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Aspirin mono-therapy continuation does not result in more bleeding after knee arthroplasty

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Abstract
Purpose Current clinical practice guidelines sometimes still recommend stopping aspirin five to seven days before knee arthroplasty surgery. Literature regarding multimodal blood management and continuation of anti-platelet therapy in this type of surgery is scant. The study hypothesis was that knee arthroplasty under low-dose aspirin mono-therapy continuation does not cause more total blood loss than knee arthroplasty performed without aspirin. Blood loss would be measured by haemoglobin (Hb) and haematocrit (HTC) levels drop at day 2 or day 4 for patients who benefit from multimodal bleeding control measures.
Methods A database of all patients undergoing knee arthroplasty between 2006 and 2014 was analysed. Demographic, surgical and complete blood workup data were collected. A retrospective comparison study analysed both groups in terms of blood loss, by mean calculated blood loss as haemoglobin or haematocrit drop between the pre-operative Nadir value and the postoperative day 2 and 4 value. A group of 198 (44 UKA and 154 TKA) patients underwent surgery without interrupting their aspirin therapy for cardiovascular prevention. Mean (SD) age was 71 (8) and the mean (SD) BMI was 29 (5.5) kg/m^2. The control group consisted of 403 (102 UKA and 301 TKA) patients who were not under aspirin, or any other anti-platelet agent. Mean (SD) age was 65 (10) ($p < 0.05$) and the mean (SD) BMI was 29 (5.0) kg/m^2 (n.s.). All patients in the control group were randomly selected.
Results There were no differences in terms of visible (early) or hidden (late) blood loss as measured by Hb drop in between both groups. There is no difference in transfusion rates.
Conclusions Modern multimodal blood management provides sufficient blood loss prevention during and after knee arthroplasty to allow physicians to continue low-dose aspirin mono-therapy for cardiovascular prevention.
Level of evidence III.

Keywords Total knee arthroplasty · Unicompartmental knee arthroplasty · Blood loss · Haemoglobin · Aspirin

Introduction

Joint arthroplasty is considered a high-risk procedure both for bleeding and for venous thromboembolic events (VTE) (4,15). Knee arthroplasty can result in substantial bleeding ranging, according to different authors, from 500 to 1500 ml of estimated blood loss [12, 25, 26]. When hidden blood loss is considered and a calculated blood loss (CBL) formula, based on haemoglobin changes, is used, volumes of 1000–2000 ml can be observed [18, 23, 31, 34]. Transfusion rates after TKA can range as high as 63–94 %, according to some authors [2, 10, 31].

Aspirin, an irreversible cyclo-oxygenase (COX) enzyme inhibitor, is frequently used for treating common health problems as well as for cardiovascular prevention at both the primary (preventing first occurrence of disease) and secondary level (preventing recurrence of disease). Aspirin is not only a non-steroidal anti-inflammatory drug but also an anti-platelet agent (4, 27). It works by inhibiting the synthesis of thromboxane A2 (TXA2), a potent stimulator of platelet aggregation, and therefore inhibits platelet pooling

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for 8–10 days [15, 29]. Because of its anti-platelet effect, aspirin is often used for thromboprophylaxis following cardiac stent procedures but has also been reported to reduce the frequency of venous thrombosis (VTE), pulmonary embolism (PE) and occlusive arterial events [5]. In many studies on aspirin continuation, a bleeding event (minor or major) was documented [23, 26].

The American Academy of Orthopedics Surgeons (AAOS) in its 2011 guidelines recommends discontinuing anti-platelet therapy prior to undergoing elective hip and knee replacement surgery (moderate recommendation grade) [23]. Similarly, recent clinical practice guidelines on aspirin use for primary prevention in patients with coronary disease as well as a guideline for primary prevention of arterial thromboembolism by the American College of Chest Physicians (ACCP) propose stopping aspirin seven to 10 days before surgery [13, 21]. The side effects of abruptly interrupting aspirin therapy can be important. Aspirin withdrawal causes a more rapid return of platelet aggregation and a platelet rebound phenomenon in the setting of acute aspirin withdrawal. This rebound period is characterized by increased thromboxane production, decreased fibrinolysis, an increase in fibrin strength and a resultant clinical prothrombotic state [6, 14]. Preoperative aspirin cessation might increase the risk of acute cardiovascular events up to 10.2 and 6.1 % for lower limb ischaemic events after surgery [8, 9, 11]. A meta-analysis of 50,279 patients taking low-dose aspirin for secondary prevention showed that the risk of arterial thromboembolism after aspirin withdrawal was threefold higher than in those who continued taking it [8].

