Clinical Interventions in Aging

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ORIGINAL RESEARCH

Preoperative Drug Monitoring in Management of Patients with Hip Fracture on Treatment with Direct Oral Anticoagulants

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Purpose: Aim of the present study was to evaluate whether monitoring direct oral anticoagulant (DOAC) levels may improve management of anticoagulated patients who need surgery for hip fracture.

Patients and Methods: A total of 147 out of 2231 (7.7%) patients with hip fracture admitted to a tertiary teaching hospital were on DOACs (group A), whereas 206 patients matched for age, sex, and type of fracture not on anticoagulant or P2Y12 platelet inhibitors were considered as control group (group B). Patients on DOACs were divided into two subgroups: A1 in which intervention was scheduled in relation to the last drug intake according to current guidelines, and A2 included patients in whom time of surgery (TTS) was defined according to DOAC levels. Neuraxial anesthesia was considered with DOAC levels <30 ng/mL, general anesthesia for levels in the range 30–50 ng/mL.

Results and conclusions: TTS was significantly lower in controls than in DOAC patients: surgery within 48 hours was performed in 80.6% of group B versus 51% in group A ($p<0.0001$). In A2, 41 patients underwent surgery within 48 hours (56%) in comparison to 32 A1 patients (45.1%; $p=0.03$). TTS and length of hospitalization were on average 1 day lower in patients with assay of DOAC levels. Finally, 35/39 (89%) patients with DOAC levels <50 ng/mL had surgery within 48 hours (26 under neuraxial anesthesia, without any neurological complication, and 13 in general anesthesia).

Conclusion: DOAC assay in patients with hip fracture may be useful for correct definition of time to surgery, particularly in patients who are candidates for neuraxial anesthesia. Two-thirds of patients with DOAC levels <50 ng/mL at 48 hours from last drug intake underwent uneventful neuraxial anesthesia, saving at least 24 hours in comparison to guidelines.

Keywords: fragility fractures, oral anticoagulants, DOAC assay, safety

Introduction

Hip fracture is a severe disabling condition in the elderly, leading to a 1-year over-mortality close to 20%, significantly higher than mortality reported in the age-matched general population.[1,2] Due to population aging, the global number of hip fractures is expected to increase four-fold between 1990 and 2050 with an estimated 5,000,000 cases per year.[3,4] Early surgery, within 24–48 hours from trauma, is associated with a lower rate of complications and decreased early and 1-year mortality.[5–8] Not less than 10% of patients with hip fracture are on chronic anticoagulant therapy at the moment of trauma. The increased risk of bleeding associated with anticoagulation is a well-known factor for surgical delay in patients with hip fracture, and several studies suggest that in patients treated with direct anticoagulants (DOACs) surgery is performed at least 12–24 hours later in comparison to non-anticoagulated patients.[9–13] Reversal therapy was not considered due the high costs related to idarucizumab administration for dabigatran antagonism. Moreover, andexanet is still not approved for reversal Xa inhibitors effects before surgery. Current guidelines suggest that, in patients at high risk of bleeding, surgery may be safely performed 48 hours after the last dose of anti-factor Xa inhibitors (rivaroxaban,

Received: 15 October 2023
Accepted: 9 April 2024
Published: 29 April 2024

apixaban, edoxaban), while for dabigatran a longer delay should be considered in subjects with impairment of renal function.[14–16] When neuraxial anesthesia is considered, treatments should be delayed by a further 24 hours. In elderly patients drug interactions or age-related impairment of elimination mechanisms may modify pharmacokinetics of DOACs. Half-life may increase from 1.4- to 4.4-fold in comparison to times reported in the Summary of Product Characteristic.[17] The use of DOAC monitoring may help to schedule safe time to surgery and proper anesthesiologic procedure. According to literature serum levels below 50 ng/mL are associated with a low risk of bleeding, and neuraxial anesthesia may be considered safe for levels <30 ng/mL.[18–20]

The aim of this study was to investigate whether DOAC measurement may influence the time to hip fracture surgery in comparison to standard guidelines. Moreover, we evaluated how DOAC levels may guide the choice of anesthesiologic strategy in the case of early surgery. Finally, we studied the effects of DOAC treatment on the risks of in-hospital complications or mortality.

