Lo SCALPELLO (2020) 34:117-122
doi number: 10.36149/0390-5276-174

Are femoral fracture patients taking NOACs more complicated than those with warfarin or antiplatelet?

Filippo Caternicchia[1], Pietro Cimatti[2], Emilio Martini[3], Maria Lunardelli[3], Calogero Alfonso[1]

[1] Department of Orthopedics and Traumatology, University Hospital "S. Orsola Malpighi", Bologna, Italy; [2] Department of Reconstructive orthopedic surgery and innovative techniques, Rizzoli Orthopedic Institute, Bologna, Italy; [3] Department of Continuity of care and disability, Geriatrics, University Hospital "S. Orsola Malpighi" Bologna, Italy

Summary

Objective. The purpose of this study is to compare hospital outcomes in patients being treated with NOACs, undergoing fixation of hip fracture, compared to patients treated with clopidogrel, aspirin, or warfarin.
Methods. We collected data from 370 patients who underwent hip fracture surgery. The sample was divided into 4 groups: NOACs, warfarin, clopidogrel/aspirin and not taking anticoagulation. We compared outcome measures including time to surgery, length of stay (LOS), transfusion rate, and blood loss.
Results. 363 hip fractures met the inclusion criteria. The total blood loss of group 1 (NOACs) was higher compared to the other groups with an increase in the number of red blood cell (RBC) transfused units ($p < 0.001$).The mean total blood loss of NOACs group was higher in patients undergoing surgery after 48 hours from admission compared to before 48 hours, but not statistically significant ($p < 0.483$). Group 1 had a time to surgery ($p < 0.0005$) and LOS ($p < 0.0005$) greater than the other groups.
Conclusions. The time of suspension of NOAC in patients with hip fracture undergoing surgery is important. Failure to understand this parameter puts the patient at risk of a longer hospital stay and greater total blood loss.

Key words: NOACs, hip fracture, outcomes, warfarin, antiplatelet

Received: July 26, 2020
Accepted: September 16, 2020

Correspondence
Filippo Caternicchia
Department of Orthopedics and Traumatology, University Hospital "S. Orsola Malpighi", via G. Massarenti 13, 40138 Bologna, Italy
E-mail: filippo.caternicchia@ior.it

Conflict of interest
The Authors declare no conflict of interest

How to cite this article: Caternicchia F, Cimatti P, Martini E, et al. Are femoral fracture patients taking NOACs more complicated than those with warfarin or antiplatelet? Lo Scalpello Journal 2020;34:117-22. https://doi.org/10.36149/0390-5276-174

Introduction

Hip fractures in the elderly population represent a major social and health problem of considerable importance. Epidemiological data are different in relation to the geographical area examined. The incidence varies from 55 to 439/100,000 [1,2]. More than 250,000 hip fractures are observed annually in the United States [3]. The effects of increased population life expectancy, and consequent comorbidities, suggest an increase in the number of hip fracture cases. Different risk factors can be associated with hip fractures and influence their epidemiological data. Age and gender are certainly among the most significant risk factors. Hip fractures are more frequent in elderly people with partial dependence on ADL (Activities of daily living) and cognitive impairment [4]. 1-month mortality ranges from 5 to 10% [5]. Female are

