Original Research Article

SAGE Open Medicine

SAGE Open Medicine
Volume 11: 1–6

DOI: 10.1177/20503121231162410
journals.sagepub.com/home/smo
SAGE

Assessing operative delay and complications in hip fracture patients on anticoagulants and antiplatelets

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Abstract

Objectives: Hip fractures represent a prevalent geriatric cause of morbidity and mortality. The presence of multiple comorbidities requiring the use of an anticoagulant or antiplatelet medication adds complexity to management and influences outcomes. International guidelines suggest expedited surgery within 48 h; however, anticoagulant and antiplatelet medications commonly cause delays. Research exploring health outcomes in this group is unclear. Therefore, we aimed to determine the impact of anticoagulant and antiplatelet medications on operative delay and overall complications in hip fracture patients.

Methods: A retrospective cohort study of hip fractures was performed at a tertiary hospital over a 3-year period from 1st January 2018 to 31st December 2020. Data collected included demographics, time to surgery, length of stay, postoperative blood transfusion, venous thromboembolism, acute coronary syndrome, stroke, infections in hospital and 120-day mortality. Patients were categorised based on the use of direct oral anticoagulants, warfarin and antiplatelet medications.

Results: In total, 474 patients were included and 43.5% were on an anticoagulant or antiplatelet medication. Patients on these medications had more than twice the rate of operative delay (41.7% versus 17.2%, $p < 0.001$) with the greatest in the direct oral anticoagulant group (92.7% delay). After controlling for age and gender, this was still significant for direct oral anticoagulant ($p < 0.001$) and antiplatelet group patients ($p = 0.02$). These patients also had a 20% increased overall complication rate ($p < 0.001$). On subgroup logistic regression, the increased complication rate was noted in the direct oral anticoagulant group ($p = 0.006$) and the antiplatelet group ($p < 0.001$) but not in the warfarin group ($p = 0.25$). Time to surgery beyond 48 h was associated with a double increase in the odds of a postoperative complication ($p = 0.005$).

Conclusion: There is a significantly greater delay to surgery in hip fracture patients on anticoagulant or antiplatelet medications as well as a higher incidence of complications. Guidelines to expedite early safe surgery in this high-risk patient group are required.

Keywords

Hip fractures, operative delay, morbidity, mortality, anticoagulants, antiplatelets

Date received: 26 July 2022; accepted: 13 February 2023

Introduction

Hip fractures represent a prevalent geriatric cause of morbidity and mortality. On average, the worldwide incidence of hip fractures is 200–300/100,000, and peaks in Denmark at 574/100,000.[1] In Australia, hip fractures occur in 199/100,000, which equates to approximately 20,000 people per year.[2] International data show that 1-year mortality for fragility hip fractures ranges from 6% up to 30%.[3]

Based on extensive literature, current guidelines suggest expedited surgery within 48 h to minimise morbidity and mortality.[4–6] Delaying surgery beyond 48 h for hip fractures leads to an increased risk of hospital-acquired infections, venous thromboembolism (VTE) and length of hospital admission.[3] According to the Australian hip fracture registry annual report in 2018, 24% of patients did not have surgery within 48 h. 'Issues with anticoagulation' were cited as the

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reason for this delay in 17% of cases highlighting this as a modifiable factor.[7]

Many older patients with hip fractures have medical comorbidities such as cardiac arrhythmias, ischemic heart disease, VTE and stroke. These often require management with anticoagulant or antiplatelet medications. The use of anticoagulant medications, in particular direct oral anticoagulants (DOACs), is increasing. In the United States, in patients over the age of 65 years, 6.5% were on DOACs in 2019 compared to 0.5% in 2010.[8] Furthermore, anticoagulant therapies are associated with an increased Charlson comorbidity index, which reflects added complexity.[9]

There are few uniform recommendations for the use of antiplatelet and anticoagulant medications (especially DOACs) during hip fracture surgery.[10] It is unknown whether the timing of surgical intervention in patients prescribed DOACs for hip fractures has a deleterious effect on patient or healthcare utilisation outcomes.[11] Delay to surgery is balanced against potentially increased risk of patient complications, but this practice is currently variable.

The number of comorbid elderly hip fracture patients on anticoagulants is expected to rise. This highlights the importance of assessing the influence of these medications on delays and complications.

