Effect of Prothrombin Complex Concentrates on Time to Surgery in Patients with Hip Fracture Anticoagulated with Vitamin K Antagonists: A Retrospective Cohort Study

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Abstract

Objectives: To determine the time to surgery (TTS) among patients with acute hip fracture who are anticoagulated with vitamin K antagonists (VKAs) who receive prothrombic complex concentrate (PCC) compared to those who do not receive PCC.

Method: We conducted a retrospective cohort study of consecutive patients with an acute hip fracture presenting to the emergency department (ED) of the Jewish General Hospital, a 637-bed tertiary care hospital center in Montreal, Quebec, between January 1st, 2015 and March 1st, 2020. Eligible patients were identified via the ED electronic database. Inclusion criteria were: (1) > 18 years of age; (2) acute hip fracture and admission for surgical repair; (3) VKA use and international normalized ratio (INR) > 1.5 at admission. Follow-up was limited to index hospitalization. The primary outcome of TTS, reported in hours, was defined as the time from hospital admission to the time of surgery. Mann-Whitney U test was used to assess any difference in median TTS between the two groups.

Results: A total of 53 patients were included in our cohort of which 43.4% (23/53) received PCC with a median time to first dose of 25.5 hours (IQR 19.4-51.6). 84.9 % (45/53) received vitamin K with a median time to the first dose of 16 h (IQR 7.5-26.7). The median TTS in the PCC and no PCC groups was 51.8 h (IQR 26.8–71.4) vs. 63.5 h (IQR 49.4-73.2) respectively (p=0.71).

Conclusion: This study did not identify shorter TTS between patients who received PCC and those who did not. Median TTS in both groups surpassed the recommended 48h benchmark, and PCC and vitamin K administration timing was suboptimal. These findings demonstrate a significant care gap among this vulnerable population and represent a call for future initiatives to ensure a more streamlined and multidisciplinary approach to anticoagulation management starting at the onset of presentation.

Résumé

Objectifs: Déterminer le délai avant l'intervention chirurgicale (DAIC) parmi les patients présentant une fracture aigüe de la hanche qui suivent une anticoagulothérapie par des antagonistes de la vitamine K (AVK) et qui reçoivent un concentré de complexe prothrombique (CCP) par rapport à ceux qui ne reçoivent pas le CCP.

Méthodologie: Nous avons mené une étude de cohorte rétrospective de patients consécutifs présentant une fracture aigüe de la hanche à leur arrivée à l'urgence de l'Hôpital général juif, un centre hospitalier de 637 lits de soins tertiaires situé à Montréal (Québec), entre le 1er janvier 2015 et le 1er mars 2020. Les patients admissibles ont été repérés par l'intermédiaire de la base de données électronique du service des urgences. Les critères d'inclusion sont : 1) personne âgée de plus de 18 ans; 2) fracture aiguë de la hanche et hospitalisation en vue d'une réparation chirurgicale; 3) prise d'AVK et rapport international normalisé (RIN) supérieur à 1,5 lors de l'admission à l'hôpital. Le suivi se limite à l'admission initiale. Le critère d'évaluation principal du DAIC, indiqué en heures, est défini comme étant le délai entre l'admission à l'hôpital et le moment de l'intervention chirurgicale. Le test U de Mann-Whitney est utilisé pour évaluer toute différence dans les DAIC médians entre les deux groupes.

Résultats: Au total, 53 patients font partie de la cohorte dont 43,4 % (23/53) ont reçu le CCP, le délai médian avant la première dose étant de 25,5 heures (écart interquartile [EI] de 19,4 à 51,6), et 84,9 % (45/53) ont reçu de la vitamine K, le délai médian avant la première dose étant de 16 heures (EI de 7,5 à 26,7). Le DAIC médian est de 51,8 heures (EI de 26,8 à 71,4) pour le groupe recevant le CCP et de 63,5 heures (EI de 49,4 à 73,2) pour celui ne recevant pas le CCP (p = 0,71).

Conclusion: Cette étude révèle une tendance vers des DAIC plus courts chez les patients recevant le CCP que chez ceux qui ne le reçoivent pas. Le DAIC médian dans les deux groupes est supérieur au délai de référence recommandé de 48 heures, et le moment où le CCP et la vitamine K sont administrés est sous-optimal. Ces constatations montrent une lacune importante en matière de soins chez cette population vulnérable et représentent un appel à des initiatives visant à assurer une approche simplifiée et multidisciplinaire de la prise en charge de l'anticoagulothérapie qui commence dès l'arrivée du patient à l'hôpital.

