

Article

Platelet Aggregation Inhibitors and Anticoagulants Delay Surgery for Hip Fractures

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Abstract: Background: we aimed to analyze the influence of antithrombotic medication in delaying surgery for fragility hip fractures; Method: a total of 312 consecutive hip fracture cases over 55 years who underwent surgery in our Orthopedic Clinic; Results: of these, 90 patients received chronic antithrombotic medication. There were no differences between the medicated group and controls (n = 222) regarding age, gender, type of fracture and haemoglobin at admittance. However, median time to surgery was significantly longer in the medicated group: 4(3–6) days compared to 2(1–4) ($p < 0.0001$). By type of medication, time to surgery was: 3(1–4) days for acetylsalicylic acid (n = 44), 6(5.25–7.75) days for clopidogrel (n = 15), 4.5(4–7) days for acenocoumarin (n = 18) and 5(4–7.25) days for novel direct oral anticoagulants (n = 13). The Charlson comorbidity index was significantly higher in the medicated group: 5 [4–5] versus 4 [3–5]. There were no differences in transfusions except for fresh frozen plasma, which was administered more in the medicated patients; Conclusions: the prevalence of platelet aggregation inhibitors and anticoagulant use among fragility hip fracture patients is high, with almost a third using some form of antithrombotic medication. This may significantly lengthen time to surgery.

Keywords: aged; anesthesia/methods; anticoagulants; hip fractures/drug therapy; hip fractures/surgery; length of stay; platelet aggregation inhibitors; time to treatment

1. Introduction

Hip fractures are a constant presence in the emergency orthopedic department. They occur mainly in the elderly, frail population and pose a healthcare and socioeconomic burden [1,2].

These are comprised of fractures located at the femoral neck or the trochanteric region, following low energy trauma (fall from standing). Treatment options are fairly standardized, and surgery can be performed under general or neuraxial anesthesia [1,3–5]. Such fractures are generally

recommended to be operatively treated within 48 h to minimize complications, improve survival and decrease costs [1,2].

Chronic use of antithrombotic medication is increasing, especially in this target population. In the form of platelet aggregation inhibitors and anticoagulants these may pose a threat for emergency surgery, potentially leading to increased blood loss, transfusions and limiting neuraxial anesthesia options [4].

The current recommendations aim to reverse the anticoagulant effect to more permissive cutoff values and thus avoid postponing surgery as much as possible [5–8].

We aimed to analyze the influence of antithrombotic medication on delaying surgery for fragility hip fractures in the elderly.

2. Materials and Methods

We performed a retrospective review of electronic and paper patient charts of all cases of hip fracture older than 55 admitted to our clinic from April 2018 to December 2019. We recorded: age, gender, type of fracture (intracapsular—femoral neck and extracapsular—trochanteric and subtrochanteric regions), type of treatment (no surgery, arthroplasty or internal fixation), comorbidities (Charlson index [9]), length of stay in hospital, time to surgery, Hb (hemoglobin) at admittance and postoperatively, transfusions (where applicable) and antithrombotic medications: platelet aggregation inhibitors—acetylsalicylic acid and clopidogrel; anticoagulants—acenocoumarin (vitamin K antagonists) and novel direct oral anticoagulants—DOACs (apixaban, rivaroxaban or dabigatran).

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by our local emergency clinical county hospital ‘Pius Brinzeu’ Timisoara ethics committee for scientific research (no 182/2020). All patients gave their informed consent for data processing at hospital admission.

The statistical analysis was performed using MedCalc Statistical Software version 19.1 (MedCalc Software, Ostend, Belgium). Data were tested for normal distribution with the Shapiro-Wilk test. Descriptive statistics were calculated for all data as means and standard deviation for normal distributed data, median and interquartile range for non-normally distributed data and as numbers and percentage for categorical data. Differences between patients’ demographic and clinical characteristics were assessed with the independent t-tests, Mann-Whitney tests and chi-squared tests. One-way ANOVA and Kruskal-Wallis tests were performed to identify the differences between different parameters across groups. Tukey-Kramer and Dunn post-hoc analysis was performed to identify the effect of antithrombotic medication on duration of hospitalization. A significance level of 0.05 was set for all tests.