The correct peri-operative management of aspirin is still a remaining challenge, finding the balance between the bleeding risk and the potential thromboembolic complications of an aspirin withdrawal syndrome (8). Multimodal blood reduction measures are part of the peri-operative management in most of the arthroplasty centres around the world (18, 23, 31). The hypothesis of this retrospective study was that current multimodal blood management is sufficiently performing to reduce visible and hidden blood loss enough to allow low-dose aspirin mono-therapy continuation in the peri-operative phase of TKA surgery.

Materials and methods

A prospective database with blood tests performed preoperatively at day 2 and day 4 was available for all patients undergoing primary knee arthroplasty from 2006 to 2014 in our department. In this study, patients undergoing minimally invasive (MI) knee arthroplasty for osteoarthritis, by a single surgeon (ET), in the Saint Luc University Hospital, Brussels, Belgium, were retrospectively reviewed for blood loss. The data were retrieved from the operating software for patients' medical records of our institution (Medical Explorer v3r9 Saint-Luc Hospital, 2008). One group of 198 (44 UKA and 154 TKA) patients operated on under low-dose aspirin continuation was selected from all consecutive cases. These patients were under aspirin mono-therapy for cardiovascular prevention and had followed the advice not to stop their aspirin treatment. The other group consisted of a random sample of 403 (102 UKA and 301 TKA) patients operated on without having ever been under aspirin. The Ethical Committee of the Saint Luc University hospital, Brussels, Belgium, approved this retrospective study (B4032011111567).

The inclusion criterion for the group under aspirin was ongoing, peri-operative low-dose aspirin therapy. The inclusion criteria for the group without aspirin were absence of current or recent aspirin therapy, no history of cardiovascular events (myocardial infarction or stroke), no bleeding events, no history of deep vein thrombosis (DVT) or pulmonary embolism (PE), a Lee score of I (postoperative cardiovascular events risk score), or an American Society of Anesthesiologist score (ASA) of 1 or 2. The exclusion criteria for both groups were previous high tibial osteotomy or arthrotomy except for open meniscectomy, presence of metallic hardware, known bleeding disorders, diagnosis other than osteoarthritis, and use of anti-aggregation therapy like clopidogrel-containing products or anticoagulation therapy (anti-vitamin K or heparin) before surgery. Demographic data and baseline characteristics of both study groups at baseline are given in Table 1.

Multimodal blood management protocol

General anaesthesia was used for all included patients with intensive per-operative temperature monitoring and prevention of hypothermia. At induction 1 g of tranexamic acid was administered to all patients. Prior to incision, the tourniquet was inflated to 280 mmHg and released after implantation of all components. An identical minimally invasive medial approach was performed in both groups. A mean (SD) incision length of 12 (2) cm was made for the UKA and a mean (SD) length of 16 (4) cm was made for the TKA. All UKA patients received a cemented ZUK (Zimmer, Warsaw, USA) with metal backing of the tibial component. An extramedullary guide was used on the tibial side with a spacer technique for the femoral side. All TKA patients received a cemented, posterior stabilized Vanguard (Zimmer Biomet, Warsaw, USA) prosthesis with resurfacing of the patella. An extramedullary guide was used on the tibial side and the femoral hole was plugged in every TKA. Bovie coagulation was used on the soft tissue areas and nothing was used on the bony surfaces. No drains were used.

Table 1 Demographic data and baseline characteristics of both study groups

Variables	Total	With aspirin	Without aspirin	*P*
Number of patients	601	198	403	
Mean age (SD)	67 (10)	71 (8)	65 (10)	<0.05
Mean BMI (SD)	29 (5)	29 (5.5)	29 (5)	n.s.
Gender				
Women	390	113	277	
Men	211	85	126	
Type of prevention aspirin use				
Primary	121	121	0	
Secondary	77	77	0	
Dose of aspirin				
80 mg	138	138	0	
100 mg	46	46	0	
160 mg	12	12	0	
330 mg	2	2	0	
History of cardiac events				
Total	121	106	0	
Myocardial infarction	37	37	0	
Stroke	10	10	0	
Other	74	74	0	
History of bleeding events	55	55	0	
History of thrombosis events				
Total	40	40	0	
Deep vein thrombosis	30	30	0	
Pulmonary embolism	10	10	0	
Diabetic				
Type 1	2	2	0	
Type 2	46	46	0	
Renal failure	15	15	0	
Tobacco use				
Current	19	19	0	
History	35	35	0	
Antihypertensive treatment	163	163	0	
Knee arthroplasty				
UKA	146	44	102	
TKA	455	154	301	
Lee score				
I	530	127	403	
II	59	59	0	
III	10	10	0	
IV	2	2	0	
ASA score				
1	50	2	48	
2	515	160	355	
3	36	36	0	
Postoperative anti-thrombosis prevention				
Enoxaparin	49	7	42	
Nadroparin	522	180	342	
Rivaroxaban	30	11	19	

