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Early Surgical Fixation for Hip Fractures in Patients Taking Direct Oral Anticoagulation: A Retrospective Cohort Study

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Abstract

Introduction: Currently, evidence-based guidelines regarding delay to theatre for urgent surgical intervention in patients taking direct oral anticoagulants (DOACs) are lacking. Therefore, this study aims to investigate the effect of DOACs on patient outcomes receiving early (<48 hours) versus delayed (>48 hours) surgery for neck of femur fractures. **Methods:** A retrospective cohort study was conducted at a tertiary teaching hospital. Treatment groups were hip fracture patients taking DOACs on admission and receiving surgery in <48 hours (n = 17) and >48 hours (n = 11). A control cohort of hip fracture patients not taking DOACs (n = 56) was matched to the <48 hours treatment group for comparison. Patient demographics were recorded and key outcome measures included perioperative hemoglobin levels, transfusion rates, time to surgery, 90-day mortality, hematoma rates, and length of stay in hospital. **Results:** There was no significant difference in perioperative hemoglobin levels, transfusion rates, or hematoma between groups. Patients taking DOACs and receiving early surgery had significantly longer time to surgery compared to the non-DOAC control (32.21 $\pm$ 7.83 vs 25.98 $\pm$ 11.4, $P = .01$). No deaths were recorded in the early DOAC group at 90 days, compared to 4 (36%) in the late DOAC group ($P = .04$). **Discussion and Conclusions:** Our study suggests hip fracture patients taking DOACs on admission is not a reason to delay surgery. However, given the lack of literature in this area, further prospective research with larger patient numbers is required to definitively guide clinical practice.

Keywords

hip fractures, anticoagulants, orthopedics, blood loss, surgical, osteoporosis

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Introduction

Use of direct oral anticoagulants (DOACs) is constantly increasing.[1] Indications for use include treatment and prophylaxis of deep vein thrombosis or pulmonary embolism and prevention of systemic embolization in non-valvular atrial fibrillation.[2] DOACs provide a stable pharmacokinetic profile and do not require routine drug monitoring, directly addressing shortcomings in managing Warfarin. Five DOACs are certified for use; Rivaroxaban, Betrixaban, Edoxaban-factor Xa inhibitors, and Dabigatran, a direct thrombin inhibitor.[3-7]While Warfarin can be easily reversed and reliably monitored, DOACs prove more difficult to reverse and have no clear biochemical markers to allow therapeutic monitoring.[8-10] Reversal agents are available for Dabigatran (Idarucizumab), Apixaban, and Rivaroxaban (Andexanet alfa), however, are expensive and generally reserved for emergencies.[7,10] Consequently, surgical delay to allow drug clearance is the only feasible option to reverse the anticoagulant effects of DOACs. Guidelines are in place for ceasing DOACs prior to elective surgery; however,

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there is uncertainty when emergency surgery is required.[3-5] In addition, recent data show that elderly hip fracture patients are prone to prolonged elimination half-lives of DOACs, with almost 50% having therapeutic levels at the time of surgery.[11]

Hip fractures place a substantial burden on the healthcare system, and with an ageing population, numbers are predicted to increase.[12] The current guidelines recommend early surgery within 48 hours, with more recent literature suggesting surgery within 24 hours is beneficial.[13,14] Extensive research has shown that delay to surgery is associated with increased morbidity, mortality, and length of stay in hospital.[15-19] Despite these findings, patients on DOACs have increased delays to surgery compared to patients on no anticoagulation or on vitamin K antagonists. Average time to surgery for DOAC patients has been shown to vary from 35 hours to 66.9 hours.[9,20,21]

Three recent studies have investigated the outcomes of hip fracture surgery within 48 hours in patients taking DOACs.[22-24] All found no difference in perioperative blood loss; however, Schuetze et al[23] found patients taking DOAC medication prior to surgery had a 3.4-fold increase in intraoperative transfusion.