more affected [4], although males seems to be affected by higher mortality [6].
The data available in the literature suggest that hip fractures are associated with high costs of hospitalization and rehabilitation.
Surgery remains the gold standard of treatment in hip fracture patients and the orthopedic surgeon determines the most appropriate treatment. The timing of surgical treatment (Time to surgery) can influence the outcome. It has been consolidated for years that early treatment within 48 hours allows for earlier mobilization and rehabilitation [7].
Many elderly patients with hip fractures, however, have several comorbidities, among which the most frequent are cardiovascular disease that require treatment with anticoagulants and can lead to delayed surgery [8].
The clinical outcome is generally poor with a one-year mortality of around 36% [9].
Anticoagulation with warfarin translates into an increase in the "International normalized ratio (INR)". In these patients, surgery must be postponed until the INR value is not less than 1.5. Discontinuation of drug treatment with warfarin is recommended, combined with the administration of vitamin K, to allow surgery to be anticipated [10].
Warfarin therapy is associated with a delayed onset of action, numerous drug interactions with other drugs or foods, a narrow therapeutic window, unpredictable response, and need for frequent monitoring of coagulation [11].
In recent years, the panorama of anticoagulant therapy has been revolutionized by the appearance of non-vitamin K inhibiting drugs: new oral anticoagulants (NOACs).
NOACs have high levels of efficacy and safety and their clinical use is increasing [12]. NOACs have been shown to be equal or better to VKA (vitamin K antagonists) for prophylaxis and treatment of thromboembolic events. They have been associated with fewer major bleeds, especially in terms of safety, including intracranial hemorrhage, thus providing a superior benefit for stroke prevention in patients with atrial fibrillation [15]. NOACs can be prescribed with a fixed dose and offer the advantage of not requiring periodic checks of anticoagulant activity. Limitations, despite these advantages, remain with NOACs: their dependence on renal and hepatic function for their clearance [14].
The characteristics of oral administration, simple dosage without a necessary monitoring, short half-life, uncomplicated switching or bridging and proven safety outweigh the disadvantages, make NOACs a valid option for short- or long-term anticoagulation.
The lack of laboratory monitoring is certainly one of the strengths of these drugs [15].
The purpose of the present study is to compare the outcomes of surgical treatment in patients hospitalized with hip fracture, both intracapsular and extracapsular, treated with NOACs, compared to patients treated with drug with warfarin, aspirin, and clopidogrel. In particular, we analyzed the time to surgery, length of stay, total blood loss, and number of transfused red blood cell units, to understand if these parameters are influenced by the laboratory blood value of the NOAC at the time of surgery (laboratory cut-off below the threshold blood value or above).

Materials and methods

In this retrospective cohort study, data were collected from 370 patients who underwent surgery for hip fracture in the period from 01/01/16 to 09/30/2019 at the Orthopedics and Traumatology department of the University Hospital S. Orsola Malpighi in Bologna, Italy.
The fracture patterns included were: intracapsular femoral neck fracture, trochanteric fracture, and subtrochanteric fracture.
Retrospective analysis excluded patients with pathological fractures (bone metastases, Paget's disease) or secondary to major trauma and patients with coagulation diseases (liver disease, hemophilia, Von Willebrand syndrome).
Patients who received conservative treatment were excluded from the analysis.
In accordance with the therapeutic diagnostic path of the patient with hip fracture at the time of admission, the following data were collected: age, sex, weight, height, BMI (body mass index), type of fracture, drug treatment with antiplatelet therapy (aspirin, clopidogrel) or anticoagulant (warfarin or NOACs).
The severity of comorbidities was quantified using the Charlson Comorbidity Index.
Cognitive status was assessed through the Short Portable Mental Status Questionnaire (SPMSQ).
The functional status of the patient referred to the pre-fracture period was measured using the Score Standardized Audit of Hip Fracture in Europe (SAHFE) and disability using the Activities of Daily Living (ADL) score and Barthel scale.
The following data were collected during the hospital stay: date of admission and surgery, type of surgery performed (intramedullary nail osteosynthesis, hemiarthroplasty, total hip arthroplasty or osteosynthesis with plate and screws), classification of American Society of Anesthesiologists (ASA) score, hemoglobin value (Hb) the first day of hospitalization, Hb value on the first postoperative day, Hb value on the fourth postoperative day, number of transfused red blood cells (RBC) units during hospitalization.
Data relating to the time elapsed between entry (defined since arrival in the emergency department) and surgical intervention (Time to surgery). We also analyzed the length of stay (LOS), defined as the time spent from hospitalization to discharge.
The data on bleeding complications were collected from the notes of the clinical diary during the hospital stay and included the following 4 groups: rectorrhagia or melena, hematemesis, hemorrhagic stroke, blood loss from the surgical wound.
The amount of blood loss during the postoperative period was calculated by the method of Good et al. [16].

