

# The Use of a Surgical Patch Coated With Human Coagulation Factors in Surgical Routine: A Multicenter Postauthorization Surveillance

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**Summary.** Local hemostyptic agents are of great value to significantly reduce bleeding complications and various devices have become available for clinical use. The aim of this multicenter postauthorization surveillance was to study the surgeons' expectations regarding efficacy and safety of the surgical patch coated with human coagulation factors (TachoSil) under routine clinical conditions. A total of 408 patients had been included in this trial and the patients had to have an expected increased bleeding risk either due to patient related hemorrhagic risk factors or operations associated with an expected increase of bleeding complications. The main types of surgical interventions were operations on the liver (26%), vascular system (16%), gastrointestinal tract (10%), heart (8%), kidney (7%), thorax (7%), spleen (4%), and pancreas (4%). Other operations (18%) were reported in the fields of neurosurgery, urology, gynecology, dermatology, and on the thyroid gland. Based on subjective assessments the results have shown that TachoSil has met the

surgeons' expectations to be efficacious and safe as a hemostatic treatment in a broad variety of surgical interventions. The observed benefits far exceed the frequencies of complications and many of the observed benefits easily translate into cost savings. In almost 50% of the cases the surgeons thought that the use of the topical hemostat TachoSil may have led to savings in blood component therapy. The savings of intra- and postoperative transfusions may lead to less frequent transfusion-related adverse effects and the lower probability of postoperative complications is of clinical importance. In particular, it is worth mentioning that based on the surgeons' assessment, the use of TachoSil may have helped to save the organ in 17% of the cases. Thus, these clinically relevant benefits may offer opportunities for improvements of hemostasis in patients at risk for bleeding complications and may facilitate the management of excessive bleeding.

**Keywords:** Surgical patch—Local hemostasis—Postoperative bleeding.

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Adequate hemostasis is a prerequisite for success of any surgical procedure, but particularly so in the case of visceral organ surgery where apparently insignificant ooze can result in significant hemorrhage. Control of intraoperative hemorrhage is primarily achieved using the traditional techniques such as compression, suture ligation or clamps and electrocautery. In many cases, however, severe

bleeding cannot be avoided despite meticulous use of these techniques. In particular, in the case of traumatized spleen or kidney or underlying coagulopathies, adequate hemostasis frequently cannot be achieved. Furthermore, there is a broad variety of congenital or acquired hemostatic dysfunctions that may cause severe bleeding complications. The most common of these are summarized in Tables 1 and 2.

Local hemostyptic agents have proven to significantly reduce bleeding complications and various devices have become available for clinical use. Some devices are simulating in vivo hemostasis by sealing the wound with physiologic components such as clotting factors and collagen. Collagen sponges or fleeces and various glues have been developed, one of which is TachoSil, a follow-up product of TachoComb H.<sup>1</sup> This ready-to-use patch consists of an absorbable collagen sponge coated on one side with human fibrinogen and thrombin,

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**TABLE 1.** The Most Common Congenital Hemostatic Defects

Vascular Dysfunctions	Platelet Disorders	Coagulopathies
Morbus Osler	Megacaryocyte production ↓ Platelet turnover ↑ Werlhof's disease Bernard Soulier syndrome Thrombasthenia Wiskott Aldrich syndrome	Hemophilia A and B F XIII deficiency Deficiencies of other coagulation factors Von Willebrand's disease

**TABLE 2.** The Most Common Acquired Hemostatic Defects

Vascular Dysfunctions	Platelet Disorders	Coagulopathies and Fibrinolytic Disorders
Drug-induced petechia	Drug-induced thrombocytopenia or platelet dysfunction	Anticoagulant therapy
Petechia associated with infectious diseases	Thrombocytopenia or platelet dysfunction due to concomitant diseases	Thrombolytic therapy  Massive transfusions Disseminated intravascular coagulation Liver diseases

thus enabling a sealing and hemostatic wound dressing. To gain experience when and how TachoSil is used by surgeons in a broad variety of indications, a postauthorization surveillance was performed and additional data were collected regarding the operating surgeon's judgment on the practicability, efficacy, and safety of TachoSil.