We seek to provide further understanding of the relationship of hip fracture patients on anticoagulants and antiplatelets with regard to operative delay and complications. Therefore, this study was designed to review operative delay associated with anticoagulant and antiplatelet use in hip fracture patients. Secondary outcomes included assessing complications and healthcare utilisation.

Methods

Design

A retrospective study of a single hospital was conducted to review all hip fracture patients admitted from 1st January 2018 to 31st December 2020. All patients managed operatively were included. Exclusion criteria were nonoperatively managed hip fractures and periprosthetic femur fractures. Observational quantitative data were collected using submitted information from the hospitals' orthopaedic service to the Australian and New Zealand Hip Fracture Registry (ANZHFR) over this period. This is a detailed registry utilised by orthopaedic, anaesthetic and orthogeriatric teams across all trauma centres in Australia and New Zealand that are involved in the management of hip fracture patients. Data from each centre are submitted on a regular basis by each hospital and compiled for research, audit and clinical governance. Data collection was done directly from the ANZHFR and the patients' electronic medical records. Data collection was supplemented by the review of patient's electronic medical record. All cases were followed from admission until 120 days postoperatively. These data were used to create a deidentified database that was password protected and stored securely.

The studied hospital did not have a site-specific formal policy about the management of anticoagulation or time to theatre during the study period. However, hospital clinicians are guided by the Australian Commission on Safety and Quality in Health Care Hip Fracture Care Clinical Care Standard.[12] This suggests patients to receive surgery within 48 h, if no clinical contraindication exists and the patient prefers surgery.

Outcomes

Demographic data, age and gender were recorded. Patients were categorised into a control group, not on any antiplatelet or anticoagulant medications, and intervention groups, which were subdivided based on the different anticoagulation and antiplatelet therapies.

Recorded complications included the following:

- wound issues requiring a return to theatre,
- postoperative blood loss requiring a transfusion,
- VTE – including deep vein thrombosis (DVT) and pulmonary embolism (PE; confirmed clinically and radiologically),
- Infection – urinary tract infections (positive urine samples taken from colonised catheters that have been in situ more than 24 h were not included), hospital-acquired pneumonia (confirmed clinically and radiologically), cellulitis, etc.,
- acute coronary syndrome (ACS) – confirmed with serial troponins,
- stroke – cerebrovascular events confirmed on imaging.

Overall complication rate was determined by combining these variables together. As guidelines recommend surgery within 48 h,[7] delay beyond 48 h from admission was recorded. Hospital length of stay and 120-day mortality rate data were also collected.

Statistical analysis

Statistical analysis was conducted using SPSS (SPSS Inc. Version 27, Chicago, IL, USA). Sample size calculations were performed using SPSS with independent sample proportions with a power value of 0.8 and significance level of 0.05. A significant difference was assessed as a 10% difference in delay which gave a minimum sample size of 450 patients. Categorical data were assessed using the chi-squared test whilst continuous data were noted to be non-parametric and therefore evaluated using the Kruskal–Wallis test and the independent samples median test. Significance was set at the 0.05 alpha level. Multivariable analysis was conducted through binomial logistic regression.

Sample size calculation was performed through SPSS power analysis. The independent samples binomial test was utilised with a single power value of 80% and the alpha significance level set at 0.05. Assessing the primary outcome of operative delay, a 20% proportion value was assigned to the control

Table 1. Univariate analysis of antiplatelet/anticoagulant group with control group.

	Antiplatelet/anticoagulant use	No use of antiplatelet/anticoagulant	*p* Value
Demographics			
Median age (IQR)	84 (77–89)	81 (72–88)	
Gender, *n* (%)			
Male	71 (34.5%)	87 (32.5%)	
Female	135 (65.5%)	181 (67.5%)	0.21
Delay >48 h	86 (41.7%)	46 (17.2%)	**<0.001**
Haemoglobin drop requiring transfusion	56 (27.2%)	49 (18.3%)	**0.02**
Wound complication requiring return to theatre	3 (1.5%)	5 (1.9%)	0.73
DVT	4 (1.9%)	12 (4.5%)	0.13
PE	6 (2.9%)	3 (1.1%)	0.16
ACS	17 (8.3%)	9 (3.4%)	**0.02**
Stroke	9 (4.4%)	5 (1.9%)	0.11
Infections in hospital	93 (45.1%)	80 (30%)	**<0.001**
Median length of stay (IQR)	29 (10–48)	17 (6–36)	**0.005**
120-day mortality	31 (15%)	24 (9%)	0.12
Overall complication rate	136 (66%)	122 (45.5%)	**<0.001**

