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Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications

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ABSTRACT

Introduction: Direct oral anticoagulation agents (DOACs) are increasingly prescribed to older adults. Concerns for perioperative blood loss dictate cessation of anticoagulation treatment and postponement of surgery until the coagulation system returns to normal state. The goal of this study is to compare the estimates of perioperative blood loss and mortality between patients using DOACs and patients receiving no anticoagultaion, in order to challenge the existing policy and question the need for surgery deferral.
Materials and methods: This is a retrospective cohort of patients (age > 65) with proximal hip fractures treated with either closed reduction internal fixation (CRIF, n = 1143; DOAC use n = 60) or hemi-arthroplasty (HA, n = 571; DOAC use n = 29). Baseline patient characteristics included age, gender, ASA score, socioeconomic level, type of surgica#1: In general a l treatment, duration of surgery and time from admission to surgery. The effect of anticoagulant prescription on percentage of hemoglobin change, odds of receiving blood transfusions and one-month and one-year mortality was evaluated separately for CRIF and HA patients.
Results: Patients receiving DOACs had similar perioperative hemoglobin change, transfusion rates and mortality, compared to subjects without anticoagulants in both CRIF and HA cohorts. DOAC patients undergoing CRIF had a longer delay to surgery (40.2 ± 26.9 vs 31.2 ± 22.2, $p = 0.003$) and higher mortality rates at one year postoperatively (26.7% vs 16.1%, $p = 0.015$).
Conclusions: DOAC use was not associated with an increased perioperative blood loss or mortality compared to controls. However, they had to wait longer for surgery, which itself was an independent predictor of mortality. It may be safe to shorten waiting time for surgery in patients using anticoagulation, with the goal to minimize surgery delay.

Introduction

Chronic oral anticoagulation use was estimated to be prevalent in 2.83 million (M) patients in the United States in the last quarter of 2014. About 1million of the above patients were using one of the four available direct oral anticoagulants (DOACs) [1]. The use of oral anti-aggregation and anti-coagulation agents is prevalent in up to 40% of the patients presenting with acute hip fractures [2]. Following a fracture, these medications are often stopped and surgery is delayed due to the concern of higher intra-operative bleeding when the medication is still active [3,4]. The drawbacks of such policy are surgery delay and higher risk of thromboembolic events [5,6], both capable of increasing the risk of mortality [7–9]. Returning to DOACs, the rationale that drug activity is associated with intraoperative bleeding is not based on firm evidence [10]. Similar assumption regarding bleeding risk associated with clopidogrel was previously overturned [11]. Moreover, it is questionable, whether preoperative bleeding from the fracture site while waiting for surgery is as clinically significant as the intra-operative blood loss, especially when the operation consists of closed reduction and fixation through limited exposure. Two recent studies failed to demonstrate higher blood loss with DOACs, though study samples were relatively small [12,13].

Current protocols for preoperative cessation of DOACs are relatively complex. Lacking direct evidence of the association drug cessation and perioperative blood loss, the protocols are based on the knowledge of drug pharmacokinetics. A working group on perioperative hemostasis, in 2013, recommended, for the perioperative management of patients using DOACs, that patients who need urgent surgery with hemorrhagic risk will be operated once the drug plasma concentration reaches 30 ng/ml or less. Above 30 ng/ml the intervention should be postponed whenever possible,

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by monitoring the drug concentration, which is expected in most cases with normal renal function go below 30 ng/ml within 12–24 hours. In a minority of the patients, especially those with impaired renal function, surgery delay to extend up to 48 h [14].

In light of the evidence suggesting higher mortality with surgery delay of 48 h or more [9,15], the pressure to expedite surgery urged to evaluate the above guidelines. A more recent paper dealing with perioperative management of patients treated with DOACS, which was published after the emergence of specific reversal options for those drugs (Idarucizumab, andexanet alfa and PER 977), some of which are already approved and some are still in different trial stages, states that depending on the urgency of surgery required, a 12-hr delay before the procedure is recommended and is typically sufficient for most patients. However, in cases of severe bleeding or emergent surgery that cannot be delayed, the clinician needs to consider reversal options that would be appropriate for the given patient and the specific DOAC [16].

The goal of this study is to compare the risk of perioperative bleeding and mortality after emergent hip fracture surgery in patients using DOACs and patients having no chronic anticoagulant prescription.

Methods

The study is a retrospective cohort of patients with proximal hip fractures operated in a single urban tertiary trauma center between 2011 and 2016. Subjects younger than 65 years, as well as subjects who received antiaggregation treatment and subjects who underwent total hip arthroplasty for intracapsular hip fractures, were excluded.