Materials and Methods

This observational single-center cohort study is part of a project of the Italian Health Ministry and Regione Toscana – RF-2010-2,316,600 – and was approved by the Ethical Committee of Regione Toscana and of Area Vasta Toscana Centro, for the approval of the studies performed in all the hospitals of Florence including AOU Careggi where the study was carried out.

At admission written informed consent was obtained to treat and collect clinical data for research purposes. The research was performed in accordance with the Declaration of Helsinki.

In the study were included all patients admitted for hip fracture in the period January 2016 to July 2021 at a single tertiary teaching trauma center in Italy and treated by a multidisciplinary team according to a previously described model.[21] Dedicated operating rooms were available 6/7 days allowing patients admitted on Saturday to undergo surgery on Monday morning, within 48 hours from trauma. Neuraxial anesthesia was usually preferred for hip fracture treatment, general anesthesia usually being reserved for conditions at high risk of hemodynamic impairment (eg, severe aortic stenosis, advanced heart failure). Patients using DOACs at the moment of trauma were divided into two subgroups, the first enrolled before September 2018 in whom surgery was scheduled according to existing guidelines (group A1) and the second, analyzed prospectively, undergoing systematic drug levels monitoring when DOAC assay became available (group A2). A group of patients matched for age, gender, and type of fracture who were not taking anticoagulant therapy or antiplatelet P2Y12 inhibitors were considered as control group (group B). In group A2 surgery was scheduled when drug levels were associated with a lower risk of bleeding, eg below 50 ng/mL. Neuraxial anesthesia was performed with DOAC levels <30 ng/mL, general anesthesia for levels in the range 30–50 ng/mL.

Demographic data, type of fracture, time from last DOAC dose, and time between trauma and surgical intervention were registered. Blood count, clotting time (prothrombin and activated partial thromboplastin time), and renal function were evaluated before and after surgery. In the postoperative period, the need for blood transfusion, intercurrent complications (acute myocardial infarction, pneumonia, sepsis, surgical site infection, deep venous thromboembolism, heart failure, delirium, anemia), and in-hospital mortality were recorded. Time to surgery, hemorrhagic complications, length of hospitalization, and finally in-hospital mortality were compared among groups.

Plasma samples were collected 48 hours after last drug dose intake to allow surgery within 48 hours from trauma, or as soon as possible in patients admitted later.

Whole venous blood was collected in tubes with citrated whole blood (3.2%, 0.109 M). Tubes were centrifuged at room temperature at 1500 *g* for 15 min, and the supernatants were used to assess the circulating levels of each DOAC. Results were available in less than 3 hours from sample collection.

Diluted thrombin time, calibrated for dabigatran (Hemosil, Thrombin Inhibitor Assay, Werfen, Italy), was used to measure dabigatran concentrations. The linearity of the test was 20–2000 ng/mL and the detection limit was 2 ng/mL. The reference values were 61–143 ng/mL at C-trough levels and 117–125 ng/mL at peak level.

Apixaban, rivaroxaban, and edoxaban levels were assessed by using specific chromogenic assay able to measure the anti-Xa activity (Hemosil Liquid anti-Xa, Werfen, Italy). The assay used apixaban, rivaroxaban, and edoxaban-specific calibrators. The linearity of the test was 15–1000 ng/mL for apixaban, 20–1000 ng/mL for rivaroxaban, and 20–850 ng/mL for edoxaban.

The detection limits were 6 ng/mL for apixaban and 10 ng/mL for rivaroxaban and edoxaban. The reference values for apixaban 2.5 mg ×2: 11–90 ng/mL (trough) and 30–153 ng/mL (peak); apixaban 5 mg ×2: 22–177 ng/mL (trough) and 59–302 ng/mL (peak). For rivaroxaban, the reference values were 6–239 ng/mL (trough) and 22–535 ng/mL (peak). The reference values for edoxaban 60 mg were 19–62 ng/mL (trough), and for edoxaban 30 mg 15–45 ng/mL (trough).

Statistical Analysis

Continuous variables were reported as mean and standard deviation. Non-continuous variables were reported as frequency of distribution. Statistical analysis of continuous data was performed using the Student *t*-test, while non-continuous data were analyzed using χ^2 test or the Fisher exact test when appropriate. A probability value of 0.05 was considered statically significant.

Results

In the study were included 2321 patients with fragility hip fracture. One hundred and forty-seven were on treatment with oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) at the moment of trauma. Two hundred and six patients matched for age, sex, and type of fracture were considered as control group.

