Gelatin Matrix Use Reduces Postoperative Bleeding After Total Knee Arthroplasty

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**abstract**

Bleeding after total knee arthroplasty can result in significant morbidity and increases the need for blood transfusion. The proper use of intraoperative adjunctive topical hemostatic agents can enhance hemostasis perioperatively, potentially reducing blood transfusions. In this prospective study, 157 consecutive patients undergoing primary total knee arthroplasty received FLOSEAL (FLOSEAL Hemostatic Matrix; Baxter Healthcare Corporation, Hayward, California), a gelatin thrombin hemostatic matrix, 5 mL (74 patients) or 10 mL (83 patients). All patients received warfarin as thromboprophylaxis starting the day after surgery. Data were extracted via hospital chart review from 100 consecutive patients who underwent total knee arthroplasty and immediately preceded the FLOSEAL groups and did not receive FLOSEAL (control group). Postoperative drainage was significantly lower in the FLOSEAL 5 mL (236.9 mL) and 10 mL (120.5 mL) groups compared with the control group (430.8 mL; \( P < .0001 \) for both). The FLOSEAL 10 mL group had significantly less drainage than the FLOSEAL 5 mL group (\( P < .0001 \)). The predicted probability of transfusion in the FLOSEAL 5 mL group was not significantly different compared with the control group (6.0% vs 7.6%, \( P = .650 \)). The predicted probability of transfusion was lower in the FLOSEAL 10 mL group compared with the control group (0.5% vs 5.5%; \( P = .004 \)). Within the FLOSEAL 10 mL group, application of FLOSEAL either before or after tourniquet release had a similarly significant effect on drainage volume and predicted probability of blood transfusion. No differences in outcomes were observed by type of anesthesia used. No adverse events occurred related to FLOSEAL use. [Orthopedics. 2015; 38(2):e118-e123.]

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Total knee arthroplasty (TKA) is associated with significant intra- and postoperative blood loss, resulting in hematoma, increased pain, and delayed recovery, which increases hospital length of stay and costs.\textsuperscript{1,2}

High-volume bleeding postoperatively may increase the need for blood transfusion, which has the additional risks of transfusion reactions and transmission of infection.\textsuperscript{3-6} Infection rates have been reported to be significantly higher in patients receiving allogeneic blood transfusion compared with no blood transfusion, resulting in longer hospital stay and 3 to 4 times higher costs than in patients without infection.\textsuperscript{1,7}

Surgeons may use various strategies for blood conservation, including perioperative hemodilution, hypotensive anesthesia, intraoperative blood salvage, specialized cautery, and allogeneic and autologous blood transfusion. In addition, use of a tourniquet during surgery may reduce intraoperative bleeding, but considerable blood loss still may occur postoperatively. Surgeons also can use topical hemostatic agents, which can enhance hemostasis perioperatively.

FLOSEAL Hemostatic Matrix (Baxter Healthcare Corporation, Hayward, California) is a combination of cross-linked bovine gelatin granules and topical human thrombin. When exposed to wet surfaces, the gelatin granules swell by approximately 10% to 20% to produce a gentle tamponade effect that physically restricts blood flow, and the high concentrations of thrombin react rapidly with the patient’s fibrinogen, forming a stable clot.\textsuperscript{8-11} Studies have reported the effectiveness of FLOSEAL in a variety of surgical procedures,\textsuperscript{10,12-17} controlling most bleeds within 2 minutes and across a range of bleeding severities from diffuse oozing to spurting bleeding.\textsuperscript{8,11} FLOSEAL is indicated in surgical procedures (other than ophthalmic procedures) as an adjunct to hemostasis when control of bleeding by ligature or conventional methods is ineffective or impractical.\textsuperscript{8} However, there have been few reports of its use in orthopedic surgery.\textsuperscript{18-20}

This study was designed to evaluate the hemostatic efficacy of the use of FLOSEAL in primary TKA, the effect of dosage (5 mL vs 10 mL), and the effect of method (timing of tourniquet release and application of FLOSEAL).

**MATERIALS AND METHODS**

**Study Design**

This was a prospective, historical controlled study. Patients undergoing primary TKA were eligible to participate. Those undergoing revision arthroplasty, partial knee arthroplasty, or surgery lasting more than 2 hours were excluded. Institutional review board approval was obtained, and all prospective patients provided informed consent. The study was registered at clinicaltrials.gov, identifier #NCT00958945.

