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Expedited surgery does not increase transfusion rates for patients with geriatric hip fracture taking factor Xa inhibitors

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Abstract

Objectives: Geriatric patients who sustain hip fractures and are taking factor Xa inhibitors (Xa-I) experience surgical delay. Our institution developed a pharmacokinetic protocol to formally guide and expedite surgical timing for these patients. The protocol is based on the patient's renal function and timing of last Xa-I dose. For patients with impaired renal function, longer wait times are recommended. The purpose of this study was to determine the effects of this protocol for patients with geriatric hip fracture taking Xa-I.

Design: Retrospective cohort study.

Setting: Level 1 trauma center.

Patients/Participants: A total of 164 patients aged 65 and older who were taking Xa-I before admission and underwent hip fracture surgery; 68 patients in the Standard group (2014–2018) and 96 patients in the Expedited group (2020–2022, after protocol implementation).

Intervention: Hip fracture surgery.

Main Outcome Measurements: Time to surgery (TTS), transfusion rate, blood loss, 90-day complication rates.

Results: The median TTS was significantly shorter in the Expedited group (28.6 hours, interquartile range 21.3 hours) than in the Standard group (44.8 hours, interquartile range 21.1 hours) ($P < .001$). There were no differences in overall transfusion rates. Multivariable regression analysis demonstrated that time to surgery was not predictive of transfusion rate in all patients (OR 1.00, 95% CI 0.99–1.02, $P = .652$). There were no differences in blood loss or rates of 90-day complications.

Conclusion: Geriatric patients with hip fractures and taking factor Xa inhibitors may warrant earlier surgery without an increased risk of transfusion or bleeding.

Level of Evidence: Therapeutic Level III.

Key Words: hip, fracture, geriatrics, trauma, apixaban, rivaroxaban, anticoagulant

1. Introduction

Geriatric patients who sustain hip fractures may be taking anticoagulants because of various medical comorbidities such as atrial fibrillation, venous thromboembolism, or history of cerebrovascular accident. Factor Xa inhibitors such as apixaban and rivaroxaban have been increasingly prescribed in recent years because they can be administered orally at fixed doses and do not require regular laboratory monitoring, which is a disadvantage of oral anticoagulants like vitamin K antagonists (warfarin).[1] There is limited evidence on perioperative management of factor Xa inhibitors in the setting of urgent hip fracture surgery. Existing literature has shown that patients with hip fracture who are taking factor Xa inhibitors experience delayed time to surgery and potentially increased mortality rates compared with patients who are not taking factor Xa inhibitors.[2–9] However, delayed surgery has not been shown to decrease transfusion rates, bleeding, or complications.[3,5,10,11] Recently published guidelines for patients with atrial fibrillation receiving factor Xa inhibitors recommend waiting 48 hours after the last dose to undergo surgery with high bleeding risk (eg, hip fracture surgery) to minimize blood loss.[12] However, the study does not provide recommendations for patients with decreased renal function because factor Xa inhibitors are renally cleared.

Patients with hip fracture are recommended to undergo surgery as soon as medically optimized to minimize morbidity and mortality, with a trend toward shorter recommended times to surgery in recent years.[13–15] Therefore, there is an ongoing challenge of balancing timely hip fracture surgery with

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appropriate perioperative management of factor Xa inhibitors to minimize bleeding and complications. To address this challenge, our institution developed a pharmacokinetic protocol to formally guide appropriate surgical timing and expedite surgery for these patients. Our hypothesis was that patients with geriatric hip fracture taking factor Xa inhibitors who undergo surgery during protocol implementation experience decreased time to surgery without increased transfusion rates, bleeding, or complications compared with patients who underwent surgery before protocol implementation.

2. Materials and Methods

2.1. Patient Selection

Institutional review approval was obtained for the use of patient data for research purposes (IRB STUDY2390; Principal Investigator: Carol Lin). This study was approved by the committee on research ethics at the primary institution in accordance with the Declaration of the World Medical Association. All data were retrospectively collected from a single Level 1 trauma center. Patients were identified from an existing orthopaedic trauma registry and a prospective orthopaedic database for all geriatric fractures. Inclusion criteria were patients aged 65 and older who presented with a femoral neck, intertrochanteric, or subtrochanteric fracture (OTA/AO classification 31A, 31B, and 32) and were taking a factor Xa inhibitor before admission. Patients were excluded if they were not directly admitted to our institution and were transferred from an outside hospital because the time since their last factor Xa inhibitor dose would be increased by the time taken to transfer the patient to our institution. Patients were also excluded if they sustained their hip fractures greater than 1 week before admission or sustained pathologic fractures.