## METHODS

### Study Design

This postauthorization surveillance was designed as a prospective, one-armed multicenter cohort trial with strict noninterventional character, the latter meaning that, obeying the contraindications as stated in the product specifications, the decision to use or not to use TachoSil in a specific case was exclusively driven by the surgeon's individual judgment and on his responsibility. To avoid product handling problems, the participation in the trial was restricted to surgical departments in hospitals on the condition that they had already used TachoSil or a precursor product. Surgeons were urged that only those operations should be included in which, either because of patient related risk factors for bleeding or according to the type of surgery, a significant risk of bleeding was expected. Patients with known hypersensitivity against any of the components of TachoSil were excluded.

### Recruitment

Surgeons in Germany and Switzerland had been invited to participate in this surveillance and the period of patient recruitment was between November 2004 and December 2005. According to national regulations, the study was announced to the competent federal authorities and organizations, who also received a list of the surgeons participating in this surveillance.

### Statistical Analysis

Statistics for categorical data were based on absolute and relative frequencies and their analysis using Chi-square test and Mann-Whitney U-test. For continuous values the mean, standard deviation, maximum, minimum as well as 25% and 75% quartiles were calculated. If the surgeon did note multiple locations where TachoSil was placed, the evaluation considered only the obviously most significant one. Comments of the surgeons were summarized to convey their key messages only.

## RESULTS

Until the end of 2005, 408 completed case record forms had been returned. Five cases had to be excluded because the type of operation did not comply with the requested high risk of blood loss. Thus, 403 cases were left for analysis and evaluation.

A total of 116 centers in Germany and Switzerland submitted completed case record forms, the majority of them reporting on 3 cases. All participating surgeons had already worked with TachoSil or TachoComb H, about 50% of them had experience with TachoSil or TachoComb H in at least 50 operations and only about 6% did try TachoSil for the first time.

### Type of Surgery

The main types of surgical interventions were operations on the liver (26%), vascular system (16%), gastrointestinal tract (10%), heart (8%), kidney (7%), thorax (7%), spleen (4%), and pancreas (4%). Other operations (18%) were reported in the fields of neurosurgery, urology, gynecology, dermatology, and on the thyroid gland.

Of the 403 operations, the majority (n = 360) were performed as open procedures, 41 minimal invasive, and in 2 cases a planned combination of open and minimal invasive approach was chosen. Minimal invasive surgery was predominantly preferred in gynecologic and abdominal surgery, but 13 of the total 41 minimal invasive operations had to be continued as open procedures due to intraoperative problems. All cardiac interventions were performed under extracorporeal circulation. The mean duration of all operations was slightly shorter than 3 hours, the durations ranging from 20 minutes to almost 10 hours.

### Data on Patients

Fifty-eight percent of the operated patients were men and 42% women, with a broad range of age from 3 years to 97 years. According to the inclusion criteria of this surveillance, the operations had to be associated with a higher risk for bleeding or the patient's individual bleeding risk had to be increased. The risk factors for bleeding and the percentages of patients who had one or more of these are summarized in Table 3. These risk factors were patient related and/or due to the type and circumstances of the operation. Thus, several patients had a combination of these risks.

### Preoperative Measures

- To preoperatively normalize the coagulation parameters, 5% of the 403 patients received platelet concentrates, 11% fresh-frozen plasma, 3% coagulation factors, and 6% were antagonized with protamine sulfate. For compensation of an expected intra- or postoperative massive blood loss, about one sixth of the patients received 1 or more infusions of packed cells (52 patients) or blood substitutes (22 patients) preoperatively.

**TABLE 3.** Frequency of Risk Factors for Bleeding

Risk Factor	n = 403
Hereditary coagulation disorder	2%
Disseminated intravascular coagulation	11%
Platelet dysfunction	14%
Hepatic disorders	15%
Malignancy	47%
Medication affecting coagulation	67%
Other reasons*	25%

\*Including, among others, severe hypertension, sepsis, kidney failure, chemotherapy.

- The mean hemoglobin or hematocrit values of the patients with infusions were initially 8.9 g/dL or 27.8%, respectively, whereas the average of these parameters in the patients not getting an infusion was 12.7 g/dL or 38.7%, respectively.

