Reducing blood loss after total knee replacement
A FIBRIN SOLUTION

K. R. Reinhardt,
H. Osoria,
D. Nam,
M. A. Alexiades,
M. P. Figgie,
E. P. Su

From Hospital for Special Surgery, New York, New York, United States

Blood loss during total knee replacement (TKR) remains a significant concern. In this study, 114 patients underwent TKR, and were divided into two groups based on whether they received a new generation fibrin sealant intra-operatively, or a local infiltration containing adrenaline. Groups were then compared for mean calculated total blood volume (TBV) loss, transfusion rates, and knee range of movement. Mean TBV loss was similar between groups: fibrin sealant mean was 705 ml (281 to 1744), local adrenaline mean was 712 ml (261 to 2308) (p = 0.929). Overall, significantly fewer units of blood were transfused in the fibrin sealant group (seven units) compared with the local adrenaline group (15 units) (p = 0.0479). Per patient transfused, significantly fewer units of blood were transfused in the fibrin sealant group (1.0 units) compared with the local adrenaline group (1.67 units) (p = 0.027), suggesting that the fibrin sealant may reduce the need for multiple unit transfusions. Knee range of movement was similar between groups. From our results, it appears that application of this newer fibrin sealant results in blood loss and transfusion rates that are low and similar to previously applied fibrin sealants.

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While advances in the design and fixation of implants have improved the survival and function of total knee replacements (TKR), blood loss from the procedure remains a concern, with estimates ranging from 800 ml to 1700 ml during the peri-operative period.1,2 Allogenic blood transfusion following TKR has been reported to be as high as 50%.3 Transfusion of allogenic blood, however, is not without risk, and has been shown in TKR to be associated with higher rates of infection, fluid overload, and increased length of stay.4 Pre-operative donation of autologous blood prior to TKR has been advocated as a means to reduce reliance on allogenic blood for post-operative transfusion, and has been effective to some degree.3 Yet not all patients will require transfusion of their autologous blood after surgery, and up to 45% may be wasted.3,4

To minimise the risks and limit the costs, efforts have focused on peri-operative blood conservation strategies during the procedure. Methods including systematic administration of tranexamic acid and clamping of knee drains to tamponade the joint cavity, have not always proven effective.5,6 Some studies report reduced blood loss and lower post-operative transfusion rates when a peri-articular injection containing adrenaline was used during TKR7-10 but intra-articular adrenaline lavage was not shown to be effective.11 Alternatively, topical fibrin sprays applied to the exposed tissues and bony surfaces during TKR has shown promise as a haemostatic option.12-15 Many fibrin sealants are commercially available, and typically contain human pooled allogenic fibrinogen, factor XIII, thrombin, and antifibrinolytic agents, such as aprotinin or tranexamic acid.16 These agents achieve their local hemostatic effect by reproducing the last step in the coagulation cascade. The fibrin sealant shown to be effective in reducing blood loss during TKR in prior studies (Quixil; Omrix Biopharmaceuticals) contains the clot stabilising agent, tranexamic acid.13,14 Due to safety concerns of intravenous tranexamic acid associated with thrombotic complications including myocardial infarction and seizures during cardiac surgery,17,18 a new generation of fibrin sealant (Evicel; Johnson & Johnson) has been developed that does not contain tranexamic acid, and instead achieves clot stability by eliminating plasminogen. Despite concern from the cardiac literature, recent studies in the orthopaedic literature have not found an increased risk of thromboembolic complications with the use of tranexamic acid during TKR.19,20 Nonetheless, there are no prior reports on the use of this new generation fibrin sealant (Evicel; Johnson & Johnson) in...
reducing blood loss during TKR and there are none comparing blood loss with a fibrin sealant versus local infiltration with adrenaline during TKR.

The purpose of this study, therefore, was to compare the total blood volume (TBV) loss in patients undergoing primary TKR with the intra-operative application of a fibrin sealant (Evicel; Johnson & Johnson) versus a local soft-tissue infiltration containing adrenaline. Secondary aims included a comparison of the rate of allogenic blood transfusions, and an assessment of knee range of movement between groups.

