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Chronic anticoagulation therapy and acute hip trauma

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ABSTRACT

Regardless of the association between hip fracture surgery and mortality, morbidity and bleeding risks, there are still significant contradictions in various published articles concerning hip fracture surgery outcomes when patients are prescribed anticoagulant medication. The primary objective of this study was to investigate if patients prescribed anticoagulants experienced delayed surgery when compared to non-users. The secondary goal was to investigate if patients prescribed anticoagulants underwent an extended hospital stay and complications such as increased bleeding, mortality and a higher rate of comorbidities when compared to non-users. Data from proximal hip fracture patients were prospectively collected at a level I university trauma center. From 1 January, 2020, through 1 January, 2021, 519 eligible patients were identified. Anticoagulant medication upon admission, time prior to surgery, hospitalized days, 30-day mortality rates, 1-year mortality, blood transfusion requirement and various comorbidities were noted. 222 of the 519 hip fracture patients were prescribed anticoagulants. Of the 222 patients, 75% were females and 25% were males. In total, 46% required a blood transfusion, with no significant differences between the anticoagulated and non-anticoagulated patients. 50% of the anticoagulated group and 42% of the control group required perioperative blood transfusion. Neither the 30-day nor the 1-year mortality rate showed statistically significant differences between the groups. However, the time to surgery and the length of hospital stay was significantly longer in the anticoagulated group. Comorbidities were found in 87% of the patients: in 95% of the anticoagulated group and in 81% of the non-anticoagulated group. Patients prescribed anticoagulants at the time of hip fracture experienced delayed surgery, longer hospital stays and more comorbidities when compared to patients not on anticoagulants. Neither a blood transfusion requirement, 30-day mortality rate nor a 1-year mortality rate showed no significant difference between the two cohorts.

Keywords: ***Anticoagulants – adverse effects; Hip fractures – drug therapy/surgery; Postoperative complications – Prevention & control;***

INTRODUCTION

Hip fractures are one of the major burdens in orthopedic surgery and one of the most common fractures occurring among elderly patients. Low-energy trauma, such as senior patients falling from standing height, commonly results in proximal femoral fracture (PFF) which is associated with high morbidity and mortality rate (18). Many such patients require long-term nursing care. *Pedersen* et al. found there were 140,000 hip fracture patients admitted to nursing homes in the United States annually (17).

Today, due to the increasing life expectancy worldwide, a higher proportion of the population reaches 65 years or more. It is more likely a larger group of individuals suffer from osteopenia and osteoporosis, consequently increasing fracture risk. Hip trauma among the elderly is thus considered a worldwide epidemic with socioeconomic factors and a burden upon the public health system. Retrospective research by *Chatziravdeli* et al. describes the burden of hip trauma treatment on public health and how hip trauma patients prescribed anticoagulation medication often require delayed surgery and more postoperative care. They found the excess financial burden from the baseline costs of 447,904.60€ to be 4,074.64€ for those operated on within 48 hours and 45,654.14€ for those with delayed surgery (4).

In addition to warfarin, the new DOACs (Direct Oral Anticoagulants), also known as NOACs (New Oral Anticoagulants) such as rivaroxaban, dabigatran and apixaban are becoming increasingly favorable. A study from 2019 by *Schuetze* et al. describes one-third of all patients with PFF ingest oral anticoagulants and DOACs appeared to have 3 to 4 times increased risk of blood transfusion (20). Warfarin is the longest-used anticoagulant and its antidote, Vitamin K, is also more affordable than reversible agents used for DOACs. However, warfarin comes with disadvantages; it requires monitoring and interacts with various drugs. After ceasing warfarin therapy, it usually takes several days to decrease the INR (International Normalized Ratio) value, since it has an indirect coagulation effect (13). DOACs, on the other hand, do not require monitoring and have fewer drug interactions than when compared to warfarin (1).