The following variables were recorded for all patients: sex, age, transfusion (yes/no), blood loss, length of stay, type of anesthesia, and pre- and postoperative hematocrit and hemoglobin levels. Intraoperative blood loss was determined at the end of surgery by totaling the blood volume in the suction canister and the volume of blood in the gauzes. Postoperatively, blood loss was measured by the volume collected in the drains and was assessed every 12 hours until the drain was removed or the patient was discharged.

**Patients and Surgical Methods**

All patients were treated at a single institution (Eisenhower Medical Center, Rancho Mirage, California). All operations were performed with a consistent technique in a bloodless field with use of a pneumatic tourniquet. FLOSEAL was applied either before or after tourniquet release in the presence of blood. In the prospective treatment arm, 74 consecutive patients were treated with adjunctive FLOSEAL 5 mL during surgery. For all patients in this group, FLOSEAL was applied with the tourniquet inflated. A further 83 consecutive patients were treated with FLOSEAL 10 mL. In this group, the product was applied with the tourniquet inflated in the first 49 consecutive patients and after the tourniquet was deflated in the remaining 34 consecutive patients (Figure 1). Data were extracted via hospital chart review from 100 consecutive patients who immediately preceded the

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**Figure 1:** Study design. Overall study population, subgroup analysis, and dosage comparison. FLOSEAL, FLOSEAL Hemostatic Matrix, Baxter Healthcare Corporation, Hayward, California.
**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=100)</th>
<th>FLOSEAL&lt;sup&gt;a&lt;/sup&gt; 5 mL Group (n=74)</th>
<th>FLOSEAL 10 mL Group (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>47</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>73 (10)</td>
<td>72 (9)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>Right knee surgery, %</td>
<td>47</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Preoperative hemoglobin, mean (SD), g/dL</td>
<td>14.2 (1.4)</td>
<td>13.6 (1.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13.7 (1.2)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preoperative hematocrit, mean (SD), %</td>
<td>42.6 (4.2)</td>
<td>41.2 (4.3)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41.1 (3.2)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type of anesthesia, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>9</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>General and spinal</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Spinal</td>
<td>91</td>
<td>62</td>
<td>67</td>
</tr>
</tbody>
</table>

<sup>a</sup> Student’s t test was used to compare the control group with each treatment group.
<sup>b</sup> FLOSEAL Hemostatic Matrix, Baxter Healthcare Corporation, Hayward, California.
<sup>c</sup>P<.05.
<sup>d</sup>P<.01.

FLOSEAL groups. These patients did not receive FLOSEAL during TKA (control arm; Figure 1). A drain was placed, and the wound was closed over the drain. All patients received warfarin as thromboprophylaxis starting the day after surgery.

In all groups, standard hemostasis was applied during surgery. In the treatment groups, FLOSEAL was applied to the bleeding internal aspects of the operative field before skin closure, according to the manufacturer’s instructions. After FLOSEAL was applied to the wound and sources of bleeding, the product was approximated for about 2 minutes with gentle pressure using a wet gauze or sponge. Excess product that was not incorporated into the clot was removed by gentle irrigation.

Patients received blood transfusion if their hemoglobin level was less than 8.0 g/dL or less than 9.0 g/dL with associated symptoms (weakness, dizziness, fainting, slow capillary refill, shortness of breath, or hypotension).

**Statistical Analysis**

Groups were compared with 2-sample Student’s t tests with equal or unequal variance, the chi-square test, and Fisher’s exact test. Logit regression models were also used to test whether each treatment was associated with differential chances of having a transfusion, controlling for preoperative hematocrit level, sex, age group, and type of anesthesia. Multiple regression models were used to test whether each treatment was associated with differential drain output on day 1, controlling for preoperative hematocrit level, sex, and type of anesthesia. All analyses were performed with Stata version 10.1 software (StataCorp LP, College Station, Texas). P≤.05 was considered significant for all analyses.

Post hoc power analyses were performed and confirmed that the study had sufficient power to detect the effects measured, including drainage effects one-third to one-half of the size detected in the study (2-sided test, prespecified alpha=.05, power 1−beta=1).

**RESULTS**

Demographic and surgical characteristics for the FLOSEAL and control groups are shown on Table 1. Demographic variables were similar between groups, except for preoperative hematocrit and hemoglobin levels.

