Use of a haemostatic matrix (Floseal®) does not reduce blood loss in minimally invasive total knee arthroplasty performed under continued aspirin

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Background. Aspirin is being used for primary and secondary cardiovascular prevention. It has been proposed that aspirin should be discontinued 5 to 7 days before surgery. However, discontinuation might increase the risk of cardiac and thrombo-embolic co-morbidity. Aspirin also increases the risk of bleeding during and after total knee arthroplasty. This study evaluated if the intra-articular use of a haemostatic matrix (Floseal®) might decrease blood loss in total knee arthroplasty performed under continued aspirin use.

Materials and methods. We retrospectively compared matched pairs in two groups (80 patients in each group). Patients in both groups were taking aspirin: one group was managed with conventional haemostasis (with bovie electrocoagulation), while the other group was treated with an intra-articular haemostatic matrix as an adjunct to electrocoagulation. The outcomes compared were haemoglobin and haematocrit levels at days 2 and 4 after surgery as surrogates for blood loss, transfusion rate, surgical time, and length of stay in the hospital.

Results. No differences were observed between the two groups for haemoglobin and haematocrit levels on days 2 and 4. There were no differences in transfusion rate, surgical time or length of stay in hospital between the two groups.

Discussion. The present study shows that the use of Floseal® has no effect on reducing either visible or hidden blood loss after total knee arthroplasty with peri-operative continuation of aspirin use, as assessed by a drop in haemoglobin or haematocrit.

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

Introduction

Total knee arthroplasty (TKA) has been proven to be one of the best procedures for treating severe osteoarthritis of the knee. It can restore mobility and stability of the knee joint, relieve pain and re-establish the normal axis of the lower limb. Despite all these benefits, like any surgical procedure, TKA can be a source of complications. Intra-operative and post-operative blood loss can be such a complication. Bone and soft-tissue bleeding following TKA can be a major cause of morbidity leading to hypovolaemia, transfusion, pain, cardiac co-morbidity, slower rehabilitation because of haematoma formation, stiffness, wound breakdown and, potentially, an increased risk of infection[1-5]. Blood loss can be "visible", and estimated during the surgical procedure by a visual evaluation of the amount of aspirated blood during surgery, by weighing used sponges or by observing the amount of blood in the post-operative drain. Blood loss can also be "hidden" and happen after the operation (or after the removal of drains); it can either infiltrate into soft tissues or remain in the joint space as a haematoma. When a technique allows only an approximation of blood loss by the anaesthetist or surgeon, the observed blood loss is called estimated blood loss. Total blood loss is, however, a combination of visible and hidden blood loss. To include both visible and hidden blood loss, an alternative technique is to measure peri-operative blood loss by a calculated blood loss formula via changes in haemoglobin (Hb) and haematocrit changes. Studies have shown that total blood loss is 40% to 50% more than the estimated blood loss and that calculated blood loss approximates reality much more accurately. Reported estimates of blood loss during TKA still vary from 300 to 1,500 mL despite conventional methods of haemostasis such as bovie electrocautery[6,7].

Aspirin is an anti-platelet agent that is frequently used for treating common health problems (fever, headaches and arthritis) as well as for primary or secondary cardiovascular prevention (myocardial infarction and stroke). In addition, it is often used for thromboprophylaxis following cardiac stent procedures and after surgery in low-risk patients. The current literature about surgery while taking aspirin is mixed. It is well known that anti-platelet therapy, including aspirin, contributes to bleeding complications during surgery[8,9]. Aspirin inhibits platelet pooling for 10 days and, therefore, increases the risk of bleeding

during surgery. Stopping the anti-platelet therapy peri-operatively has been advocated to minimise the risk of complications related to post-operative bleeding. A recent consensus on peri-operative management of anti-platelet therapy suggests that acetylsalicylic acid given for primary prevention should be stopped 5-7 days before any type of surgery[10]. On the other hand, cessation before surgery may increase the thrombotic risk from aspirin withdrawal[11] and the risk of acute cardiovascular syndromes up to 10.2%[12]. For these reasons, several authors propose that the practice of empirically discontinuing aspirin pre-operatively should be abandoned[13,14].