Keywords: vitamin K antagonist; prothrombin complex concentrate; hip fracture; perioperative medicine

Introduction

Managing patients with hip fractures is a significant public health problem worldwide.[1,2] There are an estimated 30,000 hip fractures annually in Canada, associated with a cost of $2.3 billion.[3] With an aging population, these numbers are projected to rise,[1,4] and the strain placed on hospitals will continue to increase. Large retrospective studies demonstrated that surgical intervention within 24 hours for hip fracture was associated with improved morbidity and mortality,[5,6] and surgery as early as 6 hours has been shown to reduce morbidity.[7] In Canada, surgical intervention within 48 hours is considered best practice, but less than two-thirds of patients with an acute hip fracture meet this benchmark.[8]

Anticoagulation has been identified as one major barrier to achieving the ideal time to surgery.[9-12] To minimize the risk of perioperative bleeding, current guidelines from the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommend that surgery be postponed until the patient's international normalized ratio (INR) reaches a value below 1.5.[13] Among Vitamin K Antagonist (VKA) users, where therapeutic target INR is typically between 2.0-3.0, specific interventions may be required to achieve this value; vitamin K and/or prothrombin complex concentrates (PCC) can be used to reverse anticoagulation effectively and rapidly. Despite these readily available agents, a recent systematic review and meta-analysis demonstrated that patients taking VKAs have significant delays to surgery.[14] While the optimal strategy to achieve reversal of VKA effect in the context of perioperative management of hip fractures remains controversial, previous reports have demonstrated that vitamin K is safe and efficacious in reducing INR and enabling surgery within 37.7-44 hours of presentation, i.e., within the 48h benchmark, for patients with acute hip fractures.[15,16] An alternative reversal strategy is the use of vitamin K with PCC. PCC rapidly normalizes INR within 15 minutes

and lasts up to 6 hours post-administration.[17] A recently published case-control study showed the safety of rapid reversal with PCC and early surgery for VKA patients with hip fractures.[18] However, evidence is scarce addressing whether PCC reduces time to surgery (TTS).[17,19] This study aims to evaluate whether patients taking VKAs and presenting with acute hip fractures have reduced TTS when administered PCC compared to those who did not receive PCC.

Methods

We conducted a retrospective cohort study of consecutive patients with an acute hip fracture resulting from low-energy mechanism presenting to the Emergency Department (ED) of the Jewish General Hospital (JGH), a large 637-bed tertiary care center in Montreal, Quebec, between January 1st 2015 and March 1st 2020. Annually, over three hundred patients undergo hip fracture repair at the JGH. No institutional perioperative VKA reversal protocol was available during this period. Patients were identified via the ED electronic database. Inclusion criteria were (1) 18 or older, (2) anticoagulated with a VKA, and (3) planned surgical hip repair during the same admission at the JGH. Patients were excluded if they had an INR < 1.5 at the time of presentation, were transferred from or to another hospital, or required other surgical interventions. In addition, two groups were devised based on whether or not PCC was administered before surgery. The study was approved by the JGH research ethics committee.

Our primary outcome was TTS, defined as the time from ED presentation to the time of surgery. Our secondary outcomes were: hospital length of stay (LOS) (time from ED admission to discharge), time to the first dose of PCC (time from ED admission to the first dose of PCC), time to the first dose of vitamin K (time from ED admission to the first dose of vitamin K), time to INR ≤1.5 (time from ED admission to INR ≤1.5), the total number of blood transfusion and proportions of acute venous thromboembolism (VTE), stroke, major bleeding per the International Society on Thrombosis and Hemostasis (ISTH) definition, and death during the admission. Hospital electronic medical records (EMR) were accessed for data collection. Baseline patient characteristics included: age, sex, American Society of Anesthesia (ASA) classification, admission hemoglobin, hemoglobin on the day of surgery, postoperative hemoglobin, number of blood transfusions, admission platelet count, and creatinine clearance (CKD-EPI equation). Anticoagulation-related characteristics included: indication for anticoagulation [Atrial fibrillation (AF), mechanical heart valve, or VTE], CHADS2 score, admission INR, INR on the day of surgery, and vitamin K use. Surgical-related characteristics included: date of surgery, day of the week, time of admission, time of surgery, date of admission and discharge, type of surgery [hemiarthroplasty, open reduction internal fixation (ORIF), closed reduction and percutaneous pinning (CRPP)], and pre and postoperative specialist consultations (internal medicine, thrombosis/hematology, cardiology).

