Evaluation of the efficacy of a haemostatic matrix for control of intraoperative and postoperative bleeding in major lung surgery: a prospective randomized study

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Abstract

OBJECTIVES: This prospective randomized study was designed to assess the safety and efficacy of a haemostatic matrix in intraoperative bleeding control and prevention of postoperative bleeding after major lung surgery.

METHODS: One hundred and twenty patients undergoing major lung resection and presenting with intraoperative persistent active bleeding have been prospectively enrolled and randomly assigned to receive [Floseal® group (FG)] or not (control group) the application of Floseal® to the bleeding site and to the site of the hilar dissection. To evaluate the efficacy of the product, several intraoperative and postoperative data were compared between the two groups.

RESULTS: No adverse event related to the haemostatic matrix application occurred. The intraoperative haemostasis rate at 3 (primary end-point), 6 and 10 min was significantly higher and the mean time to haemostasis was significantly shorter in the FG. The quantity of chest drain fluids did not show significant differences at 24, 48 and 72 h between the two groups. Postoperative haemoglobin-level variation was significantly lower in patients of the FG (−0.7 ± 0.66 vs −2.3 ± 5.87 g/dl; P = 0.04). Similarly, haematocrit variation was lower in the haemostatic group (−2.6 ± 2.19 vs −4.2 ± 3.71; P = 0.006). The chest drain duration resulted significantly shorter in the FG (10.3 ± 5.05 vs 13.3 ± 6.28 days; P = 0.005). In-hospital stay was shorter in the FG (6.4 ± 2.9 vs 8.1 ± 5.42 days; P = 0.044).

CONCLUSIONS: In conclusion, the application of Floseal® in major lung resections proved safe and effective in increasing the intraoperative successful haemostasis rate and in reducing postoperative variation in haemoglobin and haematocrit levels. The sealant use was also related with a significantly shorter chest drain duration and hospitalization.

Keywords: Major lung surgery • Complications • Lobectomy

INTRODUCTION

Adequate haemostasis is fundamental for the final success of every surgical procedure. In oncological thoracic surgery, this represents a crucial issue due to the need to perform extended lymphadenectomy [1] and because dissection has to be conducted close to high-flow vessels potentially infiltrated by the tumour [2]. Sometimes, the presence of scar tissue and adhesions related to previous chemotherapy or pleuro-pulmonary infection may represent an additional risk factor for bleeding [3].

Intraoperative and postoperative bleeding may be responsible for increased operative time, blood product transfusions, reoperation, prolonged intensive care unit stay and, potentially, mortality.

Meticulous surgical technique represents the primary approach for bleeding control [4, 5]. Moreover, the use of topical haemostatic agents may increase the haemostasis efficacy potentially leading to a better perioperative outcome. Several products have been tested over the last two decades and some of them have been proved to significantly improve intraoperative bleeding control and to reduce blood loss and related surgical complications [6].

Among these, Floseal® (Baxter Healthcare Corporation, Freemont, CA, USA) has been reported as one of the most effective haemostatic sealants developed in recent years. It has been designed for use in
actively bleeding fields and is indicated in surgical procedures as an adjunct to standard technique when control of bleeding by ligature, suture or other conventional procedures is ineffective or impractical.

Floseal consists of a bovine-derived gelatin matrix component and a human-derived thrombin component. Following its first use in a clinical trial reported in 2000 in the USA, the spectrum of its application has been enlarged in different surgical disciplines [7-13]. However, so far, the efficacy of this haemostatic agent has never been assessed in thoracic surgery by a prospective clinical evaluation.

For this reason, the purpose of the present study was to evaluate the efficacy of the Floseal matrix for intraoperative bleeding control and prevention of postoperative bleeding in patients undergoing major lung resection within the setting of a prospective randomized controlled trial.