The utility of a haemostatic matrix (HM), such as Floseal® (Baxter, Deerfield, IL, USA), has recently been tested in TKA but without clinical significance[15]. Floseal® is a haemostatic agent 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. The aim of this study was to evaluate whether the use of Floseal® as an adjuvant to conventional haemostasis reduces blood loss significantly in patients under anti-platelet therapy because of their higher risk of bleeding. We hypothesised that Floseal® applied during TKA surgery would reduce visible blood loss, as measured by the absence of a drop in Hb at day 2 after surgery in patients under continued aspirin therapy. A second hypothesis was that hidden blood loss, measured as a drop in Hb between postoperative day 2 and day 4 would also be reduced by the use of Floseal® in the aspirin group. Primary outcome criteria were: 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 and length of stay (LOS) in hospital, as an indicator of both speed of rehabilitation as well as 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, all under continued aspirin therapy, treated either with or without a HM, in a university hospital. The study was approved by the ethics committee of the hospital (Saint Luc University Hospital, Brussels, Belgium). Between 2006 and 2014, within a group of 1,200 consecutive patients undergoing primary knee arthroplasty performed by a single surgeon (ET) according to the inclusion criteria, TKA was performed either with a HM (n=450) or without the HM (n=750). During the 2-year period in which the HM was used, all consecutive patients had Floseal® applied to the bleeding areas of the knee 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 and after surgery on day 2, day 4, day 21 and 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 failure and use of anticoagulation medication other than aspirin. Patients were excluded from the retrospective data analysis if data were missing because the patient had left the hospital before the blood test on day 4, because he/she did not have blood work done on day 21 or day 42 or because demographic data, such as body mass index or pre-operative alignment, were missing. Two groups were formed; one group with 80 patients who underwent TKA under continued aspirin use and were treated with HM [HM (+) group] and a second group of patients, who were exactly matched with group one, who also underwent TKA while continuing to take aspirin but in whom the HM was not used [HM (−) group].

Characteristics of the study group

The following demographic data were collected for each TKA patient operated with or without the HM: age, sex, body mass index, type of anaesthesia, American Society of Anesthesiology (ASA) score and post-operative prophylaxis of deep vein thrombosis (Table I). Patients were stratified by gender, age (40-49, 50-59, 60-69, 70-79, 80-89 or 90-99 years), body mass index (≤24.9, 25-29.9, 30-34.9 or ≥35), post-operative prophylaxis of deep vein thrombosis (enoxaparin, nadroparin and rivaroxaban), anaesthesia (general anaesthesia) and ASA score (ASA 2 and 3). The TKA patients under aspirin treated with the HM were than compared to TKA patients under aspirin not treated with the HM in our database in order to match each patient exactly.

Surgical technique

General anaesthesia was given to all patients. Multimodal blood management was used consisting of peri-operative normothermia, administration of 1 g of tranexamic acid intravenously at induction and careful surgical dissection and electrocoagulation of known bleeders as well as compression bandaging after surgery. Prior to incision, the tourniquet was inflated to 280 mmHg and released after implantation of all components,

including the definitive liner. The 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, in the treatment group, 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 not covered 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), nadroparin (n=144) or rivaroxaban (n=12), 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 post-operatively on day 2, day 4, day 21 and day 42. Nadir values were compared. Gender differences for 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 patients' 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.

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

	Total	HM (+) group	HM (−) group	p-value
Number of patients	160	80	80	1.00
Sex F/M	100/60	50/30	50/30	1.00
ASA score 2	132	66	66	1.00
ASA score 3	28	14	14	1.00
Mean (SD) age [years] (range)	71.6 (8.5) (50-89)	71.8 (8) (57-89)	71.4 (8.5) (50-88)	0.78
Mean (SD) BMI [kg/m²] (range)	30 (5) (16-47)	30 (5) (16-42)	30 (5) (19.5-47)	0.75
Enoxaparin	4	2	2	1.00
Nadroparin	144	72	72	1.00
Rivaroxaban	12	6	6	1.00

HM: haemostatic matrix; ASA: American Society of Anesthesiology; SD: standard deviation; BMI: body mass index.

Secondary outcomes

Surgical time was retrieved from the anaesthetist's database. 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's 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 80 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 mean drop of 2.4 g/dL was observed for the HM (+) group and 2.3 g/dL for the HM (−) group. No differences were seen between the two groups in visible or hidden blood loss, evaluated respectively as a drop in Hb from the pre-operative day to day 2 and from day 2 to day 4. Results according to gender are shown in Table III. Among men and women, no differences were observed for Hb levels at day 2, 4, 21 or 42 between the two groups.

The results for haematocrit levels are presented in Table IV. No significant differences were seen between the two groups in the blood loss evaluated through the haematocrit.

Transfusion rates are presented in Table V. The transfusion rate for the HM (+) group was 1.3% (1 woman) while that for the HM (−) group was 2.5% (1 man and 1 woman) (p=1.00). In 21/80 patients in the HM (+) group and in 22/80 patients in the HM (−) group the pre-operative Hb level was between

13-11 g/dL, previously cited as a key level[1]. Of those patients, 79.5% were female. In 2/80 patients in the HM (+) group and 4/80 patients in the HM (−) group the pre-operative Hb level was lower than 11 g/dL[2]; 77.5% were female. Of the patients with a Hb between 11-13 g/dL, none underwent transfusion. For patients with a pre-operative Hb <11 g/dL, one out of two in the HM (+) group underwent transfusion as did one out of two in the HM (−) group.