In context of these varied findings, we aim to provide further evidence on the safety of early hip fracture surgery in patients taking DOACs. A cohort of patients taking DOACs and operated on within 48 hours will be directly compared to those having surgery after 48 hours and a control group. We investigated whether surgery within 48 hours of admission for hip fracture patients taking DOACs has any effect on morbidity and mortality. Our primary hypothesis was there would be no difference in perioperative blood loss in hip fracture patients taking DOACs and receiving early surgery. Furthermore, there would be no difference in transfusion rates, hematoma rates, or mortality.

Methods

This study was a retrospective cohort study performed at the Princess Alexandra Hospital, a tertiary teaching institution in Brisbane, Australia. A low negligible risk ethics exemption was provided from Metro South Queensland Health.

Data were obtained from the hospital neck of femur research database. The database was created through retrospective chart reviews, data entry during the patient's admission, and follow-up appointments. Information was obtained from a combination of paper and electronic medical records. Data collected included key demographic, medical, surgical, timing, laboratory values, and follow-up information.

Our study identified hip fracture patients taking DOACs on admission between January 2012 and December 2017. These patients were categorized into 2 treatment groups: those that received early surgery (<48 hours) and late surgery (>48 hours). A control cohort of patients not taking DOACs was matched to the <48 hours treatment group using age, American Society of Anaesthesiologists (ASA) score, gender, surgery type (arthroplasty vs other fixation), time to surgery (<48 hours), and dementia status. Patients were excluded from analysis in both treatment and control groups if they had no operation and were taking antiplatelet agents (Aspirin, Clopidogrel, Prasugrel, Ticagrelor, and Dipyridamole) or Warfarin.

Primary outcomes included blood loss; measured as greatest hemoglobin value minus lowest hemoglobin value from admission to postoperative day 2; blood transfusion rates; acute length of stay in hospital (from admission to orthopedic ward discharge); total length of stay (from admission to hospital discharge including rehabilitation); time to surgery; 90-day mortality; reoperation and hematoma rates.

Statistical analysis was performed using GraphPad Prism version 7.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. If normally distributed, a 2-sided *t* test with Welch correction was used and if non-normally distributed the Mann-Whitney *U* test was used. Discrete variables were analyzed using $\chi 2$ and Fisher exact for expected values <5. Statistical significance was defined as $P < .05$.

Results

A total of 1214 patients were treated for hip fractures at the Princess Alexandra Hospital from January 2012 to December 2017. 28 patients were identified to be taking DOACs on admission, 17 receiving surgery within 48 hours, and 11 receiving surgery after 48 hours. A control cohort of 56 patients not taking DOACs and receiving surgery within 48 hours was matched to the early surgery treatment group.

Group characteristics have been outlined in Table 1. Rivaroxaban was the most commonly used DOAC in early and late surgery groups. A female predominance was observed in early DOAC and control groups compared to the late DOAC group. Additionally, increased numbers of arthroplasty and intracapsular fractures were noted in early DOAC and control groups.

Perioperative hemoglobin loss was highest in the late DOAC group, followed by the non-DOAC control and finally the early DOAC group (31.91 ± 18.94 vs 30 ± 11.54 vs 26.47 ± 16.26), although these differences were not significant (Figure 1). No hematomas occurred in either group and there was no significant difference in transfusion rates.

Patients discharged to private rehabilitation facilities were lost to follow-up and were removed from analysis of total length of stay values. This was 5, 1, and 4 patients from the <48 hours DOAC, non-DOAC control, and >48 hours DOAC groups, respectively. No significant difference was found between the resulting total length of stay values.

Within the study period, there were 2 reoperations required for the early DOAC group; 1 for washout of a superficial wound infection and 1 total hip replacement conversion of a recurrently dislocating hemiarthroplasty. Two patients returned to theatre in the control group; 1 for a periprosthetic fracture and 1 for a collapsed proximal femoral nail. No late DOAC patients returned to theatre.

Interestingly, time to operation was longer in the early DOAC group compared to the non-DOAC control (32.21 hours vs 25.98 hours; $P = .01$). There was no significant difference in acute length of stay in hospital or wound infection rates (Table 2). There was no mortality difference in hospital

Table 1. Group Characteristics for Patients Taking DOACs and Receiving Early Surgery <48 Hours From Admission, Late Surgery >48 Hours From Admission and a Non-DOAC <48 Hours Control Group.