3. Results

A total of 388 patients were identified based on medical coding (ICD-10). From these, 30 subjects were excluded for incomplete data, miscoding, delay due to administrative reasons, non-acute fractures, pathologic fractures, revisions, infections. A total of 358 patient charts were individually reviewed and 7 more patients were excluded due to specific medical conditions.

In total, 351 patients (aged 77.53 \pm 9.16 years, 28.8% males) met the inclusion criteria. Of these, 106 (30.2%) were receiving chronic antithrombotic medications (either antiplatelet or anticoagulant). The most common indication for clopidogrel and anticoagulation were atrial fibrillation, followed by stroke, arterial stents, pacemakers and artificial valves. Indication for acetylsalicylic acid was not recorded in the majority of cases. Dosing for acetylsalicylic acid was 100mg once a day, for clopidogrel 75mg once per day, for acenocoumarin aiming for a therapeutic target of INR (international normalized ratio) between 2 and 3 and for DOACs based on drug-specific recommended administration. Because of the low number, DOAC patients were analyzed as a group: 11 apixaban, 2 rivaroxaban and 2 dabigatran. The baseline characteristics are presented in Table 1.

Table 1. All hip fracture patients.

	Antithrombotic (n = 106)	No Medication (n = 245)	p
Age, years (mean \pm SD)	78.45 \pm 8.63	77.14 \pm 9.37	NS
Gender			
Male, n (%)	32 (30.19)	69 (28.16)	NS
Female, n (%)	74 (69.81)	176 (71.84)	NS
Hb at admittance, g/dL	12.22 \pm 1.92	11.77 \pm 1.80	0.03
Charlson index, points (median [IQR])	5 [4–5]	4 [3–5]	<0.0001
Charlson index survival (median [IQR])	21 [21–53]	53 [21–77]	<0.0001
Type of fracture			0.04
Intracapsular, neck, n (%)	43 (40.57)	72 (29.39)	
Extracapsular, trochanteric region, n (%)	63 (59.43)	173 (70.61)	
Surgically treated, n (%)	90 (84.91)	222 (90.61)	NS

Baseline characteristics of all hip fracture patients.

A total of 312 patients (88.89%) underwent surgery in our clinic. The remaining opted for conservative treatment, were deemed unfit for surgery, were transferred to a different clinic or died. The surgically treated DOACs group included: 9 apixaban, 2 rivaroxaban and 2 dabigatran. A total of 75 femoral neck fractures were treated by uncemented hemiarthroplasty and the rest by total arthroplasty (cemented or uncemented). Fractures of the trochanteric region were fixed using an intramedullary implant, with a long nail for the subtrochanteric fractures. Transfusions were administered at variable thresholds between 7 and 9g/dL of Hb. The surgically treated patients were classified as follows: Group 1—(study) patients who were on antithrombotic medication at the moment of presentation in the clinic (n = 90) and Group 2—(controls) patients without such medication (n = 222). The demographic and clinical characteristics of the surgically treated patients are presented in Table 2, according to their antithrombotic medication.

When compared to Group 2, the median time to surgery was significantly longer in Group 1 ($p < 0.0001$). The post-hoc analysis showed that those patients treated with clopidogrel, acenocoumarin and DOACs needed significantly more time to surgery than those without such treatment. Patients treated with clopidogrel and DOACs needed significantly more time to surgery compared to patients treated with acetylsalicylic acid ($p < 0.05$). Because in our service the standard practice is to perform hip arthroplasty only during the day operating time and not during calls (evenings, nights, weekends), time to surgery for these patients is longer than for those with fractures of the trochanteric region. This difference was significantly larger for patients on clopidogrel, acenocoumarin and DOACs. The hospitalization time was also significantly higher in Group 1 patients compared to Group 2 ($p < 0.0001$). The post-hoc analysis showed a significantly increased hospitalization time in patients treated with clopidogrel, acenocoumarin and DOACs compared with those without medication ($p < 0.05$).

