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Early surgery is feasible in patients with hip fractures who are on clopidogrel therapy

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Objective: Timing of surgery in hip fracture patients using antiplatelet agents is a controversial issue. Clopidogrel is an antiplatelet drug widely used in the treatment of many diseases. In this study, we aimed to investigate the outcomes of early surgery in hip fracture patients using clopidogrel.

Methods: Elderly patients with femoral neck fractures who underwent open surgery between 2009 and 2014 were evaluated. Two hundred and eleven patients were included in the study. Patients were separated into 3 groups. Group 1 was constituted of patients using clopidogrel who had been operated on within 48 h after admission (n=74), Group 2 was constituted of patients using clopidogrel who had been operated on after the fifth day of admission (n=55), and Group 3 was constituted of patients not using clopidogrel who had been operated on within 48 h after admission (n=83). Length of hospital stay, amount of blood transfusion, rate of complication, and mortality rate were assessed for comparison of groups.

Results: Age, sex, preoperative hemoglobin values, and ASA scores were not different between the groups. Amount of blood transfusions was higher in Group 1 ($p=0.023$). Duration of hospital stay was longer in Group 2 ($p<0.01$), as was complication rate (25.4%) ($p<0.01$). Mortality within 30 days and within the first 3 months post-surgery was significantly higher in Group 2 ($p=0.031$, $p<0.01$; respectively).

Conclusion: Surgery should not be postponed in hip fracture patients using clopidogrel.

Keywords: Clopidogrel; early surgery; hip fracture.

The incidence of hip fractures is increasing throughout the world due to the advancing age of populations and is expected to exceed 6 million cases per year by 2050.[1] Hip fractures represent an important cause of morbidity and mortality in the elderly, with reported mortality rates of 7.95% and 5.75% among elderly men and women, respectively, in the first 3 months following the fracture.[2] The timing of surgery in these patients is known to be closely associated with both short- and long-term morbidity and mortality.[3] Generally, a delay of no longer than 72 h after admission is recommended for surgical intervention in hip fractures, even in patients with concomitant conditions. Accordingly, surgery performed within the first 24–48 h after admission has been shown

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to shorten the duration of hospital stay and decrease mortality rates.[3]

A significant proportion of patients with hip fractures receive clopidogrel treatment, due to co-existing cerebrovascular or cardiac conditions. Via blocking the P2Y12 receptor, clopidogrel inhibits platelet activation and aggregation throughout the lifespan of platelets (i.e., 5–7 days). Early discontinuation of clopidogrel is directly associated with an increased number of complications such as stent thrombosis, myocardial infarction, and even death.[4] Despite evidence showing increased risk of bleeding with clopidogrel in patients undergoing cardiothoracic surgery,[5] no significant increase could be detected in patients undergoing peripheral arterial or carotid surgery.[6] Clopidogrel is often discontinued 5–10 days prior to hip fracture surgery, due to both a potential increase in the risk of hematoma due to regional anesthesia and due to perioperative risk of bleeding. In patients requiring earlier surgical intervention, blood and blood product transfusions are commonly administered on the basis of a potential increase in the risk of bleeding.[7] However, there is no consensus in the literature regarding the timing and risk of bleeding in hip fracture patients receiving clopidogrel treatment,[8] and there is scarce data on this topic in the literature.

In this study, we compared 2 strategies in patients undergoing surgical intervention for hip fractures, i.e., discontinuation of clopidogrel treatment and delay of surgery until the termination of the action of clopidogrel on platelets or performing the surgery within the first 48 h after admission while the patient is still receiving clopidogrel. Additionally, a control group consisting of clopidogrel-free patients who received intervention within the first 48 h after admission was used to compare the safety of early surgical intervention.

