Use of a haemostatic matrix does not reduce blood loss in minimally invasive total knee arthroplasty

Pierre-Emmanuel Schwab, Emmanuel Thienpont

Department of Orthopaedic Surgery, University Hospital Saint Luc-UCL, Brussels, Belgium

Background. Blood loss can increase morbidity and the risk of transfusion after total knee arthroplasty (TKA). This study evaluated the difference in blood loss between minimally invasive TKA performed with and without intra-articular use of a haemostatic matrix (Floseal®).

Materials and methods. We retrospectively compared matched pairs in two groups (76 patients in each group): one group received conventional haemostasis (with bovie electrocoagulation), the other group was treated with an intra-articular haemostatic matrix (HM) as an adjunct to electrocoagulation. The outcomes compared were haemoglobin (Hb) and haematocrit levels at days 2 and 4 after surgery as a surrogate for blood loss, transfusion rate, surgical time, preoperative and postoperative range of motion (ROM) at days 21 and 42 and length of stay (LOS) in hospital.

Results. No differences were observed for Hb levels at day 2 or day 4 between men in the two groups. In women, however, the mean Hb at day 2 was 11.1 g/dL (SD 1.3) for TKA with HM and 12.0 g/dL (SD 0.9) for TKA without HM ($p<0.001$), while that at day 4 was 10.6 g/dL (SD 1.3) for TKA with HM and 11.4 g/dL (SD 1.2) for TKA without HM ($p<0.001$). The haematocrit was higher for TKA without HM at day 2 ($p=0.001$) and day 4 ($p=0.008$). The transfusion rate for TKA with HM was 2.6% and for TKA without HM 0% ($p=0.497$), while the mean surgical time was 93 minutes (SD 12) *vs* 87 minutes (SD 14), respectively ($p=0.0055$). There were no differences in preoperative or postoperative ROM at days 21 and 42 between the two groups. The LOS was longer for TKA with HM than for TKA without HM (4.5 days and 4 days, respectively, $p=0.011$) influenced by the longer stay for the transfused patients.

Discussion. The present study showed that the use of Floseal had no effect on reducing either visible or hidden blood loss after TKA, as assessed by a drop in Hb or haematocrit and that hidden blood loss was more important in women treated with the HM.

Keywords: blood loss, knee arthroplasty, haemostatic matrix, haemoglobin.

Introduction

Total knee arthroplasty (TKA) is an excellent procedure for treating severe osteoarthritis. Bone and soft-tissue bleeding following TKA can be a major cause of morbidity, leading to transfusions, pain, decreased range of motion, increased length of hospital stay and slower recovery[1-5]. Reducing blood loss and transfusions after TKA is one of the most important aims in modern knee arthroplasty. Reported estimates of blood loss during TKA still vary from 500 to 1,500 mL despite conventional methods of haemostasis such as bovie electrocautery[6,7]. In addition to electrocautery, many other forms of haemostatic control and blood salvage strategies have been proposed to avoid allogeneic transfusions including; the use of a tourniquet, sealing the intramedullary femoral canal, controlled peri-operative hypotension, loco-regional anaesthesia, autologous blood transfusion, intra-operative blood salvage and the use of erythropoietin[8-11]. Systemic and topical appliance of tranexamic acid is another proven strategy[12,13].

Over the past few years haemostatic matrices (HM) have been developed. The general purpose of these topical agents is to help to decrease bleeding when ligature or conventional procedures of coagulation are ineffective or impractical. The currently existing topical haemostatic agents are composed of fibrin or thrombin. Floseal® (Baxter, Deerfield, IL, USA) is a HM made of two components: a mechanical component and a chemical component. The mechanical component is a bovine-derived gelatin matrix, consisting of cross-linked gelatin granules, which is supposed to be adhesive and sealing. The chemical component is human-derived thrombin, which is supposed to achieve haemostasis. Review articles suggest that Floseal® decreases blood loss in a range of operations including adenoidectomy, trans-sphenoidal pituitary surgery, endoscopic sinus surgery, laparoscopic

partial nephrectomy, and vascular, cardiac and spinal surgery[14-20].