Descriptive statistics with means with standard deviation (SD) or medians with interquartile range (IQR) were used to analyze continuous data and count or proportion for categorical data. The Mann-Whitney test was used to assess the difference in median TTS. For secondary outcomes, the proportion of major bleeding was compared between the two groups using the χ^2 test and Fisher's exact test to compare proportions of VTE, stroke, and death. The median LOS between groups was compared using the Mann Whitney U test. The results were considered significant at two-sided $p < 0.05$. The SAS/STAT® software was used.

Results

Between January 1st 2015 and March 1st 2020, 1700 patients presented with a hip fracture. In total, 72 patients prescribed VKAs presented with a hip fracture; the final study population included 53 patients after exclusions. Reasons for exclusion were: VKA initiated in the postoperative period (8/19), non-surgical management (5/19), INR < 1.5 (2/19), transferred from another hospital (2/19), and hip fracture from fall while admitted (2/19). Baseline patient-, anticoagulation-, and surgery- specific characteristics between the PCC and no PCC groups are presented in Table 1. Median age was 88 years (IQR 83-91) and 49.1% (26/53) of patients were female. Median ASA class was 3 (range 1-5) and the most common indication for anticoagulation was AF 92.5% (49/53) with median CHADS2 score of 3 (IQR 2-4). Median admission INR was 2.5 (IQR 2.2-3.0). ORIF was the most frequent surgery performed in 66% (35/53) of patients. Overall, characteristics were similar between both groups; however, the PCC group had a smaller proportion of patients with a creatinine clearance above 50 mL/min [47.8% (11/23) vs. 63.3% (19/30)], lower hemoglobin at admission (median 111 vs. median 128) and more hemi arthroplasty as their surgical procedure [39.1% (9/23) vs. 16.7% (5/30)].

Within the cohort, 43.4% (23/53) received PCC and 87.0% (20/23) of those who received PCC also received

Table 1. Patient Characteristics

VKA Anticoagulation Group	PCC group n= 23	No PCC group n= 30	Total n= 53
Patient Characteristics			
Median Age, years (IQR)	87 (78-91)	88 (83-92)	88 (83-91)
Female Sex, count (%)	10 (43.5)	16 (53.3)	26 (49.1)
Median ASA Class (range)	3 (1-5)	3 (2-4)	3 (1-5)
Creatinine Clearance, count* (%)			
> 50 mL/min	11 (47.8)	19 (63.3)	30 (56.3)
= 31-49 mL/min	6 (20.1)	7 (23.3)	13 (24.5)
< 30 mL/min	3 (13.0)	1 (3.3)	4 (7.6)
Dialysis	3 (13.0)	3 (10.0)	6 (11.3)
ASA Class, count (%)			
1	1 (4.3)	0 (0.0)	1 (1.9)
2	1 (4.3)	3 (10.0)	4 (7.6)
3	14 (60.1)	21 (70.0)	35 (66.0)
4	7 (30.4)	6 (20.0)	13 (24.5)
5	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin Admission (g/L), median (IQR)	111 (108-129)	128 (119-136)	123 (110-135)
Anticoagulation Characteristics			
Admission International Normalized Ratio, median (IQR)	2.5 (2.3-3.3)	2.5 (2.1-3.0)	2.5 (2.2-3.0)
OR day International Normalized Ratio*, median (IQR)	1.3 (1.2-1.3)	1.3 (1.2-1.4)	1.3 (1.2-1.4)
Indication for Anticoagulation, count ** (%)			
Atrial Fibrillation	21 (91.3)	27 (90.0)	48 (90.6)
Venous Thromboembolism	0 (0.0)	2 (6.7)	2 (3.8)
Mechanical Heart Valve	1 (4.3)	0 (0.0)	1 (1.9)
Antiphospholipid Syndrome	0 (0.0)	0 (0.0)	0 (0.0)
> 1 Indication	1 (4.3)	1 (3.3)	2 (3.8)
CHADS 2 score (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	2 (9.5)	3 (10.7)	5 (10.2)
2	5 (23.8)	9 (32.1)	14 (28.6)
3	10 (47.6)	7 (25.0)	17 (34.7)
4	2 (9.5)	6 (21.4)	8 (16.3)
5	2 (9.5)	2 (7.1)	4 (8.2)
6	0 (0.0)	1 (3.6)	1 (2.0)
Surgical Characteristics			
Type of Surgery (%)			
Hemi Arthroplasty	9 (39.1)	5 (16.7)	14 (26.4)
Open Reduction Internal Fixation	13 (56.5)	22 (73.3)	35 (66.0)
Closed Reduction Percutaneous Pin	1 (4.4)	3 (10.0)	4 (7.6)

* missing data (1 PCC; 5 no PCC)

** One patient with > 1 indication for anticoagulation included atrial fibrillation, was counted in the appropriate CHADS2 category

vitamin K. 47.2% (25/53) of patients received vitamin K alone, 5.7% (3/53) received PCC alone and 9.4% (5/53) received neither PCC nor vitamin K. Reversal agents administered in each group is outlined in Table 2. No patients received fresh frozen plasma. The median time from ED presentation to the first PCC dose was 25.5 h (IQR 19.4-51.6) and 16h (IQR 7.5-26.7) to the first vitamin K dose. Among all patients, only 41.5% (22/53) had a formal recommendation to administer PCC before surgery.