Table 2 Haemoglobin levels in the two study groups

Hb (g/dl) (SD)	UKA		*P*	TKA		*P*
	With aspirin	Without aspirin		With aspirin	Without aspirin	
Preop	13.7 (1.4)	13.9 (1.3)	n.s.	13.4 (1.7)	13.6 (1.3)	n.s.
Day 2	13.0 (1.1)	13.0 (1.2)	n.s.	11.6 (1.4)	11.8 (1.3)	n.s.
Day 4	12.6 (1.4)	12.9 (1.3)	n.s.	11.2 (1.4)	11.3 (1.4)	n.s.
Day 21	13.1 (1.4)	13.3 (1.2)	n.s.	12.1 (1.5)	12.4 (1.2)	<0.05
Day 42	13.3 (1.3)	13. (1.1)	n.s.	12.8 (1.6)	12.9 (1.2)	n.s.
Difference Preop and Day 2	0.9 (0.8)	0.9 (0.9)	n.s.	1.8 (1.1)	1.9 (1.1)	n.s.
Difference Day 2 and Day 4	0.3 (0.8)	0.1 (0.9)	n.s.	0.4 (0.7)	0.4 (0.7)	n.s.

Table 3 Calculated blood loss in the two study groups

	UKA		*P*	TKA		*P*
	With aspirin	Without aspirin		With aspirin	Without aspirin	
CBL (cc) (SD)	369 (213)	508 (289)	n.s.	858 (479)	866 (455)	n.s.

The rehabilitation program 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 enoxaparin ($N = 49$), nadroparin ($N = 522$) or rivaroxaban ($N = 30$). Dose was 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.

Primary outcomes

Hb and HTC levels were determined for each patient before and after surgery and on postoperative days 2 and 4 through blood tests for both groups. Transfusions, if any, and number of units transfused, were noted in the prospective database. The American Association of Blood Banks clinical practice guideline on transfusion recommends the use of restrictive protocols in which transfusion is considered only in patients whose haemoglobin level is ≤8 g/dL. The guideline recommends the use of clinical symptoms as well as haemoglobin levels in determining when to use transfusion [3, 7, 10, 20]. These criteria were strictly applied and the decision to transfuse was taken by our internist (JCY). HTC levels and drop in HTC levels were also compared between both groups. Total blood loss (TBL), including 'visible' and 'hidden' blood loss, was estimated as calculated blood loss (CBL) using the change in HTC, according to Gross et al. [18] with the following formula:

$$\text{CBL} = \text{Total Blood Volume (TBV)} \times (\text{HTC initial} - \text{HTC final})/\text{HTC mean}$$

The patient's total blood volume (TBV) was calculated as:

$$\text{TBV} = 0.3669 \times \text{height (in m}^3\text{)} + 0.03219 \times \text{weight (in kg)} + 0.6041$$

for men and

$$\text{TBV} = 0.3561 \times \text{height (in m}^3\text{)} + 0.03308 \times \text{weight (in kg)} + 0.1833$$

for women [31].

Secondary outcomes

Tourniquet and total surgical time recorded by the anaesthetist were collected for analysis. Hospital stay (LOS) was considered in order to evaluate the impact of blood transfusion on LOS, if any.

Statistical analysis

Sample characteristics are presented as numbers, means, standard deviations and ranges. The normal distribution of the data was assessed by the Kolmogorov–Smirnov test. Abnormally distributed data were analysed using nonparametric statistical tests for continuous data, such as the Mann–Whitney *U* test for independent samples and Student's *t* test for dependent samples. Comparison of observed proportions was performed using Chi-square and Fisher's exact test for categorical data. Statistical analysis was conducted with SPSS 21 Statistical Software (SPSS Inc, Chicago, IL, USA) and significance was set at $P < 0.05$. Based on previous publications on blood loss, sample size was considered sufficient [30].

Table 4 Transfusion rates in the two groups

	UKA		*P*	TKA		*P*
	With aspirin	Without aspirin		With aspirin	Without aspirin	
Total number of patients	44	102		154	301	
Number of patients transfused	0	0	n.s.	3	3	n.s.
Number of units transfused	0	0	n.s.	4	3	n.s.
Patient with preoperative haemoglobin between 13 and 11 g/dL						
Number	7	19		42	77	
Number transfused	0	0	n.s.	0	0	n.s.
Patient with preoperative haemoglobin <11 g/dL						
Number	2	1		8	5	
Number transfused	0	0	n.s.	3	3	n.s.

