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Original article

Clinical implications of anticoagulant oral therapy in elderly patients with hip fracture

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Abstract. *Background and aim:* Proximal femur fractures (PFFs) are among the most common fractures, especially in the elderly population. A PFF often represents a life-changing event. Their dramatic effects are attributable not only to the massive hemorrhages caused by the fracture, but also and due to the high risk of dramatic complications. These risks are supposed to be even higher for patients under oral anticoagulant treatment. In this study we evaluated how oral anticoagulant therapy effected patient's prognosis. *Methods:* Ours was a case-control review of geriatric-aged patients treated surgically for proximal femur fractures between 2013 and 2019. Cases were divided in 2 groups depending if they were (Group A) or were not (Group B) under oral anticoagulant therapy at the moment of hospitalization. *Results:* 200 cases were included in our study: 100 in Group A and 100 in Group B. Surgical delay was significantly higher for cases under oral anticoagulant treatment compared to the other cases. Group A cases were transfused with a significantly higher frequency and with more blood units compared to Group B ($p=0.0300$; $p=0.013$). Combined cardiological and vascular complications occurred in 21 cases (10.5%), being significantly more common in Group A (16) than Group B (5), as testified by a chi-square test ($P=0.011$). *Conclusions*: Cases under oral anticoagulant therapy are fragile patients with a higher risk to develop massive hemorrhages. For this reasons, it is mandatory to achieve an early stabilization of patient's clinical conditions and then perform surgery as soon as possible. (www.actabiomedica.it)

Key words: Hip Fractures, Oral Anticoagulant, Warfarin, NOACs, Transfusions

Introduction

Proximal femur fractures (PFFs) are among the most common fractures, especially in the elderly population (1,2). In fact, more than three quarters of hip fractures occur in patients over the age of 75 (3). As western countries' population has been continuously increasing through the decades, these injuries are now more frequent than ever (2,4). While global yearly incidence of PFFs 1.3 million back in 1990, the number is estimated to rise and range between 7.3 and 21.3 million by 2050 (5).

On the single patient's perspective, a PFF often represents a life-changing event especially for those who already have multiple comorbidities at the moment of fracture (6). Only 40-60% of cases regain the activity level they used to have before the injury and most of their activities of daily living could be restricted or precluded (7). These dramatic effects are attributable not only to the challenging rehabilitation programs, but also to the high risk of peri-operative and post-operative complications to which those fragile patients are inevitably subjected. In fact, PFFs in old and complex patients are associated with a pronounced risk of

cardiovascular, pulmonary, thrombotic and bleeding complications (8). From a medical point of view, daily geriatric evaluations can be effective to provide a closer survey and the best standard of treatment for the single patient (9, 10).

From a surgical point of view, instead, studies in literature support the idea that surgical timing represents a key factor for post-operative prognosis (11). Ideally, operative treatment should take place within the first 24h from the trauma, since after 48 hours the risk of systemic and local complications increases and mortality within a year becomes significantly higher (11, 12).

Looking beyond the single case, PFFs as a whole also represent a major burden for the accounts of hospitals and national health care systems. Several days of hospitalization, daily blood tests and radiological investigations presuppose high charges for each case with hip fracture, not to mention the expenses of surgery itself. Furthermore, costs per capita inevitably increase in case of major complications, which extend hospitalization and make necessary additional diagnostic and therapeutic measures (13, 14).

Complex instable patients therefore represent both a challenge for medical personnel an important source of expense for their organization. Nowadays, an increasing share of elderly people is under oral anticoagulant treatment due to previous thromboembolic accidents. Those cases, particularly after a hip fracture, are subjected to massive bleeding, hemodynamical instability and, potentially, fatal complications (15).

In this study we evaluated the pre-operative, intra-operative and post-operative course of cases under oral anticoagulant treatment, comparing them to cases who did not use those drugs. Particular attention was given to surgical timing, number of blood units transfused through the hospitalization, post-operative complications and survival rates.