The disadvantage of clopidogrel when compared to other anticoagulants is there is no known reversing agent, therefore, it can only be reversed by the production of new platelets within seven days from the last dosage. There is some concern clopidogrel may have an increased risk of bleeding in acute cases (5). Thus, it is recommended to interrupt clopidogrel for 5–10 days prior to a hip fracture surgery, which is done by more than 40% of UK orthopedic departments (8).

Guidelines from NICE (National Institute of Health and Care Excellence) recommend hip surgery is performed on the same day as admission and, if not, the day following (16). A retrospective cross-sectional study from 2019, published by *Caruso* et al., shows a delay in surgery and a significant increase in mortality in the warfarin group when compared to the control group within one year from the surgery. The delay in surgery is described as mostly being due to reaching the target INR value <1.5. This delay can be reduced by prescribing Vitamin K and prothrombin complex concentrate, preoperatively (2). Supporting *Caruso* et al., in 2011, *Dettoni* also found patients prescribed warfarin therapy, when compared to non-users, had a higher preoperative and postoperative risk of complications (7).

The primary purpose of this study was to examine if patients prescribed anticoagulants who sustain a PFF experienced delayed surgery when compared to non-users. Furthermore, we aimed to estimate the association between anticoagulant use and prolonged length of hospital stay, the presence of comorbidities and complications such as the increased need for blood transfusion, 30-day mortality and the 1-year mortality following a PFF.

PATIENTS AND METHODS

This research was approved by the Regional Research Ethics Committee, University of Pecs Clinical Center. Patients admitted to the level I orthopedic trauma department with the diagnosis of S7200 or S7210 between 1 January, 2020, and 1 January, 2021, of which, were identified in the electronic medical records. There was no age limit set. Data

regarding age, sex, use of anticoagulants, time to surgery, hospitalized days, blood transfusion, mortality within 30 days and one year and comorbidities were evaluated. The patients were divided into two cohorts based on whether they were anticoagulated at the time of the hip fracture or not: anticoagulated and non-anticoagulated groups. Statistical workup was done using Pearson's Chi–squared test, Kruskal–Wallis rank sum test, and Fisher's exact test. Significance was set at $P \leq 0.05$.

RESULTS

During the prospective study period, 614 hip fracture patients were identified. 93 cases with insufficient data were excluded. 521 patients were found relevant to this study.

Anticoagulants

The 521 patients were reduced to 519 due to insufficient data regarding anticoagulant use. Of the 519 extracted patients, 222 were prescribed anticoagulants at the time of the fracture. There were 75% female and 25% male patients. The anticoagulated group was divided into three groups based on the type of anticoagulant drug prescribed; 1. Platelet aggregation inhibitors; 2. Other anticoagulants than platelet aggregation inhibitors; 3. Both 1 and 2. The results in *Table 1* show most patients used platelet aggregation inhibitors from the anticoagulated group. Group 4 represents patients with no anticoagulant use.

Table 1 *Subgroups based on the anticoagulated status. NA: data not available*

Type of anticoagulant	N=521
1 - Platelet aggregation inhibitors	120 (23%)
2 - Other anticoagulants than platelet aggregation inhibitors	94 (18%)
3 - Both 1 and 2 use	8 (1.5%)
4 - No anticoagulant use	297 (57%)
NA	2

Time to surgery

When dividing the patient group into two cohorts, anticoagulated and non-anticoagulated, we could estimate the time to surgery for each group. The time to surgery was reported in hours, from the admission to the hospital until the onset of surgery (the surgical delay). A mean of two days was estimated for the entire patient group of 466, with a statistically significant difference (p–value = 0,001) between the anticoagulated group with a mean of 2.57 and the control group with a mean of 1.63 days (*Figure 1.*).