In TKA, blood loss can be "visible", and estimated during the surgical procedure or in the post-operative drain, or it can be "hidden" and happen in the days after surgery by infiltration of tissues with blood, often manifested as swelling or haematoma. Blood loss can be evaluated either by an estimation of the loss or by measurements of the drop of haemoglobin (Hb) and haematocrit as surrogates of blood loss[21]. Control of the typical areas of bleeding in TKA with the bovie is not always easy and diffuse oozing is often observed despite haemostatic therapy. Furthermore, a post-operative rise of blood pressure or the second phase of post-surgical fibrinolysis could induce a release of the bovie-induced coagulation plug leading to late and hidden blood loss[6,22,23].

The aim of this study was to evaluate the added value in terms of blood loss of Floseal® as an adjuvant to conventional haemostasis for patients undergoing minimally invasive TKA. The hypothesis was that Floseal® applied during surgery to the bleeding areas of the knee would reduce visible blood loss, as measured by a drop in Hb at day 2 after surgery, more than conventional coagulation with the bovie alone. Another hypothesis was that hidden blood loss, measured as a drop in Hb between post-operative day 2 and day 4, would also be reduced by the use of Floseal®. Primary outcome criteria were, therefore, post-operative day 2 and day 4 Hb and haematocrit levels as well as blood transfusion requirements. Gender differences in blood loss were also to be investigated. Secondary outcomes were surgical time, post-operative range of motion to evaluate the influence of haematoma and swelling on a patient's recovery and, finally, length of stay (LOS) in hospital as an indicator of speed of rehabilitation and the impact of transfusion on LOS.

Material and methods

This was a retrospective comparison study of patients with a diagnosis of primary knee osteoarthritis undergoing minimally invasive TKA either with or without HM in a university hospital. The study was approved by the ethics committee of the hospital (B403201111567). Between 2008 and 2011, within a group of 758 consecutive patients undergoing primary knee arthroplasty according to the inclusion criteria, 270 TKA were performed with HM and 488 TKA without HM. During the period that HM was used all consecutive patients had Floseal® applied to the bleeding areas during surgery as an adjunct to specific bovie coagulation of the bleeding zones. All information on knee arthroplasties carried out in our institution are collected in a prospective database; blood tests are performed pre-operatively, on day 2, day 4, day 21 and on day 42. The data were retrieved from the operating software for patients' medical records of our institution (Medical Explorer v3r9 Saint Luc Hospital, 2008). The inclusion criterion was tricompartmental arthritis without prior open surgery except meniscectomy. Exclusion criteria were previous high tibial osteotomy, extra-articular deformities, presence of metallic hardware, bleeding disorders, renal or hepatic insufficiency, use of anti-aggregation or anticoagulation medication, alcohol and/or tobacco. Patients were excluded from the retrospective data analysis if data were missing because the patients had left the hospital before the blood test on day 4 or had not had the test on day 21 or day 42 or because demographic data, such as body mass index (BMI) or pre-operative alignment were missing. Two groups were formed: 76 patients who underwent TKA and were treated with HM were selected because of the presence of all data on file and exactly matched with 76 patients who underwent TKA without HM.

Characteristics of the study group

The following demographic data were collected for each TKA patient operated with a HM: age, sex, BMI, type of anaesthesia, ASA score, prophylaxis of deep vein thrombosis, preoperative alignment and laterality (Table I). Patients were stratified by gender, age (40-49, 50-59, 60-69, 70-79, 80-89 or 90-99), BMI (≤24.9, 25-29.9, 30-34.9 or ≥35), anaesthesia (general anaesthesia) and ASA score (all ASA 2). The TKA patients treated with HM database were then compared to TKA patients not treated with HM in the database in order to match each patient exactly.