	Early <48 hours DOAC, n = 17	<48 hours control, n = 56	Late > 48 hours DOAC, n = 11
Demographics			
Mean age (SD)	84.29 (5.38)	84.09 (3.06)	82.18 (12.25)
Female n (%)	14 (82.35)	47.00 (83.93)	5 (45.45)
Mean ASA (SD)	3 (0.50)	3.22 (0.67)	3.36 (0.42)
Private residence on admission n (%)	17 (100)	44 (78.57)	9 (81.82)
Independent mobility on admission n (%)	9 (52.94)	15 (26.79)	4 (36.36)
Medical complications			
Dementia, n (%)	2 (11.76)	7 (12.50)	1 (9.09)
DOAC			
Apixaban n (%)	5 (29.41)	–	0 (0)
Dabigatran n (%)	3 (17.65)	–	5 (45.45)
Rivaroxaban n (%)	9 (52.94)	–	6 (54.55)
Surgery			
Arthroplasty vs open reduction internal fixation n (%)	9 (52.94)	28 (50.00)	3 (27.27)
Surgeon experience: consultant vs trainee n (%)	10 (58.82)	23 (41.07)	5 (45.05)
Fracture type			
Intracapsular n (%)	9 (52.94)	25 (44.64)	3 (27.27)

Abbreviations: ASA, American Society of Anaesthesiologists; DOAC, direct oral anticoagulation.

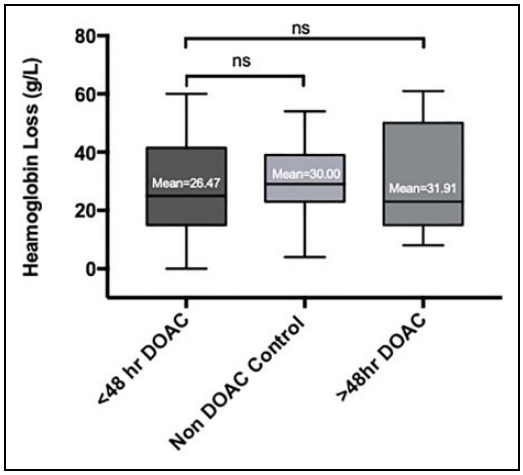

Figure 1. Hemoglobin loss between admission and postoperative day 2 for hip fracture patients taking direct oral anticoagulation (DOAC) receiving early surgery (<48 hours), late surgery (>48 hours), and a non-DOAC <48 hours control group. No significant difference was identified between groups.

or at 30 days, but the late DOAC group had a higher 90-day mortality of 36.36% compared to 0% in the early DOAC group ($P = .04$).

Discussion

This study suggests that hip fracture surgery within 48 hours for patients taking DOACs does not increase perioperative blood loss or transfusion rates. The mean hemoglobin loss in the early DOAC group of 26.47 ± 16.26 was not significantly different to the non-DOAC control values of 30 ± 11.54 and within range of values quoted in the literature of 16 to 31.1 g/L.[25,26] These findings are consistent with the majority of recent studies concerning early hip fracture surgery in patients taking DOACs, further advocating for early surgery in this patient group.[22,23]

DOAC patients delayed for surgery >48 hours had a significantly higher 90-day mortality compared to those receiving early surgery. Although increased mortality is a known risk factor for late surgery, the late DOAC group had a higher ASA, increased preoperative medical complications and lower preadmission mobility which may have caused the delay to surgery and resultant increase in 90-day mortality.[15-18]

Early DOAC patients had significantly longer time to surgery than non-DOAC patients, despite having lower ASA ratings and higher mobility scores prior to admission. Such a delay may reflect concerns about intraoperative bleeding or delay related to medical clearance for surgery in anticoagulated patients. Such findings have been reproduced multiple times within the literature.[9,20,21]

Three recent retrospective studies have addressed preoperative DOAC use and early hip fracture surgery. Nineteen hip fracture patients taking DOACs and receiving surgery within 48 hours were compared to a non-DOAC case-matched control. Findings revealed no difference in blood loss or transfusion rates but increased delay to surgery and increased readmission rates for DOAC patients.[22] Seventy-eight patients receiving non-warfarin anticoagulants (including 29 taking DOACs) and receiving surgery within 48 hours or greater than 48 hours were compared. Between DOAC patients, no difference in blood loss or transfusion requirement was identified; however, the authors did not disclose patient numbers in each group or compare to a non-anticoagulated control.[24] Fifty-three patients

Table 2. Comparison of hip Fracture Surgery Outcomes for Patients Taking DOACs and Receiving Early Surgery (<48 Hours), Late Surgery (>48 Hours) and a non-DOAC <48 Hours Control Group.