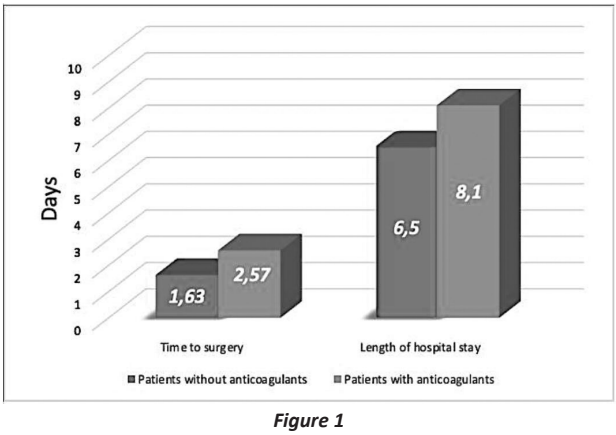

Figure 1
Time to surgery and the LOS in days for both groups

Length of hospital stay

The anticoagulated group showed a mean of 8.1 days hospitalized, while the control group was hospitalized a mean of 6.5 days. In total, the minimum number of days hospitalized was one day, and the highest number of days was 37 for the control group and 25 days for the anticoagulated group. The patients prescribed anticoagulants, on average, had a longer LOS (length of hospital stay) when compared to non-users.

Mortality

Mortality was estimated both for the total patient group and the calculated differences between the anticoagulated and the control group. The 30-day mortality rate of the anticoagulated group was 9.6%, and the control group had a slightly similar mortality rate of 9%, giving a p–value of 0.816. In total, 47 patients succumbed. The 1-year mortality rate, on the other hand, was increased among the anticoagulated patients. 27% of the anticoagulated patients expired within one year, and 18% of the patients from the control group, in total 72 patients died. Still, with a p–value of 0,063, it failed to achieve statistical significance. Additionally, 47 of the total 337 patients succumbed within one year, meaning they were already noted expired in the hospital or within the 30-day columns. 21 of these were anticoagulated, and 26 of them were not. There was no existing mortality data regarding 182 patients due to the fact, when mortality data were collected, only deaths occurring at the hospital of Pécs were found (*Table 2.*).

Table 2 *Patients' characteristics, time to surgery, hospitalized days, blood transfusion, and deaths within 30-days and one year. (Pearson´s Chi-Squared test and Wilcoxon rank sum test.) 0, N= Control group 1, N= Anticoagulated group*

			anticoagulant			
Characteristic	**N**	**Overall** N=519	**0.** N=297[1]	**1.** N=222[1]	**p-value**	**q-value[2]**
Sex	519(100%)				0.017[3]	0.024
1		160(31%)	104(35%)	56(25%)		
2		359(69%)	193(65%)	166(75%)		
time to surgery	466(90%)				**<0.001[4]**	<0.001
N (% not missing)		466(90%)	259(87%)	207(93%)		
Mean(SD)		2.05(2.18)	1.63(1.88)	2.57(2.40)		
Median(IQR)		2.00(1.00,3.00)	1.00(0.00,2.00)	2.00(1.00,3.00)		
Miniumum; Maximum		0.00;23.00	0.00;12.00	0.00;23.00		
NA		53	38	15		
Hospitalized days	518(100%)				**<0.001[4]**	<0.001
N (% not missing)		518(100%)	296(100%)	222(100%)		
Mean(SD)		7.2(4.0)	6.5(4.1)	8.1(3.7)		
Median(IQR)		6.0(5.0,9.0)	6.0(4.0,8.0)	8.0(6.0,10.0)		
Miniumum; Maximum		1.0;37.0	1.0;37.0	1.0;25.0		
NA		1	1	0		
Needed transfusion	517(100%)				0.088[3]	0.104
1		235(45%)	125(42%)	110(50%)		
2		282(55%)	171(58%)	111(50%)		
NA		2	1	1		
Death 30 days	506(97%)				0.816[3]	0.816
1		47(9.3%)	26(9.0%)	21(9.6%)		
2		459(91%)	262(91%)	197(90%)		
NA		13	9	4		
Death within 1 year	337(65%)				0.063[3]	0.082
1		72(21%)	35(18%)	37(27%)		
2		218(65%)	139(70%)	79(58%)		
4		47(14%)	26(13%)	21(15%)		
NA		182	97	85		

Blood transfusion

Of 517 patients, 235 (45%) required blood transfusion perioperatively. Of these, 110 (50%) belonged to the anticoagulated group. 125 (42%) patients received blood in the control group.