Surgical technique

General anaesthesia with a femoral nerve block was used for all patients. Prior to incision, the tourniquet was inflated to 280 mmHg and released after implantation of all components, including the definitive liner. A

Table I - Characteristics of the patients in the two groups.

	Total	TKA with HM	TKA without HM	p-value
Number of patients (N)	152	76	76	
Sex F/M	114/38	57/19	57/19	1.0
Laterality (R/L)	74/78	37/39	37/39	1.0
Mean (SD) age [years] (range)	68.5 (10) (47-92)	68.5 (10) (47-87)	68.5 (10.5) (47-92)	0.949
Mean (SD) BMI [kg/m^2] (range)	30.2 (6.3) (19-47)	29.3 (5.2) (21-45)	31.2 (7.1) (19-47)	0.067
Enoxoparin	4	2	2	1.0
Nadroparin	148	74	74	1.0

TKA: total knee arthroplasty; HM: haemostatic matrix; F: female; M: male; R: right; L: left; SD: standard deviation; BMI: body mass index.

skin incision, a mean of 16 cm long (SD, 2 cm) (range 12-20 cm), was made in flexion for both groups. A mini-parapatellar approach without eversion of the patella and without femorotibial dislocation was used for all procedures. Intramedullary alignment was used on the femoral side and extramedullary alignment for the tibia. The femoral hole was plugged in every TKA and the same cemented PS implant with resurfacing of the patella (Vanguard, Biomet, Warsaw, IN, USA) was used. After electrocoagulation, Floseal® was applied on potential bleeding sites: the femoral insertion of the posterior cruciate ligament, the lateral genicular artery after resection of the meniscus, the posterior capsule of the knee joint, the bony surfaces uncovered by the implant as well as the pinholes (femur and tibia). The entire content of a 10 mL vial containing the active product (Floseal®) was used. The HM remained in place for 3 minutes and was then gently rinsed from the knee as recommended by the manufacturer (Baxter). In the control group bovie coagulation was used on the soft tissue areas and nothing on the bony surfaces. The rehabilitation programme was identical for both groups with full weight bearing without aids and active range of motion exercises from day 1. Thrombosis prophylaxis consisted of low molecular weight heparin for 21 days after surgery with either enoxoparin (N=4) or nadroparin (N=148), with the dose adapted according to the weight of the patient. Criteria for discharge were a dry wound, oral pain medication, no need for blood transfusion, ambulation without aid and at least 90° of active flexion.

Outcomes

Primary outcomes

Hb and haematocrit levels were determined pre-operatively and on day 2, day 4, day 21 and day 42 and nadir values were compared. Gender differences in the primary end-points were studied. Pre-operative Hb levels and the presence of anaemia before surgery were analysed. Transfusions, if any, and number of units transfused were noted in the prospective database. The transfusion threshold was set at a restrictive level of 8 g/dL but all patients were seen by an internist who decided independently on the indication for transfusion depending on the individual patient's co-morbid conditions and symptoms of anaemia. Finally, hidden blood loss, measured as a drop in Hb level between day 2 and day 4, was compared.

Secondary outcomes

Surgical time was retrieved from the anaesthetists' database. Pre-operative and post-operative range of motion at day 21 and day 42 were recorded. The time spent in hospital was also recorded to determine whether the use of the HM had any impact on the LOS.

Statistical analysis

The sample characteristics are presented as numbers, means, standard deviations and ranges. The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Non-normally distributed data were analysed using non-parametric statistical tests for continuous data, such as the Mann-Whitney U test. For normally distributed data, we used unpaired Student t tests for comparisons between groups and continuous data. Observed proportions were compared using the chi-square test and Fisher's exact test for categorical data. Statistical analyses were conducted with SPSS 21 statistical software (SPSS Inc, Chicago, IL, USA) and significance was set at $p<0.05$. Based on previous publications about Floseal®, two groups of 76 patients could give the statistical analysis sufficient power.