Materials and Methods

This single-center retrospective study was approved by our local ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Our study consisted of a case-control review of cases over 65 years of age who were treated in our institution for fracture of proximal femur between April 2013 and May 2019. Inclusion criteria were patients' age (over 65), radiographical diagnosis of femur fractures – whether they were medial or lateral – and surgical treatment with prostheses or internal fixation with intramedullary nails. Exclusion criteria were periprosthetic fractures, concurrent imaging evidences of fractures involving other regions of the femur and conservative treatment.

Cases were divided in 2 groups: Group A for those who were under oral anticoagulant therapy at the moment of hospitalization, and Group B for those who were not under treatment at the moment of fracture.

For each patient we collected personal data, like age and gender, as well as pre-operative, intra-operative and post-operative information. Among the pre-operative data, we evaluated the eventual type of oral antithromboembolic treatment received, the type of fracture according to the AO/OTA classification and the time interval between diagnosis and surgical treatment.

Intra-operatively, interventions were characterized according to both the type of surgical approach and anesthesia performed. After surgery, for each case, we recorded how many cases required post-operative intensive care and how long did hospitalization last on average. Daily CBC and coagulation analysis were evaluated. We counted the number of packed red blood cells units transfused before, during and after surgery in order to maintain patients' hemodynamic situation acceptable and stable.

Patients spent their days in our hospital in our orthopedic ward, where they were evaluated daily by our orthopedic surgeons and by our orthogeriatric unit.

Postoperative follow-up consisted of serial orthopedic office visits and post-operative X-rays. Those clinical and radiographical evaluations have been carried out within 1, 3, 6 and 12 months after surgery. New visits were then scheduled every six months for the next 2 years. After three years, the frequency was furtherly decreased and patients were asked to attend clinical evaluations and X-Rays once a year.

Each complication with grade II or higher according to the Clavien – Dindo Classification was reported.

STATISTICS. Statistical analysis was performed using Stata SE 13 (StataCorp LLC, College Station, TX). Statistical significance was set at 0.05 for all endpoints.

Results

We collected 200 cases who suffered from proximal femur fracture and were treated with surgery in our institution between April 2013 and May 2019. Among those 200 patients, 100 were under oral anticoagulant therapy at the moment of hospitalization, whereas the remaining 100 were not receiving such treatment when diagnosed with fracture. 66 cases used Warfarin and 34 had Novel Oral Anticoagulant Drugs (NOACs).

The mean age was 83 years for the whole population, 82 for Group A and 84 for Group B.

Female-to-male ratio was 2.03 and 2.57 respectively for Group A and Group B.

Time between radiographical diagnosis and surgical intervention was on average 48 hours. Surgical delay was higher for cases under oral anticoagulant treatment (58 hours) compared to other cases (39 hours); the difference between the values of the two groups was statistically significant according to the results of a t-student test (T=-6.070, P=0.0001). This suggests cases treated with NOACs required significantly more time to be made ready for surgical treatment.

Before surgery, 19 of our 200 cases (9.5%) required blood transfusion by reason of pre-operative anemization. This occurrence was significantly more frequent in Group A (14%) than Group B (5%), as testified by a chi-square test (P=0.0300). The different pre-operative transfusion rate was equally significative (P=0.013).

Lateral fractures were most common than medial fractures not only in the whole population, but also in both groups. Fracture distribution obviously influenced the type surgical treatment that was carried out. Reduction and internal fixation with intramedullary nails was the most common surgical treatment, while anesthesia was performed most frequently with a general approach or subarachnoid block. 5 patients, 4 belonging to group A and 1 to group B, required peri-operative monitoring in our intensive care ward.

Once surgery was performed, hospitalization lasted on average 8.0 days, without any significant difference between the who groups (p=0.109).

131 of our 200 cases (65.5%) suffered from major intra-operative or post-operative anemization which required prompt treatment with blood transfusions in order to preserve hemodynamic stability and maintain good values of hemoglobin.

On average, through their post-operative phase, each patient of Group A required 1.94 pints of blood, whereas the mean value for cases in Group B was 1.25. This difference was statistically significant according to a t-student test for independent variables (P=0.0032).

After the intervention, 6 cases (3%) had an infection of the surgical site, 6 patients (3%) developed local hematoma and 10 (5%) were diagnosed with pneumonia (5%). 15 patients suffered from mechanic complications or implant failures, as described in detail in TAB 1. The risk of all the aforementioned complications was not significantly different between the two groups.

