TITLE

Primary joint replacement surgery: is the risk of major bleeding higher in elderly patients? A retrospective cohort study.

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ABSTRACT:

Introduction: Pharmacological prophylaxis for venous thromboembolism is recommended for the vast majority of patients undergoing major orthopedic surgery. Increased risk of bleeding after the use of these agents has been widely documented in general population. Conversely, the frequency of this complication has not been studied in the subpopulation of elderly patients. The purpose of this study is to determine whether the risk of major bleeding after major orthopedic surgery is higher in elderly patients, compared to those operated at a younger age. ***Methods***: We performed a retrospective cohort study including patients who underwent total hip and total knee arthroplasty during five consecutive years. Patients with other causes of bleeding were excluded. Medical records were reviewed in order to determine the occurrence and manifestation of major bleeding. A nested case-control analysis was used to determine which age group had the greatest odds ratio (OR) for major bleeding. Then, we compared two cohorts grouped by age. Relative risks (RR) and confidence intervals (CI) were calculated and a multivariate analysis was performed. ***Results***: A total of 1048 patients were included in the analysis. Of these, 56% corresponded to hip joint replacements and 44% to knee joint replacements. The case control analysis reported that patients who were 70 years or older at the time of surgery had the highest OR (2.61) for major bleeding, therefore a limit of 70 years old was established to create two cohorts. At the time of surgery 553 (53%) patients were 70 years or older while 495 (47%) were younger. Patients who were ≥70 years old showed an increased risk of major bleeding: RR 2,42 (95% CI: 1.54-3.81). After total hip arthroplasty the RR was 2,61 (95%CI: 1.50-4.53) and after total knee arthroplasty was 2.25 (95% CI: 1.03-4.94). After the multivariate analysis, age continued to be independently associated with a higher risk of major bleeding. ***Conclusion***: This study allows to conclude that patients who are 70 years or older are at a higher risk of major bleeding after major orthopedic surgery than younger patients. Therefore, the use of appropriate strategies to mitigate the risk in this group of patients is encouraged.

KEY WORDS

Aged, Aged, 80 and over, Postoperative Hemorrhage, Anticoagulants, Arthroplasty, Replacement, Hip, Arthroplasty, Replacement, Knee.

INTRODUCTION

The use prophylactic anticoagulant agents is one of the most effective strategies to prevent the onset of venous thromboembolism following major orthopedic surgery (1–4). However, thromboprophylaxis has been associated with an increased risk of major bleeding, intracranial bleeding and fatal bleeding (5–7).

With aging, the onset of comorbidities and impairment of hepatic, renal and cardiac function increases not only the risk of developing thromboembolic events but also the incidence of major bleeding (7–10). Therefore, appropriate pharmacologic prophylaxis for elder patients undergoing primary joint replacement is critical to reduce morbidity, mortality and additional costs (1,7,11).

Despite that numerous studies have assessed the efficacy and safety of different anticoagulant agents in general population (12–14), there is still a lack of evidence regarding its use in special populations such as elderly patients, considering that patients who are candidates to major orthopedic surgery are frequently older than 65 years (10,15,16).

Based on physiological changes, some guidelines recommend the administration of adjusted doses according to age, body mass index and renal or hepatic function (1,17). However, the effect of age on the risk of bleeding and thrombotic events after major orthopedic surgery has not been clearly identified. In the literature, age is both described to increase this risk independently (5,18,19) or not to be associated at all (8,9). To our knowledge there are no studies that assess directly the risk of bleeding after joint replacement surgery in elderly patients. Thus, the aim of this study is to identify the risk of major bleeding after hip or knee replacement surgery in patients 70 years or older, in comparison to those who are younger at the time of surgery.

MATERIALS AND METHODS

A retrospective cohort study including consecutive patients who underwent primary total hip or total knee joint replacement between January 2009 and July 2013 was performed. All patients diagnosed with degenerative joint disease were included. Patients who received simultaneous bilateral arthroplasty, patients with chronic use of anticoagulant therapy, congenital or acquired coagulation disorders, active cancer or requiring a second surgical intervention during hospitalization were excluded. Patients were followed until hospital discharge.

All patients were screened for medical risks and contraindications for surgery before the procedure. All hip replacements were performed through a mini-incision posterolateral approach and knee replacements through either a mid-vastus or a medial parapatellar approach with the use of a tourniquet. After surgery, pharmacologic prophylaxis was prescribed according to institutional guidelines. Postoperative hemoglobin was measured at 6 hours after skin closure and blood transfusion was decided according to this result and clinical signs and symptoms.

Main outcomes were major bleeding and/or thromboembolic disease. Major bleeding was defined according to European Medicines Agency (EMA) (Table 1) (17). Thromboembolic disease was defined as the presence of deep vein thrombosis confirmed by Doppler ultrasound, pulmonary embolism confirmed by CT Angiography and/or ventilation/perfusion scan or death caused by thromboembolism.

