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ORIGINAL STUDY

Anticoagulant use and its effect on bleeding and complications in total knee arthroplasty

Ingrid RADOVANOVIC, Joseph QUEALLY, Syah BAHARI, James SPROULE, John MCELWAIN

From Adelaide and Meath National Hospital, Dublin, Ireland

Currently, there is very limited literature on the effect of long term anticoagulants on total knee arthroplasty. The primary purpose of this study was to determine the effect of warfarin and clopidogrel on the transfusion rate, intra-operative blood loss, and post-operative blood loss for total knee arthroplasty. The secondary purpose was to determine their effect on post operative wound complications and length of stay. Data was collected retrospectively from medical charts between 2003-2008 and case matched to a control group. The patients on warfarin had a higher rate of blood transfusion, blood loss, and length of hospital stay compared to the clopidogrel and control groups.

Keywords : knee arthroplasty ; warfarin ; clopidogrel ; blood transfusion.

INTRODUCTION

Anticoagulants are now widely used in the prevention of thrombotic events in patients with coronary artery disease, cardiac arrhythmias, cerebrovascular disease, valvular heart disease, previous pulmonary embolism and post coronary stenting (*1,7,8,13*). Clopidogrel, an inhibitor of platelet aggregation (*11*) and warfarin, an inhibitor of the synthesis of vitamin K- dependent clotting factors (*12*), are two commonly used agents. The use of these agents has increased dramatically in recent years, especially among the elderly population. These patients are at an increased risk of perioperative bleeding and it's associated complications as has been demonstrated by studies in the cardiothoracic literature with regards to emergency procedures (*2-6,10*). Consequently, the current American College of Cardiology/American Heart Association guidelines recommend that clopidogrel be discontinued 5-7 days prior to both urgent and elective cardiothoracic surgery (*1*).

Currently there are no guidelines in place regarding the management of patients on anticoagulants undergoing elective total knee arthroplasty. Similarly, evidence on the effect of long term anticoagulation on perioperative bleeding and its complications in total knee arthroplasty is limited (*12*). In our practice, to reduce the potential increased risk of perioperative bleeding, we advise patients to discontinue their anticoagulant prior to elective total knee arthroplasty as per the American College of Chest Physician's guidelines (*9*). The evidence to date on the effect of anticoagulants on patients

■ Ingrid Radovanovic, MRCSI, Registrar.
■ Joseph Queally, MRCSI, Registrar.
■ Syah Bahari, MRCSI, Registrar.
■ James Sproule, FRCSI, Registrar.
■ John McElwain, FRCSI, Consultant.
Department of Trauma & Orthopaedic Surgery, Adelaide and Meath National Hospital, Dublin, Ireland.
Correspondence : Ingrid Radovanovic, Apt 401 565 Proudfoot Lane, London, Ontario, N6H 0A1, Canada.
E-mail : ingasps@hotmail.com

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undergoing surgical procedures while on an anticoagulant is limited mainly to cardiothoracic studies. The majority of these studies describe patients who are commenced on clopidogrel as a result of an acute ischaemic event and are typically on clopidogrel for a short period (5-7 days) prior to coronary artery bypass surgery (*2,3.4,5,6,10*). Limited data is available regarding the effect of prolonged clopidogrel or warfarin use on perioperative bleeding. The aim of this study was to assess the effect of long-term anticoagulant use on perioperative bleeding in elective total knee arthroplasty (TKA). We specifically assessed the two most common anticoagulants (warfarin and clopidogrel) used in our patient population.

METHODS

Patient Population

Twenty patients on warfarin and 10 patients on clopidogrel who underwent elective total knee arthroplasty were included in the study. Inclusion criteria included patients on long term warfarin or clopidogrel (> 3 months) who underwent total knee arthroplasty under spinal anaesthesia over a 6 year period (2003-2009). Patients had to discontinue clopidogrel for at least 5 days prior to surgery while those on warfarin had to discontinue their medication (typically for 3-5 days) until a target INR less than 1.4 had been reached. Exclusion criteria included patients with a known history of anaemia or bleeding disorders. Indications for anticoagulation included atrial fibrillation, ischaemic heart disease, valvular heart disease, and previous thromboembolic events (Table I). Patients in the anticoagulant groups were compared to a control group of patients who were not on an anticoagulant. The patients in the control group were matched for sex and age.