MATERIALS AND METHODS

The trial was conducted between March 2010 and December 2011 at the Department of Thoracic Surgery of the ‘Sant’ Andrea Hospital in Rome. This prospective, randomized, single-institution study was intended to evaluate the efficacy of Floseal in association with standard care versus Standard Care (SC) alone in controlling intraoperative and postoperative bleeding in patients undergoing major lung resection (lobectomy, pneumonectomy, sleeve lobectomy—artery or bronchus). Exclusion criteria included age <18 years old, cancer recurrence, pleural adhesions, oral anticoagulant therapy, platelet aggregation disorders, known coagulopathy, severe obesity (BMI >30), other malignant disease, concomitant abdominal surgery, liver disease, immune system disorders or hypersensitivity to any component of the investigational product. Patients concurrently participating in other clinical trials and/or having received another investigational drug or device within the last 30 days were also excluded.

The trial conformed to the ethical principles of the Declaration of Helsinki and was in accordance with the guidelines for good clinical practice. The study was also approved by the local ethical committee. Written informed consent was obtained from each patient before the operation.

Lung resections were performed through a lateral muscle-sparing thoracotomy. Division of incomplete fissures was performed by stapling devices [Gastrointestinal anastomosis (GIA) 75 or 80 mm]. Vascular sutures were generally performed by ligature for vessels with calibre <10 mm and by vascular staplers (Endo-GIA 45 mm) for vessels with calibre >10 mm.

In some patients presenting with good postoperative general and respiratory status, discharge was done with a chest tube connected to the Heimlich valve if one or more of the following conditions were present: incomplete lung re-expansion, mild par enchymal air leaks, chest fluid drainage >250 cc/24 h, persistent haematic drainage without anaemization.

Patients with moderate-to-severe air leaks and patients with persistent haematic drainage and concurrent anaemization were not considered for discharge.

Trial design

Patients undergoing major lung resection (lobectomy, pneumonectomy, sleeve lobectomy) during the study period were considered eligible for the trial if a persistent intraoperative active bleeding occurred and no exclusion criteria were present. Persistent active bleeding was considered to be each case of pulsatile or continuous bleeding that was still present after primary haemostatic treatment with simple compression or electrocoagulation for 2 min.

Patients enrolled in the study were randomly assigned to receive (Floseal group) or not to receive (SC group) the haemostatic product as an adjunct to the standard surgical procedures.

In the SC group, haemostasis was performed by direct pressure, sutures and/or electrocoagulation, applied through two different systems: monopolar and bipolar.

After informed consent, patient enrolment into the trial took place in the operation theatre once it was established that persistent active bleeding occurred during the operation. The randomization sequence was computer generated and enclosed in a series of sealed envelopes provided to the investigators. Treatment allocation was ascertained for each eligible patient by opening the next available sealed randomization envelope of this series.

Patients of the Floseal group received application of the haemostatic matrix according to the following modalities:

- to the bleeding site at the occurrence of intraoperative active haemorrhage, in addition to standard techniques used for haemostasis. In these cases, the Floseal sealant was applied independently of the success or failure of the haemostasis performed by conventional techniques. In case of haemostasis failure, the haemostatic agent was reapplied. The number of haemostatic applications was recorded.
- to the site of hilar dissection at the end of major lung resection.

Study outcome measures included the following:

- During the surgical procedures: rate of successful intraoperative haemostasis in a range from 3 to 10 min (at 3, 6 and 10 min) and time to reach haemostasis. A successful haemostasis rate at 3 min was the primary end-point.

- After the surgical procedures: evaluation of fluid drainage for the first 72 h (at 24, 48, 72 h), rate of transfusion of blood products, number of transfusions, postoperative haemoglobin (Hb)-level variation, postoperative haematocrit variation, rate of surgical revision for bleeding, rate of patients requiring Intensive Care Unit stay, chest drain duration, length of hospital stay.

- Incidence and types of adverse events were also recorded.

- Time to haemostasis was defined as the time required to obtain successful haemostasis in a single bleeding site. This time was recorded by the operative room nurses according to the surgeon’s observation.

- Success or failure of haemostasis was observed by the operative surgeon and recorded by the operative room nurses. Success of haemostasis was defined as haemostasis occurring within 10 min of product application. Postoperative management of patients and outcome measures data registration were performed by surgeons and nurses who were aware of the intraoperative treatment modalities. Patients were not informed about the treatment option received.

- Mechanical thromboprophylaxis with graduated compression stockings was used in patients of both groups with specific risk factors for venous thromboembolism. No postoperative pharmacological prophylaxis was administered to patients of this study because of the intraoperative and, in some cases, postoperative bleeding and the early patient mobilization.