Statistical Analysis

Sample size was calculated assuming a 1:1 ratio between patients <70 and ≥ 70 years old, alpha error of 5% and power of 80%. The minimum detectable relative risk (RR) was established as 1.8, with a confidence interval of 95% at 2 queues. Assuming an expected frequency of patients with major bleeding of 8% in the study group and a 5% of losses, a minimum of 400 patients in each group was defined.

A case-control analysis was carried out to identify the highest odds ratio (OR) for major bleeding at different age groups (60, 65, 70 and 75), in order to determine the age limit to divide the sample into two cohorts. After this analysis, it was found that the OR for major bleeding increased with age, however, from 75 years and over there was no longer statistically significance. Accordingly,

the limit age to divide the two study groups was set at 70 years old. A homogeneity test was performed to confirm that groups were comparable. The RR and 95% confidence interval for major bleeding was calculated and a chi-square ($\chi 2$) test was used to assess statistical significance (p-value less than 0.05). A logistic multivariate regression analysis was established to evaluate the association of other variables (different from age) with major bleeding using a p-value < 0.05.

RESULTS

A total of 1062 patients were identified. Of these, fourteen were excluded: 5 patients had history of active cancer, 1 patient had simultaneous bilateral arthroplasty, 4 patients did not receive pharmacologic prophylaxis according to institutional guidelines and 4 patients had incomplete medical records (Figure 1).

Among 1048 patients included in the analysis, 553 (53%) were older than 70 years, 495 (47%) were hip replacements, average body mass index (BMI) was 26.76 kg/m^2 and mean preoperative hemoglobin was 14.48 g/dL (Table 2).

In the group of patients younger than 70 years, creatinine clearance levels were higher compared to older patients, however this difference was not statistically significant (P=0.3). In both groups preoperative and postoperative hemoglobin levels were similar. There were no significant differences in major bleeding associated with the pharmacological agent prescribed.

Ninety patients (8.58%) met at least one criterion for major bleeding. From these, 24 patients younger than 70 years (4.85%) and 65 patients older than 70 years (11.75%) required transfusion in the postoperative period ($p < 0.005$). Within the ≥70 years old cohort, three cases of surgical site bleeding and 2 cases of gastrointestinal bleeding were reported (Table 3). Relative risk of major bleeding in patients ≥70 years was 2.42 (95% CI: 1.54 – 3.81).

In the analysis performed by type of surgery, 66,7% of major bleeding events among the <70 years cohort and 63.6% from the ≥70 years old cohort, were patients who underwent hip replacement surgery, and for knee replacement surgery, major bleeding events were present in 36.4% and 33.3%, respectively (Table 5). Relative risk after hip arthroplasty was 2.61 (95% CI: 1.50-4.53) and 2.25 (95% CI: 1.03-4.94) after knee arthroplasty (Figure 2).

According to the multivariate analysis, age was an independent risk factor for major bleeding and other variables, such as gender, BMI, creatinine clearance and type of pharmacologic prophylaxis were not statistically significant.

Overall prevalence of pulmonary embolism was 0.76%: 3 cases were identified in patients aged 70 years and older and 5 cases in patients aged less than 70 years. One case of deep vein thrombosis

was observed in the group of older patients and three cases in the other group. During the study period 3 deaths occurred, but none were related to bleeding or pulmonary embolism.

DISCUSSION

As life expectancy increases, the demand for joint replacement surgery in elderly patients is also growing (16,20,21). Even though elderly patients are considered at higher risk for bleeding and venous thromboembolism (5,7,10) most studies that assess safety and efficacy of VTE prophylaxis after major orthopedic surgery did not include an independent analysis or special considerations for this population (6,13,14,22–26). Therefore, recommendations of dose adjustments are only based on the assumption of a physiological impairment of renal and hepatic function that occurs with age, but not on objective evidence of the increased risk of bleeding in this group of patients (15,27–29).

In this study, an association between the occurrence of major bleeding events after major orthopedic surgery and age older than 70 years was found. The increased risk of bleeding within this group of patients was statistically significant, not only in the overall analysis, but also in the analysis by type of surgery. This difference between cohorts was found to be independent of renal function, preoperative hemoglobin or type of anticoagulant. These results are comparable to those reported by Ahmed et al., where the rate of blood transfusion increased with age and preoperative hemoglobin, age and weight were found to be independent predictors of blood transfusion requirement (19). Similarly, Pola et al., reported higher rate of blood transfusion in patients older than 75 years old (8 out of 20 patients) compared to those younger than 75 years old (16 out of 65), but did not find a statistically significant difference with younger patients due to small sample size ($p=0.1$) (18).