We then divided the sample into 4 groups: patients taking NOACs (group 1), warfarin (group 2), clopidogrel or ASA (group 3) and patients taking none of the previous medications (group 4).
Group 1 patients were further divided into two sub-categories based on the laboratory value of the drug at the time of surgery: subgroup 1, if the blood level of the drug is below the threshold value; subgroup 2, if it is above. Cut-off values have been indicated by the Laboratory of CBC and Clinical Chemistry of our Institute.

Statistical analysis

Descriptive and demographic analysis was carried out using Microsoft Excel.
All data were treated confidentially. Patients were identified in the database through their initials and date of birth. Informed consent was obtained with the patient when cognitively intact or with family members if the patient had cognitive impairment. In statistical analysis, continuous data are reported as mean ± standard deviation (SD) and categorical data as frequencies (%). The categorical variables were compared using contingency tables with a χ^2 test according to Pearson or the Fisher's exact test.
The continuous variables were compared with parametric tests such as the Student Test (t-test) or with the Fisher Test f.
The analysis of the continuous variables of the 2 subcategories of group 1 (NOACs) were compared with non-parametric tests (Mann Whitney).
A value of $p < 0.05$ was considered to be statistically significant. Statistical processing was performed using SPSS 26.0 software (SPSS® inc., Chicago, IL, USA) for Windows® 10 (Microsoft Corp.).

Results

363 (98.10%) of 370 patients with hip fracture analyzed met the inclusion criteria; 78 males (21.49%) and 285 females (78.51%). The average age of the population was 85.95 years +/- 5.63. The median was 86.0 years.
The data relating to the BMI (Body mass Index), Barthel index, Charlson index, SAHFE score, ASA, ADL in the groups are summarized in Table I.
At the time of admission, 162 patients had an intracapsular neck fracture (44.62%), 190 a trochanteric fracture (52.34%), and 11 a fracture classified as subtrochanteric (3.03%) (Tab. II).
Group 1 was composed of 43 patients (11.8%), group 2 48 patients (13.2%), group 3 117 patients (32.2%), and group 4 155 patients (42.7%).
Comparing the 4 groups with each other, we found no statistically significant differences in mean age, BMI, Barthel Index, or ADL ($p < 0.5$).

Table I. Sample description, average of BMI, Barthel index, Charlson index, *SAHFE Score* (Standardized Audit of Hip Fracture in Europe), and ADL (Activities of daily living) in the statistical sample.

Parameter	Value (medium)
BMI	23.58
Barthel index	73.93
Charlson index	6.11
SAHFE score	1.93
ADL	4.27

In group 1 (NOACs), 26 (60.47%) patients were being treated with Apixaban, 11 (25.58%) with Edoxaban, and 6 (13.95%) with rivaroxaban.
Total blood loss was higher in patients undergoing surgery with intramedullary nail osteosynthesis (928 ml) followed by hemiarthroplasty (882 ml), total hip arthroplasty (529 ml) and osteosynthesis with plate / screws (136 ml) (Tab. II).
Furthermore, blood loss and number of transfused RBC transfused units were higher in group 1 (NOACs) than in the other groups ($p < 0.001$) (Tab. III). The difference in total blood loss was more evident between group 1 and group 4 ($p < 0.0005$).
Of the 43 patients taking NOACs, at the time of surgery 19 (44.18%) had the laboratory value of the drug below the threshold value (subgroup 1); the remaining 23 patients (55.82%) were above the threshold value (subgroup 2).
Subgroup 2 showed a greater blood loss than subgroup 1 ($p < 0.017$), but there were no significant differences in terms RBC transfused units between the two subgroups ($p < 0.14$).
Regarding the onset of major bleeding complications, there were 8 significant episodes, 4 of which occurred in group 1 and 4 in group 4 ($p < 0.08$).Patients in group 1 (NOACs) had longer time to surgery than the other groups with an average of 67.12 hours ($p < 0.0005$).
Group 1 patients who underwent surgery after 48 hours showed an average blood loss of 243.07 ml higher than patients in the same group undergoing surgery before 48 hours, but this difference was not significant ($p < 0.315$).
A major blood loss, not statistically significant, was also found in patients undergoing surgery after 48 hours in group 2 ($p < 0.082$), group 3 ($p < 0.400$), and group 4 ($p < 0.088$).
The length of stay (LOS) was greater in group 1 with an average of 15.58 days ($p < 0.0005$).