Table 1. Data of our cases, overall and sorted by group: Group A (oral anticoagulant treatment) and Group B (controls).

DATA	TOTAL	GROUP A (Anti-coagul.)	GROUP B (No Anti-coagul.)
NUMBER	200	100	100
AGE (mean age at surgery, in years)	83 (7)	84 (6)	82 (7)
GENDER			
M	61 (30,5%)	33 (33%)	28 (28%)
F	139 (69,5%)	67 (67%)	72 (72%)
FRACTURE TYPE			
Medial	76 (38%)	36 (36%)	40 (40%)
Lateral	124 (62%)	64 (64%)	60 (60%)

Table 1. (*Continued*)

Table 1. Data of our cases, overall and sorted by group: Group A (oral anticoagulant treatment) and Group B (controls). (*Continued*)

DATA	TOTAL	GROUP A (Anti-coagul.)	GROUP B (No Anti-coagul.)
SURGICAL RECONSTRUCTION			
Three screws	10 (5%)	7 (7%)	3 (3%)
Intramedullary Nails	106 (53%)	56 (56%)	50 (50%)
Endoprostheses	54 (27%)	29 (29%)	25 (25%)
Total Hip Arthroplasty	30 (15%)	8 (8%)	22 (22%)
ANESTHESIA			
Spinal anesthesia	102 (51%)	39 (38%)	63 (63%)
General anesthesia	79 (39,5%)	49 (49%)	30 (30%)
General + Plexus anesthesia	9 (4,5%)	5 (5%)	4 (4%)
Spinal + Plexus anesthesia	9 (4,5%)	6 (67%)	3 (33%)
Local anesthesia	1 (0,5%)	1 (1%)	0 (0)
SURGICAL DELAY (mean duration, in hours)	48	58	39
HOSPITALIZATION (Days)	8	8,3	7,8
PATIENTS TRANSFURES BEFORE SURGERY	19 (9,5%)	14 (14%)	5 (5%)
BLOOD UNITS PER PATIENT BEFORE SURGERY	0.20	0,3	0,09
PATIENTS TRANSFURES AFTERS URGERY	131 (65,5%)	69 (69%)	61 (61%)
BLOOD UNITS PER PATIENT AFTER SURGERY	1,59	1,94	1,25
POST-OPERATIVE CLINICAL MONITORING IN INTENSIVE CARE REGIME	5 (2,5%)	4 (4%)	1 (1%)
COMPLICATIONS			
Local infections	6 (3%)	3 (3%)	3 (3%)
Hematomas	6 (3%)	4 (4%)	2 (2%)
Pneumonias	10 (5%)	6 (6%)	4(4%)
Cardiac and vascular complications	21 (10.5%)	16 (16%)	5 (5%)
Atrial Fibrillation	5 (2,5%)	4 (4%)	1 (1%)
Acute Heart Failure	7 (3,5%)	7 (7%)	0 (0)
Stroke	2 (1%)	1 (1%)	1 (1%)
Acute Kidney Injury	3 (1,5%)	1 (1%)	2 (2%)
Pulmonary Embolism	4 (2%)	3 (3%)	1 (1%)
MECHANIC AND LOCAL BIOLOGIC COMPLICATIONS	15 (7,5)	7 (7)	8 (8)
Luxation	5 (2,5%)	1 (1%)	4 (4%)
Nail Cut-out	1 (0,5%)	1 (1%)	0 (0%)
Pseudoarthrosis and Union Delay	4 (2%)	2 (2%)	2 (2%)
Periprosthetic fracture	6 (3%)	4 (4%)	2 (2%)

Combined cardiological and vascular complications - such as pulmonary embolism, atrial fibrillation, heart failure, stroke and pre-renal acute kidney injury – occurred in 21 cases (10.5%) and were significantly more common in Group A (16; 8%) than Group B (5; 2.5%), as testified by a chi-square test (P=0.0112). This finding suggests that cases who were under treatment with Warfarin or NOACs had a statistically higher risk to develop at least one major cardiovascular complication after surgery.