Patients and methods

Patients undergoing open surgery for femoral neck fractures due to advanced age between 2009 and 2014 were retrospectively evaluated. Patients on clopidogrel treatment at the time of admission/fracture were compared with those individuals who were not on clopidogrel or any other anti-aggregating agent. Patients were assessed by anesthesiology and cardiology specialists, and clopidogrel was discontinued in all patients after admission. Clopidogrel was reinstituted within a maximum duration of 48 h after admission based on bleeding status and recommendations by the cardiologists. Perioperatively, all patients were given low molecular weight heparin at a prophylactic dose (40 mg/day), which was continued until the patients were mobilized. Patients receiving clopidogrel were categorized into 2 groups: those surgically treated within the first 48 h after admission and those who underwent surgery after Day 5 after admission. The control group consisted of clopidogrel-free patients who were operated on within the first 48 h after admission (Table 1). Clopidogrel treatment was re-initiated 2 days after surgery. Exclusion criteria included use of anticoagulants or antiplatelet agents in conjunction with clopidogrel, presence of blood dyscrasia or hemoglobinopathy, pathological fractures, discontinuation of clopidogrel before presentation to the study site, and use of blood transfusion prior to surgery.

After written informed consent was obtained from the patients, an adequate amount of platelet and erythrocyte suspensions were prepared. After optimal presurgical preparation, a Watson-Jones incision was made while the patient was in a supine position, with the greater trochanter located on the side of the surgical table. The muscles were separated using appropriate dissection techniques, the joint capsule was longitudinally opened along the femoral neck, and the surgical intervention was performed. All patients received antibiotic prophylaxis with first-generation cephalosporins. A total of 151 patients received cementless bipolar partial prosthesis, while 60 had cemented bipolar partial prosthesis. Aspiration drainage tubes were removed on postoperative Day 1, and exercises to strengthen the hip and knee muscles were initiated. All patients were encouraged to ambulate within the first 24 h as soon as they could tolerate the pain.

Patients were compared in terms of age, gender, time of surgery, volume of postoperative blood transfusions, complications, ASA score, duration of hospital stay, and mortality.

Statistical analyses were performed using Kruskal-Wallis analysis of variance, Pearson's chi-square test, and Mann-Whitney U test. SPSS 16.0 statistical software for Windows was used for the analyses. A p value of less than 0.05 was considered statistically significant.

Results

A total of 211 patients were included in the study. Group 1 consisted of 24 patients with clopidogrel use who were operated on within the first 48 h after admission, Group 2 consisted of those patients who were operated on after the fifth day after admission, while Group 3 consisted of 82 patients with no use of antiplatelet agents who did not meet the exclusion criteria.

No significant differences between the groups were found in terms of age, gender, preoperative hemoglobin

Table 1. Distribution of study participants.

	Clopidogrel Operated <48 h (SD)	Clopidogrel Operated ≥5 days (SD)	Controls Operated <48 h (SD)	p
Age	76.53 (7.62)	75.53 (7.03)	79.81 (7.47)	0.24
Preop duration (days)	1.79	5.82*	1.68	0.02
Preop HGB	11.89 (1.161)	12.18 (1.26)	12.48 (1.36)	0.64
ASA score	3.30 (0.656)	3.45 (0.722)	3.18 (0.645)	0.38
Hip fractures (n)	74	55	82	

*The group responsible for the statistically significant difference.

levels, and ASA scores (Table 1). Although patients in Group 1 were found to have a longer duration of surgery, the difference did not reach statistical significance (Table 2). Similarly, although lower hip scores were noted in patients in Group 2—i.e., delayed surgery group—the difference was not significant. Length of hospital stay was significantly longer in Group 2 than in other groups ($p<0.01$). Significantly higher need for blood transfusions was found among patients in Group 1 who underwent early surgery following discontinuation of clopidogrel ($p=0.023$). In Group 2, those who underwent delayed surgery after discontinuation of clopidogrel, a significantly higher 30-day and 3-month mortality rate was found ($p=0.031$ and $p<0.01$, respectively). With regard to anesthesia techniques, a more frequent use of general and peripheral (sciatic-femoral nerve) anesthesia was found in Group 1 and Group 2, while spinal anesthesia was more frequent in Group 3 (Table 2). Complications occurred at a significantly higher frequency (25.4%) in Group 2 ($p<0.01$) than in other groups, with 4 of these complications being serious complications requiring follow-up in the intensive care unit. One patient died on postoperative Day 2. One patient in Group 1 also experienced complications requiring intensive care,

Table 2. Results in study groups.