Trial product(s)

Floseal® is a highly viscous topical gel that consists of a bovine-derived gelatin matrix component and a human-derived thrombin...
component. It has been designed to work on wet, actively bleeding tissue and conforms to irregular wound surfaces. Both components work independently and synergistically to promote clot formation at the bleeding site. While the thrombin converts fibrinogen into fibrin monomers that polymerize to form a fibrin clot, the gelatin matrix seals the wound. It has been proven to control bleeding from oozing to pulsatile flow.

Statistical analysis

Descriptive statistics were applied to outcome measures. Percentage rates were compared between the two groups by the z test. Quantitative measurements were compared between the two groups using the Mann–Whitney U-test. Continuous data are presented as mean ± standard deviation. Confidence intervals (95%) were used to quantify the extent of the observed differences. All statistical comparisons were based on a two-sided test on a 5% significance level. Data were analysed through Stata/SE 12.1 software.

Sample size. Based on previous studies of haemostatic products [7, 14, 15], it was estimated that 75% of patients receiving the haemostatic agent and 45% of those receiving standard care alone would achieve haemostasis after 3 min. To show a difference between the two treatment options at a power of 90% with a significance level of 5%, a sample size of 120 patients was required for this trial (60 per treatment group).

RESULTS

One hundred and twenty patients fulfilled the inclusion criteria during the study period and were included in the trial. Seventy (58.3%) were male and 50 (41.7%) were female with ages ranging between 25 and 79 years (mean 65.1 years). Sixty patients of these were randomly assigned to the Floseal group, and 60 patients to the SC group (control group). During the same period, 789 patients underwent lung resection in our institution.

Patients’ characteristics of the two study groups including sex and presence of main comorbidities (diabetes, COPD, smoking history, cardiovascular disease) and preoperative antiaggregant therapy are reported in Table 1. Eleven patients in the haemostatic group and 9 in the control group took antiaggregant therapy for primary prevention of vascular disease before operation. This therapy was interrupted in all patients at least 7 days before surgery and not shifted to low weight heparin. Three patients in the Floseal group and 4 in the control group received mechanical thromboprophylaxis with graduated compression stockings because of the presence of varicose veins (2 patients of the Floseal group and 2 of the control group) or obesity (1 patient in the Floseal group and 2 in the control group).

Major lung resections performed in the 120 patients included lobectomy, bilobectomy, sleeve lobectomy and pneumonectomy. The distribution of the surgical procedures in the two study groups is reported in Table 2.

Intraoperative bleeding sites and their distribution were similar between the two groups (Table 3). Floseal application was associated with a significantly higher successful haemostasis rate: 98% (59/60) vs 76% (46/60) (P < 0.001, 95% CI 0.105–0.328). A shorter mean time to reach haemostasis was observed in patients of the Floseal group (3.6 ± 0.5 vs 6.4 ± 0.7 min, P < 0.001). Haemostasis at 3 min was achieved in 78% of Floseal group patients (47/60) and in 58% (35/60) of the control group patients. This difference was statistically significant (P = 0.019, 95% CI 0.037–0.363). Haemostasis at 6 min was achieved in 92% (55/60) of patients receiving Floseal application and in 72% (43/60) of patients of the standard care group (P = 0.005, 95% CI 0.066–0.334).

In the Floseal group, one haemostatic application to the intraoperative bleeding site was performed in 42 patients, and two applications were required in 18 patients. One dose of the haemostatic agent was applied to the site of the hilar dissection in all patients. No patient presented multiple sites of intraoperative active bleeding. An average of 2.3 doses per patient was used in the haemostatic group. No patient required reoperation for haemostasis revision.