2.2. Time-to-Surgery Protocol

The orthopaedic trauma and anesthesiology departments at our institution collaborated to establish a pharmacokinetic-based protocol to formally guide surgical timing and expedite surgery for patients with hip fracture taking factor Xa inhibitors (Fig. 1). Because factor Xa inhibitors are renally cleared, the protocol is based on the patient's preoperative renal function and time since the last dose. For patients with normal renal function—defined as having a creatinine clearance (CrCl) of 50 or greater, the protocol recommends waiting 24 hours after the last dose. In patients with decreased renal function—defined as a CrCl of less than 50 but greater than or equal to 30, the protocol recommends waiting 48 hours after the last dose. In patients with severely decreased renal function—defined as a CrCl of less than 30, the protocol recommends multidisciplinary clinical judgment for appropriate surgical timing. The protocol was developed throughout 2019. Therefore, the Standard (preprotocol) group consisted of patients who underwent surgery from 2014 to 2018, and the Expedited (postprotocol) group consisted of patients who underwent surgery from 2020 to 2022.

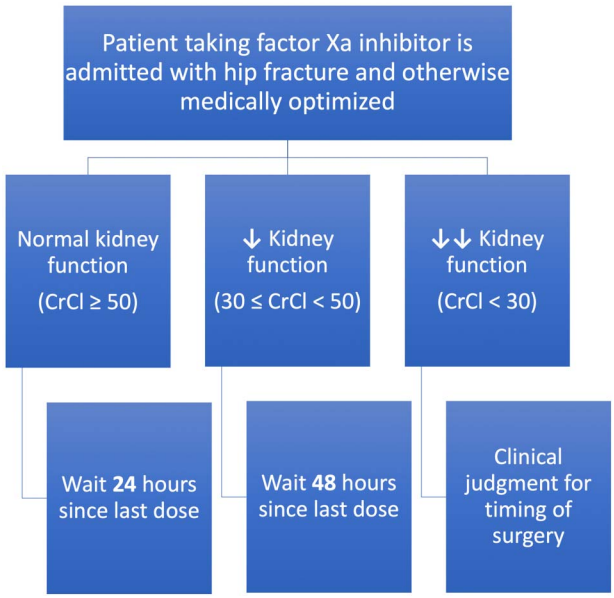

Figure 1. Pharmacokinetic-based protocol for patients who are taking factor Xa inhibitors undergoing surgery for hip fractures.

2.3. Data Collection

Chart review was performed to record patient demographics, type of factor Xa inhibitor, reason for anticoagulation, concurrent clopidogrel use, age-adjusted Charlson Comorbidity Index (CCI), American Society of Anesthesiologists (ASA) classification, preoperative creatinine clearance (CrCl), fracture type, implant choice, primary anesthesia type, time to surgery (TTS), length of stay, transfusion rates, blood loss, and 90 day postoperative rates of readmission, reoperation, mortality, and complications. Transfusion thresholds were at the discretion of the patient's anesthesiologist or hospitalist. Two measures of blood loss were calculated. Preoperative blood loss was defined as the difference between the preoperative hemoglobin (Hgb) on admission and the lowest preoperative Hgb. Overall blood loss was defined as the difference between the preoperative Hgb on admission and the lowest postoperative Hgb within the first 4 postoperative days. Recorded complications were cerebrovascular accident, myocardial infarction, deep venous thrombosis or pulmonary embolism, gastrointestinal bleed, pneumonia, and postoperative surgical site drainage or infection requiring intervention. Interventions included both surgical (eg, debridement) and nonsurgical (eg, compressive wrap or incisional vacuum dressing) treatment modalities.