Results

Primary outcomes

For UKA patients, both groups had the same preoperative haemoglobin level and no differences were observed post-operatively at days 2, 4, 21 and 42.

For TKA patients, both groups had the same preoperative haemoglobin level without significant difference. In addition, there were no differences between patients with and without aspirin for visible (between preoperative and day 2) and hidden blood loss (between day 2 and day 4). Nevertheless, there was a difference in the mean (SD) haemoglobin level between the groups at day 21: 12.1 (1.5) g/dL in patients with aspirin and 12.4 (1.2) g/dL in patients without aspirin ($P < 0.05$). At day 42, there were no differences between both groups. The results are presented in Table 2.

For UKA and TKA, there were no differences in terms of calculated blood loss (total blood loss: visible and hidden blood loss) between patients with and without aspirin. The results are presented in Table 3.

Transfusions occurred only in patients who underwent total knee arthroplasty, both with and without aspirin. Three patients in each group (a total of six patients) with a preoperative haemoglobin level below 11 g/dL required transfusion. There were no differences in terms of transfusion between the two TKA groups (n.s.). No patients with a preoperative level above 11 g/dL were transfused. The results are presented in Table 4.

There were no differences in visible and hidden blood loss between TKA under aspirin for primary or secondary prevention as described by the American College of Chest Physicians [13]. The results are presented in Table 5.

Secondary outcomes

There were no differences in terms of surgical time and length of hospital stay between the aspirin and control group for both UKA and TKA. Nevertheless, there was a significant difference between the two TKA groups regarding the tourniquet time: 59 min for patients under aspirin and 65 min for patients without aspirin ($P < 0.05$). For the UKA group, there were no differences between both groups for tourniquet time. The results are presented in Table 6.

Table 5 Haemoglobin levels between patients who take aspirin for primary or secondary prevention in TKA

Hb (g/dl) (SD)	Primary prevention	Secondary prevention	*P*
Preop	13.3 (1.6)	13.5 (1.7)	n.s.
Day 2	11.6 (1.4)	11.7 (1.5)	n.s.
Day 4	11.2 (1.5)	11.1 (1.4)	n.s.
Day 21	12.0 (1.4)	12.2 (1.7)	n.s.
Day 42	12.7 (1.6)	13.1 (1.5)	n.s.

Discussion

The most important finding of this retrospective study was that with current multimodal blood management low-dose aspirin mono-therapy could be continued in the peri-operative period of knee arthroplasty. There is no difference between patients with and without aspirin in terms of visible and hidden blood loss, either for unicompartmental or for total knee arthroplasty.

Knee arthroplasty is an interesting study model to analyse the risks or benefits of continuing low-dose aspirin in the peri-operative setting. TKA is a surgical procedure that is considered at risk both for bleeding and for thromboembolic events [13]. Current literature is still suggesting that the bleeding risk is higher than the risk of peri-operative thrombotic events, including myocardial infarction and stroke. Therefore, the current consensus is still to stop aspirin 5–7 days before knee arthroplasty [13, 23].

Table 6 Secondary outcomes in the two study groups

	UKA		*P*	TKA		*P*
	With aspirin	Without aspirin		With aspirin	Without aspirin	
Procedure time min (SD)	73 (10)	77 (19)	n.s.	100 (19)	103 (22)	n.s.
Tourniquet time min (SD)	46 (15)	49 (15)	n.s.	59 (23)	65 (19)	<0.05
Length of hospital stay days (SD)	3 (1)	3 (1)	n.s.	4 (2)	4 (1)	n.s.

Preoperative haemoglobin level is known to be a risk factor for transfusion after knee arthroplasty [2, 33]. Patients with preoperative haemoglobin levels lower than 13 g/dL [29] or lower than 11 g/dL [17] are more likely to have blood transfusions after knee arthroplasty. In this study, no patients with a haemoglobin level between 13 and 11 g/dL received transfusion. For UKA, none of the patients were transfused. As shown in a previous study, UKA is a safe procedure in terms of blood loss and risk of transfusion [30]. Nevertheless, for TKA there were three patients in each group, with a preoperative haemoglobin level lower than 11 g/dL, who received transfusion after surgery. Knee arthroplasty under aspirin continuation is a safe procedure for patients with preoperative haemoglobin higher than 11 g/dL; moreover, it does not lead to a greater risk of transfusion in patients with a preoperative haemoglobin level lower than 11 g/dL.