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**Table 1:** Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Floseal group (n = 60)</th>
<th>SC group (n = 60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (63.3%)</td>
<td>35 (58.3%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female</td>
<td>22 (36.7%)</td>
<td>25 (41.7%)</td>
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</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (10%)</td>
<td>5 (8.3%)</td>
<td>0.75</td>
</tr>
<tr>
<td>No</td>
<td>54 (90%)</td>
<td>53 (91.7%)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (18.3%)</td>
<td>9 (15%)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>49 (81.7%)</td>
<td>51 (85%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (25%)</td>
<td>17 (28.3%)</td>
<td>0.68</td>
</tr>
<tr>
<td>No</td>
<td>45 (75%)</td>
<td>43 (71.7%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (85%)</td>
<td>52 (86.7%)</td>
<td>0.79</td>
</tr>
<tr>
<td>No</td>
<td>9 (15%)</td>
<td>8 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative antiaggregation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (18.3%)</td>
<td>9 (15%)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>49 (81.7%)</td>
<td>51 (85%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2:** Type of resection

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Floseal group (n = 60)</th>
<th>SC group (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sleeve lobectomy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3:** Intraoperative bleeding sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Floseal group (n = 60)</th>
<th>SC group (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Chest wall</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Lung parenchyma</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Sub-clavian artery</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchial arteries</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
The mean quantity of chest drain fluids at 24, 48 and 72 h in patients of the two groups are reported in Table 4. Differences between the Floseal and the control group were not significant at all three times.

The mean preoperative Hb level was 13.4 ± 1.19 g/dl in the Floseal group and 13.4 ± 1.24 g/dl in the SC group. Postoperative Hb-level variation was significantly lower in patients of the Floseal group when compared with patients of the control group (-0.7 ± 0.66 vs -2.3 ± 5.87 g/dl; P = 0.04).

Similarly, haematocrit variation was lower in the haemostatic group (-2.6 ± 2.19 vs -4.2 ± 3.71; P = 0.006). The mean preoperative haematocrit was 40.6 ± 3.4 in the Floseal group and 40.1 ± 3.4 in the control group.

Intensive Care Unit stay was required in 2 patients of the Floseal group (3.3%) and in 3 patients of the control group (5%). Blood transfusion was required in 2 patients of the SC group (2 units of packed red cells in 1 patient and 1 unit in the other). One patient of the Floseal group required transfusion of blood products (2 units of packed red cells).

Postoperative complications rate was 8.3% in the Floseal group including air leaks in 2 patients, parenchymal atelectasis requiring bronchial aspiration in 1, atrial fibrillation in 1 and recurrent laryngeal nerve palsy in 1. In the SC group, there were complications in 6 patients (10%) including air leaks in 3, renal failure in 1, pneumonia in 1 and atrial fibrillation in 1. No adverse events or complications related to the sealant application occurred.

Chest drain duration was significantly shorter in the Floseal group (10.3 ± 5.05 vs 13.3 ± 6.28 days; P = 0.005). In-hospital stay was shorter in the Floseal group (6.4 ± 2.9 vs 8.1 ± 5.42 days; P = 0.044).

## DISCUSSION

Effective control of intraoperative bleeding and prevention of postoperative bleeding represent crucial issues in major thoracic surgery.

The standard surgical technique including sutures and electrocoagulation still represents the main tool for haemorrhage control. Direct pressure without additional procedures can be sufficient to stop the bleeding in the case of a small injury to low-pressure vessels as the pulmonary artery and veins.

Adequate management also requires preoperative risk assessment. In some cases, preoperative evaluation anticipates an increased operative bleeding risk, due to chronic antiaggregant or anticoagulant therapies, low haematic platelet levels or coagulation disorders [16].

In the last years, advances in technology have allowed the development of new devices and products with the aim of achieving safer, faster and more effective haemostasis. The use of some haemostatic agents has been proven to improve surgical haemostasis, to decrease the perioperative blood loss and, therefore, to decrease blood transfusion requirement in different fields of surgery [6, 7, 14, 17, 18].

The number of available options for management of intractable haemorrhage has expanded rapidly over the past decades and adequate knowledge of such products has improved the level of safety and efficacy of surgical haemostasis. These include gelatin sponges, collagen sponges, oxidized cellulose, thrombin, fibrin glues, collagen patches coated with fibrinogen and thrombin and others.

Significant advantages in bleeding control have been reported in cardiac surgery within the setting of randomized trials by the use of collagen patches coated with fibrinogen and thrombin and of other fibrin sealants [14, 18].