**Patients and methods**

Operative records of two fully trained orthopaedic surgeons were reviewed to identify patients who underwent unilateral primary TKR between April 2010 and September 2011. Criteria included those patients who underwent cemented posterior-stabilised TKR for a diagnosis of osteoarthritis, were between the ages of 20 and 90 years, and had not donated any autologous blood pre-operatively. Excluded patients had a known diagnosis of coagulopathy or bleeding disorder, the presence of abnormal coagulation values on routine pre-operative testing, ongoing use of clopidogrel prior to surgery, bilateral knee replacement, or prior ipsilateral knee surgery, bilateral knee replacement, or prior ipsilateral knee replacement. A thigh tourniquet was used on all patients. Two groups were formed based on whether application of a fibrin sealant (Evicel; Johnson & Johnson) or a local infiltration containing adrenaline was undertaken intra-operatively. The peri-articular injection contained 30 cc bupivacaine 0.5% with adrenaline (1:200,000, total dose 0.182 mg), 1 cc 8 mg morphine, 22 cc sodium chloride 0.9%, methylprednisolone 40 mg 1 cc, Benadryl 25 mg 0.5 cc, and cefazolin 500 mg. No intra-articular wound drains were used and no patients received tranexamic acid. The study protocol was approved by the Institutional Review Board.

Demographic data in Table I demonstrates blood haemoglobin and haematocrit levels measured pre-operatively from routine laboratory testing conducted within one week prior to surgery. These levels were also assessed post-operatively within two hours following surgery, and on each post-operative day during the hospital stay. The volume of allogenic blood transfusions during the post-operative period, as well as the haematocrit level at which each transfusion was initiated (i.e. transfusion trigger) was also collected for each patient. Standard criteria for blood transfusion at the authors’ institution include:

1. A haemoglobin level less than 8 g/dl that is not due to iron, folate or B12 deficiency (and is clinically symptomatic).
2. Active bleeding in a clinically unstable patient.
3. A haemoglobin level less than 10 g/dl and coexisting cardiac, pulmonary or cerebrovascular disease, or symptoms of decreased oxygen delivery. Knee range of movement, defined as total arc of knee movement (°), was noted from private office documentation pre-operatively, from physical therapy progress notes during the inpatient hospital stay post-operatively, and from private office documentation at the six week follow-up visit.

All patients received prophylaxis against deep venous thrombosis (DVT) post-operatively, which consisted of early mobilisation, lower limb intermittent compression devices, and warfarin dosed according to the prothrombin time for a total of six weeks, with a goal range of 1.8 to 2.3 per institutional policy.

**Calculation of total blood loss.** The primary outcome was TBV loss which was calculated according to the following formula:

\[ \text{TBV loss (mL)} = \text{Predicted Blood Volume (PBV)} \times (\text{Haematocrit pre-op} - \text{Haematocrit post-op}) + \text{Volume of Red Blood Cell (RBC) transfused} \]

Where PBV and Volume of RBC transfused are defined as follows:

\[ \text{PBV in men} = 0.3669 \times H^3 + 0.03219 \times W + 0.6041 \]
\[ \text{PBV in women} = 0.3561 \times H^3 + 0.03308 \times W + 0.1833 \]

\( H \) = height in metres, \( W \) = weight in kg

Volume of RBC transfused (ml) = Volume of transfusion (ml) / haematocrit transfusion trigger

The haematocrit transfusion trigger has been defined as the haematocrit level at which each particular transfusion is initiated. One unit of allogenic blood transfusion represents the equivalent volume of 200 ml of RBCs, and one unit of autologous blood transfusion represents a volume of 180 ml of RBCs as previously determined.

In total, 114 patients were included in the study protocol, with 57 patients in each of the two groups (Table I). The demographics and pre-operative clinical details of the groups are shown in Table I. There were no significant differences between the groups for baseline demographics, including age, gender, BMI and ethnicity distribution.