ACS: acute coronary syndrome; DVT: deep vein thrombosis; IQR: interquartile range; PE: pulmonary embolism.
Note: Significance of bold was to highlight the key statistically significant results within the table.

group to reflect the hip registry incidence. A 60% delay was assigned to the intervention group based on a three-fold increased delay in the systematic review by You et al.[1] A 1:10 group size ratio was utilised based on the approximate prevalence of DOAC or warfarin use as 10% of hip fracture patients.[1]

The subsequent minimum sample size to be adequately powered was 10 patients on DOACs and 93 control group patients. This study was performed over a larger period to ensure a greater sample size for analysis.

Results

From 1st January 2018 to 31st December 2020, a total of 475 patients were admitted with hip fractures. All operatively managed patients were included in the study as the singular inclusion criteria. The number of patients included in the study were 474. The median age was 82 years with a 2:1 proportion of females to males. In all, 206 patients (43.5%) were on an anticoagulant or antiplatelet medication, whilst 268 patients (56.5%) were not on any anticoagulant or antiplatelet medication. The median age across both groups was comparable as shown in Table 1. This table highlights the key differences in outcomes between these two groups, whereas Table 2 provides a detailed breakdown of various anticoagulant and antiplatelet groups. There were 141 patients on antiplatelet agents (29.7%), 41 patients on DOACs (8.6%), 21 patients on warfarin (4.4%) and there were 3 patients on clexane.

Operative delay

Operative delay greater than 48 h was twice as frequent in the patients on antiplatelet or anticoagulant medications compared to the control group ($p < 0.001$). This was noted in 92.7% of patients on DOACs, 55% of patients on warfarin, 26.2% of patients on antiplatelets and 17.2% in the control group (Table 2). Patients on clexane did not have an operative delay; however, the results for these patients were statistically insignificant owing to a small sample size. On subgroup logistic regression analysis, controlling for age and gender, there was a statistically significant operative delay across the agents including DOACs ($p < 0.001$), warfarin ($p < 0.001$) and antiplatelets ($p = 0.02$) (Table 3).

Complication rate

An overall complication rate was assessed as a composite of outcomes including ACS, DVT, PE, significant postoperative reduction in haemoglobin requiring a blood transfusion, stroke, hospital-acquired infections and significant wound complications requiring a return to theatre. This overall complication rate was 20% greater in the patients on an antiplatelet or anticoagulant medication ($p < 0.001$).

On subgroup logistic regression analysis, the increased complication rate was noted in the patients on DOACs ($p = 0.006$) and antiplatelet agents ($p < 0.001$) but not in the warfarin group ($p = 0.25$). Increasing age also had a weak association with an increased complication rate (odds ratio (OR): 1.04, $p < 0.001$) (Table 3). The specific complications that were significantly related to DOACs included stroke (OR 5, $p = 0.02$) and hospital-acquired infections (OR 3, $p = 0.001$). For patients on antiplatelet medications, the specific complications included ACS (OR: 2.6, $p = 0.04$) and a haemoglobin drop requiring a transfusion (OR: 1.03, $p = 0.02$).

When operative delay was analysed as a predictor variable in logistic regression assessing complication rate, it was significantly associated with doubled odds of a complication occurring ($p < 0.005$). In this analysis, as can be noted in Table 4, DOACs no longer had a significant association with

Table 2. Breakdown analysis of antiplatelet and anticoagulant use.

Anticoagulation type	None	Antiplatelet	DOAC	Warfarin	Total
Frequency	268 (56.5%)	141 (29.7%)	41 (8.6%)	21 (4.4%)	474 (100%)
Median age (IQR)	81 (72–88)	83 (77–89)	86 (80–89)	85 (78–88)	82 (74–88)
Gender, *n* (%)					
Male	87 (32%)	52 (37%)	12 (29%)	6 (29%)	158 (33.3%)
Female	181 (68%)	89 (63%)	29 (71%)	15 (71%)	316 (66.6%)
Operative delay >48 h	46 (17.2%)	37 (26.2%)	38 (92.7%)	11 (55%)	132 (27.8%)
Median length of stay, days (IQR)	17 (6–36)	30 (9–48)	27 (11–50)	19 (12–40)	21 (7–41)
120-day mortality	24 (9%)	23 (16.3%)	4 (9.8%)	4 (19%)	55 (11.6%)
Overall complication rate	122 (45.5%)	92 (65.2%)	30 (73.2%)	13 (61.9%)	258 (54.4%)

DOAC: direct oral anticoagulant; IQR: interquartile range.

