical evidence that TachoComb should have better hemostatic properties than does TachoSil in arterial bleeding. Both TachoSil and TachoComb can be used with heparin administration, but significant prolongation of the time to hemostasis is to be expected for both products. TachoSil should be preferred to TachoComb due to the potential lower risk of side effects when using the former.

Key Words: Hemostasis, Hemostatic agents, TachoSil, TachoComb.

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Bleeding is a common and significant issue in most surgical procedures, especially arterial bleeding with difficult access as in cases of a redo surgery or trauma. Therefore, a number of hemostatic drugs and devices have been developed to promote hemostasis.

The major types are fleece bound such as Surgicel, Surgicel-fleece, and TachoComb, and liquid such as CoSeal, FloSeal, and Tisseel. The various types of hemostatic aids have different performance profiles that make them suitable for different purposes. In general, the fleece-bound products are applicable in areas with difficult access as in the posterior aspect of anastomoses on the aorta and the pulmonary trunk. The liquid types are particularly useful in case of many suture lines and after general impediment of the coagulation system such as after the use of hypothermia. TachoComb has been developed for use on large bleeding surfaces such as after surgical or traumatic liver and kidney resection. In addition, the product has gained popularity for use on large areas of leaking lung tissue; TachoComb has even been used for bleeding from low pressure hollow organs, such as the atria and the right ventricle. Also, in case of diffuse bleeding, e.g., from myocardial surfaces after dissection of adherences during redo procedures, these products are of great use. TachoComb provides homeostasis by creating a fibrin clot, which adheres to the tissue when applied to a bleeding tissue surface. It releases the antifibrinolytic agent aprotinin along with the coagulation factors fibrinogen and thrombin to hamper fibrinolysis and initiate the final steps in the blood coagulation process, respectively. However, an increase in the number of reported cases of immunologic responses with anaphylaxis caused by the TachoComb contents (aprotinin and bovine thrombin) after repeated use along with a report stating that the use of aprotinin during cardiac surgery is associated with renal failure encouraged the manufacturer to develop a new version of the product—TachoSil with no aprotinin contents and thrombin being sourced from human instead of bovine origin, intuitively assuming that this would reduce the risk of anaphylactic reactions and meanwhile preserving the hemostatic properties.

However, an impact of the changed composition on the characteristics and activity of TachoComb/TachoSil cannot be excluded until it has been specifically investigated. Hemostatic agents are usually compared in a clinical trial and TachoSil and TachoComb have been tested in several studies in different organ systems proving the products’ hemostatic efficacy. However, there is paucity in the data about the efficacy in cardiac surgery of TachoSil by comparison with the predecessor, TachoComb. This study aimed to disclose any potential difference in hemostatic efficacy of the two products.

Hypothesis

The null hypothesis was that TachoComb has statistically significantly better hemostatic properties than TachoSil in the pig with and without administration of heparin.
MATERIALS AND METHODS

Study Design

The study was performed in an acute setting. A series of stab wounds were applied to the thoracic aorta and randomly covered with either TachoSil or TachoComb. All experiments were subdivided into two sessions where both hemostatic agents were investigated. Session 1 was conducted on the thoracic aorta without heparin administration and session 2 was also conducted on the thoracic aorta but with heparin administration (Fig. 1). Session 1 was repeated twice resulting in two identical subsessions (a and b). The incisions matching each session on the thoracic aorta are marked 1a, 1b, and 2 in Figure 1. In session 2, we administered 20,000 IU of heparin to inhibit the coagulation cascade in the pig. As assessment of the change in coagulation properties, blood activated coagulation time (ACT) was measured before and 3 minutes after heparin administration. Blood pressure was monitored and kept as stable as possible during the application of patches to reduce bias from this source.

Study Randomization and Blinding

The procedures were conducted in pairs. Before each pair of procedures, TachoSil and TachoComb were randomized by a third party in an A and a B patch blinded to all persons performing the procedures. The two products look exactly alike, so it was not possible to distinguish A from B during surgery. In addition, it was randomized by coin flipping, whether the first patch to be applied in the first procedure was to be product A or B. If the first procedure was randomized to start with application of product B, the subsequent procedure would start with application of product A.