Patients on DOACs (A) and controls (B) were comparable for age (A: 84.7±6 years vs B: 84.1±8.5 years), gender (A: 73.9% females vs B: 76.2% females), type of fracture, and finally comorbidities (at least 2 comorbidities were present in 64.5% of group A versus 60.7% of group B). Anemia (defined as Hb <10 g/dL) was more frequent at admission in patients with DOAC (A: 29.7% versus B: 20.9%); nevertheless, these patients during hospitalization needed less frequently transfusion than did the control group (A: 39.3% versus B: 46.1%). Time to surgery was significantly lower in controls than in DOAC patients: surgery within 48 hours was performed in 80.6% of group B versus 51% in group A; $p<0.0001$. Only 1 patient (0.6%) in the DOAC group died during hospitalization in comparison to 6 (2.9%) in the control group as reported in Table 1. It must

Table 1 Characteristics of Patients taking DOACs and Controls

	Controls	DOAC	p
Number	206	147	
Age (mean±SD)	84.1±8.5	84.7±6	ns
Sex (number and % female)	157 (76.2%)	102 (73.9%)	ns
30 days mortality	6 (2.9%)	1 (0.6%)	ns
Preserved BADL (n, %) **0–4** **5–6**	 68 (33%) 138 (67%)	 53 (36%) 94 (64%)	ns
Previous functional capacity **0** **1**	 55 (26.7%) 151 (73.3%)	 46 (34%) 91 (66%)	ns
Time to surgery (n, %) **- <48 hours** **- >48 hours**	 166 (80.6%) 40 (19.4%)	 75 (51%) 72 (49%)	<0.0001
Mortality	6 (2.9%)	1 (0.6%)	ns
Type of fracture **- femur neck** **- per trochanteric** **- sub trochanteric**	 107 (51.9%) 93 (45.2%) 6 (2.9%)	 77 (55.8%) 55 (39.8%) 6 (4.3%)	ns

(*Continued*)

Table 1 (Continued).

	Controls	DOAC	p
Type of intervention (n, %) **- prosthesis** **- nail**	 82 (39.8%) 124 (60.2%)	 64 (43%) 83 (57%)	ns
Hb at admission <10 g/dL (n, %)	43 (20.9%)	41 (29.7%)	ns
Creatinine >1.5 mg/dL (n, %)	14 (6.8%)	6 (4%)	ns
Transfusions (n, %)	95 (46.1%)	54 (39.3%)	ns
Dementia (n, %)	52 (25.2%)	14 (10.1%)	0.002
Hypertension	141 (68.4%)	87 (63%)	ns
Persistent atrial fibrillation	49 (23.8%)	70 (50.7%)	<0.0001
COPD	27 (13.1%)	16 (11.6%)	ns
Diabetes	37 (18.0%)	14 (10.1%)	0.03
Cancer	42 (20.4%)	18 (13%)	0.05
Heart failure	16 (7.8%)	20 (14.5%)	ns
Coronary artery disease	31 (15.0%)	17 (12.3%)	ns
Peripheral artery disease	32 (15.5%)	25 (18.1%)	ns
Comorbidities >2	125 (60.7%)	89 (64.5%)	ns

Abbreviations: BADL, basic activity daily living; Hb, hemoglobin; COPD, chronic obstructive pulmonary disease; ns, not significant.

be emphasized that less than 5% of surgery delay was related to clinical instability in each group, and that in controls late surgery was related to organization problem in 14% of patients.

DOAC Measurement

Patients on DOAC treatment were divided into two subgroups: the first in which intervention was scheduled in relation to the last drug intake according to current guidelines (group A1) and the second included patients in whom timing of surgery was aided by DOAC monitoring (median time of the assay from last dose was 49 hours) (group A2).

In Table 2 clinical features of the two groups are reported.

They did not differ for age (A1: 84.6±5.07 years vs A2: 84.7±7 years) or gender (A1: 71.8% females vs A2: 75% females). Regarding the type of fracture, neck femur fracture was the most frequent in both groups, with a slight prevalence in A2 (48% vs 41%). Dabigatran was the most frequent drug in group A1, and apixaban in group A2. In both groups, the indication for anticoagulation was non-valvular AF in more than 90% of patients. Late surgery >48 hours was related to clinical instability in respectively 5% and 4%.