No significant differences were found between the two groups for age, gender, type of fracture/surgery and Hb. The Charlson comorbidity index was significantly higher in Group 1 compared to Group 2 ($p < 0.0001$). The estimated 10-year survival was significantly lower in Group 1 compared to Group 2 ($p < 0.0001$). Patients receiving acetylsalicylic acid and acenocoumarin had a significantly higher index and lower estimated survival rate than those without such medication ($p < 0.05$). There were no differences in transfusions except for fresh frozen plasma, which was administered significantly more in patients on platelet aggregation inhibitors and anticoagulant medication ($p < 0.0001$) (Table 3).

Table 2. Surgically treated patients.

	Group 1 (n = 90)	Acetylsalicylic Acid (n = 44)	Clopidogrel (n = 15)	Acenocoumarin (n = 18)	DOACs (n = 13)	Group 2 (n = 222)	p *
Age, years (mean \pm SD)	78.41 \pm 8.86	78.54 \pm 8.79	76.67 \pm 8.96	79.11 \pm 9.45	79 \pm 8.95	76.86 \pm 9.46	NS (0.18)
Gender							NS
Male, n (%)	27 (30)	13 (29.55)	2 (13.33)	8 (44.44)	4 (30.77)	61 (27.48)	
Female, n (%)	63 (70)	31 (70.45)	13 (86.67)	10 (55.56)	9 (69.23)	161 (72.52)	
Charlson Index, points (median [IQR])	5 [4–5]	5 [4–5]	5 [4–5]	5 [4–5]	5 [4–5]	4 [3–5]	<0.0001
Charlson index survival, (median [IQR])	21 [21–53]	21 [11.5–53]	21 [21–53]	21 [21–53]	21 [21–53]	53 [21–77]	<0.0001
Type of fracture							NS
Intracapsular, neck, n (%)	31 (34.44)	16 (36.36)	3 (20)	5 (27.78)	7 (53.85)	60 (27.03)	
Extracapsular, trochanteric region, n (%)	59 (65.56)	28 (63.64)	12 (80)	13 (72.22)	6 (46.15)	162 (72.97)	
Time to surgery, days (median [IQR])	4 [3–6]	3 [1–4]	6 [5.25–7.75]	4.5 [4–7]	5 [4–7.25]	2 [1–4]	<0.0001
Intracapsular, neck	4 [3–6.75] (n = 31)	3 [2–4] (n = 16)	10 [7–13.75] (n = 3)	5 [4–5.5] (n = 5)	7 [5.25–8] (n = 7)	3 [2–5] (n = 60)	0.03
Extracapsular, trochanteric region	4 [3–6] (n = 59)	3 [1–5] (n = 28)	6 [5–7] (n = 12)	4 [3–7.25] (n = 13)	4 [4–4] (n = 6)	2 [0–3] (n = 162)	<0.0001
Length of stay, days	17 [13–20]	14.5 [10–18]	19 [16.25–21]	17 [15–19]	19 [14.75–26.25]	13.5 [10–16]	<0.0001

Baseline characteristics for surgically treated patients. *—refers to Group 1 vs. Group 2 comparison.

Table 3. Transfusions.