Results

Primary end-points

The results for mean (SD) Hb levels and their range are presented in Table II. A drop of 1.8 g/dL was observed for the HM group and 1.2 g/dL for the control group. No differences were seen between the two groups in hidden blood loss, evaluated as a drop in Hb from day 2 to day 4. Results according to gender are shown in Table III. Among males, no differences were observed for Hb levels at day 2 or day 4 between the two groups. Among the women, however, the mean Hb level at day 2 was 11.1 g/dL (SD, 1.3 g/dL) for TKA with HM and 12.0 g/dL (SD, 0.9 g/dL) for TKA without HM ($p<0.001$). On day 4, the mean Hb level was 10.6 g/dL (SD, 1.3 g/dL) for TKA with HM and 11.4 g/dL (SD, 1.2 g/dl) for TKA without HM ($p<0.001$).

The results for haematocrit levels are presented in Table IV. The haematocrit was higher in patients who underwent TKA without HM at both day 2 ($p=0.001$) and day 4 ($p=0.008$).

Transfusion rates are presented in Table V. The transfusion rate for TKA with HM was 2.6% while that for TKA without HM was 0% ($p=0.497$). Both transfused patients were female.

Table II - Haemoglobin levels in the two study groups.

Hb [g/dL]	TKA with HM			TKA without HM			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	13.3	1.6	9.1-18	13.4	1.3	10.5-17.1	0.727
Day 2	11.5	1.5	7.7-15.0	12.2	1.1	10.1-15.5	0.001
Day 4	11.0	1.6	7.8-16.0	11.7	1.2	9.2-14.7	0.015
Day 21	12.1	1.4	8.8-15.8	12.5	1.1	10.1-15.6	0.046
Day 42	12.6	1.2	9.4-15.9	13.0	1.4	9.4-16.5	0.120

Hb: haemoglobin; TKA: total knee arthroplasty; HM: haemostatic matrix; SD: standard deviation; Pre-op: pre-operative.

Table III - Mean haemoglobin levels in relation to gender.

	Men TKA with HM			Men TKA without HM			p-value	Women TKA with HM			Women TKA without HM			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*		*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	14.6	1.8	10.9-18.0	14.6	1.4	12.4-17.1	0.966	12.8	1.2	9.1-15.0	13.2	1.2	10.5-15.8	0.143
Day 2	12.6	1.4	10.0-15.0	13.1	1.2	11.3-15.5	0.299	11.1	1.3	7.7-13.2	12.0	0.9	10.1-15.0	<0.001
Day 4	12.4	1.7	9.4-16.0	12.6	1.2	10.7-14.7	0.697	10.6	1.3	7.8-12.8	11.4	1.0	9.2-13.8	0.001
Day 21	13.2	1.3	10.4-15.8	13.4	1.0	11.5-15.2	0.630	11.7	1.2	8.8-14.6	12.3	1.1	10.1-15.6	0.005
Day 42	13.3	1.5	10.7-16.5	14.1	1.1	12.5-15.9	0.144	12.3	0.9	9.4-14.1	12.6	1.3	9.4-15.9	0.203

Haemoglobin expressed as g/dL. TKA: total knee arthroplasty; HM: haemostatic matrix; SD: standard deviation; Pre-op: pre-operative.

Table IV - Mean haematocrit levels in the two groups.

Haematocrit in %	TKA with HM			TKA without HM			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	40	4	26-51	40	3	32-49	0.486
Day 2	35	4	24-45	37	3	31-46	0.001
Day 4	33	4	23-45	35	4	27-43	0.008
Day 21	38	7	27-81	38	3	31-46	0.425
Day 42	39	6	30-80	39	3	30-47	0.742

TKA: total knee arthroplasty; HM: haemostatic matrix; SD: standard deviation; Pre-op: pre-operative.

Table V - Transfusions rates in the two groups.