2 cases of Group A and 1 case of Group B died during their hospitalization due to the aforementioned major cardio-vascular complications. Overall survival for Group A patients was 75% after 1 year, 64% after 2 years and 36% after 5 years. Group B cases, for their part, had a survival rate of 83%, 70% and 49% respectively 1, 2 and 5 years after surgery. Population's survival through the months is represented graphically using Kaplan Meier curves (FIG 1). Although our outcomes suggest a shorter life expectancy for cases under oral anticoagulant treatment, the difference between the two groups was not enough to provide a strong statistical evidence (P=0.1902). Considering cases belonging to Group A alone, cases who underwent surgery within the first 48 hours after the injury had a significantly higher mortality rate 1 years after surgery, according to a chi-square test for independent variabilities (P=0.006) (FIG 2).

Considering Group A alone, the use of Warfarin or NOACs did not seem to effect the risk of major post-operative complications nor overall survival.

The mean follow-up was 41 months (8-96).

Discussion

Proximal femur fractures (PFFs) represent one of the most threatening injuries in orthopaedics and trauma surgery (1-4). Clinical management is particularly challenging in old patients. Cases who have multiple comorbidities and require complex drug therapies are particularly subjectable to develop anemization and hemodynamic instability, with higher risk of major complications and lower survival rates. In western countries, an increasing share of elderlies make recourse to oral anticoagulant drugs in order to treat or prevent thromboembolic events. Although effective, these therapies expose patients to a significantly higher tendency to bleed. When a person under Warfarin or NOACs gets a hip fracture, there is a high risk of massive blood loss and hemodynamic instability. Furthermore, in reason of their age and their previous medical history, those cases often suffer from a number of other diseases which tend to increase their clinical instability. The management of both medical and surgical treatment must therefore be carefully planned (3, 8-12).