All patients in both treatment and control groups were placed on either low molecular weight heparin subcutaneously (or intravenous heparin where indicated) on admission prior to surgery. All procedures were performed by the senior author (JPM). All patients undergoing total knee arthroplasty had standard tourniquet control, three drain placement and limb compression bandaging afterwards. All patients were recommenced on their respective anticoagulant on the first day after surgery. Bridging low molecular heparin was discontinued in the warfarin group when the INR returned to a level > 1.5.

The patients were retrieved retrospectively from our pre-assessment clinic database from 2003 to 2009. Demographic and outcome data was collected from retrieved patient charts. Our primary outcome was transfusion rate and wound complications (infection, haematoma and wound ooze) related to perioperative bleeding of the anticoagulant groups compared to their respective control group. Secondary outcomes included blood loss, operating time and length of stay.

For continuous variables, we compared the study arms using the Student paired t test. For categorical variables we compared the study arms using the chi square test. Post operative complications were documented as a binary number where 0 meant no complication occurred and 1 indicated a complication had occurred. Analysis was performed using Analyze-It-Software (Analyze-It, Leeds, UK). A p value < 0.05 was considered significant.

RESULTS

The control groups were matched to their respective treatment groups to control for age and sex. Regarding our primary outcome for transfusion rate, patient on warfarin were more likely to require a blood transfusion (40%, $p = 0.03$) compared to those not on anticoagulant (13%), despite discontinuation of the anticoagulant preoperatively (Table I). In agreement with an increased requirement for transfusion, perioperative blood loss was greater in patients on warfarin undergoing total knee replacement, although the difference was not statistically significant ($p = 0.0839$). However, the increased requirement for a blood transfusion was not accompanied by an increased risk of wound complications in patients undergoing total knee replacement procedures (see Table I).

Patients undergoing total knee replacement who discontinued their clopidogrel preoperatively were not at an increased risk of requiring a blood transfusion relative to the respective control group (Table I). In agreement with this, there was no significant difference in perioperative blood loss ($p = 0.324$) or complications associated with perioperative bleeding. Overall the risk of wound complications was equal between all groups ranging between 20-30%.

In terms of secondary study outcomes, the operating time was significantly longer in the warfarin (129 min, $p = 0.0254$) and clopidogrel group

Table I. — Patient characteristics and outcomes for total knee arthroplasty

Patient Characteristic	Warfarin (n = 20)	Clopidogrel (n = 10)	Control (n = 30)
Male, number (%)	8 (40%) p = 0.36	6 (60%) p = 0.46	14 (47%)
Age (years), mean +/- SD	71 ± 9 p < 0.05	70 ± 12 p < 0.05	70 ± 9
Indication for anticoagulation			
Atrial Fibrillation	12	0	1
Deep vein thrombosis	3	1	0
Valvular Heart Disease	0	0	0
Artificial Valve	0	0	0
Study Outcomes			
Transfusion			
Yes	8 (40%)	2 (20%)	4 (13%)
No	12 (60%) p = 0.03	8 (80%) p = 0.6	26 (87%)
Transfusion (units/patient)			
Units 0	12	8	26
1	0	0	0
2	4	1	4
3+	4	1	0
Perioperative blood loss (mL) (intra-op + post-op)	779 (194 +585) p = 0.0839	864 (276 + 569) p = 0.324	557 (63 + 494)
Wound Complication			
Ooze	5	1	8
Haematoma	0	0	0
Infection	2	1	1
Wound Complication Occurrence			
Yes (%)	6 (30%)	2 (20%)	9 (30%)
No (%)	14 (70%) p = 0.9401	8 (80%) p = 0.5165	21 (70%)
Operative time (min)	129 p = 0.0254	123 p = 0.0582	104
Length of stay (days)	21 p = 0.0001	15 p = 0.0132	10

p values refer to the comparison of the anticoagulant group versus the control group.

(123 min, p = 0.0753) compared to the control group (104 min). The length of stay was longer in the warfarin group compared to the clopidogrel and control groups (21, 15, 10 days respectively).