	Clopidogrel Operated <48 h (SD)	Clopidogrel Operated ≥5 days (SD)	Controls Operated <48 h (SD)	p
Male/Female (n)	33/41	26/29	37/45	0.084
Blood transfusion (u)	3.16 (1.253)*	2.40 (1.30)	2.25 (1.224)	0.023
Duration of surgery (min)	60.26 (7.831)	59.20 (7.896)	58.08 (8.277)	0.213
Length of hospital stay (days)	8.13 (3.457)	14.53 (4.327)*	7.53 (4.411)	<0.01
Haris hip fracture	81.80 (13.165)	78.27 (17.228)	83.27 (7.631)	0.059
Mortality, n (%)				
30-days	2 (2.7)	4 (7.2)*	1 (1.2)	0.031
3-months	4 (5.4)	7 (12.7)*	3 (3.6)	<0.01
Anesthesia, n (%)				
General	33 (44.6)	22 (40.0)	17 (20.7)	
Spinal	0 (0.0)	14 (25.4)	36 (43.9)	
Peripheral blockade	41 (55.4)	19 (34.6)	29 (35.3)	
Complications (n)				
Myocardial ischemia	1 (died on day 3)	2	0	
CVA	0	1 (died on day 2)	0	
Pulmonary embolism	0	0	1	
Atrial fibrillation	0	1	0	
LRTI	0	1	1	
Wound site infection	3	1	0	
Non-infectious discharge	3	4	4	
Decubitus ulcers	0	3	0	
Urinary tract inf.	1	1	2	
Total, n (%)	8 (10.8)	14 (25.4)*	8 (9.7)	<0.01

*The group responsible for the statistically significant difference.

and this patient died on postoperative Day 3. Only three patients in Group 2 had decubitus ulcers, which were successfully managed using appropriate wound care methods. Three patients in Group 1 had superficial infections, which were treated with antibiotics and wound care. In 1 patient in Group 2, a deep infection (methicillin-resistant *S. aureus*) occurred, which was managed with a 2-stage revision surgery. Three patients in Group 1, 4 in Group 2, and 4 in Group 3 had non-infectious discharge at the site of surgical wound. After discontinuation of low molecular weight heparin, discharge disappeared in these cases. Lower respiratory tract infection occurred in 1 patient each in Group 2 and Group 3 who were treated at the chest disease unit. One patient each in Group 1 and Group 2 and 2 patients in Group 3 developed urinary tract infections (due to *E. coli*), who were treated with appropriate antibiotics (Table 2).

Discussion

Timing of surgery in patients sustaining a hip fracture while receiving antiplatelet treatment has been a subject of controversy. As compared to those who advocate performing a surgical intervention while platelets are still under the effect of these agents, others recommend a delay period of at least 5 days to allow for the recovery of platelet aggregation functions before surgery.[7] In the absence of evidence-based guidelines for hip replacement surgery in such cases, outcomes in patients undergoing cardiac surgery while receiving clopidogrel treatment are generally used as a substitute marker for decision-making processes. Of the patients undergoing coronary stent implantation during clopidogrel use, 5% have been found to require non-cardiac surgery.[9] Although an increased risk of bleeding was shown in patients on clopidogrel treatment,[10] it has also been found that premature discontinuation of clopidogrel in this group of patients was also associated with increased risk of cardiovascular complications perioperatively.[9] In guidelines issued by the American Cardiology Society, American Thoracic Society, and European Cardiology Society, an emphasis is placed on the duration and dose of clopidogrel treatment.[11] In the guidelines of the European Cardiology Society, discontinuation of clopidogrel 5 days prior to elective surgery is recommended to reduce the risk of bleeding. In addition, the European Cardiology Society recommends the delay of elective surgery for 6 weeks to 12 months depending on the type of the stent in order to prevent stent thrombosis in patients who underwent stent implantation.[12]

In this study, no serious complications due to clopidogrel use were observed in patients undergoing early surgery for hip fractures. Conversely, an increased duration of hospital stay as well as increased 30-day and 90-day mortality rates were detected in patients for whom surgery was delayed to allow for the disappearance of the effect of clopidogrel on platelets. There was an increased need for blood transfusions among patients for whom early surgery was performed after discontinuation of clopidogrel. Again, there was a higher incidence of complications among patients who underwent delayed surgery after discontinuation of clopidogrel.