Baseline patient-, anticoagulation-, and surgery- specific characteristics between the PCC and no PCC groups are presented in Table 2. Overall, characteristics were similar between both groups; however, the PCC group had a smaller proportion of patients with a creatinine clearance above 50 mL/min [47.8% (11/23) vs. 63.3% (19/30)], lower hemoglobin at admission (median 111 vs. median 128) and more hemi arthroplasty as their surgical procedure [39.1% (9/23) vs. 16.7% (5/30)].

The median TTS (Figure 1) in the PCC and no PCC groups was 51.8 h (IQR 26.8–71.4) vs. 63.5 h (IQR 49.4-73.2) respectively (p=0.71). However, median TTS for the study cohort was 58 h (IQR 37.1-72.8) and only 34.0% (18/53) proceeded to surgery within 48h: 47.8% (11/23) in the PCC group vs 23.3% (7/30) in the no PCC group (p=0.062) (Figure 2).

The proportion of major bleeding in the PCC group was 8.7% (2/23) vs. 16.7% (5/30) in the no PCC group (p =0.343). Blood transfusions were similar between both groups, 43.4% (10/23) vs. 40.0% (12/30) (p=0.799). Median LOS was 13.5 days (IQR 10.5-27.4) in the PCC group compared with 15.7 days (IQR 12.3-27.3) in the no PCC group (p = 0.653). Secondary outcomes are outlined in Table 3.

Discussion

Our study did not demonstrate that the administration of PCC to patients taking VKAs resulted in a significant difference in TTS in hip fracture surgery. However, more patients in the PCC group had surgery within 48h than those in the no PCC group. These results align with the findings of two other studies[17,19] addressing this poorly elucidated question. One prospective study demonstrated significant differences in TTS between VKA patients who received PCC

Table 2. PCC and Vitamin K Administration Characteristics

VKA Anticoagulation Group	PCC Group n= 23	No PCC Group n= 30	Total n= 53
Number of Patients Who Received Vitamin K (%)	20 (87.0)	25 (83.3)	45 (84.9)
Median time to 1st dose Vitamin K, hours (IQR)	18.0 (7.4-25.9)	15.8 (9.6-27.6)	16 (7.5-26.7)
Median time to 1st dose PCC, hours (IQR)	25.5 (19.4-51.6)	NA	NA

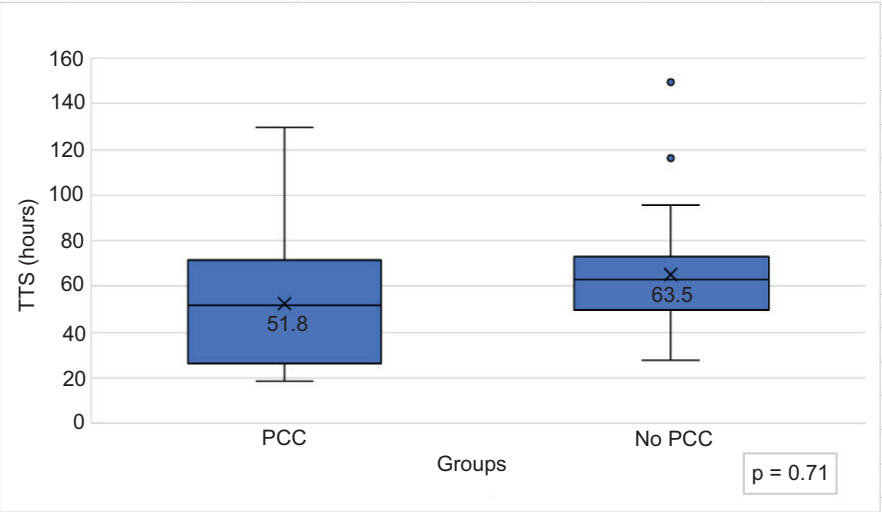

Figure 1. Median Time to Surgery in the PCC versus no PCC groups.

