

## RESEARCH ARTICLE

# Evaluation of Clopidogrel Safety in Geriatric Patients with Hip Fracture: A Retrospective Study

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**Objective:** To evaluate the risk of bleeding in elderly patients undergoing early hip fracture surgery with/without clopidogrel administration.

**Methods:** This was a retrospective study, and patients over 65 years with fresh hip fracture were enrolled. For the patients taking clopidogrel, early surgical treatment was performed without 5–7 days waiting time. The patients were divided into groups according to their fracture type and the surgical method. Within each fracture/surgery group, the patients were further divided into subgroups according to whether they had clopidogrel administration. The patients' age, gender, American Society of Anesthesiologists (ASA) score, hemoglobin level at admission, and the time from admission to surgery were compared in the different groups. The bleeding outcomes, such as intraoperative blood loss and blood transfusion status, as well as secondary outcomes, such as operation duration and length of hospital stay, were also compared in these groups.

**Results:** There were no statistically significant differences in patients' baseline characteristics and outcomes, including intraoperative blood loss, blood transfusion rate, operation duration and length of hospital stay, between the clopidogrel-administrated patients and the control patients. However, the percentage of patients taking general anesthesia was significantly higher in clopidogrel group than that in control group ( $P = 0.01$ ). Similar intraoperative blood loss was found in the subgroups of hemi-hip replacement, internal fixation for intertrochanteric fracture of the femur (fracture type A1-2, short pin), and internal fixation of femoral neck fracture with cannulated nails. For the internal fixation of femoral neck fracture with cannulated nails, the blood loss is significantly less in both subgroups than that with other two surgical methods. Moreover, the total hip arthroplasty, with the highest bleeding risk among all the surgical methods involved, was rarely chosen to treat geriatric hip fracture in this study.

**Conclusion:** This study indicated that compared with patients without clopidogrel administration, elderly patients with hip fractures who receive clopidogrel as long-term anti-platelet therapy are relatively safe for surgery in less than 5–7 days after discontinuation of clopidogrel.

**Key words:** Blood transfusion; Clopidogrel; Geriatric; Hip fracture; Intraoperative blood loss

## Introduction

The incidence of hip fractures in elderly people over 65 years is increasing with the aging population. According to statistics from the World Health Organization, there are approximately 6 mn newly diagnosed hip fracture

cases each year<sup>1</sup>. Sadly, hip fractures are still a major source of morbidity and mortality in the elderly population. Mortality rates of hip fracture cases within 3 and 12 months are estimated to be 13% and 24%, respectively<sup>2</sup>. Therefore, surgical treatment in time is crucial for the prognosis of hip

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fractures in elderly patients due to its frequent consequences, such as deep vein thrombosis, pneumonia, pressure ulcers, and malnutrition. Moreover, multiple studies have demonstrated that delaying surgery may increase the incidence rate of complications and short- or long-term mortality<sup>3-10</sup>.

Clopidogrel is an irreversible inhibitor of platelet aggregation which can block adenosine diphosphate (ADP) from binding to the platelet receptor (P2Y<sub>12</sub>) and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex<sup>11,12</sup>. Clopidogrel is commonly used in patients with coronary heart disease, cerebrovascular disease, and peripheral artery disease. Since the half-life of clopidogrel is 8 h and the average life span of platelets is 7–10 days, the administration of clopidogrel should be stopped for 5–7 days preoperatively as to reduce the risk of bleeding caused by clopidogrel<sup>13-15</sup>. However, surgical treatment of elderly patients with hip fractures who take clopidogrel therapy is a dilemma: if clopidogrel administration is stopped for 5–7 days, the incidence of surgical complications, short-/long-term mortality may rise; while if early surgical treatment for hip fractures is performed, the risk of bleeding could be increased. Therefore, currently there is no consensus on the appropriate timing of surgical treatment for elderly patients with hip fractures who take clopidogrel therapy.