The study cohort was divided into two smaller cohorts by type of the surgery. First cohort included subjects with intertrochanteric fractures and femoral neck fractures managed with closed reduction internal fixation techniques ("CRIF" cohort). Second cohort included patients with femoral neck fractures treated with hemiarthroplasty ("HA cohort"). The rationale for the above division is that in the CRIF group the majority of blood loss in the perioperative period had probably occurred from the fracture site prior to surgery, without significant bleeding during the surgery or afterwards, when the fracture was fixed. Conversely, with hemiarthroplasty, the intraoperative blood loss could be equal or even exceed the blood loss from the fracture site. According to this reasoning, waiting for the coagulation system to return to normal prior to surgery may be more important in the HA group, compared to CRIF.

According to guidelines for anticoagulation cessation in the institution at which this study was conducted, patients taking Rivaroxaban and Apixaban were operated after 24–36 hours, given that the patient had a normal kidney function [17]. Similarly, patients using Dabigatran were operated at least 12–24 hours since last tablet [18]. In both drug groups, when creatinine clearance was low, the operation was further delayed until decrease of the drug blood levels below the therapeutic range [14].

The available baseline demographic information were age, gender and socio-economic grade (from 1 to 20 according to mean income per living area, provided by the Central Bureau of Statistics). Medical data included ASA (American Society of Anesthesiologists) score, preoperative hemoglobin levels, surgery type, admission time and surgery time. In many patients several hemoglobin values were recorded prior to surgery and three days after surgery. We choose highest preoperative hemoglobin value and lowest postoperative hemoglobin value within three days from surgery for estimation of perioperative blood loss.

Anticoagulation exposure data was taken from the patients' chronic medication lists on admission and served for divison of the study population into three groups: no anticoagulant use (control group), coumadin and DOACs (apixaban, rivaroxaban and dabigatran). Concurrent use of aspirin and antiplatelet agents (clopidogrel, prasugrel and ticagrelor) was recorded to evaluate for possible confounding effect in multivariate analysis. There was no information about time of last dosing of the medication or its blood levels at the time of surgery, but it was safely assumed that all patients were operated according to the medication cessation protocols [17,18].

Outcome data included percent perioperative hemoglobin change (difference between pre- and post-operative hemoglobin levels divided by preoperative hemoglobin level and multiplied by 100), blood transfusions within one week from surgery and mortality (at one month and at one year postoperatively).

Statistical analysis started from univariate exploration of study variables, checking for normal distribution of continuous variables and error values and outliers. Next, a bivariate analysis of baseline demographic and medical factors was performed in order to present difference between the exposure groups. ANOVA with Bonferroni correction was performed for comparison of continuous variables (age, time from admission to surgery, duration of surgery and preoperative hemoglobin), followed by pairwise comparisons of each anticoagulation groups with patients using no anticoagulation. Nominal and ordinal variables were compared using chi-square test. Alpha and beta parameters were set at 0.05 and 0.2, respectively.

Percentage of hemoglobin change was calculated as difference between preoperative and postoperative hemoglobin divided by preoperative hemoglobin and the multiplied by 100. The resulting values distributed normally and were therefore compared between the control group and each anticoagulation group using t-test. Blood transfusion therapy in this patient cohort was administered when Hb level was below 7 g/dL, when Hb level was 7–9 in patients with ischemic heart disease, acute renal failure, tachycardia, shortness of breath, syncope; or in cases of acute ongoing bleeding with significant hemoglobin decrease. Percent of patients who received at least one transfusion, percent of patients who died within one month and percent of patients who died within two months were compared between the study groups with chi-square test. Next, a multivariate regression analysis was done to adjust the above outcomes for baseline variables. Linear regression was used to predict the percent of perioperative hemoglobin change, and logistic regression was used to predict the odds of receiving blood transfusions and to die within one month and one year from surgery. Only variables that were significantly different between patient groups were included in regression analysis.

The study was approved by the medical center institutional review board. Data query was performed by the quality control unit. Data analysis was done using R - the open-source statistic software. The results were presented according to the STROBE guidelines for reporting observational research studies.

Results

A total of 3455 patients with hip fractures underwent surgery during the study period. Patients younger than 65 (n = 424) and patients who received only anti-aggregation agents (n = 1317) were excluded. The remaining 1714 patients (1143 in CRIF group and 571 in HA group) were included in the final patient cohort. Of these, 1466 received no anticoagulation prior to admission, 159 received coumadin and 89 received DOACs.

In the CRIF group, there were 60 patients using DOACs (14 (23%) with aspirin and 5 (8.3%) with clopidogrel). In the HA group, there were 29 patients using DOACs (4 (14%) with aspirin and none (0%) with clopidogrel).

Patient baseline characteristics are presented in Table 1. Patients receiving DOACs who underwent CRIF were older than

Table 1
Baseline characteristics of patients.