DISCUSSION

This study clearly demonstrates that patients on the anticoagulant warfarin over a prolonged period prior to elective total knee arthroplasty are at risk for increased perioperative bleeding and blood transfusion even though they discontinue warfarin preoperatively as per the American College of Chest Physicians' guidelines (9). This did not translate to an increase in wound complications related to bleeding. In contrast to this, patients on clopidogrel undergoing total knee replacement, who discontinued it preoperatively were not at an increased

risk of blood transfusion or perioperative wound complications relative to control.

Despite an increase in the prevalence of anticoagulated patients presenting for total knee arthroplasty, a literature review only identified one study that investigated the effect of preoperative anticoagulation on perioperative bleeding in patients undergoing lower limb arthroplasty (*12*). Rhodes *et al* investigated the effect of discontinuing warfarin preoperatively in total knee arthroplasty (*12*). Unlike our study, they did not specifically compare a chronically anticoagulated patient group with a chronically non-anticoagulated group, but evaluated the effect of discontinuing warfarin preoperatively in patients on long term warfarin. They retrospectively compared 39 patients who had their warfarin discontinued preoperatively with 38 patients who continued to take their warfarin as normal. They found no difference in the rates of postoperative blood transfusions and complications related to perioperative bleeding, leading them to conclude that discontinuing warfarin was not necessary in patients undergoing TKR. Taking into account our findings, this seems to suggest that patients undergoing total knee arthroplasty on warfarin are at an increased risk of perioperative bleeding, but this risk is not affected by the patient discontinuing their warfarin preoperatively.

Our finding that clopidogrel does not increase the risk of perioperative bleeding and it's associated sequellae if it is has been discontinued for 5 days preoperatively prior to surgery is similar to the findings of a number of cardiothoracic surgery studies which have evaluated the effect of preoperative clopidogrel on perioperative bleeding in coronary artery bypass graft procedures (*2,3.4,5,6,10*). In a recent systematic review, Carrel *et al* concluded that there is a moderately elevated risk of bleeding in patients who undergo coronary artery bypass (CABG) while on clopidogrel without discontinuing it preoperatively (*4*). After 5 days they concluded that the risk of perioperative bleeding reduces to control group levels. This is reflected in the American College of Cardiology/American Heart Association guidelines which recommend that clopidogrel be discontinued 5 days prior to CABG surgery (*1*). In our study, despite being off clopidogrel for at least 5 days, patients on long term clopidogrel were more likely to have perioperative bleeding, although this did not translate into a significant increased need for blood transfusion.

It is not clear why patients on warfarin are at a higher risk of perioperative bleeding, despite discontinuing the anticoagulant preoperatively until an INR < 1.4 while patients on clopidogrel are not at risk. As warfarin and clopidogrel work via different physiological pathways, (warfarin selectively inhibits vitamin K dependent factors II, VII, IX and X (*12*) whereas clopidogrel is an antiplatelet agent), a pharmacologic mechanism, not reflected in the usual bleeding time indices may be responsible. Another possibility is that patients on warfarin may have a more significant co-morbid illness profile which results in an anticoagulant state.

Limitations to this study include it being a retrospective, observational and single centre study. Secondly, we did not report complications as per severity, rather treating then as binary variables in our analysis, thus in this study wound ooze carries the same severity as a wound re-exploration. Also the analysis was not risk adjusted for medical co-morbidities, with patients in the anticoagulant groups being more likely to suffer from a co-morbid illness. This may contribute to their increased risk of perioperative bleeding. However, our conclusion remains valid, i.e. that this patient group is at a higher risk of perioperative bleeding relative to a control group.

In conclusion, the data herein demonstrates that patients on warfarin who are undergoing total knee arthroplasty are at an increased risk of perioperative bleeding and are more likely to require a blood transfusion despite the discontinuation of their anticoagulant preoperatively. Clopidogrel, once it is discontinued for 5 days preoperatively, does not increase the risk of perioperative bleeding. This is the first study to compare an anticoagulated patient group undergoing total knee arthroplasty with a non-anticoagulated group. In terms of reducing the risk of perioperative bleeding in patients on warfarin undergoing lower limb arthroplasty, we do not recommend that patients should be left off their anticoagulant for longer than recommended by current guidelines due to the accruing risk of a

thrombotic event. However, patients on warfarin should be informed prior to total knee arthroplasty of the increased risk of perioperative bleeding and the need for a blood transfusion. Strategies to reduce perioperative blood loss such as perioperative autotransfusion should also be considered in this patient group.

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