	TKA with HM	TKA without HM	p-value
Number of patients transfused	2 (2.6%)	0 (0%)	0.497
Number of units transfused	4	0	
Patients with preoperative haemoglobin <13 g/dL			
Number	27	23	0.385
Number transfused (%)	2 (7.5%)	0 (0%)	0.497
Patients with pre-operative haemoglobin <11 g/dL			
Number	6	3	0.494
Number transfused (%)	1 (17%)	0 (0%)	1.0

TKA: total knee arthroplasty; HM: haemostatic matrix; SD: standard deviation.

In 27/76 patients in the TKA with HM group, and 23/76 patients in the TKA without HM group, the pre-operative Hb level was below 13 g/dL, previously cited as a key level[1]. Of those patients, 94% were female. In 6/76 (8%) patients of the TKA with HM group, and in 3/76 (4%) in the TKA without HM group, the pre-operative Hb level was lower than 11 g/dL[2]; 89% were female. Of the patients with a Hb <13 g/dL, 7.5% in the TKA with HM group underwent transfusion whereas 0% in the TKA without HM group did so. For patients with a preoperative Hb <11 g/dL, 17% in the TKA with HM group underwent transfusion and 0% in the TKA without HM group did so.

Secondary end-points

The mean surgical time for TKA with HM was 93 minutes (SD 12) *vs* 87 minutes (SD 14) for the group without HM (p=0.006).

The results for range of motion are presented in Table VI. There were no differences between the two groups in pre-operative or post-operative range of motion at day 21 and 42. The results for hospital stay are also presented in Table VI. Patients in the TKA with HM than for TKA groups stayed longer in hospital than did patients in the TKA without HM group (4.5 days and 4 days, respectively, p=0.011) because of the longer stay of transfused patients in the former group.

Discussion

The major finding of this retrospective study with matched pairs is that preventive application of Floseal® in areas at risk of bleeding during TKA brings no benefits in terms of blood loss compared to TKA in which the haemostatic therapy for bleeding was bovie electrocautery. It was also observed that adding Floseal® did not reduce the need for transfusions for either normal or pre-operatively anaemic patients. The post-operative range of knee movement for patients who underwent TKA with HM was no different from that of patients who underwent the operation without HM. The former group of patients did, however, stay in hospital slightly longer than patients in whom the HM was not used, because of a couple of transfusions in pre-operatively anaemic female patients in the group managed with the HM.

The reduction of blood loss after TKA is one of the most important goals today to help patients in their recovery. The purpose of this study was to contribute to the search for new ways to reduce peri-operative blood loss by applying a HM to the bleeding areas of the knee joint. These areas are often less accessible to conventional haemostatic therapies after implantation of all the

Table VI - Mean pre-operative and post-operative range of motion (ROM) and length of stay for both groups.

ROM [degrees]	TKA with HM		TKA without HM		p-value	
	Mean extension (SD)	*Mean flexion (SD)*	*Mean extension (SD)*	*Mean flexion (SD)*	*p-value extension*	*p-value flexion*
Pre-op	−2° (4°)	113° (15°)	−2° (4°)	116° (13°)	0.451	0.295
Day 21	−0.5° (3°)	110° (13°)	−1.0° (3°)	110° (15°)	0.432	0.961
Day 42	−0.5° (4°)	116° (14°)	−0.5° (5°)	116° (15°)	0.881	0.892
Mean (SD) LOS [days] (range)	4.5 (1.5) (3-11)		4 (0.8) (2-8)		0.011	

ROM: range of motion; TKA: total knee arthroplasty; HM: haemostatic matrix; SD: standard deviation; Pre-op: pre-operative; LOS: length of stay.

components and release of the tourniquet. Alshryda *et al*. tested topical tranexamic acid, an antifibrinolytic agent, as a method for decreasing blood loss[24]. They applied a saline solution of 1 g of tranexamic acid to the knee joint and showed that this technique reduced the absolute risk of blood transfusion and blood loss. With the same objective, we wanted to evaluate the capacity of Floseal® to prevent blood loss. This HM has two components, one mechanical and one chemical. The mechanical component is a bovine-derived gelatin matrix with cross-linked gelatin granules, which induce activation of primary haemostasis and the intrinsic pathway of coagulation. The chemical component consists of human-derived thrombin, which induces the transformation of fibrinogen into monomers of fibrin in the extrinsic pathway.