### Intraoperative Procedures

- In 81% of the cases, the surgeons used one or more traditional surgical hemostatic measures before the application of TachoSil. Suture and ligation was used in 51%, electrocautery in 45%, and compression or tamponade in 18%.
- The following expectations of the surgeons regarding the benefit of TachoSil were recorded. In 79% of the cases, immediate hemostasis had been expected by the use of TachoSil, followed by 39% who expected to stop bleeding from leakages, 27% who expected to avoid suture line bleeding, and in 14% it had been expected to prevent fistulization.
- The number of TachoSil patches needed per operation ranged from 1 to 7. Despite the fact that 3 different sizes of TachoSil (9.5 × 4.8 cm, 4.8 × 4.8 cm, and 3.0 × 2.5 cm) were at the surgeons' disposal, in about one third of the operations, the patches had to be cut into appropriate size and shape.
- Thirty-four percent of the patients required intraoperative transfusions. One hundred and twelve patients were treated with 1 or more packed cell infusions and 57 patients received blood substitutes.
- Drains were placed in 92% of the patients. About one fourth of the surgeons were of the opinion that they could positively change their drainage management by using TachoSil. Their main argument was that because of the reduced bleeding and blood loss, in several cases drains could be avoided at all or at least removed earlier.

### Postoperative Course

- Ninety-four percent of the patients received thromboprophylaxis, mostly with low-molecular-weight heparins, in 1 case with desirudin, and in several cases with oral anticoagulants or

**TABLE 4.** Incidences of Postoperative Complications and Treatments

Complication/Treatment	n = 403
Recurrent bleeding	4%
Unplanned drainage	2%
Additional packed cells	5%
Thrombosis	0.25%
Fistulization	2%
Unplanned re-operation	11%
Others	9%

antithrombotic therapy with aspirin and other platelet aggregation inhibitors.

- About three fourths of the patients were referred to an intensive care unit, being treated there for a mean duration of 3.7 days.

Any postoperative complication and unplanned additional treatment was carefully noted. Table 4 shows a categorized summary of the incidences.

Some patients required more than 1 intervention, for instance seven patients with severe postoperative bleeding received packed cells and had to be re-operated. About half of the unplanned re-operations were necessary in patients showing none of the complications listed in Table 4. Six patients underwent planned re-operations. Postoperative complications summarized as "Others" in the table include, among others, pneumonia, respiratory insufficiency, cardiac problems, wound infections, hematoma, and protracted wound healing.

The subjective assessments of benefit from using TachoSil by the surgeons are listed in Table 5. Multiple answers were possible.

### Overall Assessment

The overall assessment of TachoSil, related to the categories practicability, satisfaction with result and usefulness, was performed by subjective ranking and using a scale from 1 (rated best) to 10 (rated worst). Table 6 contains the summary of the answers, showing how many surgeons assigned the various ranks to these 3 categories.

Three surgeons provided further information on why they were not content with the use of TachoSil. In 1 case recurrent bleeding occurred, in another patient pancreas fistulization could not be prevented despite the use on TachoSil and one surgeon did not see an advantage of TachoSil over fibrin glue.

## DISCUSSION

This postauthorization surveillance has shown that the surgical patch coated with human coagulation

**TABLE 5.** Subjective Assessments of Benefit From Using TachoSil in the Operations Performed

Benefit	n = 403
Shorter duration of operation	83%
Lower probability of postoperative complications	81%
Less tissue damage	69%
Drain shorter in place	30%
Saving transfusions of packed cells	29%
Shorter duration of hospitalization	28%
Organ saving procedure	17%
Saving transfusion of fresh-frozen plasma	14%
Shorter duration of intensive care treatment	14%
Saving transfusions of platelet concentrates	6%

factors, TachoSil has met the surgeons' expectations to be efficacious and safe as a hemostatic treatment in a broad variety of surgical interventions. The observed benefits far exceed the frequencies of complications and many of the observed benefits easily translate into cost saving. In almost 50% of the cases the surgeons felt that the use of the topical haemostat TachoSil may have led to savings in blood component therapy (packed blood cells, fresh frozen plasma, or platelet concentrates) as summarized in Table 5. Furthermore, shorter durations of hospitalization and intensive care treatment are inevitably associated with cost saving. Thus, the use of local hemostyptic agents will play a significant socio-economic role in the future. The aspect of cost saving has also been addressed by Frilling and colleagues,<sup>2</sup> who compared the effectiveness of the surgical patch coated with human coagulation factors TachoSil with an argon beamer in patients undergoing liver resection. The authors summarized that TachoSil was well tolerated and safe as a hemostatic treatment in liver resection and that its effectiveness in the control of bleeding proved to be superior to the standard of care with argon beamer. Therefore, this method may lower the number of complications associated with liver surgery and, consequently, provide high cost effectiveness.<sup>2</sup>