Timing of surgery is of utmost importance in terms of postoperative outcome. Closely related to the timing of surgery, several studies have reported an increased incidence of medical complications such as deep vein thrombosis, infections, and skin ulcers due to prolonged bed rest, as well as delayed functional recovery due to delayed mobilization.[13] In patients who are on clopidogrel treatment prior to surgery, a decision to delay surgical intervention to allow for normalization of platelet functions is associated with an increased risk of bleeding at the site of the fracture, as well as the risks associated with delayed surgery. In a meta-analysis of 5 prospective observational studies by Simunovic et al., lower mortality was found in those undergoing early surgery (within 72 h after admission) than in those undergoing delayed surgery.[14] In another meta-analysis involving 16 observational studies, a delay of 48 h or more for surgical repair was associated with increased 30-day and 1-year mortality. Similarly, early surgery allows reduction in pain and length of hospital stay.[15] In our study, patients in Group 2 had longer duration of hospital stay, lower hip scores, higher mortality rates, and were more likely to have complications such as decubitus ulcers.

Our results show that early surgery in patients who were on clopidogrel therapy prior to surgery is not associated with serious hemorrhagic complications, consistent with the results of a retrospective cohort-analysis involving 1,118 patients reported by Collinge et al.[16]

However, in the presence of concomitant conditions such as decompensated heart failure, active infection, serious pulmonary disease, or acute coronary syndrome, the timing of surgery may be adjusted, as to allow for appropriate laboratory work-up and emergency care of such patients.

Furthermore, discontinuation of antiplatelet agents is known to result in a rebound increase in coagulation.[3] Trauma, surgical intervention, and immobility may also lead to increased coagulation in these patients. This temporary hypercoagulability peaks at 3–5 postoperative days; thus, the risk of cardiac mortality after discontinuation of clopidogrel is highest between post-

operative days 4 and 8.[17] Premature discontinuation of clopidogrel, particularly in those individuals who require continuous antiplatelet treatment, may lead to serious complications such as stent thrombosis that may ultimately lead to mortality. This may explain the increased mortality and complication rate in Group 2 in our study.

An increased risk of bleeding was found when platelets are still under the effect of clopidogrel.[2,14,18] However, most of these data are derived from cardiac interventions performed under heparin treatment. In this study, an increased need for transfusions was found among patients who underwent early surgery after discontinuation of clopidogrel, although this was not associated with increased morbidity and mortality. Lavelle et al. previously demonstrated the feasibility of hip fracture surgery performed without delay, but there was an increased need for transfusions.[19] Additionally, Nydick et al. showed that early hip fracture surgery can be accomplished without a need for increased transfusions in patients on clodipogrel therapy.[20] Collinge et al. found no associations between clopidogrel use and increased bleeding complications and increased need for transfusions in patients under clopidogrel therapy.[16] Among the patients in Group 1 in our study, there was an increase in the need for transfusions and the rate of superficial infections, which may be related to the duration of time of bleeding control.

Patients with respiratory or cardiovascular conditions generally receive spinal anesthesia. Concomitant clopidogrel therapy may lead to serious complications such as epidural hematoma in such patients. Most anesthesiologists and surgeons recommend delaying the surgery in such clinical situations. Nonetheless, since delayed surgery is associated with increased morbidity and mortality, particularly in elderly patients, platelet transfusions and an assessment of the platelet functions are recommended for safe central neural blockade in selected cases.[21] In our study, for patients undergoing early surgery during clopidogrel treatment, general anesthesia or peripheral nerve blockade (sciatic-femoral) was preferred. Spinal anesthesia that was performed in the other groups was not associated with complications. In these cases, an experienced team of anesthesiologists administered appropriate anesthesia techniques.

The retrospective nature of our study, relatively low number of patients on clopidogrel treatment (Group 1 and Group 2), and assessment of the bleeding complications based on the need for transfusions are among the potential limitations. Conversely, utilization of the same surgical technique in the study groups, as well as the categorization of patients in 2 groups based on the timing of surgery after discontinuation of clopidogrel represent the strengths of our study. Our results support the literature data which suggest that preoperative use of clopidogrel is not associated with adverse outcomes in high-risk patients undergoing hip fracture surgery.

These results show that in patients with hip fractures, surgical intervention should not be delayed to allow for the recovery of platelet functions, and an early surgery should be performed. Despite an increase in the need for blood transfusions, as reflected by a comparison between risk of bleeding and risks associated with delayed surgery, early surgery continues to be associated with low rates of morbidity and mortality.

Conflics of Interest: No conflicts declared.

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