We determined the number of patients who adhered to the protocol recommendations for each year after protocol implementation (2020–2022). Patients were considered to have adhered to the protocol if their TTS was within the recommended parameters based on preoperative renal function. If their TTS was outside of recommended parameters, then the patients were considered to have not adhered to the protocol. This did not include patients with severely decreased renal function (CrCl < 30) because there was no specifically defined cutoff for TTS, and appropriate surgical timing was based on multidisciplinary clinical judgment.

2.4. Statistical Analysis

Chi-squared or Fisher exact tests, in the case of small cell counts, were performed to compare categorical data. Student *t* tests and Mann Whitney *U* tests were performed to compare normally distributed and non-normally distributed continuous data, respectively. Multivariable logistic regression models were conducted to analyze the relationship between predictors of interest and overall transfusion rate. Included predictor variables were

deemed either statistically significant (P value $< .05$) or clinically relevant between the 2 groups. All statistical analyses were performed using R software (Vienna, Austria).

3. Results

Sixty-eight patients comprised the Standard group and 96 patients comprised the Expedited group. Patient demographics and preoperative characteristics are described in Table 1. The Expedited group had a significantly higher number of patients taking apixaban than the Standard group did (70.8% vs. 45.6%, $P = .001$). The most common reason for factor Xa inhibitor usage in both groups was atrial fibrillation (83.8% in the Standard group, 81.2% in the Expedited group). No patient in the Standard group was concurrently taking clopidogrel, but 9 patients (9.4%) in the Expedited group were also taking clopidogrel in addition to a factor Xa inhibitor. There were significantly fewer female patients in the Expedited group than in the Standard group (54.2% vs. 79.4%, $P = .001$). There were no significant differences between the 2 groups regarding age, body mass index (BMI), age-adjusted CCI, ASA classification, or preoperative renal function.

Injury characteristics, time to surgery, and length of stay are described in Table 2. There were no significant differences between the 2 groups regarding fracture type or implant choice. There was a significant difference between the 2 groups in primary anesthesia type ($P = .006$). More patients in the Expedited group underwent primarily general anesthesia than in the Standard group (86.6% vs. 67.6%). Fewer patients in the Expedited group underwent primarily neuraxial anesthesia (9.4% vs. 13.2%) and primarily regional anesthesia (4.2% vs. 19.1%). Of note, patients who underwent general or neuraxial anesthesia may have also received supplemental peripheral nerve blocks but not as their primary anesthetic regimen. The Expedited group had a significantly lower median time to surgery of 28.6 hours (interquartile range 21.1 hours) than the Standard group, which was 44.8 hours (interquartile range 21.3 hours) ($P < .001$). More patients in the Expedited group underwent surgery within 48 hours of admission than in the Standard group (80.2% vs. 58.8%) and within 24 hours of admission (29.2% vs. 14.7%). There was no significant difference in length of stay between the 2 groups.

Transfusion rates, blood loss, and 90-day complication rates are described in Table 3. There was a trend toward decreased overall transfusion rate in the Expedited group (29.2%) when compared with the Standard group (36.8%), although this did not reach statistical significance ($P = .305$). There were no significant differences between the 2 groups regarding preoperative, intraoperative, or postoperative transfusion rates. There were no significant differences in preoperative blood loss or overall blood loss. There were no significant differences in 90-day complication rates, readmission, reoperation, or mortality. Four patients (5.9%) in the Standard group developed a gastrointestinal bleeding-related complication within 90 days. One patient developed the complication during the index admission, and the other 3 patients were diagnosed with these complications during readmissions. One patient in the Expedited group developed a gastrointestinal bleed-related complication during readmission. One patient in the Standard group underwent cephalomedullary nailing for an intertrochanteric hip fracture and was readmitted 6 days postoperatively for persistent bleeding from the surgical site. There was no evidence of wound dehiscence. The patient was treated with an incisional vacuum dressing for 3 days followed by a dry dressing, with no recurrent drainage on follow-up. One patient in the Expedited group underwent hemiarthroplasty for a femoral neck fracture and was readmitted 2 weeks postoperatively for a hematoma requiring irrigation and debridement with liner exchange. No other reoperations were related to anticoagulant use. One patient in the Expedited group was found to have increasing hip ecchymosis and swelling postoperatively during the index admission, concerning for a hematoma. The patient required transfusions and was placed in a compressive thigh wrap with no further bleeding-related complications.