Comorbidities

448 of the total 517 hip fracture patients had comorbidities. 208 (95%) of these patients used anticoagulants. 240 (81%) patients from the control group also had comorbidities. Hypertension, coronary artery disease, stroke, atherosclerosis, diabetes mellitus and osteoporosis were conditions registered. Overall, the most common conditions were hypertension and coronary artery disease (*Figure 2.*)

Hypertension was found in many (384 of 517) patients. Of this, 186 (85%) belonged to the anticoagulated group and 198 (67%) to the control group. Statistically significant results were obtained with a p–value of 0.001. 144 of the 517 patients studied had coronary artery disease and 85 were anticoagulated (p–value= 0.001).

Furthermore, 40 patients were registered with stroke, and 27 were anticoagulated (p-value=0,001). Atherosclerosis was discovered in 28 of 517 examined patients, 19 from the anticoagulated group (p–value=0.005). Of the 517 studied patients, 121 had DM. The anticoagulated group with a markedly higher number of 73 patients represents 33% of the group, while the control group had 48 patients with DM, including 16% of the control group. P–value=0.001 (*Table 3.*)

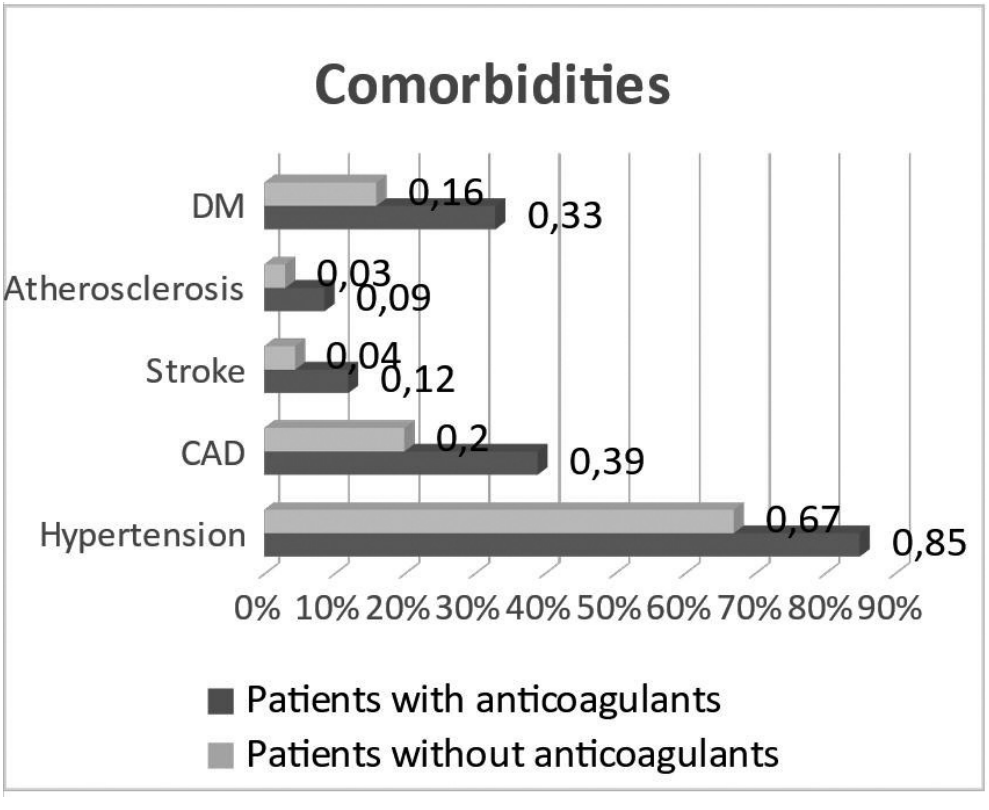

Figure 2
The prevalence of comorbidities in each studied cohort, with hypertension as the majority in both groups