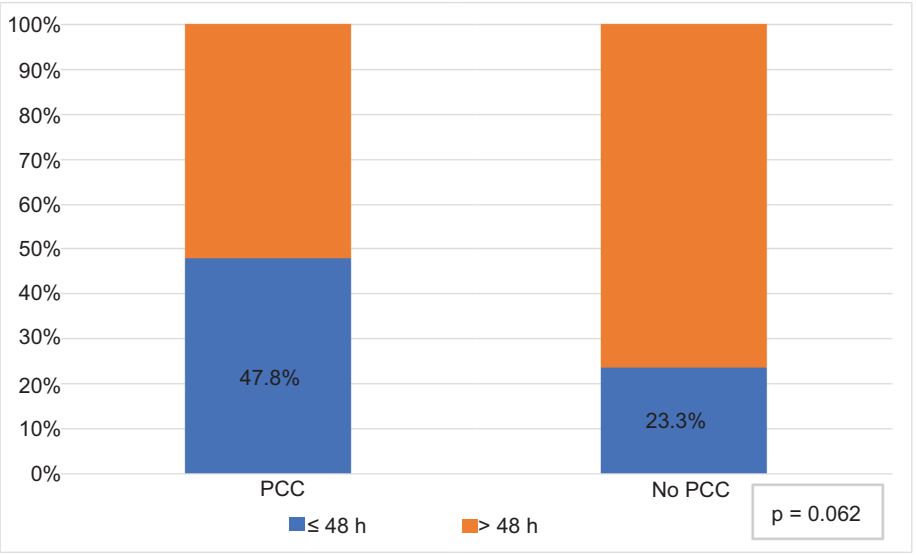

Figure 2. Proportions of Patients with Time to Surgery ≤ 48 h in PCC vs no PCC group.

Table 3. Secondary Outcomes

VKA Anticoagulation Group	PCC Group n= 23	No PCC Group n= 30	Total n= 53	P value
Hospital Length of Stay, days (IQR)	13.5 (10.5-27.4)	15.7 (12.3-27.3)	16 (11.2-27.4)	0.653
Median Time from ED presentation to first dose of PCC, hours (IQR)	25.5 (19.4-51.6)	NA	NA	NA
Median Time from ED presentation to first dose of Vitamin K, hours (IQR)	18.0 (7.4-25.9)	15.8 (9.6-27.6)	16 (7.5-26.7)	0.706
Median Time to INR ≤1.5, hours (IQR)	29.7 (21.4-52)	40.8 (33.6-49.1)	37 (24.4-49.9)	0.112
Number of Patients with Acute VTE (%)	0 (0)	1 (3.3)	1 (1.9)	1.0
Number of Patients with Acute Stroke (%)	1 (4.3)	1 (3.3)	2 (3.8)	1.0
Number of Patients with Major Bleeding by ISTH Definition (%)	2 (8.7)	5 (16.7)	7 (13.2)	0.343
Number of Patients Who Received Blood Transfusions (%)	10 (43.4)	12 (40.0)	22 (41.5)	0.799
Number of Deaths during admission (%)	3* (13)	0 (0)	3 (5.7)	0.076

* Causes of death were: congestive heart failure, renal failure and pneumonia

as compared to those who did not [21 ± 10 h (n=12) vs. 28 ± 15 h (n=50), (p=0.029)][17] and another study found that patients treated solely with PCC had similar TTS [20 h (IQR 13–25 h)] to a non-anticoagulated control group [20 h (IQR 15–33)]. They also noted significantly longer TTS for patients who received only vitamin K [45 h (IQR 31–52 h), p < 0.001].[19] Nonetheless, these results highlight that PCC is an appropriate agent to achieve hemostasis in patients using VKAs with acute hip fractures, with or without vitamin K, and can allow patients to achieve surgery within the optimal 48h benchmark.

Various factors have been associated with increased TTS in patients with acute hip fracture; in Canada, only 66% of patients proceed to surgery within the 48h benchmark.[20] A large Canadian population-based cohort of 42 230 patients requiring surgery for hip fracture assessed several characteristics previously shown to influence surgical delays.[21] The authors concluded that prescriptions for anticoagulants, among other factors, are an important and modifiable cause of delay. In a previous study from our institution, we found that median TTS was longer in patients using VKA patient [64 h (IQR 50–84)] compared to non-anticoagulated patients