Figure 2 shows the proportion of patients who adhered to the protocol each year in the Expedited group. Patients with severely

TABLE 1

Demographic, Anticoagulation, and Preoperative Characteristics

Characteristic	Standard (n = 68)	Expedited (n = 96)	P
Age (y)	84.4 ± 6.9	84.3 ± 7.9	.810
Sex (% female, n)	79.4% (52)	54.2% (52)	**.001**
Body mass index (BMI)	24.5 ± 4.2	24.1 ± 4.7	.630
Race (%, n)			.694
Asian	1.5% (1)	3.1% (3)	
Black	4.4% (3)	6.2% (6)	
White	91.2% (61)	84.4% (81)	
Other	2.9% (2)	6.2% (6)	
Type of factor Xa inhibitor (%, n)			**.001**
Apixaban	45.6% (31)	70.8% (68)	
Rivaroxaban	54.4% (37)	29.2% (28)	
Concurrent clopidogrel use (%, n)	0% (0)	9.4% (9)	**.011**
Reason for factor Xa inhibitor use (%, n)			.405
Atrial fibrillation	83.8% (57)	81.2% (78)	
DVT and/or PE	10.3% (7)	7.3% (7)	
CVA	5.9% (4)	11.5% (11)	
ASA classification (%, n)			.173
II	14.7% (10)	10.4% (10)	
III	77.9% (53)	72.9% (70)	
IV	7.4% (5)	16.7% (16)	
Age-adjusted Charlson Comorbidity Index	5.8 ± 1.7	6.6 ± 2.8	.230
Preoperative renal function (%, n)			.593
CrCl ≥ 50	75.0% (51)	67.7% (65)	
30 ≤ CrCl < 50	16.2% (11)	18.8% (18)	
CrCl < 30	8.8% (6)	13.5% (13)	

CVA, cerebrovascular accident; DVT, deep venous thrombosis; PE, pulmonary embolism.

TABLE 2

Perioperative Characteristics

Characteristic	Standard (n = 68)	Expedited (n = 96)	P
Fracture type (%, n)			.677
Femoral neck	48.5% (33)	47.9% (46)	
Intertrochanteric	51.5% (35)	50.0% (48)	
Subtrochanteric	0% (0)	2.1% (2)	
Implant type (%, n)			.850
Arthroplasty	41.2% (28)	38.5% (37)	
Cephalomedullary nailing	47.1% (32)	45.8% (44)	
Sliding hip screw	10.3% (7)	11.5% (11)	
Percutaneous screw fixation	1.5% (1)	4.2% (4)	
Primary anesthesia type (%, n)			**.005**
General	67.5% (46)	86.5% (83)	
Neuraxial	13.2% (9)	9.4% (9)	
Regional	19.1% (13)	4.2% (4)	
Median TTS (h, IQR)	44.8 (21.3)	28.6 (21.1)	**<.001**
Length of stay (d)	7.0 ± 3.5	7.2 ± 3.5	.710

IQR, interquartile range.

TABLE 3

Transfusion Results, Perioperative Blood Loss, and 90-Day Complications

Characteristic	Standard (n = 68)	Expedited (n = 96)	*P*
Transfusion rate, overall	36.8% (25)	29.2% (28)	.305
Average change in Hgb from admission to lowest preoperative Hgb (g/dL)	1.1 ± 1.1	1.1 ± 1.3	.930
Average change in Hgb from admission to lowest postoperative Hgb (g/dL)	3.0 ± 1.5	3.3 ± 1.7	.240
Preoperative transfusion	4.4% (3)	8.3% (8)	.323
Intraoperative transfusion	2.9% (2)	4.2% (4)	1.000
Postoperative transfusion	33.8% (23)	26.0% (25)	.281
Readmission	27.9% (19)	26.0% (25)	.787
Reoperation	2.9% (2)	3.1% (3)	1.000
Mortality	7.4% (5)	8.2% (8)	1.000
Complication			
Cerebrovascular accident	1.5% (1)	3.1% (3)	.642
Myocardial infarction	0% (0)	3.1% (3)	.267
Deep venous thrombosis or pulmonary embolism	1.5% (1)	3.1% (3)	.642
Urinary tract infection	20.6% (14)	26.0% (25)	.419
Gastrointestinal bleed	5.9% (4)	2.1% (2)	.233
Pneumonia	5.9% (4)	5.2% (5)	1.000
Significant drainage/infection	1.5% (1)	2.1% (2)	1.000

decreased renal function (CrCl < 30) were not included in this graph. In 2020, 27.6% (8 of 21 patients) underwent surgery within protocol parameters. This progressively increased to 38.5% in 2021 (10 of 26 patients) and 50.0% (14 of 28 patients) in 2022.