One weakness of our study lies in the fact that we did not exactly follow the application recommendations given by manufacturer of Floseal®[25] by not using it on an active bleeding site. The reason for this was that we estimated that non-accessible active bleeding is rare in TKA. However no control over bleeding is possible after the knee joint has been closed and this will influence the hidden blood loss within days after the surgery. The potential sites of bleeding in knee arthroplasty are: the uncovered bone surfaces by the implant, the instrument pinholes, the external genicular artery and the posterior capsule of the knee joint. We applied Floseal® on these different bleeding points during surgery, allowing the product to be in contact with the patient's blood because of oozing during surgery and after release of the tourniquet and we kept the product *in situ* for at least 3 minutes. The HM was then removed with physiological serum because of the potential adverse effects of leaving it in the joint, including foreign body reaction, encapsulation of fluid or haematoma, chemical synovitis or third body wear. Consequently, the mechanical effect of Floseal® on hidden blood loss could not be evaluated, as it was not left inside the knee as specifically recommended by the manufacturer to avoid complications. However the more important component, the chemical part, which activates the most important pathway of coagulation, was in contact with the bleeding sites, as recommended.

A second weakness of our study is that all of the total knee arthroplasties were performed by an orthopaedic surgeon (ET) who was very cautious about bleeding, even before the use of the HM. He did not change his general haemostatic practice, but may have reduced peri-operative bleeding to such a low level that Floseal® was not able to make a significant difference (type I error). Aglietti *et al*. showed that the ideal surgeon for minimally invasive TKA is a high-volume arthroplasty surgeon who is able to anticipate possible sources of mistakes[26]. Perhaps a junior surgeon's results, in terms of blood loss, would be improved by the use of a HM, as a less experienced surgeon tends to cause more blood loss, allowing Floseal® to have an effect. This is only a hypothesis, of course, and could be the subject of a prospective RCT.

The strength of this study lies in the fact that all conditions were comparable for both groups. Floseal® was systematically applied to the same potential bleeding areas in one group as the areas treated with bovie coagulation in the control group. Furthermore we ensured that the product was in contact with blood for each patient so that the thrombin could take effect. Kim *et al*. had already shown that Floseal® had no demonstrable effect on blood loss, as measured by drain output, following TKA[27]. Our study complements their results and shows, with different outcomes, that the HM does not have sufficient effect to stand as a blood salvage technique in TKA. In contrast to the hypothesis of this study, TKA performed without the thrombin sealant was advantageous. We believe that this finding was made because the surgeon (ET) counted on the additive effect of the HM at the bleeding areas and probably went quicker with the bovie.

Hidden blood loss is the blood retained in the wound or in adjacent tissues. Aguilera *et al.* found that the calculated mean hidden blood loss in their study was not significantly different between the group of patients who received a solution of 2 mL of fibrinogen combined with 2 mL of thrombin and the control group of patients[12]. Our results were similar to theirs because no difference in hidden blood loss was observed between the two groups: each lost 0.5 g/dL of Hb between days 2 to 4. We can, therefore, conclude that Floseal® has no effect on hidden blood loss.