Beside cost savings, there is also a clinical need for adjunctive use of local hemostyptic agents in combination with conventional techniques of hemostasis. The savings of intra- and postoperative transfusions may lead to less frequent transfusion related adverse effects and the lower probability of postoperative complications is of clinical importance. In particular, it is worth mentioning that based on the surgeons' assessment, the use of TachoSil may have helped to save the organ in 17% of the cases. Thus, these clinically

**TABLE 6.** Overall Assessment of TachoSil in the Performed Operations

Parameters Assessed	Rank 1-2	Rank 3-4	Rank 5-6	Rank 7-8	Rank 9-10
Practicability	249	139	8	5	2
Satisfaction with the surgical result	309	74	10	6	4
Usefulness	277	109	8	7	2

relevant benefits may offer opportunities for improvements of hemostasis in patients at risk for bleeding complications and may facilitate the management of excessive bleeding. This has also been confirmed for the use of TachoComb by Czerny and colleagues, who had been able to reduce the cumulative chest drain volume and the duration of chest tubes in patients undergoing complete mediastinal lymph node dissection for stage I and II non-small-cell lung carcinoma.<sup>3</sup> Improvement of hemostasis by topical hemostats also plays a significant role in thoracic surgery,<sup>4</sup> cardiac surgery,<sup>5</sup> vascular surgery,<sup>6</sup> surgical interventions in visceral organs and trauma surgery,<sup>7,8</sup> neurosurgery,<sup>9</sup> and for many types of intraoperatively occurring bleeding emergencies. However, it also relates to any patient at risk for bleeding complications such as patients suffering from congenital or acquired hemostatic disorders. Because elective procedures are increasingly performed in these patients at risk, a safe and efficacious local hemostatic agent is of great clinical importance and will be increasingly used.

Different methods of topical hemostats have become available and these can be grouped into synthetic and biologic agents. Within the biological compounds the following groups can be distinguished: liquid fibrin glue, prepare-to-use fleeces, and ready-to-use fleeces.

TachoSil is a third-generation ready-to-use device consisting of an equine collagen fleece patch carrying the tissue glue components human fibrinogen and human thrombin. It does not contain bovine material and therefore it does not carry the risk of immunologic responses. The issue of antihuman factor V antibodies after use of bovine thrombin has been addressed by Lawson and colleagues.<sup>10</sup> The authors describe a case in which exposure to a relatively pure bovine thrombin preparation resulted in the development of an antihuman factor V antibody-associated coagulopathy. This report calls into question the safety of even relatively pure bovine thrombin.<sup>10</sup> The equine collagen fleece which is one of the components of TachoSil, had been tested regarding immunogenicity by Adelman-Grill and colleagues<sup>11</sup> as early as in 1987 and the authors

have shown that this material is very unlikely to induce immune reactions upon clinical application to humans. Meanwhile, this collagen fleece has been clinically applied for almost 20 years. The other components of TachoSil, human fibrinogen and human thrombin, have been purified from human plasma. To minimize the risk of viral transmission from these components, plasma donations undergo a series of procedures that contribute to avoiding, inactivating, and eliminating potential contaminants. The procedures for selection and screening of plasma donors, and the testing of donated plasma, incorporates highly sensitive molecular techniques (e.g., polymerase chain reaction testing) and the manufacturing process for these components comprises a range of procedures, including heat treatment (e.g., pasteurization, dry or vapor heating), filtration, solvent/detergent treatment, precipitation, pH treatment, and chromatography. In 20 years of worldwide use, there have been no known cases of hepatitis or HIV transmission associated with the use of commercial fibrin sealants.<sup>12</sup> To increase the safety of these components, all plasma donations used for their production are put into quarantine for 60 days.

TachoSil may be applied directly to the bleeding surface, without the need for preparation or reconstitution. The benefits of such a device as a hemostasis adjunct has been fully confirmed by the postauthorization surveillance presented in this article. This trial included as many as 403 evaluable cases and covered a broad variety of surgical indications. Therefore, the results can be translated into many patient populations who are at risk for bleeding complications where optimizing hemostasis has become a challenge.

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