Some studies have shown that the risk of bleeding in such elderly patients will not increase in early surgery<sup>16-19</sup>. Chechik *et al.* found that elderly patients (an average age of 82 years) receiving long-term treatment with clopidogrel who underwent early surgical intervention for hip fracture appeared to be safe in terms of bleed complication<sup>18</sup>. However, some other studies suggested that the increased risk of bleeding should be taken into consideration in the selection of operative time<sup>20,21</sup>. In addition, Collyer *et al.* reported that the length of clopidogrel therapy perioperatively was in association with the incidence rate of acute coronary syndrome in the patients with a median age of 84 years, and they suggested that a more considered, individualized, evidenced-based approach is needed among this population<sup>22</sup>.

Based on the previous controversial reports, the purpose of this study was to: (i) evaluate the risk of bleeding during the surgery in elderly patients with hip fractures who take clopidogrel as long-term anti-platelet therapy, when the surgical treatment of the hip fracture starts earlier rather than discontinue the drug and wait for 5–7 days before the surgery; (ii) compare the difference of blood loss volume during seven different surgical methods for treatment of patients with hip fractures; (iii) compare other primary and secondary outcomes, including the amount of intraoperative blood loss, blood transfusion rate, operation duration, and the length of hospital stay between the patients receiving clopidogrel before the injury and the patients without medication history of clopidogrel. This study may potentially provide clinical guidance for surgeons to efficiently treat patients with hip fractures who undergo clopidogrel therapy.

## Methods

### *Ethical Approval and Patients Involved*

This research was approved by the Ethics Committee of Beijing Jishuitan Hospital. In this study, all patients over 65 years old with fresh hip fractures admitted to the Department of Trauma were enrolled. These enrolled patients were treated with clopidogrel alone or dual anti-platelet therapy with clopidogrel and aspirin due to coronary artery stent implantation, previous cardiovascular or cerebrovascular events, or history of peripheral vascular disease. All patients received comprehensive clinical assessments preoperatively. Clopidogrel administration should be stopped before surgery and aspirin could be continuously taken as usual in all groups. All patients were given low molecular weight heparin at a prophylactic dose perioperatively. Patients were encouraged to ambulate within the first 24 h as soon as they could tolerate the pain.

### *Patient Grouping Design*

Since the type of hip fracture and the surgical method have a great impact on the intraoperative blood loss, in this study, the patients were divided into different groups according to the type of fracture and the surgical method. The surgical methods for senior patients with hip fractures in our hospital include: (i) total hip arthroplasty; (ii) hemi-hip replacement for femoral neck fracture; (iii) hemi-hip replacement for intertrochanteric fracture of the femur; (iv) internal fixation of femoral neck fracture with cannulated nails; (v) internal fixation for intertrochanteric fractures of the femur (fracture type A1-2, short pin); (vi) internal fixation for intertrochanteric fractures of the femur (fracture type A1-2, long pin); (vii) internal fixation of intertrochanteric/subtrochanteric fracture of the femur (fracture type A3). In each fracture/surgery group, the patients were further divided into two subgroups according to the clopidogrel administration, including the clopidogrel group (patients taking clopidogrel with/without using aspirin) and the control group (patients not taking clopidogrel). In each fracture/surgery group, we compared the bleeding outcomes and the secondary outcomes, such as operation duration and length of hospital stay, between the clopidogrel subgroup and the control subgroup.

### *Patient Selection*

All patients were over 65 years old and were treated for fresh hip fracture at the Department of Trauma in Beijing Jishuitan Hospital from November 2016 to April 2017.

Inclusion criteria were as follows: (i) patients were >65 years old; (ii) patients were diagnosed with hip fractures by clinical examinations and radiological tests; (iii) hospital stay >48 h; (iv) patients needing surgical fracture reduction; (v) patients without serious medical problems that make them intolerant to surgery, such as cardiac or renal insufficiency, allergy, ischemic stroke, and bleeding events; (vi) patients who provided the informed consent form; (vii) availability of preoperative and postoperative clinical testing results.