Table 3 *Patients' comorbid conditions (Pearson's Chi-squared test)*

			anticoagulant			
Characteristic	**N**	**Overall** N=519	**0.** N=297[1]	**1.** N=222[1]	**p-value**	**q-value[2]**
Concomitant disease	517(100%)				**<0.001[3]**	<0.001
1		448(87%)	240(81%)	208(95%)		
2		69(13%)	57(19%)	12(5.5%)		
NA		2	0	2		
Hypertension	517(100%)				**<0.001[3]**	<0.001
1		384(74%)	198(67%)	186(85%)		
2		133(26%)	99(33%)	34(15%)		
NA		2	0	2		
CAD	517(100%)				**<0.001[3]**	<0.001
1		144(28%)	59(20%)	85(39%)		
2		373(72%)	238(80%)	135(61%)		
NA		2	0	2		
stroke	517(100%)				**<0.001[3]**	<0.002
1		40(7.7%)	13(4.4%)	27(12%)		
2		477(92%)	284(96%)	193(88%)		
NA		2	0	2		
osteoporosis	492 (95%)				0.664[3]	0.719
1		458(93%)	260(94%)	198(93%)		
2		34(6.9%)	18(6.5%)	16(7.5%)		
NA		27	19	8		

DISCUSSION

This single-center retrospective study revealed the use of anticoagulants at the time of hip fracture results in increased time to surgery, longer hospitalization and association with higher numbers of comorbidities among patients. The mean time to surgery regarding the anticoagulated patients was 2.57 days, versus 1.63 days for the non-anticoagulated group. Also, the multiple comorbidities play a significant role in the outcome since it requires more time to evaluate and prepare the patients for surgery. *Castelli* et al. observed an increase in LOS up to seven days for patients suffering from comorbidities at the time of the fracture (3). Comorbidities can also lead to an increase of surgical complications resulting in an increased hospital stay.

Whether anticoagulated hip fracture patients have poorer surgery outcomes is debatable. According to our results, it does not appear to be significantly worse, presumably, due to similar ages between the two cohorts or since concomitant diseases are affecting them both equally.

Hossain et al. and *Collinge* et al. showed no considerable elevation regarding the risk in hemorrhaging, bleeding complications and/or mortality in consideration of patients prescribed clopidogrel, aspirin or warfarin and undergoing early hip fracture surgery (5, 8). A possible explanation in support of the conflicting results implies each hospital uses different protocols, especially between countries, due to the lack of standardized international guidelines. Using different perioperative treatment protocols, including reversal agents and other hospital quality measures likely play a role. The method of surgical care of hip fractures may vary between countries and can also impact the results.

The necessity of delayed surgery once the patient is prescribed anticoagulants is also a source of controversy. A study by *Caruso* et al., in 2019 found patients prescribed

warfarin experienced increased surgical delay and decreased survival when compared to patients not prescribed anticoagulants (2). *Daugaard* et al. found patients on antiplatelets had an increased need of blood transfusion and mortality. Additionally, DOACs were only associated with a higher risk of blood transfusion (6). *Lawrence* et al. in 2016 highlighted warfarin as a "red flag" among patients who suffered a femoral neck fracture and found warfarin use to be associated with increased time to surgery, LOS and decreased survival (10). However, *Leer Salvesen* et al. in 2020 found no increased surgical delay, LOS nor bleeding complications in a group of 314 hip fracture patients on DOACs when comparing them to non-users (11).

Most of the proximal femoral fracture patients are elderly with comorbidities which require chronic anticoagulant medication. Therefore, it may be advisable to wait on surgery until the INR value is less than 1.5 reducing the risk of perioperative bleeding regarding these patients. It is also suggested in the use of vitamin K antagonists and other reversal agents, we can reach INR<1.5 faster and minimize unnecessary delays. A case-control study from *Mattison* et al. reported it is safe to use vitamin K and four-factor prothrombin complex concentrates on achieving INR values below 1.5 at a faster rate, when they analyzed 198 extracapsular PFF patients (15). Contradictory to this, *Caruso* et al. found even with the use of Vitamin K and a four-factor prothrombin complex, anticoagulant use leads to surgical delay (2).