Postoperative drainage was significantly lower in the FLOSEAL 5 mL group compared with the control group (236.9 mL vs 430.8 mL, P<.0001; Table 2 and Figure 2), and in the FLOSEAL 10 mL group compared with the control group (120.5 mL vs 430.8 mL, P<.0001; Table 2 and Figure 2). The FLOSEAL 10 mL group had significantly less drainage than the FLOSEAL 5 mL group (P<.0001). These results (predicted means) were confirmed with multiple regression analysis (Table 2).

Within the FLOSEAL 10 mL group, postoperative drainage was similar irrespective of the timing of tourniquet release, with drainage of 134.7 mL when the tourniquet remained inflated during FLOSEAL application and drainage of 102.4 mL when the tourniquet was deflated before FLOSEAL application (P=.163). Both FLOSEAL groups had significantly less drainage than the control group (P<.0001; Table 2).

The predicted probability of transfusion was significantly lower in the FLOSEAL 10 mL group compared with the control group (0.5% vs 5.5%, P=.004; Figure 3). The predicted probability of transfusion in the FLOSEAL 5 mL group was not significantly different compared with the control group (6.0% vs 7.6%, P=.650; Table 2). No significant differences in hematocrit or hemoglobin levels were observed postoperatively (Table 3), and mean inpatient hospital stay was similar in the FLOSEAL 10 mL group and the control group (3.1 days for both). No differences in outcomes were observed by type of anesthesia used. No adverse events occurred related to the use of FLOSEAL.

Analysis with propensity score matching produced the same or stronger results than those reported here. Treatment and control groups were matched on a series of covariates, including age, sex, preop-
erative hematocrit level, and preoperative hemoglobin level. Student’s t tests with matched data showed that postoperative drainage was significantly lower in the FLOSEAL 5 mL group (P < .0001) and the FLOSEAL 10 mL group (P < .0001) compared with the control group, and the FLOSEAL 10 mL group had significantly less drainage than the FLOSEAL 5 mL group (P < .0001). No statistically significant difference was noted between groups based on the timing of tourniquet release, with the predicted probability of transfusion and inpatient hospital stay similar to or stronger than those reported earlier (data not shown).

**DISCUSSION**

Topical hemostatic agents can enhance hemostasis in the perioperative period after various surgical procedures. One well-studied example is fibrin sealants, which are composed of human thrombin and human fibrinogen and mimic the final stages of the coagulation cascade. Supporting the use of fibrin sealants in the surgical setting is a Cochrane meta-analysis that reported trends for a decrease in blood loss and the risk of transfusion for these agents relative to conventional surgical hemostasis, particularly in the orthopedic setting. Fewer studies assessed FLOSEAL, which is a hemostatic matrix and not a fibrin sealant. To the authors’ knowledge, this is the first study to assess the timing of FLOSEAL application and tourniquet release in TKA. FLOSEAL and fibrin sealants have

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**Table 2**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Control Group</th>
<th>FLOSEALb 5 mL Group</th>
<th>All</th>
<th>Tourniquet Up</th>
<th>Tourniquet Down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean intra-articular drainage, mL (±SE)</td>
<td>430.8 (32.7)</td>
<td>236.9 (17.3)c</td>
<td>120.5 (8.9)c</td>
<td>134.7 (11.6)c</td>
<td>102.4 (13.3)c</td>
</tr>
<tr>
<td>Mean intra-articular drainage predicted, mL</td>
<td>367.8</td>
<td>195.6d</td>
<td>396.7</td>
<td>106.9d</td>
<td>431.6</td>
</tr>
<tr>
<td>Predicted probability of transfusion, %</td>
<td>7.6</td>
<td>6.0</td>
<td>5.5</td>
<td>0.5e</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>0.6e</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Logit regression models controlled for preoperative hematocrit level, sex, age group, and type of anesthesia. The range of control probabilities encompasses the predicted probabilities from the models comparing the control group with each treatment group. Variables in each model have different means because there are different cases in each model.

bFLOSEAL Hemostatic Matrix, Baxter Healthcare Corporation, Hayward, California.

cP < .001 compared with control (Student’s t test).

dP < .001 compared with control (Student’s t test, multiple regression models).

eP < .05 compared with control (logit regressions).
FLOSEAL was reported to be effective in various types of surgery, including vascular, cardiac, and spinal surgery.\textsuperscript{10,14,16} FLOSEAL is a bovine-derived gelatin matrix combined with a human thrombin component. The gelatin granules in FLOSEAL initiate coagulation by contact activation. When combined with human thrombin and the patient’s fibrinogen, a mechanically stable clot is formed and a gentle tamponade effect occurs.