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**Table I. Comparison of pre-operative baseline characteristics between groups**

<table>
<thead>
<tr>
<th></th>
<th>Fibrin sealant (n = 57)</th>
<th>Local adrenaline (n = 57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (yrs)</td>
<td>67 (10)</td>
<td>69 (9.6)</td>
<td>0.430</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>33 (57.9)</td>
<td>36 (63.2)</td>
<td>0.565</td>
</tr>
<tr>
<td>Caucasian (n, %)</td>
<td>44 (77.2)</td>
<td>57 (89.5)</td>
<td>0.079</td>
</tr>
<tr>
<td>Mean (SD) body mass index (kg/m²)</td>
<td>30.4 (6.1)</td>
<td>32.6 (7.1)</td>
<td>0.083</td>
</tr>
<tr>
<td>Mean (SD) haemoglobin (g/dL)</td>
<td>13.7 (1.2)</td>
<td>13.6 (1.4)</td>
<td>0.568</td>
</tr>
<tr>
<td>Mean (SD) haematocrit (%)</td>
<td>41.2 (3.3)</td>
<td>40.9 (3.6)</td>
<td>0.575</td>
</tr>
</tbody>
</table>
Furthermore, pre-operative haemoglobin and haematocrit levels were similar between groups (Table I).

**Statistical analysis.** The power calculation was based on the primary outcome of TBV loss. The expected standard deviation per group (614 ml) was derived from a previously published study, and a difference of 300 ml was chosen as clinically relevant. Therefore, in order to detect a significant difference in TBV loss with 80% power at a significance level of 5% (p < 0.05), 55 patients per group were required.

Data analysis of the primary outcome consisted of two-sample t-tests for fibrin sealant versus local adrenaline. Descriptive statistics were calculated for all independent variables and secondary outcome variables. Normally distributed continuous variables were analysed using the t-test (for continuous variables), and categorical variables were evaluated using the chi-squared and Fisher’s exact tests. All analysis was performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina).

**Results**

**TBV loss.** There was no statistically significant difference in TBV loss between patients who received the fibrin sealant and those who received the local adrenaline infiltration (Table II).

**Clinical outcomes.** During the post-operative in-hospital course, seven patients (12.3%) in the fibrin sealant group, and nine patients (15.8%) in the local adrenaline group required at least one unit of allogenic blood transfused. Overall, significantly more units of allogenic blood were transfused in the local adrenaline group compared with the fibrin sealant group (15 versus seven units of allogenic blood respectively) (p = 0.0479). The number of units of blood per patient transfused was significantly lower in the fibrin sealant group compared with the local adrenaline group (p = 0.027) (Table II).

Total arc of knee range of movement in each group during the inpatient stay and at six week follow-up is summarised in Table III. The use of a fibrin sealant had no significant effect on knee range of movement at six week follow-up (p = 0.684).

**Discussion**

The mean total blood loss across all groups in the current study was 708.8 ml (261 to 2308), which is low when compared with other studies in which calculated total blood loss was over 1000 ml during total knee replacement. The authors did not find that the addition of a newer generation fibrin sealant reduced total blood loss significantly following TKR, when compared with a local soft-tissue infiltration containing adrenaline. However, with application of a new generation fibrin sealant, there was a significant reduction in the overall number of units of blood transfused (Table II).

All consecutive patients over a relatively short time period (17 months) were considered for inclusion to meet our sample size requirements, however this study has several limitations, including its retrospective nature which risks potential selection bias. Additionally, although baseline demographics and pre-operative blood values were similar between groups (Table I), there may be potentially confounding variables that were not accounted for as the allocation of patients was not randomised. Furthermore, as two surgeons were involved in this study the potential for variability in surgical technique including the meticulousness of surgical haemostasis, may bias the results. Application of the fibrin sealant, on the other hand, was performed according to the manufacturer’s instructions. Controlled hypotensive combined spinal-epidural anesthesia was utilised in these patients, which has the effect of reducing blood loss during TKR and so could have been a

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**Table II.** Comparison of blood loss and blood transfusion between groups

<table>
<thead>
<tr>
<th></th>
<th>Fibrin sealant (n = 57)</th>
<th>Local adrenaline (n = 57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (sd) total blood loss (ml)</td>
<td>705 (309)</td>
<td>712 (519)</td>
<td>0.929</td>
</tr>
<tr>
<td>Units of blood transfused</td>
<td>7</td>
<td>15</td>
<td>0.048</td>
</tr>
<tr>
<td>Units per patient transfused</td>
<td>1.00</td>
<td>1.67</td>
<td>0.027</td>
</tr>
</tbody>
</table>