Discussion

Hip fractures represent a major health problem. Often these patients present multiple comorbidities, and multi-drug treatment can lead to difficult preoperative and postoperative management. These comorbidities often require treatment with antico-

Table II. Mean total blood loss (ml) according to type of surgery performed.

	Hemiarthroplasty	Intramedullary nail	Plate and screws	Total hip arthroplasty
Medium total blood loss for type of surgery (ml)	882.74	928.31	136.74	539.73

Table III. Sample description for patients not taking anticoagulation therapy, and those on NOAC, warfarin, or clopidogrel/aspirin therapy.

Measure	No anticoagulation	On NOACs	On warfarin	On clopidogrel / ASA	Total
No. patients (%)	**155 (42.70)**	**43 (11.80)**	**48 (13.20)**	**117 (32.20)**	**363 (100)**
Type of fracture, number (%)					
Intracapsular neck fracture	67	20	19	56	162 (44.62)
Trochanteric fracture	82	23	27	58	190 (52.34)
Subtrochanteric fracture	6	0	2	3	11 (3.03)
Type of surgery					
Hemiarthroplasty	52	20	14	53	139
Intramedullary nail	87	23	27	60	197
Plate and screws	8	0	2	2	12
Total hip arthroplasty	8	0	5	2	15
ASA score, number*					
5	0	0	0	0	0
4	8	6	7	16	37
3	127	36	38	91	292
2	16	1	2	8	27
1	0	0	0	0	0
Time to surgery					
> 48 ore	10	19	11	13	53
< 48 ore	145	24	37	104	310
Time to surgery, mean (days)	1.59	2.67	1.72	1.60	1.74
Length of stay (days)	11.64	15.58	11.92	11.41	12.07
Total blood loss, mean (ml)	757.98	1339.23	800.56	879.41	868.35
RBC transfused units, mean	0.97	1.93	1.13	1.26	1.19

agulant therapy. Different types of anticoagulants, as explained in this study, can be used.

From some years, the panorama of anticoagulant therapy has been changing with the appearance of anticoagulant drugs that do not inhibit vitamin K, namely NOACs.

An important advantage, compared to warfarin, is the wide pharmacokinetic and pharmacodynamic predictivity which does not make evaluation of coagulation more necessary than with warfarin.

Some studies in the literature have shown different advantages of NOACs over warfarin in reducing the risk of osteoporosis [17]. This would make these drugs very suitable for use in the el-