	Group 1 (n = 90)	Acetylsalicylic Acid (n = 44)	Clopidogrel (n = 15)	Acenocoumarin (n = 18)	DOACs (n = 13)	Group 2 (n = 222)	p *
Hb at admittance, g/dL	12.17 \pm 1.85	12.31 \pm 1.69	12.12 \pm 1.89	11.85 \pm 2.01	12.14 \pm 2.23	11.75 \pm 1.78	NS (0.06)
Hb postop, g/dL	10.45 \pm 1.6 (n = 84)	10.61 \pm 1.83 (n = 40)	10.57 \pm 1.36 (n = 14)	10.43 \pm 1.23 (n = 17)	9.83 \pm 1.48 (n = 13)	10.19 \pm 1.31 (n = 206)	NS (0.08)
Packed red blood cells							
n (%)	34 (37.78)	14 (31.82)	7 (46.67)	9 (50)	4 (30.77)	75 (33.78)	NS
units (median IQR)		1.5 [1–2]	1 [1–1]	2 [1–3]	1 [1–1]	2 [1–2]	0.01
Fresh frozen plasma							
n (%)	15 (16.67)	3 (6.82)	1 (6.67)	4 (22.22)	7 (53.85)	17 (7.65)	<0.0001
units (median IQR)		2 [2–2]	1 [1–1]	2 [1.5–5]	2 [1.25–2.75]	2 [1–4]	NS
Platelet mass							
n (%)	3 (3.33)	1 (2.27)	0	1 (5.56)	1 (7.69)	5 (2.25)	NS
units (median IQR)		1	–	8	2	2 [1.75–5.75]	NS

Comparison of transfusions for the surgically treated. *—refers to Group 1 vs. Group 2 comparison.

4. Discussion

Platelet aggregation inhibitors and anticoagulant use at the time of hospital admittance for a fragility hip fracture is high. In our study population, almost one-third of patients were using some form of antithrombotic medication. This had a significant effect on the delay of surgery.

We offer a local perspective from a single level 1 trauma center. Time to surgery, use of platelet aggregation inhibitors and anticoagulant medication and type of anesthesia have regional differences [1–8]. Madsen et al. found that antithrombotic medication use in general increased 2.3 times from 19% to 43%, with the highest increase seen for anticoagulants. Age, sex and higher Charlson index were associated with the use of antithrombotic medication [4].

Hip surgery consists of either fracture fixation or arthroplasty. It is considered a delayed emergency/major surgery with a high risk of bleeding. For anticoagulated patients, the delay is based on the type of blood-thinning medication used, current guidelines and product label information: acetylsalicylic acid—no delay; clopidogrel—5 days for neuraxial anesthesia, less for orthopedic surgery; acenocoumarin—INR < 1.5 for neuraxial anesthesia, higher values for orthopedic surgery yet no consensus regarding cut-off value; patients with an INR >3 should receive oral vitamin K; apixaban, rivaroxaban and dabigatran—2 to 5 days with more caution required for neuraxial anesthesia than for orthopedic surgery [1,5,6].

The most used platelet aggregation inhibitors are acetylsalicylic acid and clopidogrel. Recent guidelines consider that platelet aggregation inhibitor agents should not interfere with timing of surgery but may dictate the choice of anesthesia. Currently there is strong evidence that acetylsalicylic acid does not increase the risk of bleeding during major surgery or regional anesthesia. On the other hand, clopidogrel should be stopped for 5 days before regional anesthesia such as spinal, epidural or peripheral nerve blocks [5,6]. Nonetheless, in our study, even patients on acetylsalicylic acid had a longer delay of surgery compared to controls. A study by Pean et al. showed a wide variability among orthopedic surgeons regarding management of patients with hip fracture on clopidogrel [10]. Over a quarter of surgeons continued to opt for surgery postponement even though there appears to be no difference in total blood loss, transfusion rate, or 1-year mortality among patients receiving platelet aggregation inhibitor medication [10–12].