Table 3. Binomial logistic regression for operative delay and complication rate.

Operative delay >48 h			Overall complication rate		
Factor	Odds ratio (95% CI)	*p* value	Factor	Odds ratio (95% CI)	*p* Value
DOAC	**68.9** (20.1–235.7)	<**0.001**	DOAC	**2.84** (1.4–6)	**0.006**
Warfarin	**5.8** (2.3–14.7)	<**0.001**	Warfarin	1.7 (0.7–4.3)	0.25
Clexane		0.99	Clexane	0.8 (0.7–9.5)	0.84
Antiplatelet agents	**1.8** (1.1–3)	**0.02**	Antiplatelet agents	**2** (1.3–3.1)	**0.001**
Age	0.98 (0.96–1.004)	0.11	Age	**1.04** (1.02–1.06)	<**0.001**
Gender	0.4 (0.75–2)	0.43	Gender	0.9 (0.7–1.5)	0.98

CI: confidence interval; DOAC: direct oral anticoagulant.
Note: Significance of bold was to highlight the key statistically significant results within the table.

overall complication rate whilst antiplatelet agents continued to be associated with an increased complication rate ($p=0.003$) after accounting for operative delay.

Other outcomes

There were no significant differences in 120-day mortality in the antiplatelet and anticoagulant medication groups ($p=0.12$). Median hospital length of stay was greater across all groups on anticoagulants and antiplatelets when compared to the control group; 27 days for those on DOACs, 19 days for patients on warfarin and 30 days for patients taking antiplatelets. The control group had a significantly lower hospital length of stay at 17 days ($p=0.005$). Assessing the relationship on linear regression, a significant association was noted for DOACs ($p=0.02$) and antiplatelet agents ($p<0.001$) but not for warfarin ($p=0.16$).

Discussion

This study demonstrated significant differences in operative timing and outcomes between hip fracture patients on antiplatelet or anticoagulant medications compared to those not on these medications. There was a statistically significant increase in overall complication rate and length of stay for the intervention group. Specifically, patients on DOACs were almost three times as likely to have a complication. Patients on anticoagulant or antiplatelet medications were twice as likely to incur operative delay beyond 48 h. Ninety-three percent of patients on DOACs had delayed surgery which was almost six times greater than the control group. Operative delay was associated with an increased overall complication rate, increased infection and increased stroke risk, noted across all groups. When considering the relative effect of operative delay and DOAC use, it is likely the detrimental effect of the former outweighs the latter.

The DOAC patients had the greatest proportion experiencing an operative delay, that is, more than triple the rate of the other anticoagulant or antiplatelet groups combined ($p<0.001$). All but 3 of the 41 DOAC patients had surgery at least 48 h after admission. Operative delays in this group are reflected in the literature worldwide. You et al., in their systematic review of 34 studies, noted a similar three-fold higher odds of operative delay beyond 48 h for DOAC patients compared to patients not on those medications.[13] Tran et al. and Cafaro et al. similarly report significant delays for warfarinised patients as well as DOAC patients.[8,14]

In our study, there was an increased overall complication rate for patients on anticoagulant or antiplatelet medications. In the literature, the evidence surrounding complications and outcomes is mixed with some studies reporting worse outcomes for patients on these medications whilst others demonstrate lack of significant differences. Mitchell et al. in their systematic review of 21 articles noted 18.2% of DOAC users having increased blood transfusions, 40% of users had increased length of stay whilst there was no difference in

Table 4. Binomial logistic regression for overall complication rate.