derly population which is, on average, more prone to risk of frailty fractures.
Several studies have also shown that NOACs have a safety and efficacy profile equal to or greater than warfarin, especially for treatment of atrial fibrillation and venous thromboembolism [18].
Some recent studies, thanks to these characteristics, have analyzed its effectiveness in postoperative thromboprophylaxis in total hip arthroplasty [19].
The short half-life, rapid disappearance of action, and foreseeable anticoagulant effect without the need for laboratory monitoring were strengths for their entry into the market [18]. Some problems, however, have been encountered in clinical-surgical practice with their use.
The use of these drugs should be avoided in the presence of valvulopathies as in the case of mitral valve stenosis. In the literature, however, there are conflicting data about their use in patients with liver and kidney organ failure [20].
NOACss, with the exception of dabigatran [21], do not have an effective antidote available within the National Health Service to be used in case of bleeding or overdose. This can increase surgical risk.
Despite the advantages deriving from the use of NOACs, precisely for these latter considerations the anticoagulant drug of choice today for many patients remains warfarin.
The guidelines of the European Heart Rhythm Association in March 2018 give precise indications on the modality of suspension of the NOACs in elective surgical interventions, while there are still no shared indications on the time to surgery in urgent and deferrable surgeries such as hip fractures [22].
Knowing exactly the time to surgery in a patient taking NOACs is of fundamental importance, since the outcome may depend on this.
The ability also to reverse NOACs in patients with hip fractures requiring surgery is definitely important. This is, at the moment, one of the main problems inherent with the use of NOACs and in the literature there are several studies in this regard such as the use of dialysis or infusion of prothrombin complex concentrate (PCC) and fresh frozen plasma, all with unsatisfactory results [23]. The suspension period of NOACs depends on the molecule and renal function.
The withdrawal period of the drug, as indicated by the guidelines of the European Hearth Rhythm association (EHRA), to reduce the risk of bleeding, should be equal to or greater than 48 hours.
In our study, we found that when controlling for age, gender, ASA, and type of fracture, patients taking NOACs have more blood loss than the no anticoagulation group, clopidogrel, and warfarin.
The most represented drug, in group 1, in our study was Apixaban (60.47%), followed by Edoxaban (25.58%) and Rivaroxaban (13.95%).
This result can be explained by the higher incidence of renal failure in frail elderly patients since Apixaban has a lower renal elimination.
We did not find a difference in postoperative blood loss between the group of patients being treated with clopidogrel or warfarin. We found a significant increase of transfused RBC units between the NOAC and other groups.
Although the NOACs subgroup 2 lost an average of 611.04 ml more blood than the subgroup 1, this difference was not statistically significant in terms of transfused RBC units. NOAC patients in both subgroups 1 and 2 showed more blood loss than the other groups ($p < 0.019$ and $p < 0.017$, respectively).
The data seems to confirm that patients on NOACs show more blood loss regardless of the serum level of the drug, even if a greater number of postoperative bleeding complications in the NOAC group was not observed compared to the no anticoagulation group ($p < 0.086$), and did not affect outcomes.
NOACs can, therefore, be responsible for a potential delay in time to surgery and longer length of stay, and therefore with possible influence on outcomes.
The results in the literature regarding the time to surgery and length of stay in patients treated with anticoagulants differ [24].
In our study, the NOAC group presented an average length of hospital stay and time to surgery that were higher than the other groups, as reported in literature [25].
Patients treated with NOACs who underwent surgery after 48 hours had, on average, more blood loss than patients operated before 48 hours. This data is in accordance with the guidelines of the European Hearth Rhythm Association, confirming the indication to wait at least or more than 48 hours from the suspension of the NOACs before undergoing surgery with a high risk of bleeding.
Waiting at least 48 hours, therefore, represents an advantage in terms of total blood loss. Surgery should only be performed when the laboratory value of the NOACs is below the threshold blood value or in any case very close to it.
This study certainly has some limitations. Although 90.8% of patients with hip fractures underwent surgery within 48 hours, we do not know how to define, in each individual patient of the remaining 9.2%, all the reasons for the delay in surgery. Another limitation is that the clinical data collection comes from a single hospital center, although this University Hospital Center includes an orthopedics department, a geriatric referral center and a primary level of trauma center.
The third limitation is the small number of patients on NOACs. Finally, socio-economic factors that may have influenced factors such as length of stay were not analyzed.

Conclusions

This study emphasizes the importance of achieving the threshold blood value of NOACs at the time of surgery and the importance of the period of suspension of these drugs in patients undergoing urgent or deferrable surgery such as hip fractures. It is thus important that the team managing these patients considers that there may be differences in treatment between pa-

tients receiving NOACs and patients receiving other oral anticoagulants, and these differences may influence the patient's final outcome.