Secondary end-points

The results for surgical time, tourniquet time and for hospital stay are presented in Table VI. No differences were seen between the two groups in terms of surgical time, tourniquet time or LOS.

Discussion

The major finding of this retrospective study of matched pairs is that the preventive application of Floseal® in areas at risk of bleeding during TKA in patients continuing to take aspirin brings no benefits in terms of blood loss compared to TKA in patients continuing to take aspirin in whom the only haemostatic therapy for bleeding was bovie electrocautery.

Aspirin inhibits the cyclo-oxygenase (COX) enzyme and, therefore, the production of prostaglandins[16]. There are two COX isoenzymes: COX-1 and COX-2. In platelets, COX-1 produces thromboxane A2, which allows platelets to activate and aggregate. Aspirin inhibits the COX-1 isoenzymes and, therefore, the production of thromboxane A2. This effect inhibits platelet pooling appreciably for 10 days. Some studies estimated that, as a consequence of this inhibition, aspirin increases blood loss from 1.57 to 2.08 times in arthroplasty surgery[8,9]. Current guidelines suggest stopping any anti-platelet therapy 5 to 7 days before surgery. The ASA recommends that anti-platelet therapy should be stopped approximately 1 week before surgery[17]. Korte *et al.* showed that it is preferable for patients with coronary artery disease to stop aspirin 5 to 7 days before any type of surgery. They also showed that for secondary prevention, stopping mono-therapy 5 to 7 days pre-operatively should be evaluated on a case-by-case basis when major bleeding complications are to be expected[10]. Nevertheless, aspirin has been reported to reduce the frequency of venous thrombosis, pulmonary embolism, and occlusive arterial events[18-20]. Furthermore, in a meta-analysis, Burger *et al.* showed that retrospective investigations revealed that aspirin withdrawal precedes up to 10.2% of acute cardiovascular syndromes (myocardial infarction, stroke, peripheral vascular occlusion, or cardiovascular death)[11]. Other studies recommend not stopping aspirin during surgery because of the thrombotic risk of the aspirin withdrawal syndrome (rebound of primary haemostasis after stopping aspirin)[11] and the low risk of bleeding

Table II - Haemoglobin levels in the two study groups.

Hb [g/dL]	HM (+) group			HM (−) group			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	13.6	1.5	(10.1-17.8)	13.4	1.5	(8.8-16.1)	0.36
Day 2	11.7	1.3	(9.5-15)	11.5	1.3	(9.1-14.3)	0.36
Day 4	11.2	1.4	(8.4-15)	11.1	1.2	(8.8-13.9)	0.52
Day 21	12.2	1.2	(8.6-14.9)	12.1	1.4	(7.8-15.4)	0.77
Day 42	12.7	1.4	(9.9-17.8)	12.7	1.4	(9.7-16.3)	0.86

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

Table III - Haemoglobin levels for men and women in the two study groups.

Men Hb [g/dL]	HM (+) group			HM (−) group			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	14.8	1.4	(11.8-17.8)	14.0	1.6	(8.8-16.1)	0.07
Day 2	12.2	1.2	(9.7-15.0)	11.8	1.5	(9.1-14.3)	0.28
Day 4	11.9	1.6	(9.6-15.0)	11.4	1.4	(9.6-13.9)	0.91
Day 21	12.7	0.9	(10.3-14.9)	12.7	1.6	(7.8-15.4)	1.00
Day 42	13.5	1.6	(11.1-17.8)	13.4	1.4	(10.2-16.3)	0.89
Women Hb [g/dL]	**HM (+) group**			**HM (−) group**			**p-value**
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	13.0	1.2	(10.1-15.5)	13.0	1.2	(10.1-15.3)	0.87
Day 2	11.4	1.2	(9.5-14.3)	11.3	1.1	(9.5-14.0)	0.74
Day 4	10.9	1.2	(8.4-13.8)	10.9	1.1	(8.8-13.7)	0.94
Day 21	11.9	1.2	(8.6-13.8)	11.8	1.3	(8.0-14.5)	0.89
Day 42	12.3	1.8	(9.9-14.7)	12.3	1.2	(9.7-15.0)	0.94

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

Table IV - Haematocrit levels in the two study groups.