The recent guideline for the use of aspirin in non-cardiac surgery by the ACCP proposes peri-operative antithrombotic management based on risk assessment for thromboembolism and bleeding [13]. It is recommended that patients be stratified according to their risk of thromboembolism. For high-risk patients, such as those taking aspirin for secondary prevention, it is recommended that it should be continued peri-operatively. For low-risk patients, such as those taking aspirin for primary prevention of arterial thromboembolism, stopping aspirin seven to 10 days before surgery is still recommended [13]. Our study demonstrated that for both groups, under aspirin for either primary or secondary prevention purposes, there were no differences in terms of blood loss at days 2 and 4. This study suggests that we can continue aspirin for high- and low-risk patients to minimize the risk of arterial thromboembolism in both groups. Continuing aspirin eliminates the need for accurate patient stratification and the risk of complications in a group that was estimated low risk.

This study has a number of limitations. The first and main limitation is that it is a retrospective study. These results must be confirmed by a prospective randomized study with a higher level of evidence. Nevertheless, this study shows that little blood loss is observed during modern knee arthroplasty under aspirin. All consecutive aspirin patients were included since the day it was decided to advice patients (1 January 2011) not to stop aspirin anymore before surgery. Furthermore, our large database allowed us to randomly select an important control group with patients without history of bleeding events, cardiovascular or thrombotic events and tobacco use. The patients in this control group all had a co-morbidity score ASA 1 or 2, as well as a postoperative cardiovascular risk score (LEE) of I. The findings of this study are therefore more interesting because the control group carried a minimal bleeding risk compared to the aspirin continuation group. Patients were older and with more co-morbidity since fragile patients are more often under aspirin than the healthy ones [2].

A second limitation is the difference in age of each study group. The mean age of the group under aspirin was 71 and the mean age of the group without aspirin was 65 ($P < 0.05$). The patients without aspirin that were randomly selected were younger. Ahmed et al. [2] found with a regression analysis that patient age is a significant independent factor predicting the need for blood transfusion. In this study, patients under aspirin had a higher risk of bleeding than the group without aspirin simply because of their age. Despite this great discrepancy in terms of risk, no differences in blood loss or transfusion were found. The limitation therefore becomes a strength for the study.

A third limitation is that the surgeon (ET) who performed the surgeries is a high-volume arthroplasty surgeon interested in blood reduction techniques for many years. The experience and training of the surgeon can enter in the equation of blood management and offer a protective factor against bleeding during knee surgery (15, 21, 26, 34). Zhang et al. [36] found in their study about the learning curve of minimally invasive Oxford phase 3 unicompartmental knee arthroplasty that a surgeon with a higher experience in the field of arthroplasty had a significantly lower perioperative blood loss. Aglietti et al. also showed that the ideal surgeon for minimally invasive TKA is a trained surgeon who is able to anticipate possible sources of mistakes and therefore causes less blood loss [1].

A last limitation was that all patients were under a deep venous thrombosis (DVT) prevention protocol other than aspirin. Therefore, this study did not analyse venous thromboembolic events (VTE) as an endpoint. Despite this low molecular weight heparin regime, no difference in blood loss was observed for the

group under low-dose aspirin as compared to the control group. There were no effusions or prolonged wound drainage limiting patients to leave the hospital or asking for a revision surgery. This observation emphasizes that aspirin can be continued in the peri-operative phase after knee arthroplasty, even when combined with more advanced VTE prophylaxis.

The strength of this study lies in the fact that this is, to the best of our knowledge, the first study that shows the impact of modern multimodal blood management in knee arthroplasty under aspirin mono-therapy continuation with a large sample size of 601 knee arthroplasties covering a broad population, ranging from ASA 1 to 3. Furthermore, the study was performed in standardized conditions with all patients operated on by a single surgeon, with the same implants for UKA and TKA and under the same type of anaesthesia. Blood values were prospectively obtained at 48 h which seems to be the best timing for Hb level check because of ongoing fluid shifts after surgery [34] and also at 96 h to evaluate if there is still some late hidden blood loss in TKA.

The clinical relevance of this study lies in the fact that under multimodal blood management conditions aspirin mono-therapy can be continued since bleeding will not be more important and therefore the risk for postoperative morbidity and mortality of any type of thromboembolic event due to aspirin withdrawal syndrome can be avoided.

Conclusions

The decision to stop aspirin mono-therapy, given for primary prevention, before knee arthroplasty for blood loss reduction reasons might not be justified anymore with the current multimodal blood management protocols at our disposal. Continuing aspirin during unicompartmental and total knee arthroplasty appears to be safe for the bleeding risk and protects patients from a potential withdrawal syndrome, which might cause postoperative cardiovascular, arterial and venous thrombotic events.

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