In A2, 41 patients underwent surgery within 48 hours (56%), with a median time between trauma and surgery of 2.7±1.1 days (62±25 hours). The number of patients with DOAC levels above 50 ng/mL according to time from last drug intake (less or more than 48 hours) is reported in Table 3.

In 17/56 (30%) who had last drug intake within 48 hours from trauma, plasma levels were above 50 ng/mL. Surgery was delayed by at least 24 hours to safely perform neuraxial anesthesia in 11/13 patients with apixaban levels above 50 ng/mL and in all 4 patients with dabigatran levels above 50 ng/mL. The 2 patients with elevated plasma levels underwent

Table 2 Comparison Between Patients with and without Determination of DOAC Levels

	DOAC Levels Group A2	No DOAC Levels Group A1	
	n=73	n=74	
Age (mean±SD)	85.1±7	84.6±5.1	ns
Gender M/F (n)	17/56	20/51	ns
Mortality	0 (0%)	1 (0.6%)	ns
Drug **Dabigatran** **Rivaroxaban** **Apixaban** **Edoxaban**	 13 (17%) 14 (19%) 34 (47%) 13 (17%)	 28 (38%) 19 (26%) 24 (32%) 3 (4%)	 0.002
DOAC indication **Atrial fibrillation** **Venous thromboembolism** **Heart valve prosthesis**	 69 (93%) 3 (5%) 1 (2%)	 68 (90%) 6 (8%) 1 (2%)	 ns
BADL (n, %) **0–4** **5–6**	 21 (28%) 52 (72%)	 33 (44%) 45 (64%)	 ns
Time to surgery (n, %) **Days (median±SD)** **Hours (mean±SD)** **- <48 hours** **- >48 hours**	 2.7±1.1 62±25 41 32	 3.6±2.7 86±46 34 40	 0.004 0.004 0.03
Type of fracture **- femur neck** **- per trochanteric** **- sub trochanteric**	 30 (41%) 37 (50%) 6 (9%)	 36 (48%) 36 (48%) 2 (4%)	 ns
Length of hospital stay (median±SD, days)	14±4	15±7	0.04
Hb at admission <10 g/dL (n, %)	27 (34.5%)	14 (18.6%)	0.05
Creatinine >1.5 (n, %)	3 (4%)	3 (4%)	ns
Transfusions (n, %)	28 (36.9%)	30 (40%)	ns
Dementia (n, %)	5 (7.7%)	9 (12%)	ns
Hypertension	43 (66.1%)	48 (64%)	ns
COPD	10 (15.3%)	9 (12%)	ns
Diabetes	8 (12.3%)	6 (8%)	ns
Cancer	5 (7.7%)	10 (13.33%)	ns
Heart failure	10 (%)	6 (8%)	ns
Coronary artery disease	10 (13%)	12 (16%)	ns
Peripheral artery disease	15 (23.1%)	11 (14.66%)	ns
Comorbidities >2	47 (64%)	49 (65.33%)	ns

Abbreviations: BADL, basic activity daily living; Hb, hemoglobin; COPD, chronic obstructive pulmonary disease; ns, not significant.

Table 3 DOAC Level >50 ng/mL in Relation to Time Since Last Dose

	Time from Last Dose <48 Hours (n=56)	Time from Last Dose >48 Hours (n=17)	p
Apixaban	13/28	0/6	0.05
Rivaroxaban	0/9	1/5	ns
Dabigatran	4/9	1/4	ns
Edoxaban	0/11	1/2	ns

Abbreviation: ns, not significant.

surgery within 48 hours in general anesthesia. Therefore, in patients with DOAC levels below 50 ng/mL surgery was performed without hemorrhagic complications within 48 hours in 35/39 patients (89%).

In A1, 32 patients underwent surgery within 48 hours (45.1%; p=0.03) with a median time to surgery of 3.6±2.7 days (86±46 hours) (p<0.0001). Therefore, patients with assay of DOAC levels were treated on average 1 day earlier than patients in whom guidelines were followed. Furthermore, the length of hospital stay was on average 1 day lower in A2 with respect to A1 (14±4 vs 15±7 days, p=0.04).