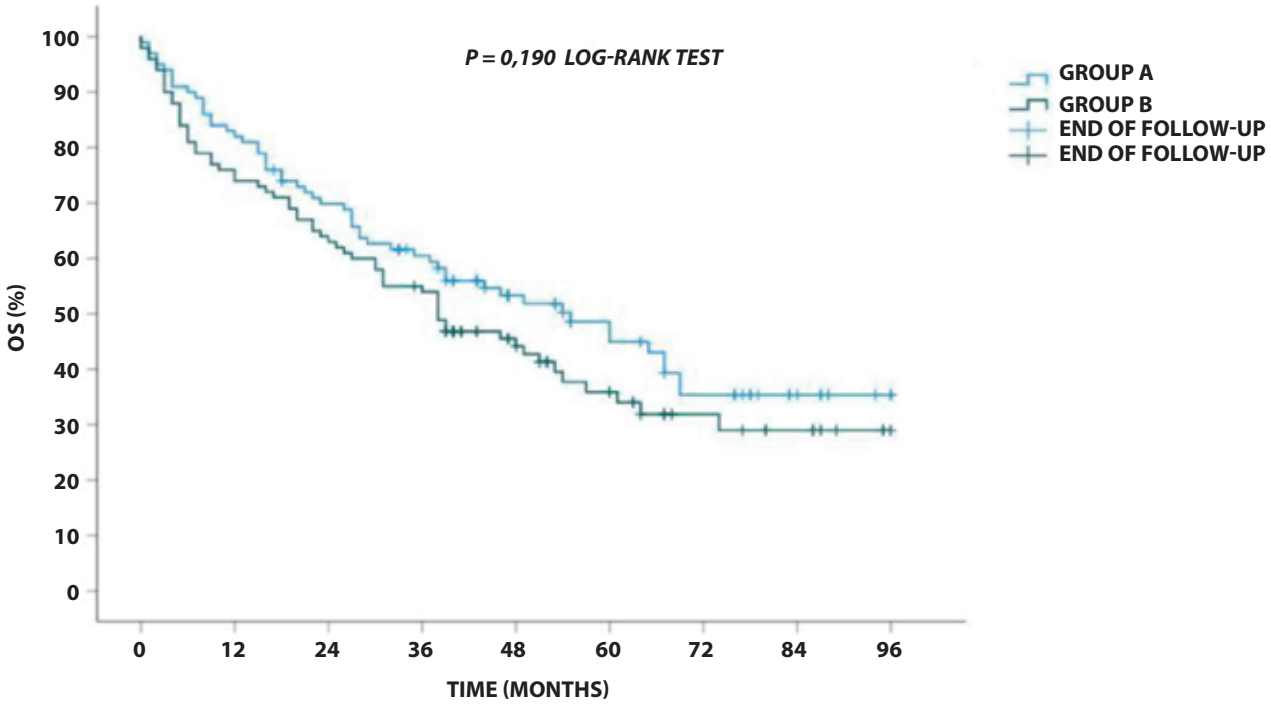

Figure 1. Kaplan Meyer survival curves for Group A (light blue) and Group B (dark blue)

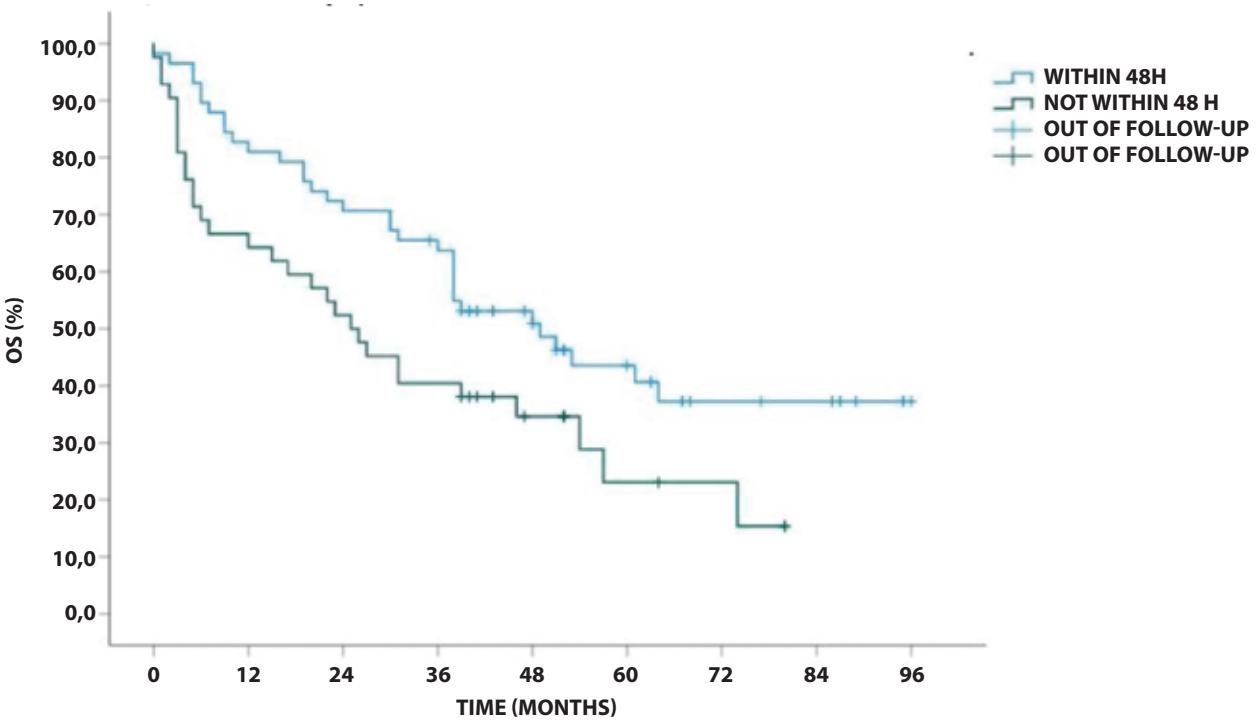

Figure 2. Kaplan Meyer survival curves for Group A cases sorted by surgical timing: treated before (light blue) or after (dark blue) 48h from the injury event.

Since the main risks for patients' health are linked to the hemorrhage that results from hip fracture, one of the main focuses in medical treatment before and after surgery should be to counterbalance the bleeding. To this date transfusion therapy represents one of the most important therapeutic approaches in this scenario (16, 17).