Multivariable logistic regression analyses were performed. Statistically significant predictor variables were sex, primary anesthesia type, type of factor Xa inhibitor, and concurrent clopidogrel use. Clinically relevant variables were age and BMI. Fracture type and implant type were initially included, but owing to a small number of patients with subtrochanteric fractures and patients who underwent percutaneous screw fixation, these 2 variables could not be successfully included in the final analysis. When controlling for the above variables, time to surgery was not predictive of overall transfusion rate (odds ratio 1.00, 95% confidence interval 0.99–1.02, $P = .537$). For each increasing year in age, there was a 7% increase in the odds of transfusion (odds ratio 1.07, 95% confidence interval 1.02–1.12, $P = .011$). Rivaroxaban was not significantly associated with an increased odds of transfusion over apixaban (odds ratio 1.34, 95% confidence interval 0.66–2.76, $P = .416$). In addition, concurrent clopidogrel use was not significantly associated with an increased odds of transfusion (odds ratio 1.65, 95% confidence interval 0.37–6.99, $P = .488$).

4. Discussion

Our institutional protocol aimed to expedite surgery for patients with geriatric hip fracture taking factor Xa inhibitors who were otherwise medically optimized. Patients who underwent surgery during protocol implementation were found to have shorter median times to surgery but not increased transfusion rates, bleeding, or 90-day complications. To our knowledge, this is the first study to evaluate outcomes of a protocol expediting hip

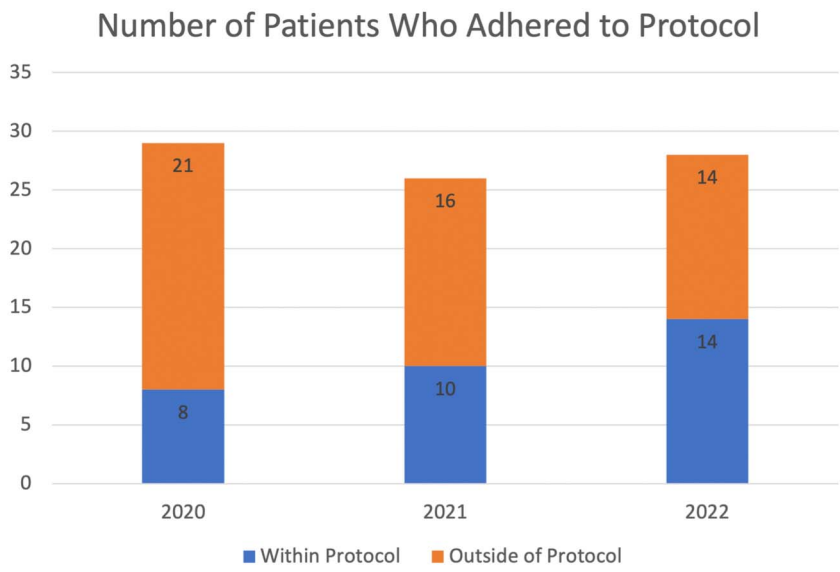

Figure 2. Overall protocol adherence rates from 2020 to 2022.

fracture surgery for patients on factor Xa inhibitors. More patients in the Expedited group were taking apixaban than in the Standard group. Increasing apixaban use and decreasing rivaroxaban use over the years may be partly explained by apixaban's decreased dependence on renal clearance than rivaroxaban (27% vs. 35%, respectively).[16] Clinicians may have preferentially prescribed apixaban if renal insufficiency was a concern, although the specific factor Xa inhibitor taken did not affect overall transfusion rates. Concurrent clopidogrel use was also not associated with increased risk of transfusion. Collinge et al[17] demonstrated that patients taking clopidogrel do not experience delays in surgery and increased risk for bleeding. Our institution does not delay hip fracture surgery for patients who are taking clopidogrel or similar antiplatelet medications, although no clear guidelines exist for patients who are on both clopidogrel and a factor Xa inhibitor.