[44 h (IQR 28–63), p = 0.0006].[11] Similar results were reported by Tran et al. from Ottawa.[22] Due to limitations of the EMR, specific reasons for delay could not be assessed in our sample population. However, we noticed long times to administration of vitamin K and/or PCC (16h and 25h, respectively). Though it is possible that clinicians waited to observe the effect of vitamin K on INR before administration of PCC, the median time from PCC administration to OR was quite narrow [4.3h (IQR 3.42 to 8.26)], suggesting that it was more likely the time of OR that dictated PCC administration. Regardless, the plausibility of such confounding factors influencing how clinicians approach VKA reversal in the urgent perioperative setting highlights the need for clear guidelines and protocols to remove heterogeneity from patients' care and standardize the process. In fact, following the implementation of a hip fracture-specific VKA reversal protocol, Ahmed et al. showed reduced median TTS from 73h (IQR 46-105) in the pre-protocol group to 37.7 (IQR 28-45) in the post-protocol group ($p < 0.001$) along with an increase in the proportion of patients being operated within 48 hours from 30 to 80%.[15] Similarly, Moores et al. showed a reduction of mean TTS from 70.36 h (± 61.9 h) to 46 h (± 37.9h) (p=0.03)[16] with the introduction of a standardized regimen for VKA reversal. In addition to protracted times to administration of PCC, we also identified that only 40% of our patients had a formal recommendation to administer PCC in a perioperative internal medicine consultation. This reflects the need for developing and implementing an anticoagulation reversal protocol specific to VKA patients with hip fractures; we believe this to be a modifiable contributor to delayed TTS. As previously highlighted in other studies, a multidisciplinary panel of experts; including surgeons, anesthesiologists, thrombosis experts, and internists, is needed to unify guidelines that are acceptable to all stakeholders.[23]

With the increasing prescription of oral anticoagulation,[24] this care gap will likely widen. Experts have noted a rise in anticoagulant-related adverse drug events (ADE)[25,26] related to transcription errors,[27] off-label under- or over-dosing,[28] drug-drug interactions,[29] and lack of clinician familiarity.[25] A large proportion of anticoagulation-associated ADEs occur during the perioperative period[30,31] as complex risk assessments and multiple steps, clinician groups, and care transitions are involved. To face this issue, guidelines recommend using institution-specific protocols for perioperative anticoagulant management,[32] and experts advocate for developing anticoagulation stewardship programs.[25,33] It is noteworthy that VKAs continue to play a key role in managing and preventing VTE in specific patient populations. For example, they have been shown superior to Direct Oral Anticoagulants (DOACs) for stroke prevention in patients with mechanical valves[34] and for secondary prevention of thrombosis in triple-positive antiphospholipid syndrome.[35] They also remain the standard of care for treating unusual site thrombosis,[36] for patients at extremes of weight[37] and patients with end-stage renal disease.[38] It is thus essential that clinicians continue to receive guidance from expert panels and societies and their local institutional experts on how to best manage VKAs, including in the perioperative setting.

Our study has limitations; as a single-center retrospective cohort, there is restricted generalizability and exposure to various sources of bias. Potential confounders, such as patient comorbidities, individual clinician practice, healthcare systems-related factors, and presentation timing, such as weekday shifts vs. evening/weekend, could have impacted TTS independently from PCC administration. Additionally, these factors could have also impacted anticoagulation management itself. Moreover, our small number of patients may have impacted our study results, and definitive conclusions cannot be drawn, notably related to clinical outcomes.

Conclusion

This study did not identify a difference in TTS between patients who received PCC and those who did not. A larger proportion of patients who received PCC met the 48-hour benchmark for surgical hip fracture repair. However, timing and proportion of PCC administration was suboptimal; demonstrating a significant, yet modifiable, care gap among this population. We call to action future initiatives to standardize VKA management in the perioperative setting and prospective studies to better define this relationship and its impact on clinical outcomes.

Statement on Informed Consent and/or Research Ethics Board approval

Approval for the conduct of this study was obtained from our local Research Ethics Board.

Contributions of Authors to the Manuscript

Dr Teresa Cafaro has participated in the conception and design of the study, procurement of data, data analysis,

drafting of the original manuscript and critical review of the original manuscript.

Dr Nour Rached-d'Astous has participated in the conception and design of the study, procurement of data, data analysis, and drafting of the original manuscript.

Dr Pallavi Ganguli has participated in procurement of data, analysis of data and critical review of the original manuscript.

Dr Maral Koolian has participated in the conception and design and critical review of the original manuscript.

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Conflict-of-interest

None of the authors have any conflict of interest to declare.