In addition to this findings, whether the risk of bleeding in patients older than 70 years is due to an increased susceptibility to the administration of anticoagulants, to a decreased tolerance to blood loss or to physiological impairment of renal function that occurs with age (15,28,30), the exact mechanism of this phenomena remains to be established.

Despite major bleeding was defined according to all four EMA criteria (17), the vast majority of our cases were classified only by requirement of blood transfusion of 2 or more units. Although preoperative and postoperative hemoglobin levels did not differ significantly between groups, older patients were transfused more frequently than younger patients. It is possible that this observation can be attributed to a lack of a standardized protocol for blood transfusion, that physicians could

be more likely to prescribe transfusions to older patients or that these patients are more susceptible to develop physiological changes with blood loss. Even though age, weight and preoperative hemoglobin have been demonstrated to be risk factors for blood transfusion (9,18,19), identification of blood transfusion criteria needs to be established, since this intervention represents increased morbidity and costs (9,18).

The inability to determine indications for transfusion in this cohort of patients could be the most important weakness of this study. Conversely, the sample size, that allowed us to find significant differences in both procedures and the cohort design study that also allowed to homogenize the sample and isolate age as an independent variable, were identified as main strengths.

The outcomes reported in study confirm that patients over 70 years old are at higher risk of major bleeding after MOS. Despite some limitations, the strength of these results should encourage physicians to implement strategies to balance the risk in this special population.

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Figure 1. Diagram of patient selection.

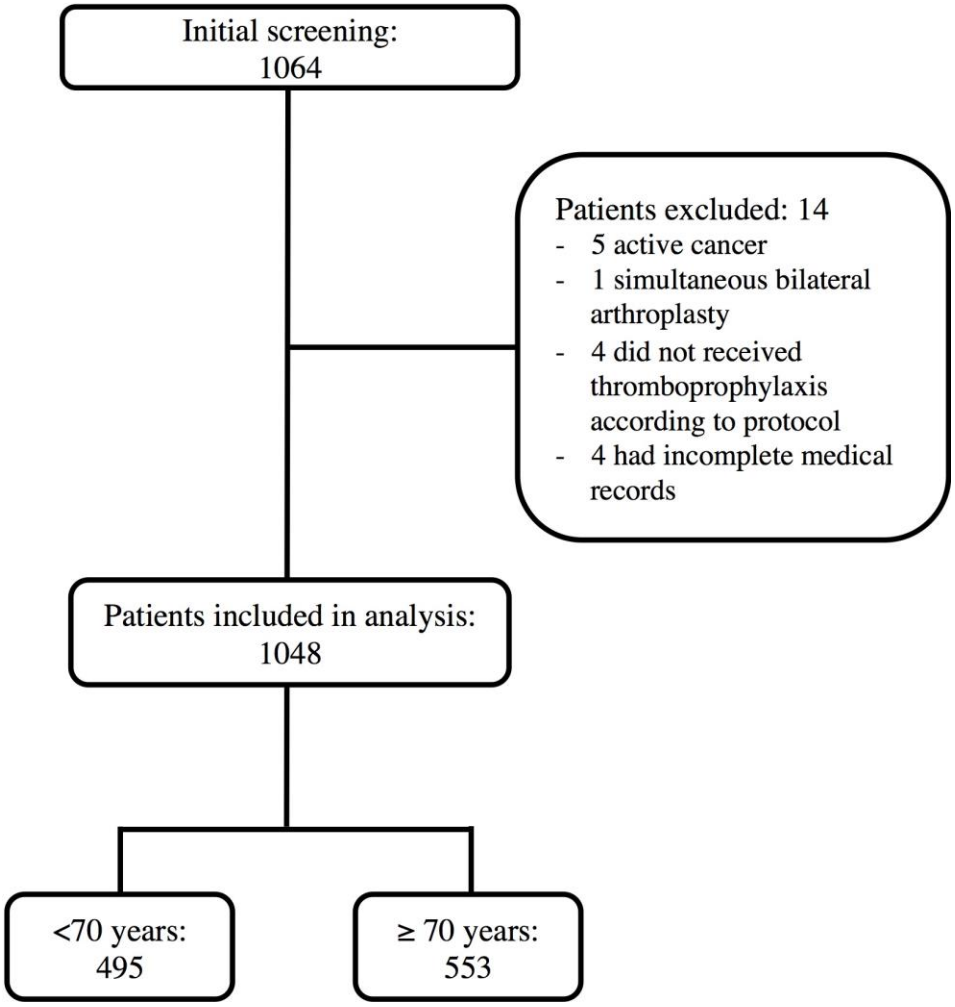

Figure 2. Graph of relative risk for major bleeding after major orthopedic surgery in patients older than 70 years.