Outcomes of patients undergoing hip fracture surgery with general or neuraxial anesthesia have been extensively studied. Patients who are taking factor Xa inhibitors are recommended to wait 3 days from their last dose before proceeding with neuraxial anesthesia to minimize risk for hemorrhagic complications, such as spinal epidural anesthesia.[18] This delay conflicts with the need to expedite surgery for otherwise medically optimized patients with hip fracture. In our cohort, more patients in the Expedited group underwent general anesthesia than patients in the Standard group. A recent large, multicenter randomized controlled trial demonstrated that for older patients undergoing hip fracture surgery, neuraxial anesthesia did not result in improved survival or mobilization at 60 days compared with general anesthesia.[19] However, this trial does not address long-term outcomes and transfusion or bleeding-related outcomes.

Reported transfusion rates for patients on factor Xa inhibitors and undergoing hip fracture surgery vary widely in existing literature, and our reported transfusion rates for both patient groups fall within this range.[3,9–11,20,21] While transfusion thresholds may have evolved throughout the study period, our study demonstrated that even with a decreased median time to surgery, patients in the Expedited group trended toward lower transfusion rates. Patients in the Expedited group also experienced similar amounts of preoperative and overall blood loss as patients in the Standard group. Our findings support expediting hip fracture surgery for patients on factor Xa inhibitors without an increased risk of transfusion or blood loss. These patients experienced low rates of thrombotic complications, gastrointestinal bleed, or significant postoperative drainage and infection, which is also comparable with rates reported in other studies.[3,21]

This study design has several limitations, including its retrospective nature and division of patients into 2 groups based on the year they were treated. We purposely did not include patients who underwent surgery in 2019 because the protocol was gradually implemented and not at a single time point. This limits the number of patients in our analysis and may not capture other changes in patient care during that time. Although we investigated overall protocol adherence rates, we cannot make definitive conclusions regarding specific reasons for surgical delay. Protocol adherence rates in our cohort increased since implementation, but half of the patients in 2022 with normal or decreased renal function continued to demonstrate delayed times to surgery that were outside of protocol recommendations. Multiple factors can contribute to surgical delay, including additional need for medical optimization, operating room availability, surgeon availability, and discussions for goals of care before surgery. Furthermore, we cannot make definitive conclusions or recommendations for patients with severely decreased renal function because these patients are expected to require additional medical optimization such as dialysis before surgery. The longitudinal nature of the study introduces the possibility of evolving treatment algorithms outside of our protocol, such as varying transfusion thresholds and recommended type of anesthesia. Transfusion thresholds were at the discretion of the patient's hospitalist or anesthesiologist. Usage of tranexamic acid, or TXA, was also at the discretion of the patient's surgeon or anesthesiologist and was not captured in this study. Our study did not investigate patients who were taking dabigatran, another orally administered anticoagulant that acts as a direct thrombin inhibitor. Dabigatran is more reliant on renal function for clearance than apixaban or rivaroxaban, so existing guidelines typically recommend waiting longer periods of time before proceeding with surgery.[12] Our preliminary chart review revealed only 1 patient who was taking dabigatran and met inclusion and exclusion criteria. Future studies would benefit from dedicated analyses of patients taking dabigatran in conjunction to patients taking factor Xa inhibitors.

In conclusion, implementation of a pharmacokinetic-based time-to-surgery protocol for patients with geriatric hip fracture taking factor Xa inhibitors has been shown to decrease time to surgery without increasing the risk of transfusion, bleeding, or 90-day postoperative complications. Despite protocol implementation, a significant number of patients still did not undergo surgery within protocol recommendations. This may be due to several reasons including additional medical optimization and resource constraints. Further research is needed to determine long-term outcomes, outcomes in patients taking dabigatran, and outcomes for patients with severely decreased renal function because they likely metabolize factor Xa inhibitors at a slower rate.

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