References

1. Polok K, Pilecki Z, Kutaj-Wąsikowska H, Kutryba B, Sunol R, Pilecki G, et al. Admission to surgery time in Polish patients with hip fractures: temporal trends in the last decade and association with duration of hospitalization and in-hospital mortality. Polish Arch Intern Med. 2020;130. https://doi.org/10.20452/pamw.15342
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis Int. 2006;17(12):1726–33. https://doi.org/10.1007/s00198-006-0172-4
3. Hopkins RB, Burke N, Von Keyserlingk C, Leslie WD, Morin SN, Adachi JD, et al. The current economic burden of illness of osteoporosis in Canada. Osteoporos Int. 2016;27(10):3023–32. https://doi.org/10.1007/s00198-016-3631-6
4. Papadimitropoulos E, Coyte PC, Josse RG, Greenwood CE. Current and projected rates of hip fracture in Canada. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1997;157 10:1357–63.
5. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, Salanti G, et al. Timing matters in hip fracture surgery: patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One. 2012;7(10):e46175. https://doi.org/10.1371/journal.pone.0046175
6. Pincus D, Ravi B, Wasserstein D, Huang A, Paterson JM, Nathens AB, et al. Association Between Wait Time and 30-Day Mortality in Adults Undergoing Hip Fracture Surgery. JAMA. 2017;318(20):1994–2003. https://doi.org/10.1001/jama.2017.17606
7. Borges FK, Bhandari M, Guerra-Farfan E, Patel A, Sigamani A, Umer M, et al. Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial. The Lancet. 2020;395(10225):698–708. https://doi.org/10.1016/S0140-6736(20)30058-1
8. Sobolev B, Guy P, Sheehan KJ, Kuramoto L, Sutherland JM, Levy AR, et al. Mortality effects of timing alternatives for hip fracture surgery. Can Med Assoc J. 2018;190(31):E923–E32. https://doi.org/10.1503/cmaj.171512
9. Tran T, Delluc A, de Wit C, Petrcich W, Le Gal G, Carrier M. The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. Thromb Res. 2015;136(5):962–5. https://doi.org/10.1016/j.thromres.2015.09.017
10. Caruso G, Andreotti M, Marko T, Tonon F, Corradi N, Rizzato D, et al. The impact of warfarin on operative delay and 1-year mortality in elderly patients with hip fracture: a retrospective observational study. J Orthop Surg Res. 2019;14(1):169. https://doi.org/10.1186/s13018-019-1199-5
11. Cafaro T, Simard C, Tagalakis V, Koolian M. Delayed time to emergency hip surgery in patients taking oral anticoagulants. Thrombosis Res. 2019;184:110–4. https://doi.org/10.1016/j.thromres.2019.11.005
12. You D, Xu Y, Ponich B, Ronksley P, Skeith L, Korley R, et al. Effect of oral anticoagulant use on surgical delay and mortality in hip fracture. Bone Joint J. 2021;103–B(2):222–33. https://doi.org/10.1302/0301-620X.103B2.BJJ-2020-0583.R2
13. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43(3):263–309. https://doi.org/10.1097/AAP.0000000000000763
14. Xu Y, You D, Krzyzaniak H, Ponich B, Ronksley P, Skeith L, et al. Effect of oral anticoagulants on hemostatic and thromboembolic complications in hip fracture: A systematic review and meta-analysis. J Thromb Haemostas. 2020;18(10):2566–81. https://doi.org/10.1111/jth.14977
15. Ahmed I, Khan MA, Nayak V, Mohsen A. An evidence-based warfarin management protocol reduces surgical delay in hip fracture patients. J Orthop Traumatol. 2014;15(1):21–7. https://doi.org/10.1007/s10195-013-0274-7
16. Moores TS, Chatterton BD, Walker MJ, Roberts PJ. Standardised warfarin reversal expedites time to theatre for fractured neck of femur surgery and improves mortality rates: a matched cohort study. Adv Orthop. 2018;2018:4791214. https://doi.org/10.1155/2018/4791214
17. Buecking B, Eschbach D, Bliemel C, Oberkircher L, Struewer J, Ruchholtz S, et al. Effectiveness of vitamin K in anticoagulation reversal for hip fracture surgery--a prospective observational study. Thromb Res. 2014;133(1):42–7. https://doi.org/10.1016/j.thromres.2013.10.031