	Closed reduction internal fixation (n = 1143)			Hemiarthroplasty (n = 571)		
	No anticoagulants (n = 977)	DOACs (n = 60)	p-value	No anticoagulants (n = 489)	DOACs (n = 29)	p-value
Age	82.7 ± 8.0	86.1 ± 5.7	0.001	82.8 ± 7.6	86.2 ± 7.1	0.02
Gender (% men)	22%	26.7%	0.5	31.5%	44.8%	0.2
Socio-economic level	16.5%	8.3%	0.1	14.6%	12.5%	0.95
low	35.3%	29.2%		31.2%	33.3%	
middle	48.2%	62.5%		54.2%	54.2%	
high						
ASA score	58%	22%	<0.001	51.4%	31%	0.05
1-2	42%	78%		48.6%	69%	
3-4						
Duration of surgery	110.7 ± 48.9	122.0 ± 58.0	0.09	126.2 ± 39.8	143.7 ± 38.5	0.02
Preoperative Hb	11.9 ± 1.6	11.7 ± 1.7	0.3	12.3 ± 1.5	12.1 ± 1.6	0.6
Time from admission to surgery	31.2 ± 22.2	40.2 ± 26.9	0.003	36.6 ± 25.8	42.3 ± 27.3	0.3
% Surgeries within 48 hours	82%	74%	0.2	77.5%	74%	0.9

*Significance $p < 0.05$ compared to controls.
DOAC - direct oral anticoagulation medications, ASA score – American Society of Anesthesiology score.

controls ($p = 0.001$), had significantly higher burden of chronic disease, as reflected by ASA score ($p < 0.001$) and were operated after a significant delay (40.2 ± 26.9 vs 31.2 ± 22.2, $p = 0.003$). In the HA group, the DOAC patients were similarly older than controls and more of them had ASA scores of 3 or 4, but they did not experience as higher surgery delay compared to controls. Duration of surgery was significantly longer in DOAC patients undergoing HA (143.7 ± 38.5 vs 126.2 ± 39.8, $p = 0.022$) (Table 1).

Percent Hb change was similar between DOACs and controls, in both HA and CRIF cohorts (Table 2). Rates of blood transfusions were similar between patients using DOACs and patients using no anticoagulation in CRIF and HA. One-year mortality was higher among DOAC patients who underwent CRIF, compared to controls ($p = 0.015$).

Linear regression showed that age, higher ASA score and longer duration of surgery were significant predictors of percent hemoglobin change in CRIF group, while in the HA group these were only age and higher ASA score (Table 3). A multivariate logistic regression showed that in the CRIF patients, age, ASA score and duration of surgery were significant determinants of blood transfusions. In the HA group, the determinants of the need for blood transfusion higher ASA score and longer duration of surgery (Table 4). One-year mortality in both CRIF and HA groups was increased by older age, higher ASA score and longer surgery delay, whereas female gender had a protective effect (Table 4).

Discussion

The objective of this study was to compare estimates of perioperative bleeding and mortality between subjects receiving direct oral anticoagulation medications and patients receiving no anticoagulation. The results show similar hemoglobin values and hemoglobin change, as well as similar blood transfusion rates between these two groups, regardless of the type of surgery they had. Adjusted mortality risk was similar between patients using DOACs and patients using no anticoagulation, in both study cohorts (HA and CRIF). However, surgery delay, which was an independent predictor of mortality, was higher among patients using DOACs.

The results advocate challenge of the existing policy of surgery delay in patients using DOACs and undergoing CRIF. As mentioned previously, the concern with expediting the surgery in these

Table 2
Blood loss estimates and mortality of the patients treated with DOACs and the controls.

	Closed reduction internal fixation (n = 1143)			Hemiarthroplasty (n = 571)		
	No anticoagulants (n = 977)	DOACs (n = 60)	p-value	No anticoagulants (n = 489)	DOACs (n = 29)	p-value
% Hb change	24.0 ± 10.8	22.6 ± 9.7	0.332	21.0 ± 9.2	21.7 ± 10.4	0.698
% Subjects who required blood transfusion	7.9%	8.3%	0.807	7.4%	10.3%	0.472
% One-month mortality	4.4%	6.7%	0.343	6.1%	6.9%	0.698
% One-year mortality	16.1%	26.7%	0.047	21.1%	13.8%	0.479

DOAC - direct oral anticoagulation medications.

Table 3
The effect of demographic and treatment characteristics on perioperative percent hemoglobin change (linear regression).

	Closed reduction internal fixation (n = 1143)		Hemiarthroplasty (n = 571)	
	Beta coefficient	p-value	Beta coefficient	p-value
DOAC use	−1.42	0.340	0.73	0.70
Age	0.11	0.019	0.12	0.04
Female gender	1.02	0.222	1.34	0.15
ASA 3-4	−1.81	0.012	−2.23	0.01
Duration of surgery in minutes	0.02	0.008	0.01	0.26

DOAC - direct oral anticoagulation medications, ASA score – American Society of Anesthesiology score.