Htc [%]	HM (+) group			HM (−) group			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Pre-op	40	4	(31-52)	40	4	(25-47)	0.38
Day 2	35	3	(29-44)	34	4	(26-42)	0.12
Day 4	34	4	(26-45)	33	3	(26-42)	0.41
Day 21	37	3	(27-43)	37	4	(23-46)	0.80
Day 42	39	4	(31-51)	38	3	(31-47)	0.61

Htc: haematocrit; HM: haemostatic matrix; SD: standard deviation; Pre-op: pre-operative.

Table V - Transfusions rates in the two groups.

	HM (+) group	HM (−) group	p-value
N. of patients transfused (%)	1 (1.3%)	2 (2.5%)	1.00
N. of units transfused	2	2	
Patients with pre-operative haemoglobin between 11-13 g/dL			
N.	21	22	
N. transfused (%)	0 (0%)	0 (0%)	1.00
Patients with pre-operative haemoglobin <11 g/dL			
N.	2	4	
N. transfused (%)	1 (50%)	2 (50%)	1.00

HM: hemostatic matrix; N: number.

Table VI - Surgical time, tourniquet time and length of hospital stay in the two study groups.

	HM (+) group			HM (−) group			p-value
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	
Surgical time [minutes]	103	19	70-192	105	20	68-181	0.48
Tourniquet time [minutes]	59	24	0-111	63	22	0-115	0.21
LOS [days]	4	2	3-14	5	2	2-11	0.37

HM: hemostatic matrix; SD: standard deviation; LOS: length of hospital stay.

in surgery while taking a low dose of aspirin[13,14]. In another clinical study of high-risk patients undergoing non-cardiac surgery, Oscarsson *et al*. showed that low-dose aspirin reduced the risk of post-operative major adverse cardiac events[21].

A far as we know, there are few studies of TKA under aspirin. The purpose of the present study was to find a new process of blood salvage to retain the benefits of aspirin while counteracting its disadvantages. Alshryda *et al*. tested topical tranexamic acid, an antifibrinolytic agent, as a method for decreasing blood loss[22]. 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 reduce blood loss in TKA in patients taking aspirin. The mechanical component of Floseal® induces 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. We hypothesised that the chemical component of the topical haemostatic agent would help palliate the deficiency of haemostasis caused by the inhibition of platelets.

One weakness of our study lies in the fact that we did not follow the application recommendations given by manufacturer of Floseal® exactly[23], 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 surgery. The potential sites of bleeding in knee arthroplasty are: the bone surfaces not covered 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. The product was, therefore, in contact with the patient's blood because of oozing during surgery and after release of the tourniquet; 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 a 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.

The strength of this study lies in the fact that all conditions were comparable for the two 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. Our study joins the current literature about Floseal®. In a randomised controlled trial in which Kim *et al*. evaluated the use of the thrombin-based sealant Floseal® during primary TKA, 196 patients were randomised to receive the topical spray intra-operatively[24]. No clinically significant differences were found between post-operative drain outputs, haemoglobin changes, transfusion rates, or post-operative complications. In another recent retrospective study, we showed that the use of Floseal® had no effect on reducing either visible or hidden blood loss after TKA[15]. Our study complements current findings and shows, with different outcomes, that the HM does not have sufficient effect to stand as a blood salvage technique in TKA performed in patients receiving aspirin.

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 a group of patients who received a solution of 2 mL of fibrinogen combined with 2 mL of thrombin and the control group of patients[25]. Our results were similar to theirs because no difference in hidden blood loss was observed between the two groups: the loss was consistently from 0.4 to 0.5 g/dL of Hb between days 2 to 4. We can, therefore, conclude that Floseal® has no effect on visible and hidden blood loss during aspirin therapy.

Salido *et al*. demonstrated in their study that patients with a low pre-operative hemoglobin (<13 g/dL) were at higher risk of needing allogeneic transfusion[1]. Nevertheless, in our study no patients with a pre-operative Hb between 11 and 13 g/dL required transfusion in either of the two groups, despite the fact that all the patients were receiving aspirin. This observation suggests that multimodal blood management is a protective factor against blood loss and transfusion, even in patients taking anti-platelet therapy. Multimodal blood management could be the solution to maintain anti-platelet therapy during TKA to avoid the risks associated with the interruption of these drugs. Our study also suggests that the transfusion risk cut-off with this modern method of blood management would have to be 11 g/dL.

Furthermore, the experience of the surgeon can be a part of the equation of blood management.

Conclusions

This study on the use of a HM in TKA with continuation of peri-operative aspirin use showed that the application of Floseal® had no effect on reducing either visible or hidden blood loss after TKA, as measured by a drop in Hb or haematocrit.

Funding

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

Authorship contributions

PES and ET both designed the study and wrote the paper.

The Authors declare no conflicts of interest with the present study.

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Arrived: 22 February 2015 - Revision accepted: 24 March 2015
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