18. Mattisson L, Lapidus LJ, Enocson A. Is fast reversal and early surgery (within 24 h) in patients on warfarin medication with trochanteric hip fractures safe? A case-control study. BMC Musculoskelet Disord. 2018;19(1):203. https://doi.org/10.1186/s12891-018-2126-3
19. Jay-Caillierez L, Friggeri A, Viste A, Lefevre M, Decullier E, Bernard L, et al. Safety and efficacy of a strategy of vitamin K antagonist reversal with prothrombin complex concentrates compared to vitamin K in patients with hip fracture. Can J Surg. 2021;64(3):E330–E38. https://doi.org/10.1503/cjs.002120
20. Sheehan KJ, for The Canadian Collaborative Study on Hip F, Filliter C, Sobolev B, Levy AR, Guy P, et al. Time to surgery after hip fracture across Canada by timing of admission. Osteoporosis International : With other metabolic bone diseases. 2018;29(3):653–63. https://doi.org/10.1007/s00198-017-4333-4
21. Pincus D, Wasserstein D, Ravi B, Byrne JP, Huang A, Paterson JM, et al. Reporting and evaluating wait times for urgent hip fracture surgery in Ontario, Canada. CMAJ. 2018;190(23):E702–e9. https://doi.org/10.1503/cmaj.170830
22. Tran T, Delluc A, de Wit C, Petrcich W, Le Gal G, Carrier M. The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. Thromb Res. 2015;136(5):962–5. https://doi.org/10.1016/j.thromres.2015.09.017
23. Flemons K, Marcil G, Kachra R, et al. Barriers to Implementing Internist Recommendations for perioperative anticoagulation management by surgical teams: a qualitative study. Can J Gen Intern Med. 2022;17(1):14–28. https://doi.org/10.22374/cjgim.v17i1.525
24. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. EP Europace. 2021;24(6):887–98. https://doi.org/10.1093/europace/euab303
25. Burnett AE, Barnes GD. A call to action for anticoagulation stewardship. Research and Practice in Thromb Haemos. 2022;6(5):e12757. https://doi.org/10.1002/rth2.12757
26. Geller AI, Shehab N, Lovegrove MC, Rose KO, Weidle NJ, Goring SK, et al. Emergency visits for oral anticoagulant bleeding. J Gen Intern Med. 2020;35(1):371–3. https://doi.org/10.1007/s11606-019-05391-y
27. Piazza G, Nguyen TN, Cios D, Labreche M, Hohlfelder B, Fanikos J, et al. Anticoagulation-associated adverse drug events. Am J Med. 2011;124(12):1136–42. https://doi.org/10.1016/j.amjmed.2011.06.009
28. Zhang X-L, Zhang X-W, Wang T-Y, Wang H-W, Chen Z, Xu B, et al. Off-Label Under- and overdosing of direct oral anticoagulants in patients with atrial fibrillation: a meta-analysis. Circulation: Cardiovasc Qual Outcomes. 2021;14(12):e007971. https://doi.org/10.1161/CIRCOUTCOMES.121.007971
29. Li A, Li MK, Crowther M, Vazquez SR. Drug-drug interactions with direct oral anticoagulants associated with adverse events in the real world: A systematic review. Thromb Res. 2020;194:240–5. https://doi.org/10.1016/j.thromres.2020.08.016
30. Moesker MJ, de Groot JF, Damen NL, Huisman MV, de Bruijne MC, Wagner C. How reliable is perioperative anticoagulant management? Determining guideline compliance and practice variation by a retrospective patient record review. BMJ Open. 2019;9(7):e029879. https://doi.org/10.1136/bmjopen-2019-029879
31. Henriksen JN, Nielsen LP, Hellebek A, Poulsen BK. Medication errors involving anticoagulants: Data from the Danish patient safety database. Pharmacol Res Perspect. 2017;5(3):e00307. https://doi.org/10.1002/prp2.307
32. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. 2012;141(2):e326S–e50S. https://doi.org/10.1378/chest.11-2298
33. Koolian M, Wiseman D, Mantzanis H, Kampouris N, Kerzner RS, Kahn SR. Anticoagulation stewardship: Descriptive analysis of a novel approach to appropriate anticoagulant prescription. Res Pract Thromb Haemo. 2022;6(6):e12758. https://doi.org/10.1002/rth2.12758
34. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206–14. https://doi.org/10.1056/NEJMoa1300615
35. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018;132(13):1365–71. https://doi.org/10.1182/blood-2018-04-848333
36. Abbattista M, Capecchi M, Martinelli I. Treatment of unusual thrombotic manifestations. Blood. 2020;135(5):326–34. https://doi.org/10.1182/blood.2019000918
37. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemo. 2016;14(6):1308–13. https://doi.org/10.1111/jth.13323
38. Ribic C, Crowther M. Thrombosis and anticoagulation in the setting of renal or liver disease. Hematology. 2016;2016(1):188–95. https://doi.org/10.1182/asheducation-2016.1.188