With FLOSEAL, the gelatin matrix and thrombin work additively through 2 independent mechanisms to restrict blood flow and form a stable clot. The gelatin granules swell 10% to 20% to produce a tamponade effect. The matrix is resorbed by the body within 6 to 8 weeks, consistent with normal wound healing.\textsuperscript{9} The human thrombin works to convert the patient’s fibrinogen to fibrin monomers and a fibrin clot. The consistency of FLOSEAL allows it to conform to irregular wound geometry.\textsuperscript{8}

The results of the current study showed that drain output for both FLOSEAL groups was significantly lower than that for the control group, and predicted probability of transfusion was significantly lower in the FLOSEAL 10 mL group compared with the control group. Application of FLOSEAL either before or after tourniquet release had a similarly significant effect on drainage volume and predicted probability of blood transfusion, suggesting that the timing of application of FLOSEAL did not affect the results. The optimal dose of FLOSEAL during TKA remains to be determined, but preliminary data from this study suggest that 10 mL might be more efficacious than 5 mL, as determined by outcome measures of drainage and transfusion. No differences in outcome were observed by type of anesthesia used. No safety concerns were observed with the use of FLOSEAL in these patients.

Other studies assessed the efficacy of FLOSEAL in TKA. A recent retrospective chart review of 184 patients treated with FLOSEAL and 165 control subjects who underwent TKA reported that the use of FLOSEAL significantly reduced postoperative decreases in hemoglobin compared with conventional hemostatic methods, with a mean difference of 0.96 g/dL.\textsuperscript{18} In this study, change in hemoglobin level was used as a surrogate to estimate blood loss. Blood transfusions were infrequent in both groups. Similarly, beneficial effects on hemoglobin levels were reported in a small study of patients with hemophilia who received FLOSEAL in TKA,\textsuperscript{20} with a change in hemoglobin levels of approximately 2 g/dL pre- and postoperatively in the FLOSEAL group compared with the control group (3.8 g/dL vs 5.8 g/dL), and a 25% reduction in both the amount of blood transfused and postoperative drainage in patients in the FLOSEAL group compared with the control group.\textsuperscript{20}

Consistent with these reports, a retrospective study of 121 patients undergoing TKA reported no significant differences between the FLOSEAL group and the control group in drain output at 24 hours (711 mL vs 702 mL, $P=.823$) or transfusion rates.\textsuperscript{19} However, a significant difference in hemoglobin levels between groups was observed on the first and second postoperative days.

**CONCLUSION**

In summary, the current prospective study indicated that the use of FLOSEAL in TKA provided safe and improved control of blood loss and reduced the predicted probability of postoperative blood transfusion in the FLOSEAL 10 mL group. This may reduce postoperative extravasation of blood into the tissues as well as apparent blood loss, thereby preventing the formation of hematoma, and may have economic benefits as well. Further study is needed to determine the optimal dose of FLOSEAL for use in TKA, and a randomized multicenter prospective trial is recommended.

**REFERENCES**


<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Control Group (n=100)</th>
<th>FLOSEAL\textsuperscript{5} 5 mL Group (n=74)</th>
<th>FLOSEAL 10 mL Group (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative, mean (SD), g/dL</td>
<td>14.2 (1.4)</td>
<td>13.6 (1.5)</td>
<td>13.7 (1.2)</td>
</tr>
<tr>
<td>Postoperative, mean (SD), g/dL\textsuperscript{b}</td>
<td>11.4 (1.5)</td>
<td>10.6 (1.4)</td>
<td>10.9 (1.2)</td>
</tr>
<tr>
<td>Difference</td>
<td>2.8</td>
<td>3.0</td>
<td>2.8</td>
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\textsuperscript{a}Student’s t test was used to compare pre- and postoperative hemoglobin levels in each treatment group. 
\textsuperscript{b}FLOSEAL Hemostatic Matrix, Baxter Healthcare Corporation, Hayward, California.
\textsuperscript{c}Postoperative day 1.
bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res. 2011; 11:135.