In an article published in 2023 by *Levack* et al., 55 years or older proximal femoral fractured patients were evaluated, of which, 210 patients were undergoing warfarin therapy and 420 patients served as the matched control cohorts. The study revealed those patients treated with warfarin increasingly experienced delayed surgery and a greater number of post-operative complications when compared to matched controls without warfarin therapy (12).

A study by *Jørgensen* et al. studied the association between clopidogrel use and fracture risk. They found patients on recommended clopidogrel dosages had an increased risk of fractures, as well as osteoporotic fractures. It is still not known how clopidogrel affects bone metabolism. It is suggested the inhibiting effect of the platelets affects certain pathways in the osteoblasts and both osteoblasts and osteoclasts express P2Y12 receptors, potentially affecting bone remodeling (9).

A retrospective analysis representing 531 isolated hip fracture/PFF patients above 60 years-old was performed by *Lott* et al., from October 2014 through September 2016. It involved a comparison of the hospital quality outcomes between an anticoagulated group with either of the following: clopidogrel, warfarin, factor Xa inhibitors including rivaroxaban and apixaban, dabigatran and aspirin and a non-anticoagulated group. Initially, their results showed an increase in the mean LOS and time to surgery for the anticoagulated patients. After controlling for age, Charlson comorbidity index and the type of anesthesia used, they concluded anticoagulation alone is not independently responsible for exposing patients to increased risk, since the results were not significant (14).

No significant differences were found in our study regarding the mortality. The 1-year mortality showed a difference between the anticoagulated and the control group; however it was not statistically significant.

Most guidelines regarding hip fractures recently recommend surgery is performed within 48 hours from the time of the fracture. The Norwegian national quality indicator recommends surgery ideally within 48 hours from admission (19). This has been proven to be crucial in reducing postoperative complications and mortality. Surgical delay and comorbidities appear to be the main factors contributing to hip fracture complications among patients prescribed anticoagulants. A stricter management of comorbidities is important to diminish the postoperative complications and mortality. This can include measures such as more frequent screening for the different comorbidities as well as greater focus on reducing modifiable risk factors such as high blood pressure, elevated low-density lipoprotein cholesterol and osteoporosis. Additionally, more research regarding the antidotes of the various anticoagulants is essential.

Limitations of the study are numerous. Data were collected during the COVID restrictions, which may have influenced surgery delay data. The sample may be regarded heterogeneous since it involves fractures which required different types of surgeries. However, we feel the cohort is sufficiently large enough to minimize this bias. Mortality data were collected only from the hospitals in Pécs and the outcomes based on those data must be observed with discretionary caution. Our study only divides the anticoagulated cohort into "platelet aggregation inhibitors" and "other anticoagulants in addition to platelet aggregation inhibitors", hence, there is no sub-analysis performed for each anticoagulant, representing another limitation.

We believe further studies are needed to be able to establish an internationally accepted guideline regarding the management of patient prescribed anticoagulant therapy at the time of hip fracture.

CONCLUSION

Hip fracture patients are considered a vulnerable population with high morbidity and mortality rates. With the increase of the geriatric population and the comorbidities, the number of hip fractures is also increasing. More individuals require chronic anticoagulant therapy, which further causes challenges in treating an acute hip fracture.

Our study found there is delayed surgery, increased LOS and an increase in comorbidities in patients prescribed anticoagulants when suffering from a hip fracture compared to non-users at our department. However, the anticoagulated patients did not appear to be at substantially increased risk for perioperative bleeding. There were no significant differences in the 30-day mortality and 1-year mortality between the two cohorts.

We found published literature represents conflicting results. This highlights the importance of more accurate and understandable guidelines regarding perioperative procedures and the consequences for anticoagulated hip trauma patients.

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