Table 4
The adjusted risk of blood transfusion and one-year mortality in the patient groups.

	Closed reduction internal fixation (n = 1143)		Hemiarthroplasty (n = 571)	
	Adjusted odds of blood transfusion OR (95%CI)*	Adjusted odds of one-year mortality OR (95%CI)**	Adjusted odds of blood transfusion OR (95%CI)*	Adjusted odds of one-year mortality OR (95%CI)**
No anticoagulation	Reference risk	Reference risk	Reference risk	Reference risk
DOACs	0.95 (0.25:2.73)	1.35 (0.61:2.80)	1.20 (0.26:3.97)	0.55 (0.15:1.61)
Age	1.04 (1.01:1.08)#	1.06 (1.03:1.09)#	0.97 (0.93:1.01)	1.05 (1.02:1.09)#
Gender	0.97 (0.53:1.87)	0.49 (0.33:0.73)#	0.99 (0.49:2.05)	0.37 (0.22:0.60)#
ASA score 3-4	1.86 (1.11:3.15)#	2.53 (1.74:3.69)#	2.45 (1.19:5.34)#	4.02 (2.36:7.08)#
Aspirin use	0.44 (0.02:3.9)	0.59 (0.11:2.55)	NA	NA
Clopidogrel use	NA	0.43 (0.02:3.93)	NA	NA
Duration of surgery	1.018 (1.01:1.022)#	NA	1.01 (1.006:1.02)#	NA
Time from admission to surgery	NA	1.01 (1.006:1.02)#	NA	1.01 (1.001:1.02)#

*Adjusted for age, gender, ASA score, aspirin use, clopidogrel use and duration of surgery.
**Adjusted for age, gender, ASA score, aspirin use, clopidogrel use and time from admission to surgery.
#Significant at $p < 0.05$.
DOAC - direct oral anticoagulation medications, ASA score – American Society of Anesthesiology score.

patients is higher intra-operative blood loss. On the other hand, the concern with currently existing surgery delay is thromboembolic complications, with resulting morbidity and mortality. In this study, patients with DOACs did not have more bleeding than patients without anticoagulation, but they did have significantly higher mortality on one-year follow-up (26.7% vs 16.1%, p = 0.047). According to the regression analysis, the above excess mortality was explained by older age, higher comorbidity burden and longer waiting time of DOAC patients compared to controls. The medication itself did not contribute to mortality. In this setting, patients may benefit from expediting surgery.

The effect of DOACS on perioperative blood loss was recently evaluated by several retrospective studies. In a cohort of 796 elderly patients divided into 3 groups by anticoagulation use (103 received Coumadin, 47 received DOACs and 646 had no-anti-coagulation). There were no differences in blood transfusion rates and mortality between the three groups. Surgery delay was significantly higher in patients on coagulation treatment [13]. In a cohort of 19 patients using DOACs and 74 controls, no difference was found in blood transfusions, changes in hemoglobin levels, wound complications and mortality. Surgery delay was higher among patients using DOACs [12]. Another retrospective cohort of 63 patients with hip fractures using DOACs and 63 matched controls showed no differences in time to surgery, hemoglobin levels, probability of blood transfusions and short-term mortality. The latter study was principally different from the other two, because it presented DOAC patients who were operated wihtout a delay, and concluded that surgery delay does not contribute to reduction of bleeding and other complications [19]. With the above evidence and availability of reversal options for DOACS, it is probable that a 12-hr delay before the procedure may be sufficient for most patients with hip fractures [16].

The limitations of our study retrospective design and secondary data. Using the available data, it was not possible to calculate the exact blood loss for each patient, leading to choice of indirect estimates, hemoglobin levels and transfusion rates. Mortality from all causes was chosen as an outcome in this study as an indirect measure of the clinical impact of preoperative coagulability resulting from medication cessation, because the data about the number of thromboembolic events was less valid and had variable clinical significance. Time of last administration of the anti-coagulation medications and drug levels during surgery could not be ascertained. However, this data is also unavailable in most studies on the topic. Lastly, the size of our study did not allow stratification to different types of DOACs.

As a conclusion, patients receiving DOACs were not found to be at higher risk of perioperative hemoglobin levels decrease and blood transfusions compared to controls, when operated after a considerable delay. Surgery delay was associated with significantly higher risk of mortality. We therefore advocate limitation of surgery delay to 12 h from the last dose of the medication in patients undergoing CRIF. This study and the available literature suggest that expediting surgery may be safe, and may reduce overall mortality in this group.

Conflict of interest

None of the authors have conflicts of interest.

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