**Table III.** Comparison of total arc of knee movement between groups on each post-operative day (POD) and at six-week follow-up

<table>
<thead>
<tr>
<th>Mean range of movement (*) (range)</th>
<th>Fibrin sealant (n = 57)</th>
<th>Local adrenaline (n = 57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 1</td>
<td>53.4 (20 to 85)</td>
<td>57.8 (15 to 85)</td>
<td>0.106</td>
</tr>
<tr>
<td>POD 2</td>
<td>63.4 (20 to 95)</td>
<td>66.4 (33 to 90)</td>
<td>0.307</td>
</tr>
<tr>
<td>POD 3</td>
<td>66.4 (20 to 85)</td>
<td>68.5 (32 to 105)</td>
<td>0.503</td>
</tr>
<tr>
<td>6-weeks</td>
<td>103.9 (75 to 130)</td>
<td>105.7 (55 to 125)</td>
<td>0.684</td>
</tr>
</tbody>
</table>
confounding factor. Finally, co-investigators collecting data were not blinded to treatment groups.

The authors did not find a significant reduction in blood loss with use of this topical fibrin spray when compared with local infiltration with adrenaline (p = 0.929). In a prospective randomised study, Levy et al showed that application of a topical fibrin spray during TKR reduced total blood loss, reduced transfusion rates, and minimised perioperative decreases in haemoglobin.15 The agent used in that study, while not explicitly stated, was of the former generation of fibrin sealants that contained tranexamic acid as a fibrin stabilising agent. In their fibrin sealant group, 17% of patients required a transfusion, which is comparatively low when one considers the 55% transfusion rate found in the control group in that study.15 More recently, a randomised controlled trial again compared an older generation topical fibrin spray (Quixil, Omrix Biopharmaceuticals, Belgium) with an intravenous administration of tranexamic acid, which demonstrated a significant reduction in calculated total blood loss in the fibrin spray and tranexamic acid groups compared with controls.13 However they found no difference when the fibrin spray and tranexamic acid groups were compared. The mean calculated blood loss after TKR, reported in that study was 1190 ml (708 to 2067) in the fibrin sealant group, and 1225 ml ($80 to 2027) in the tranexamic acid group.13 The overall blood loss in both our groups (708.8 ml (261 to 2308)) is comparatively low, despite not finding a difference in total blood loss between the groups in our study. Blood loss totals similar to that in the current study can be found in other reports on the use of local adrenaline in TKR. For example, Gasparini et al9 reported mean calculated blood loss of 821.9 ml (SD 270.8), in a group of patients that received a peri-articular injection of dilute norepinephrine during TKR, which was significantly less than the 1270.8 ml (SD 394.5) of blood loss in their control group without norepinephrine.

There was a significant reduction in the total number of units transfused with application of a fibrin sealant suggesting a decreased need for multiple unit transfusions, compared with local infiltration with adrenaline. No prior studies have directly compared a fibrin sealant and local adrenaline in TKR for blood loss or transfusion rates. However, a number of studies compare administration of a local infiltration containing adrenaline with a control group of patients. In 2004, Lombardi et al17 noted a reduction in blood loss in TKR patients that received a peri-articular injection of bupivacaine, morphine and adrenaline when compared with control patients that received no injection, but did not show a difference in units of blood transfused between groups. Using similar agents, Anderson et al18 demonstrated a reduction in drain output during the day of surgery when compared with controls, but was unable to show a difference in post-operative haematocrit levels or volume of blood transfused.

Clinical outcomes in the early post-operative period, specifically in knee range of movement, have received attention in prior studies on older generation fibrin sealants. Knee range of movement has not been reliably shown to be significantly improved by applying a fibrin sealant after TKR when compared with controls,15 and a newer generation fibrin sealant gave no demonstrable difference up to six weeks post-operatively.

It appears that application of this newer fibrin sealant produces calculated total blood loss and transfusion rates similar to prior fibrin sealants. Furthermore, the authors have found there was a beneficial effect of this fibrin sealant in reducing blood transfusion. However, prospective randomised controlled trials are needed to determine the true efficacy of this newer generation topical fibrin spray in reducing blood loss during primary TKR, and in minimising the need for blood transfusion.

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References