Literature data assessing the role of topical haemostatics in general thoracic surgery are more limited. The use of a fibrin pad as an adjunct to conventional methods for haemostasis has been found superior to absorbable haemostatic materials in terms of a successful haemostasis rate at 4, 6 and 10 min in a multi-institutional North-American trial including patients undergoing thoracic or abdomino-pelvic surgery with mild-to-moderate soft tissue bleeding [19].

In another prospective randomized study, the topical use of tranexamic acid after lung surgery has been reported to be associated with reduced postoperative bleeding and blood transfusion volume in a group of 44 patients compared with 43 patients who did not receive the antifibrinolytic agent [20].

The Floseal sealant has been the object of study in several surgical disciplines over the last 15 years, and has been found to be an innovative, effective and versatile product.

The first clinical trial assessing the efficacy of the Floseal matrix was conducted in cardiac surgery and published in 2000 by Oz [7]. This study reported significantly higher rates of bleeding control at 3 min (72 vs 23%) and at 10 min (94 vs 60%) in patients treated with this product in comparison with the control group.

In a more recent prospective randomized Italian trial [17] including more than 200 patients undergoing cardiac surgery in each study group, the use of Floseal correlated with higher rates of successful haemostasis, shorter time to haemostasis, decreased postoperative bleeding and transfusion rates in comparison with alternative topical haemostatic agents. The haemostatic matrix in this study was used with two modalities: (i) as an adjunct to standard technique for haemostasis in those patients of the Floseal group presenting with active bleeding during the operation (about 60–65% as in the control group); (ii) in all patients of the same group, at the end of operation, with a prophylactic intent (postoperative bleeding control) independently of the occurrence of intraoperative bleeding.

The efficacy of this haemostatic sealant has been reported over the last decade in several other surgical fields including spine surgery [8], surgery for spontaneous intracerebral haemorrhages [9], renal surgery even in post-traumatic disease [10], liver resections [11] and liver and spleen rupture in the human and animal models [12, 13]. However, this product has never been evaluated in major thoracic surgery by a prospective controlled trial.

The aim of the present study was to evaluate the efficacy of Floseal either in intraoperative active bleeding control or in prevention of postoperative bleeding and related complications.

Floseal application as an adjunct to the standard surgical technique has significantly improved the efficacy of bleeding control in terms of a successful intraoperative haemostasis rate, and the mean time to reach haemostasis. Moreover, the mean loss in postoperative haemoglobin and haematocrit levels was significantly lower in patients receiving the haemostatic application.
These intraoperative and early postoperative results have been found to be associated with a shorter hospital stay and chest drain duration. Although various clinical factors may influence the latter outcome measures [21], such data suggest a favourable impact of the Floseal application on the entire postoperative course of patients presenting with persistent active bleeding during the operation.

A difference of 30% in the haemostasis rate assumed in the study design was derived from a study including patients undergoing cardiac surgery and generally receiving heparinization, in many cases with the use of extracorporeal circulation (ECC). The lower difference found in our study could be justified by the inclusion of different patients with no heparinization and ECC.

The product cost in our hospital is 258 € per dose (593 € for an average use of 2.3 doses per patient), while the cost for 1 day of hospitalization is about 800 €. A specific cost analysis was not performed in the present study; but, since a mean reduction of 1.7 days in postoperative hospitalization was reported in the Floseal group patients, these data should likely be related to lower costs [22].

We have found some important technical advantages with use of the Floseal sealant, since this product presents as a viscous gel, which allows adequate application to any type of surface and anatomical site, and also when standard surgical procedures for haemostasis are difficult or impractical. Moreover, this haemostatic agent shows very rapid action in promoting an instantaneous clot formation at the bleeding site, which is a crucial property for effective control of high-flow active haemorrhage.

Main limitations of this study include the subjective estimation of intraoperative bleeding, the inability to perform a blinded study design, and presenting with persisting active bleeding during the operation. Strengths include homogeneity of different patients with no heparinization and ECC.

In conclusion, the application of Floseal® in major lung resections proved safe and effective in increasing the intraoperative successful haemostasis rate and in reducing postoperative variation in haemoglobin and haematocrit levels. The sealant use was also related with significantly shorter chest drain duration and hospitalization.

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Conflict of interest: none declared.

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