Funding

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

References

1 Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury 2018;8:1458-60. https://doi.org/10.1016/j.injury.2018.04.015

2 Maggi S, Kelsey JL, Litvak J, et al. Incidence of hip fractures in the elderly: a cross-national analysis. Osteoporos Int 1991;1:232-41. https://doi.org/10.1007/BF03187467

3 Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. N Engl J Med 1995;23:767-73. https://doi.org/10.1056/NEJM199503233321202

4 Erratum to: Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study: consequences and predictors of frailty in WHI women. J Am Geriatr Soc 2017;53:1321-30. https://doi.org/10.1111/jgs.15006

5 Roche JJW, Wenn RT, Sahota O, et al. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. Br Med J 2005;331:1374-6. https://doi.org/10.1136/bmj.38643.663843.55

6 Iqbal MM. Osteoporosis: epidemiology, diagnosis, and treatment. South Med J 2000;93:2-18. https://doi.org/10.1097/00007611-200093010-00002

7 Tierney AJ, Vallis J. Multidisciplinary teamworking in the care of elderly patients with hip fracture. J Interprof Care 1999;13:41-52. https://doi.org/10.3109/13561829909025534

8 Hourston GJM, Barrett MP, Khan WS, et al. New drug, new problem: do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay,or poorer outcomes? HIP Int 2019; Apr 25. https://doi.org/10.1177/1120700019841351

9 Abrahamsen B, Van Staa T, Ariely R, et al. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int 2009;20:1633-50. https://doi.org/10.1007/s00198-009-0920-3

10 Watson HG, Baglin T, Laidlaw SL, et al. A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. Br J Haematol 2001;125:2944-7. https://doi.org/10.1046/j.1365-2141.2001.03070.x

11 Zimetbaum PJ, Thosani A, Yu HT, et al. Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? Am J Med 2010;123:446-53.

12 Bai Y, Guo SD, Deng H, et al. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis. Age Ageing 2018;47:9-17. https://doi.org/10.1093/ageing/afx103

13 Vílchez JA, Gallego P, Lip GY, et al. Safety of new oral anticoagulant drugs: a perspective. Therap Advanc Drug Safety 2014;5:8-20.

14 Gong IY, Kim RB. Importance of phar-14. macokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol 2013;29(Suppl 7):S24-33.

15 Conway SE, Hwang AY, Ponte CD, et al. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. Pharmacotherapy 2017;37:236-48. https://doi.org/10.1002/phar.1884

16 Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003;90:596-9. https://doi.org/10.1093/bja/aeg111

17 Tufano A, Coppola A, Contaldi P, et al. Oral anticoagulant drugs and the risk of osteoporosis: new anticoagulants better than old? Semin Thromb Hemost 2015;41:382-8. https://doi.org/10.1055/s-0034-1543999

18 Dubois V, Dincq AS, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. Thromb J 2017;15:14. https://doi.org/10.1186/s12959-017-0137-1

19 Kasina P, Wall A, Lapidus LJ, et al. Postoperative thromboprophylaxis with new oral anticoagulants is superior to LMWH in hip arthroplasty surgery: findings from the Swedish registry. Clin Orthop Relat Res 2019;477:1335-43. https://doi.org/10.1097/CORR.0000000000000714

20 Wang CL, Wu VCC, Kuo CF, et al. Efficacy and safety of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with impaired liver function: a retrospective cohort study. J Am Heart Assoc 2018;7:e009263. https://doi.org/10.1161/JAHA.118.009263

21 Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015;131:972-9

22 Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-93.

23 Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke 2011;44:771-8. https://doi.org/10.1161/STROKEAHA.111.624650

24 Lawrence JE, Fountain DM, Cundall-Curry DJ, et al. Do patients taking warfarin experience delays to theatre, longer hospital stay, and poorer survival after hip fracture? Clin Orthop Relat Res 2017;475:273-9. https://doi.org/10.1007/s11999-016-5056-0

25 Tran T, Delluc A, De Wit C, et al. The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. Thrombosis Res 2015;42:e331-5.