In our study blood units were administered with significantly higher number and frequency in cases under oral anticoagulant therapy than in control cases, both before and after surgery. Our outcomes differ from those reported by other studies, such as the ones by Schermann et al (18) and Gautier et al (19), who did not testify any significant difference between cases under NOACs or Warfarin and controls in terms of blood losses and transfusion rates. Although these outcomes could lead to different interpretations of the hemorrhagic and hemodynamic risks that come after a hip fracture, standard blood units still represent a therapeutic option whose use depends by the single physician, without any univocal standardization for therapeutic indications. Use or withdrawal of transfusion therapy inevitably depends not only on hemoglobin levels, but also on the complete overview of blood exams, included coagulation values, pressure, heart rate and the complete landscape of patient's comorbidities, recent treatments and surgeries undertaken.

From a surgical point of view, a correct timing is fundamental to provide the guarantee chances of success and minimize blood losses and therefore reduce the risk of post-operative complications (11, 14, 18, 19).

In our population surgical delay, considered as the time gap between radiographical diagnosis of hip fracture and surgical intervention, was significantly broader in cases under oral anticoagulant therapy compared to control cases. The mean time even exceeded the 48-hour standard given by literature to allow patients to have the safest possible post-operative intercourse. This finding, in line with the ones by Gautier et al and Shermann et al, suggests that cases under Warfarin or NOACs at the moment of diagnosis required significantly more time before they could be clinically stabilized and surgical intervention could be

allowed (18, 19). Post-operative time of hospitalization, for its part, did not differ between those who were under oral anticoagulant drugs and the other patients. Our results are in line with the ones by Gautier and Shermann also in terms of short-term and mid-term mortality (18, 19). In our population, the mortality rates of cases who assumed oral anticoagulants did not differ from the ones of control cases in the first weeks after surgery. On the other hand, they had a higher one-year mortality. Although the number of our population did not provide enough evidence to make our outcome statistically significant, it is consistent with the idea that cases under anticoagulant therapy are exposed to a worse long-term prognosis than general population. This tendency may be attributable to their poorer health status, often attributable to the concurrent presence of multiple diseases. Therefore, although fracture does not directly cause the death of the patient, it may represent the starting event of a progressive breakdown of an already complex clinical balance.

Our data differ from the ones by Gautier et al and Shermann et al when it comes to post-operative complications (18, 19). Unlike these two studies which did not highlight any difference between cases and controls, in our population cases under Warfarin or NOACs had a significantly higher risk to develop major thromboembolic and cardio-vascular complications after surgery. In contrast with what already described in literature, this evidence could support the hypothesis of a cause-effect link between higher risk of post-operative complications and long-term mortality (10, 11, 14, 18, 19).

We are conscious our study has some limitations. The main issues of our work are represented by its retrospective nature, which limited the number of data available and did not allow a perfect standardization of care, and by the relatively limited number of cases, which was responsible for the low statistical significance of some of our outcomes. Nevertheless, the results obtained on our population confirmed many of the current conceptions in modern literature in terms of treatment for cases under oral anticoagulant therapy at the moment of a hip fracture. Overall, medical and surgical equips should focus their practice to get an early stabilization of patient's clinical status, in order to allow a safe surgical intervention within 48 hours. Physicians should therefore consider the use of each therapeutic approach that could be useful from that point of view. Among these possibilities, we also consider the administration of antidotes for NOACs or vitamin K for those who were under Warfarin, particularly in case of remarked hemodynamic stability or significantly reduced hemoglobin levels. In parallel, hemoglobin levels and hemodynamic values should be carefully examined on a daily basis and blood transfusions should be administered in order to counterbalance the losses caused by the fracture.

In conclusion, cases under oral anticoagulant therapy are often frail patients with multiple comorbidities and have a higher risk to develop massive hemorrhages. For these reasons, it is mandatory to achieve an early stabilization of patient's clinical conditions and then perform surgery as soon as possible. The complexity of those cases is also testified by their higher long-term mortality rates, although short and mid-term rates do not differ from general population. Our data also suggested a significantly higher risk of major post-operative complications, which could represent an additional factor to explain their poorer prognosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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