Complications

In Table 4 are reported the more common complications of the two subgroups and of the control group. Average postoperative hemoglobin loss was 1.5 g/dL in all groups. Severe postoperative anemia (Hb <7.5 g/dL) needing RBC transfusion occurred in nearly 40% of patients in both groups. The incidence of delirium was similar (23.1% versus 24%), as was that of pneumonia (12.3% versus 9.3%). Both groups showed low incidence of DVT (1.5% versus 2.7%) and no cases of pulmonary embolism or stroke (0%).

Table 4 Comparison of Post-Operative Complications Between Patients with and without Determination of DOAC Levels

	Controls N=206	DOAC Levels Assay n=73	No DOAC Levels Assay n=74	p
Delirium	57 (28%)	15 (23.1%)	18 (24%)	ns
Myocardial infarction/myocardial injury	8 (4%)	5 (7.7%)	4 (5.4%)	ns
Stroke	0 (0%)	0 (0%)	0 (0%)	ns
Pneumonia	15 (7%)	8 (12.3%)	7 (9.3%)	ns
Sepsis	1 (0.6%)	0 (0%)	2 (2.7%)	ns
Deep venous thrombosis	12 (6%)	1 (1.5%)	2 (2.7%)	ns
Pulmonary embolism	1 (0.6%)	0 (0%)	0 (0%)	ns
Heart failure	7 (3.5%)	9 (13.8%)	5 (6.7%)	ns
AKI	7 (3.5%)	1 (1.5%)	1 (1.3%)	ns
Respiratory failure	10 (5%)	5 (7.7%)	2 (2.7%)	ns
Hb <7.5 g/dL	21 (10%)	26 (40%)	28 (37.3%)	0.0001

Abbreviation: ns, not significant.

Discussion

Results from our study show that the time from hospital admission to surgery was about 15 hours longer (95% CI 4–24 hours) in patients on DOACs in comparison to controls. No differences in 30-day mortality, requirement for transfusion, and incidence of postoperative deep venous thrombosis were found between patients on DOACs and controls. Using a strategy which includes DOAC level assay, time to surgery and length of hospital stay were significantly reduced (about 24 hrs each) in comparison to patients without DOAC measurement, in whom surgery was scheduled according to current guidelines. DOAC levels <50 ng/mL were found in 70% allowing surgery to be performed within 48 hours in 89% of patients (75% under neuraxial anesthesia). On the other hand, 30% of patients had DOAC levels at 48 hours since last intake >50 ng/mL, exposing them at risk of severe complications in the case of surgery under neuraxial anesthesia.

DOACs are progressively replacing VKA inhibitors in thromboembolism prophylaxis, in particular in patients affected by NVAF. Their management in patients who need urgent–emergency surgery is still a matter of debate. In the elderly, the association between anticoagulation and frailty fracture is common. Early surgery has been demonstrated to improve outcome and decrease complications in patients who need hip fracture surgery,[5–8] but it is associated with a high risk of bleeding in anticoagulated patients. The HIP ATTACK study, however, failed to show that accelerated surgery significantly lowers the risk of mortality or a composite of major complications compared with standard care.[22] In this study the median time from hip fracture diagnosis to surgery was 6 h (IQR 4–9) in the accelerated-surgery group and 24 h (10–42) in the standard-care group ($p<0{\cdot}0001$).

Current available guidelines[14–16] suggest that, in surgery (thoracic, abdominal, or major orthopedic surgery procedures) at high risk of bleeding, apixaban, rivaroxaban, and edoxaban should be discontinued 48 hours before intervention. For dabigatran, renal function is a strict determinant of the timing (from 48 to 72 hrs). Before a neuraxial block guidelines suggested to wait 72 hours for Xa inhibitors and for dabigatran in patients with a CrCl of at least 80 mL/min.[23]

Among 15,099 patients from a large German registry (Registry for Geriatric Trauma), 11% took DOACs at the time of fracture. The time-to-surgery of patients on DOACs was longer compared to patients who did not take any anticoagulation. It must be noticed that 13,770 patients (92%) were treated under general anesthesia.[24] In a small study from Norway, 15% of patients enrolled in the study were on DOACs. Most of these (90%) were operated under spinal anesthesia, with no reported difference in surgical delay (29 vs 26 h, $p=0.26$) between DOAC users and non-users. However, DOAC users operated under neuraxial anesthesia had longer surgical delay compared to DOAC users operated under general anesthesia (35 h vs 22 h, $p<0.001$). Again, perioperative blood loss, transfusion rate, risk of bleeding complications, and mortality were similar between groups.[25]

In 2018, approximately 3% of hip fracture patients in England and Wales were delayed >36 h before surgery due to DOAC therapy; virtually all patients taking DOACs were delayed >36 h before surgery.[26] Results from other studies reported longer time to surgery in patients with hip fracture under DOAC treatment but no increased perioperative blood loss or mortality compared to the controls.