Animal Preparation and Anesthesia

The study material consisted of 12 mixed Danish Landrace and Yorkshire female pigs with a body weight of ~70 kg. Before transport from the housing facility, each animal was preanesthetized with midazolam (0.5 mg/kg) and ketaminol (5 mg/kg). On arrival to the experimental facilities, preanesthesia was supplemented if required. An intravenous access was established by an ear vein. A second dose of midazolam (0.5 mg/kg) and ketaminol (5 mg/kg) was administered intravenously to allow endotracheal intubation and coupling to an anesthesia unit with ventilator (GE Datex-Ohmeda S/5 Avance). Anesthesia was maintained by 3% inhalational sevoﬂurane aiming at a constant mean alveolar concentration value just above 1.0 and analgesics was maintained by intravenous fentanyl infusion (8 μg/kg/h). Neuromuscular blockade was ensured with pancuronium 0.2 mg/kg at the start of surgery to facilitate the incisions using electrocautery. In case of any sign of inadequate pain relief like unexpected raise in heart rate and/or blood pressure, a bolus of fentanyl was administered immediately and the continuous infusion dose was raised.

Ethical Considerations

All animal experiments were conducted after approval from the Danish Inspectorate of Animal Experimentation. Likewise, the investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Each animal was killed at the day of investigation by an overdose of pentobarbital during continued anesthesia.

Pilot Procedures

We conducted a series of six pilot procedures to find the most optimal way of creating reproducible uniform lesions to the aorta. For that purpose, we invented a tool consisting of a steel tube with an adjustable scalpel inside (Fig. 2, A). The tube acted as a stop when the blade was applied to the aorta, hereby controlling the size of the lesion. The blade was adjusted with 0.3-mm variation within the reading accuracy of a ruler. We found that a lesion size of 3 mm was sufficient to create a bleeding that could not stop without intervention; a pig was exsanguinated during anesthesia with lethal outcome after one lesion. Furthermore, the bleeding could not be stopped by digital compression alone with no other hemostatic aid. This was tested in another pig using the same compression times as in the final study as described later.

In addition, we investigated the optimal time frame of initial compression when applying the hemostatic patches.
We concluded that the optimal time without heparin administration was 1 minute. If initial compression for a longer period was used, complete hemostasis could occur after one compression only, making it impossible to distinguish between products. With heparin administration, we discovered that we, despite the risk of a type 2 error, had to prolong the initial period of compression to 2 minutes to let thrombus formation take place. If we used 1 minute, the initial thrombus buildup was washed off and continuous homeostasis was hampered. In that way, there would most likely not have been a chance to find any difference between the products when using them with heparin administration.

Surgical Procedure

The right carotid artery was surgically exposed to allow insertion of a 7-F sheath that enabled blood pressure measurement and sampling of blood for ACT analysis. During the procedure, systolic blood pressure was maintained between 95 and 105 mm Hg to reduce bias in bleeding amount because of alterations in blood pressure. Lowering of blood pressure was counteracted by administration of saline or volume expanders (Voluven or Rheomacrodex). A rise of the blood pressure above the limits was dealt with by increasing the pressure above the limits was dealt with by increasing the

After each iatrogenic lesion, randomization to covering with either TachoSil or TachoComb was performed as depicted in Figure 1. Compression was applied with another custom-made instrument (Fig. 2, C). In the nonheparinized animals, the compression was initially maintained for 1 minute to allow the patch to moisten and stick to the tissue. Subsequently, the compression was removed to check for hemostasis. If hemostasis was not present, the pressure was reapplied in subsequent periods of 30 seconds until hemostasis was observed. In the heparinized animals, the initial pressure was maintained for 2 minutes.

With each intervention, the time from application of the patch to hemostasis was measured as primary endpoint. The aorta with six applied patches is shown in Figure 2, B.

Statistical Considerations

The data were analyzed on the log scale, i.e., modeling multiplicative effects, with a random level for each pig and systematic effects of heparin, hemostatic agent, and sequence within session. The ACT data were compared using Wilcoxon’s signed rank test.

RESULTS

From the original study material of 12 animals (TS 1–12), the final data set consists of 12 measurements without and 10 measurements with heparin infusion because in two animals heparin measurements were not conducted because of equipment malfunction. The ACT measurements before heparin administration ranged from 51 seconds to 354 seconds (median, 101.5) and after administration of 20,000 IU of heparin, the ACT ranged from 212 seconds to 1,500 seconds (median, 440). The time measurements in minutes from application of patches to hemostasis in all sessions are shown in Figure 3. The median times for each session are outlined in Table 1.