		Early <48 hours DOAC, n = 17	<48 hours control, n = 56	*P*	Early <48 hours DOAC, n = 17	Late >48 hours, DOAC, n = 11	*P*
ΔHb admission to postoperative day 2	Mean (SD)	26.47 (16.26)	30 (11.54)	.41	26.47 (16.26)	31.91 (18.94)	.44
Blood transfusion	Count (%)	2 (11.76%)	17 (30.36%)	.34	2 (11.76%)	1 (9.09%)	.99
Pre-op complications[a]	Count (%)	1 (5.88%)	5 (8.93%)	.68	1 (5.88%)	3 (27.27%)	.15
Acute LOS from surgery (days)	Median (IQR)	6 (5)	3.5 (5.75)	.12	6 (5)	7 (5)	.28
Total LOS from surgery (days)	Median (IQR)	27.5 (32)	26 (29)	.31	27.5 (32)	34.5 (47.25)	.49
Time from admission to surgery (hours)	Mean (SD)	32.21 (7.83)	25.98 (11.4)	.01	32.21 (7.83)	76.68 (26.06)	NA
In-hospital mortality	Count (%)	0 (0%)	3 (5.35%)	.99	0 (0%)	1 (9.09%)	.41
30-day mortality	Count (%)	0 (0%)	3 (5.35%)	.99	0 (0%)	1 (9.09%)	.41
90-day mortality	Count (%)	0 (0%)	5 (8.93%)	.58	0 (0%)	4 (36.36%)	.04
Hematoma	Count (%)	0 (0%)	0 (0%)	.99	0 (0%)	0 (0%)	.99
Wound infection	Count (%)	1 (5.88%)	1 (1.79%)	.42	1 (5.88%)	1 (9.09%)	.99

Abbreviations: DOAC, direct oral anticoagulation; IQR, interquartile range; LOS, length of stay.
[a]Includes urinary tract infection, lower respiratory tract infection, delirium, pulmonary embolism, myocardial infarct, and stroke.

taking DOACs were compared to other oral anticoagulants and a non-anticoagulated control when receiving hip surgery within 24 hours, with an average time to surgery of 10 hours. Interestingly, they found a 3.4-fold increase in intraoperative blood transfusion in DOAC patients as well as a significantly lower admission hemoglobin when compared to controls. No significant difference in perioperative blood loss or mortality was identified.[23] These transfusion rate findings were not reflected in our study. Several further studies have been performed investigating perioperative DOAC use in hip fractures, however, have included patients operated on outside the recommended 48 hours where the anticoagulant effect will likely be eliminated or significantly reduced.[27-29]

Strengths of this study involve the strict controls and exclusion criteria that were utilized at the cost of extra patient numbers. To the authors' knowledge, this is the only study to directly compare DOAC patients operated on <48 hours to those operated on >48 hours and to a non-anticoagulated control.

There are limitations identifiable in this study. Its limited time frame of 2012 to 2017 may decrease the relevance to current orthopedic practice. Given the small sample size of the study, it is only powered to observe large differences between groups and sub-group analysis between different DOAC types was unable to be performed. Medication adherence and dosage was also unable to be accounted for due to the retrospective nature of the study.

Conclusion

Our study suggests hip fracture patients taking DOACs on admission is not a reason to delay surgery. Patients receiving early surgery had no increase in hemoglobin loss, transfusion rates, or mortality. Given the variability in recent retrospective studies, further meta-analysis and prospective research is required with larger patient numbers, recording of patient renal function, and subgroup analysis of each DOAC type in order to definitively guide clinical practice. On this basis, detailed patient and drug-specific clinical guidelines could be produced.

Authors' Note

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Declaration of Conflicting Interests

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