Overall complication rate		
Factor	Odds ratio (95% CI)	*p* Value
Operative delay >48 h	**2** (1.2–3.3)	**0.005**
DOAC	1.7 (0.7–3.8)	0.24
Warfarin	1.4 (0.5–3.5)	0.54
Clexane	0.97 (0.08–11)	0.98
Antiplatelet agents	**1.9** (1.2–3)	**0.003**
Age	**1.04** (1.02–1.06)	**<0.001**
Gender	0.96 (0.6–1.5)	0.86

Note: Significance of bold was to highlight the key statistically significant results within the table.

overall blood loss, postoperative complication rates, stroke or mortality rates compared to the control group.[11]

Studies have been performed assessing DOAC patient's outcomes in the context of early surgery. Mullins et al. in their retrospective study reported that 87.3% of the DOAC patients had an operation within 36 h and their results demonstrated no statistically significant increase in transfusions or mortality differences.[15] King et al.[16] compared their DOAC patients who had an early surgery compared to those having a delay, with no difference noted in perioperative haemoglobin, transfusion rates or haematoma formation. Scheutze et al. in their study of 327 patients on anticoagulant medications undergoing surgery within 24 h noted no statistical difference in complications including infections, haematoma, acute cardiovascular events or in mortality. They did however notice 3.4 times increase in intraoperative blood transfusion.[17] Tarrant et al.[18] in an Australian study also reported no detrimental effect of early surgery on mortality, transfusions or post-op day 1 haemoglobin, thereby advocating for earlier surgery in anticoagulated patients. Furthermore, the HIP ATTACK trial did not reveal increased complications with time to surgery within 6 h.[19]

In our study, when operative delay was included as a predictive variable in logistic regression, it was a significant factor in the overall complication rate. The DOAC group was no longer statistically significant regarding overall complications in this model. This likely suggests the complications attributed to the DOAC group may be better explained by operative delay. Antiplatelet agents continued to have a significant association with complications which included ACS and haemoglobin reduction even after accounting for operative delay.

Whilst there are no clear guidelines for DOACs and hip fracture surgery, given the evidence for worse outcomes with delay in this study and outcomes comparable to control groups from early surgery in the literature, the universal implementation of early surgery should be advocated for in this population when otherwise medically cleared. Taranu et al. have proactively offered a protocol to address the operative delays with recommendations for each of the antiplatelet and anticoagulant medication group.[20] Clopidogrel patients are to be treated as non-anticoagulated and for DOAC patients, the advice is to proceed with surgery after 24 h if the renal function is normal. As advised by Taranu et al., the operative delay in the warfarin group can be mitigated by warfarin reversal.[20]

The limitation of this study is its single centre, retrospective design. Another potential limitation is the lack of control for comorbidities within certain patient groups affecting surgical timing and complications. However, the demonstrated strength of association of anticoagulants on operative delay means that this is unlikely to have altered the results. Other causes of operative delay not included in this study include theatre and surgeon availability. This would likely affect all groups similarly and thus should not affect the results.

Conclusion

This study reinforces the current literature of hip fracture patients on antiplatelet or anticoagulant medications. Patients on antiplatelet or anticoagulant medications have increased incidence of complications and operative delay. Operative delay significantly contributes to poor outcomes and complications, amplifying the preoperative risk related to advanced age and comorbidities. To safely minimise operative delay, local and international guidelines on the perioperative management of patients on these medications (especially DOACs) are required.

Acknowledgements

Not applicable.

Author contributions

- Elete, Asheesh: conceptualisation, methodology, data collection, writing – original draft preparation
- Panwar, Yash: data collection, writing – original draft preparation and editing
- Dannaway, Jasan: supervision, writing, reviewing and editing
- Chen, Jacqeuline: investigation and data collection
- Thomas, Bijoy: supervision.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

- Ethics approval gained by Human Research Ethics Committee (HREC) and Western Sydney Local Health District Research Office, NSW Health. 2021/PID03550 – 2021/ETH12267:
- Approval was obtained from the Australian and New Zealand Hip Fracture Registry.

Informed consent

Informed consent for publication was not applicable for this project. This was independently reviewed by the Human Research and Ethics Committee during the ethics approval process.

Informed consent was not sought for the present study because this is a retrospective cohort study using deidentified patient data. All hip fracture patients on admission to hospital in Australia are alerted that their deidentified data will be included in the Australian and New Zealand Hip Fracture Registry. This is an opt-out registry where a patient must actively opt out, consent from individual patients is not required to use the deidentified data in this record. A key part of the purpose of this registry is to facilitate improvement in quality of care which includes research.

Trial registration

Not applicable – this was a retrospective cohort study, not a randomised control trial.

Consent for publication

Consent for publication is not applicable (reviewed during HREC approval).

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Data availability

All data generated or analysed during this study are included in this article.

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