Vitamin K antagonists (warfarin, acenocoumarin) and DOACs (inhibitors of factor IIa or Xa) are the most used anticoagulants. Vitamin K antagonists coagulopathy is usually reversed by administration of phytomenadione. An INR < 1.5 is considered safe for elective major surgery. Hip fracture patients on vitamin K antagonists are more likely to have increased time to surgery, blood loss, length of stay and mortality up to 1 year [13,14]. However, a study by Cohn et al. observed that hip fractures admitted on warfarin seem to be at similar risk of transfusion or adverse events compared with nonanticoagulated patients. Waiting for INR normalization only delayed surgery without reducing blood loss or preventing complications. They conclude that one may consider proceeding with surgery in patients with INR above 1.5 if patients are otherwise medically optimized, but to what upper limit is currently unknown [15]. In a large cohort, vitamin K antagonists and DOACs did not increase the 30-day postoperative mortality among hip fracture patients. A subset analysis found that DOACs increased the risk of transfusion and platelet aggregation inhibitors increased the risk of both transfusion and mortality [16]. Several other recent studies identified approximately 9–16.6% of hip fracture patients to be anticoagulated. However, the absolute number of DOACs cases was relatively low [17–20]. In our study 9.9% were anticoagulated. Due to the low number of patients receiving DOACs we decided to analyze them together as a group, even though there was a predominance of apixaban (69%). Several studies found both vitamin K antagonists and DOACs delayed emergency surgery [17–20]. Patients on DOACs had similar perioperative hemoglobin change, transfusion rates and mortality compared to subjects without anticoagulants in both trochanteric – internal fixation and femoral neck – arthroplasty situations [19–22]. For DOACs surgery should therefore be reasonably delayed, until reversal agents become available [5,6].

General and regional anesthesia are both suitable for hip fracture surgery [1,3,5,6,8]. A study by Chen et al. found no difference in 30-day mortality. In-hospital mortality, acute respiratory failure, length of hospital stays, and readmissions were significantly reduced in the regional anesthesia group. On the other hand, pneumonia, heart failure, acute myocardial infarction, acute renal failure, cerebrovascular accident, postoperative delirium and deep vein thrombosis/pulmonary embolism were similar between the two techniques [3]. In our clinic, neuraxial anesthesia is the preferred technique and a previous survival analysis found similar survival to reports using general anesthesia [2]. This may be an important factor for the longer time to surgery in our patients on antithrombotic medication compared to what is generally reported in the literature [10–21]. However, new evidence suggests mostly economic but no clinical benefit in hip fracture surgery under 24 h from hospital admission [7,23].

The biggest limitation of our study is its retrospective nature with inborn confounders that cannot be controlled for. Other limitations are the lack of outcome measures and survival analysis. In addition, patients who received tranexamic acid to decrease bleeding were not accounted for. We did not take into consideration the INR, administration of vitamin K, platelet counts or the American Society of Anesthesiologists (ASA) physical status classification system.

Within such a complex environment, hip fractures should be managed as a team, with careful consideration for perioperative support, surgical technique, choice of implant, rehabilitation and hospitalization costs [24–26]. Treatment of these fractures is considered major surgery and also a major risk factor for developing deep vein thrombosis/pulmonary embolism. As a consequence, these patients receive medical thromboprophylaxis. The current standard of care is a single dose of low molecular weight heparin for up to 30 days, even in patients without previous antithrombotic medication [1,27]. For those already anticoagulated preoperatively, the same regimen should be reinstated as soon as possible after surgery [1,5,6,27]. On the other hand, the perioperative management for platelet aggregation inhibitors and oral anticoagulants is not well standardized. There are several ways this can be achieved: stopping the medication, reducing dosage or bridging to a more controllable and shorter half-life low molecular weight heparin. Bridging to subcutaneous low molecular weight heparin twice a day is the most common strategy; however, the dosage is not standardized. For clopidogrel and warfarin there may even be a potential increased risk of cardiovascular events if stopped perioperatively [11,28].

5. Conclusions

Patients on antithrombotic medication experienced significantly longer times to surgery. The biggest delay was seen with clopidogrel, followed by DOACs, acenocoumarin and acetylsalicylic acid.

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