The high variability of DOAC pharmacokinetics (related to drug interactions, renal and liver dysfunction, advanced age, and rare genetic polymorphisms) demonstrated in elderly patients limits the usefulness of current guidelines to schedule hip fracture surgery in patients in whom neuraxial anesthesia is preferred, as in our institution. DOAC monitoring can assist in the management of elderly patients with hip fracture. Till now few investigations evaluated the effects of dosing DOAC levels on time to surgery, operative bleeding, complication rates, and mortality in hip fracture. Aziz et al[27] compared 3 different strategies: 1. Nottingham University Hospitals (NUH 24): 24 hours from last DOAC dose before surgery; 2. University Hospitals of Leicester (UHL level): DOAC level measurement and surgery once below the hospital protocol threshold of 50 ng/mL. 3. 48 hours from last DOAC dose before surgery (UHL 48). Time to surgery was highest (53 hours) in the UHL level group, followed by UHL 48 at 23 hours, and the lowest in the NUH 24 group at 18 hours. Overall 90% of NUH 24 and UHL 48 groups were treated within 36 hours' target compared with 3% for the UHL level group and 93% for the control group. There was no need for transfusions in the control group, while in the three protocol groups the transfusion rate was the highest (40%) in the UHL level groups, followed by UHL 48 at 27%, and the lowest in the NUH 24 group at 23%. All patients in NUH 24 received a general anesthetic. However, this study has shown that avoiding spinal anesthetic has led to a substantial financial gain through improvement in reaching 36 hours target.

The results from present investigation confirm that DOAC treatment is associated with a significant delay in time to hip fracture surgery, that is mainly related to the high risk of hemorrhagic complications of neuraxial anesthesia before 72 after DOAC withdrawal. At variance with the study by Aziz,[27] time to surgery was about 24 hours lower in patients with measured DOAC levels, and this was associated with one day less average length of hospital stay. Surgery within 48 hours was performed in 56% of patients with drug level assay vs in 45% of patients who did not undergo assay and 80.6% of controls. It must be emphasized that the higher proportion of patients treated with dabigatran in the group without DOAC assay may contribute to the longer times to surgery.

Blood losses were similar in patients with or without DOAC assay, as well the need of RBC transfusion, which is at variance with previously reported data. Anemia (defined as Hb levels <7.5 g/dL) was, however, more frequent in DOAC patients than in controls due to a larger blood loss before hospitalization. The observation that in the DOAC group only 0.6% died during hospitalization in comparison with 2.9% of control group deserves attention. This observation agrees with current literature that reports a very low in-hospital mortality rate among patients on DOAC treatment. Several factors may be hypothesized to explain this observation. Firstly, patients on DOACs are a selected and well followed population;[28,29] secondly, impairment of renal function is a contraindication to DOAC administration, and chronic renal failure is a well-established independent factor of mortality in patients undergoing hip fracture surgery.

Limitations

This as an observational retrospective study, and inherent limitations such as a higher potential for missing data are present. Moreover, confounders may be present due to absence in the design of the study of propensity matching. However, the observational aspect carried several advantages, such as an evaluation of patients in a real-world setting. We considered together thrombin and Xa factor inhibitors: although the former has an antidote that facilitates surgery for fracture, cost-effectiveness of idarucizumab in patients with hip fracture has never been evaluated, and the use of the antidote never entered in the clinical practice.

The limited number of patients from a single center limits the statistical power of our results.

Conclusion

The results of our study suggest that DOAC assay in patients with hip fracture may be useful for a correct definition of time to surgery and anesthesiologic strategy, decreasing the risks of bleeding complications related to neuraxial anesthesia in subjects with not completely reversed anticoagulation. Given the different behavior of each drug in relation to renal function of the patient, a tailored approach is mandatory. The relatively low cost of drug assay is widely compensated by faster and safe surgery in hip fracture, favoring reducing intra-hospital complications, length of stay, and mortality. Further studies are needed to support our findings.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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