This study also showed a significant difference in blood loss between men and women but especially more blood loss for the women treated with Floseal®, both at day 2 and day 4. We also observed a difference in terms of hidden blood loss between men and women. This can be explained by differences in oestrogen levels. The mean age of patients in our study was 68.5 years (SD 10). The majority of women in our sample were post-menopausal, which induces a decrease in oestrogen levels. It is well known that oestrogen increases the levels of coagulation factor VIII and decreases those of protein S (inhibitor of factor Va and VIIIa). A lower oestrogen level decreases factor VIII and increases protein S, causing women to be hypocoagulable[28]. Potentially less time was spend on the electrocoagulation of potential surgical bleeders because of an expected blood loss reducing effect from Floseal®. If this was the case our results also suggest that, in women, mechanical haemostasis by the bovie is more efficient than the chemical haemostasis of Floseal® via its thrombin component.

A final topic of discussion is the cost of using Floseal®. Its application requires 6 extra minutes per operation. The HM is applied and then left in place for 3 minutes before it can be removed by cleansing with serum. On a typical day of surgery, with five TKA per room, this makes a time loss of 30 minutes per day. With a cost of 1 hour of operating time being 1,000 USD this adds 500 USD to the variable costs of surgery. One Floseal® kit has a fixed cost of about 2,600 USD. The total cost of using Floseal® is, therefore, about 13,500 USD per day, unfortunately without reductions in the potential costs of transfusion, time spent in hospital or risk of mobilisation under anaesthesia because of stiffness. Other haemostatic products similar to Floseal® exist. They act at different stages of the coagulation cascade but have the same goal, which is to accelerate the process of topical haemostasis. Diiorio *et al*. found no clinically important differences between patients who received an intra-operative application of platelet-rich plasma and patients who did not[29]. Some studies showed a benefit from using fibrin sealant[12], while others did not[30]. These contrasting observations highlight that others factors are involved in the control of haemostasis during and after TKA. Maybe gender is more important than previously considered.

Conclusion

This study on the use of a HM in TKA showed that the application of Floseal® had no effect on reducing either visible or hidden blood loss after TKA, estimated by decreases in Hb or haematocrit, and that hidden blood loss was more important in women treated with the HM.

Funding

This study was made possible by a scientific grant from Baxter Healthcare Corporation.

Authorship contributions

PES and ET designed the study protocol. PES collected the data, searched the literature and performed the statistical analysis. ET and PES both wrote the paper. ET gave final approval of the manuscript.

The Authors declare no conflicts of interest.

References

1) Salido JA, Marin LA, Gomez LA, et al. Preoperative hemoglobin levels and the need for transfusion after prosthetic hip and knee surgery: analysis of predictive factors. J Bone Joint Surg Am 2002; **84-A**: 216-20.
2) Fujimoto H, Ozaki T, Asaumi K, et al. Blood loss in patients for total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2003; **11**: 149-54.
3) Bierbaum BE, Callaghan JJ, Galante JO, et al. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 1999; **81**: 2-10.
4) Grosu I, Lavand'homme P, Thienpont E. Pain after knee arthroplasty: an unresolved issue. Knee Surg Sports Traumatol Arthrosc 2014; **22**: 1744-58.
5) Watts CD, Pagnano MW. Minimising blood loss and transfusion in contemporary hip and knee arthroplasty. J Bone Joint Surg Br 2012; **94**: 8-10.
6) Comadoll JL, Comadoll S, Hutchcraft A, et al. Comparison of hemostatic matrix and standard hemostasis in patients undergoing primary TKA. Orthopedics 2012; **35**: e785-93.
7) Thoms RJ, Marwin SE. The role of fibrin sealants in orthopaedic surgery. J Am Acad Orthop Surg 2009; **17**: 727-36.
8) Alcelik I, Pollock RD, Sukeik M, et al. A comparison of outcomes with and without a tourniquet in total knee arthroplasty: a systematic review and meta-analysis of randomized controlled trials. J Arthroplasty 2012; **27**: 331-40.
9) Hu S, Zhang ZY, Hua YQ, et al. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 2009; **91**: 935-42.
10) Ko PS, Tio MK, Tang YK, et al. Sealing the intramedullary femoral canal with autologous bone plug in total knee arthroplasty. J Arthroplasty 2003; **18**: 6-9.
11) Kapadia BH, Banerjee S, Issa K, et al. Preoperative blood management strategies for total knee arthroplasty. J Knee Surg 2013; **26**: 373-7.
12) Aguilera X, Martinez-Zapata MJ, Bosch A, et al. Efficacy and safety of fibrin glue and tranexamic acid to prevent postoperative blood loss in total knee arthroplasty: a randomized controlled clinical trial. J Bone Joint Surg Am 2013; **95**: 2001-7.
13) Chimento GF, Huff T, Ochsner JL Jr, et al. An evaluation of the use of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013; **28**: 74-7.
14) Ellegala DB, Maartens NF, Laws ER Jr. Use of FloSeal hemostatic sealant in transsphenoidal pituitary surgery: technical note. Neurosurgery 2002; **51**: 513-6.
15) Gall RM, Witterick IJ, Shargill NS, Hawke M. Control of bleeding in endoscopic sinus surgery: use of a novel gelatin-based hemostatic agent. J Otolaryngol 2002; **31**: 271-4.
16) Mathiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in children undergoing adenoidectomy. Otolaryngol Head Neck Surg 2004; **131**: 601-5.