Statistical Analysis

To ensure significant impairment of the coagulation system, the ACT measurements before and after heparin administration were compared using Wilcoxon’s signed rank test (p = 0.0005).

First, the influence of the hemostatic material was investigated both with and without heparin administration. The increase when using TachoSil instead of TachoComb was 14% (−13% to 49%) with heparin and 11% (−26% to 67%) without heparin (±95% confidence interval) (p > 0.05 in both).

Second, the influence of heparin on time to hemostasis was investigated. Time to hemostasis with heparin administration was significantly increased in both hemostatic products. Eighty percent (26%–156%) increased when using TachoComb (p = 0.001) and 75% (18%–158%) increased when using TachoSil (p = 0.005).

DISCUSSION

To our knowledge, this is the first study to directly compare the hemostatic efficacy of TachoComb and TachoSil in arterial bleeding from the aorta in a clinically realistic animal model.
In this study, we found no difference between TachoSil and TachoComb for primary hemostasis in an animal experimental model. In addition, we found that there was a statistically significant longer time to hemostasis during heparin treatment with both products.

No clinical or experimental studies have previously been conducted to disclose the specific effect of heparin administration on the efficacy of TachoSil and TachoComb. We confirmed an intuitively anticipated prolongation of the time to hemostasis despite the potential type 2 error introduced in the different length of the initial period of compression. Furthermore, the hemostatic properties of the two products did not seem to change because of administration of heparin. This, however, cannot be confirmed using our study design. The recommendation of the manufacturer regarding initial compression is 3 minutes to 5 minutes. This should be sufficient for the patch to adhere to the tissue in all physiologic pressure and coagulation environments.

Study Limitations

Even though it has been extensively investigated that humans and pig are similar in terms of anatomy and physiology, we know that minor differences in coagulation properties exist among mammals and that they theoretically might influence our results to some extent. However, from a practical point of view, it seems justifiable to anticipate that these findings can be translated to the human clinical scenario.

When we controlled for hemostasis by removing compression, we also introduced a confounder. When removing compression, there was an inherent risk of also removing the newly formed blood clot. Hereby, we significantly prolonged the time to hemostasis and thus making the parameter “time to hemostasis” incomparable to hemostasis times in real surgery. Nevertheless, the hemostasis time is prolonged evenly in all measurements and therefore the comparability between groups is preserved.

Our measurements have only been performed with a blood pressure ranging from 95 mm Hg to 105 mm Hg. We do not know whether a difference between products had appeared if we had measured in lower or higher blood pressures.

Other comparative studies have used a punch hole in the abdominal aorta as a standardized injury, but our pilot studies taught us that a 3-mm incision made with a scalpel blade had the optimal characteristics for this study, i.e., a traumatic injury that was within a realistic range to be repaired using TachoSil and TachoComb. The incision had to be large enough to induce bleeding that would not be able to stop without intervention or just by compression alone. Conversely, it had to be small enough to allow hemostasis without suturing. This setup was optimal for our measurements, but it is worth noting that if this type of injuries would occur in real surgery they would most likely not be repaired with TachoSil or TachoComb alone. Instead, primary suturing would have been chosen supported by a hemostatic patch if needed. Therefore, our study was conducted in a setting that mimic worst case scenario and it is therefore relevant for surgery in trauma cases.

TABLE 1. The Median Times to Hemostasis in Each Session Using TachoComb and TachoSil

<table>
<thead>
<tr>
<th>Median Time to Hemostasis (min)</th>
<th>Session 1a</th>
<th>Session 1b</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TachoComb</td>
<td>4.5</td>
<td>5.25</td>
<td>8</td>
</tr>
<tr>
<td>TachoSil</td>
<td>5</td>
<td>5.5</td>
<td>7</td>
</tr>
</tbody>
</table>

CONCLUSION

We found neither statistical nor clinical evidence that TachoComb should have better hemostatic properties than TachoSil in treating arterial bleeding. Both TachoSil and TachoComb can be used with heparin administration, but significant prolongation of the time to hemostasis is to be expected. TachoSil should therefore be preferred to TachoComb due to the potentially lower risk of adverse effects.

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REFERENCES