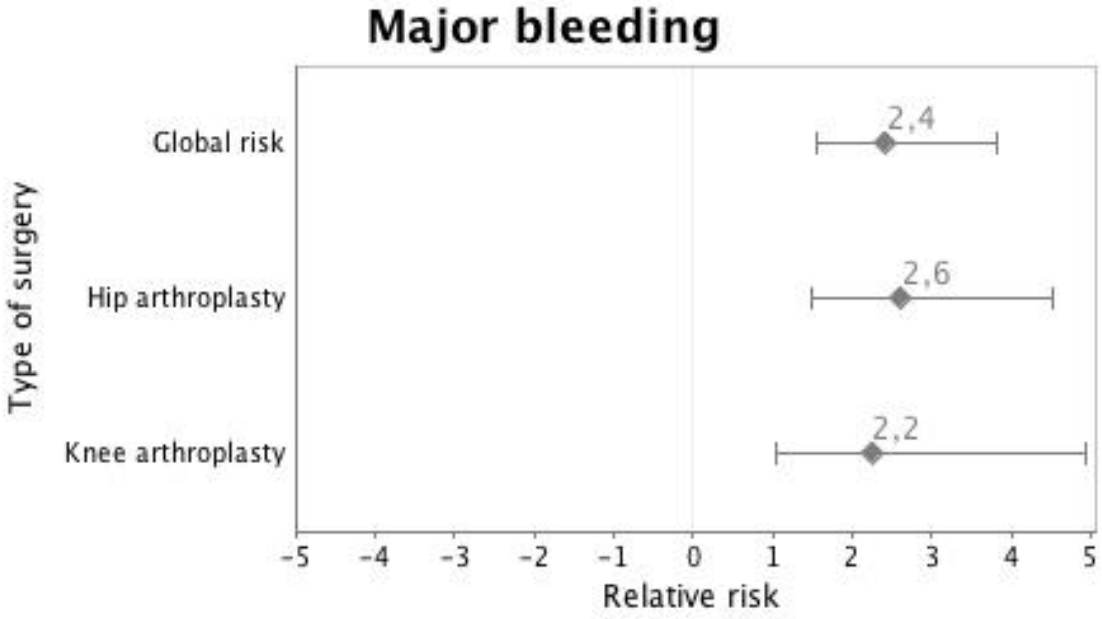

Table 1. European Medicines Agency criteria for major bleeding.

Bleeding event that meets at least one of the following criteria:	
Fatal bleeding	
Critical bleeding	Intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular or intramuscular with compartment syndrome.
Clinically overt bleeding associated with a decrease in the haemoglobin level of more than 2 g/dL	
Clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells	
Clinically overt bleeding leading to surgical intervention	

Table 2. Demographic and clinical characteristics of patients included in the study.

Variable	N (%)		*P-value*
	< 70 years	**≥ 70 years**	
Number of patients	495 (47)	553 (53)	
Age (mean)	60 years	77 years	
Sex			
Male	136 (27,8)	141 (25,5)	0,46
Female	359 (72,3)	412 (74,5)	
Body Mass Index (mean)	27,17 kg/m2	26,37 kg/m2	0,01
Type of surgery			
Hip arthroplasty	290 (58,6%)	292 (52,8%)	0,11
Knee arthroplasty	205 (41,4%)	261(47,2%)	0,32
Creatinine Clearance (mean)	90,1 mL/min	65 mL/min	0,02
Hemoglobin (mean)			
Preoperative	14,58 gr/dl	14,39 gr/dl	0,06
Postoperative	11.71 gr/dl	11.54 gr/dl	0,15
Prophylactic agent			
Dabigatran	25 (5)	33(6)	
Fondaparinux	35 (7)	33 (6)	
LMWH	109 (22)	183 (33)	
Rivaroxaban	326 (66)	304 (55)	

Table 3. Number of cases of major bleeding according to EMEA criteria.

Criteria for Major Bleeding*	< 70 years N (%)	≥ 70 years N (%)
Total of patients who presented major bleeding	24 (4.85)	66 (11.9)
Fatal bleeding	0	0
Critical bleeding	0	0
Gastrointestinal bleeding	0	2 (0.36)§
Clinically evident bleeding		
Surgical site bleeding requiring re-operation¶	1 (0.20)	2 (0.36)
Transfusion >2 RBC units	24 (4.85)	65 (11.75)

*Patients can present with more than one criterion
§Only one patient required blood transfusion of two or more RBC units.
¶All patients required blood transfusion of two or more RBC units.

Table 5. Cases of major bleeding by type of surgery.

Type of surgery	**Major bleeding N (%)**	
	< 70 years	**≥ 70 years**
Hip replacement	16 (66.7)	42 (63.6)
Knee replacement	8 (33.3)	24 (36.4)