17) Oz MC, Cosgrove DM 3rd, Badduke BR, et al. Controlled clinical trial of a novel hemostatic agent in cardiac surgery. The Fusion Matrix Study Group. Ann Thorac Surg 2000; **69**: 1376-82.
18) Renkens KL Jr, Payner TD, Leipzig TJ, et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. Spine (Phila Pa 1976) 2001; **26**: 1645-50.
19) Reuthebuch O, Lachat ML, Vogt P, et al. FloSeal: a new hemostyptic agent in peripheral vascular surgery. Vasa 2000; **29**: 204-6.
20) Richter F, Schnorr D, Deger S, et al. Improvement of hemostasis in open and laparoscopically performed partial nephrectomy using a gelatin matrix-thrombin tissue sealant (FloSeal). Urology 2003; **61**: 73-7.
21) Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br 2004; **86**: 561-5.
22) Blanie A, Bellamy L, Rhayem Y, et al. Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. Thromb Res 2013; **131**: e6-e11.
23) Guay J. Postoperative pain significantly influences postoperative blood loss in patients undergoing total knee replacement. Pain Med 2006; **7**: 476-82.
24) Alshryda S, Mason J, Vaghela M, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). J Bone Joint Surg Am 2013; **95**: 1961-8.
25) Baxter. Floseal® Hemostatic Matrix, 10 mL. Instruction for Use.
26) Aglietti P, Baldini A, Giron F, Sensi L. Minimally invasive total knee arthroplasty: is it for everybody? HSS J 2006; **2**: 22-6.
27) Kim HJ, Fraser MR, Kahn B, et al. The efficacy of a thrombin-based hemostatic agent in unilateral total knee arthroplasty: a randomized controlled trial. J Bone Joint Surg Am 2012; **94**: 1160-5.
28) Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012; **7**: CD004143.
29) Diiorio TM, Burkholder JD, Good RP, et al. Platelet-rich plasma does not reduce blood loss or pain or improve range of motion after TKA. Clin Orthop Relat Res 2012; **470**: 138-43.
30) Skovgaard C, Holm B, Troelsen A, et al. No effect of fibrin sealant on drain output or functional recovery following simultaneous bilateral total knee arthroplasty: a randomized, double-blind, placebo-controlled study. Acta Orthop 2013; **84**: 153-8.

Arrived: 8 August 2014 - Revision accepted: 24 November 2014
Correspondence: Emmanuel Thienpont
Department of Orthopaedic Surgery
Cliniques Universitaires Saint Luc
Av. Hippocrate 10
1200 Brussels, Belgium
e-mail: emmanuel.thienpont@uclouvain.be