The exclusion criteria were as follows: (i) patients were not admitted to hospital within 2 days after the injury, or no operation was performed on patients within 4 days after admission; (ii) patients used any other anticoagulant drugs, such as warfarin; (iii) patients with bilateral hip fracture; (iv) patients were allergic to the drugs commonly used during the routine treatment in our hospital; (v) patients with mental disorders, alcohol dependence, or a history of drug abuse; (vi) patients with abnormal function of liver and kidney and other important organs. Following these criteria, 282 patients were eventually included for this study.

### Data Collection and Outcomes Measurement

We recorded patients' age, gender, American Society of Anesthesiologists (ASA) score, the hemoglobin level, as well as platelet (PLT) level at admission and the time from admission to surgery by the clinical routine tests as baseline data. Intraoperative blood loss and blood transfusion status were recorded as the main outcomes. At the same time, the operation duration and the length of hospital stay were recorded as secondary outcomes.

#### ASA Score

ASA scores are used to characterize patient operative risk prior to the surgical procedure with a scale from 1–5: 1 is for “a normal healthy patient”; 2 is for “a patient with mild systemic disease”; 3 is for “a patient with severe systemic disease”; 4 is for “a patient with severe systemic disease that is a consistent threat to life”, and 5 is for “a moribund patient who is not expected to survive without the operation.” In this study, the anesthesiologists assessed the ASA scores of every patient with hip fracture before the surgery according to the ASA classification system. The ASA scores could be associated with the blood loss during the surgery.

#### Hemoglobin Level

The hemoglobin level of patients with hip fracture was measured when the patients were admitted in our hospital and detected by XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). This parameter could reflect the blood loss of patients after the injury to some extent.

#### Platelet Level

The platelet level of patients with hip fracture was measured when the patients were admitted in our hospital and detected by XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). This study was conducted in the patients taking clopidogrel, and the drug was an anti-platelet agent. The platelet level was measured as to evaluate the effects of clopidogrel on the bleeding conditions.

#### Time From Admission to Surgery

Time from admission to surgery in every patient with hip fracture was obtained from the medical records of the patient at admission and at the time of the operation, and hours as the measuring unit. This parameter was measured as to

evaluate the curing efficiency for elderly patients with hip fracture, including the bleeding status.

#### Intraoperative Blood Loss

Intraoperative blood loss from patients was calculated by combining the blood volume from a surgical aspirator and the blood left on the sterile gauze during the surgery, which was estimated by the experienced anesthesiologists.

#### Blood Transfusion Status

Blood transfusion status was recorded based on whether the patients received the blood transfusion or not during the surgery. This parameter could directly reflect the bleeding status during the surgery.

#### Operation Duration

The operation duration was recorded from the anesthesia note of each patient and was measured in minutes. This parameter could partly reflect the bleeding status during the surgery. Generally, the more blood that lost, the longer the operation would be to stop the bleeding.

#### Length of Hospital Stay

The length of hospital stay was obtained from the medical records of each patient and was measured in days. This parameter could partly reflect the bleeding status during the surgery, as the patients may need longer hospital stay when they have larger intraoperative blood loss.

#### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Chicago, IL) was used for data processing and analysis in this study. Categorical data, including gender, ASA score > III, general anesthesia, and blood transfusion rate, were summarized as frequency (percentage), and continuous data,

**TABLE 1 Fracture/surgical type and clopidogrel medication status of the enrolled patients**

Type of fracture/surgery	Clopidogrel	Control
Total hip arthroplasty	0	14
Hemi-hip replacement for femoral neck fracture	11	94
Hemi-hip replacement for intertrochanteric fracture of the femur	0	2
Internal fixation of femoral neck fracture with cannulated nails	2	29
Internal fixation for intertrochanteric fracture of the femur (fracture type A1-2, short pin)	7	99
Internal fixation for intertrochanteric fracture of the femur (fracture type A1-2, long pin)	0	7
Internal fixation of intertrochanteric/subtrochanteric fracture of the femur (fracture type A3)	0	17
Total	20	262

TABLE 2 Baseline characteristics

Characteristic	Patient groups		P value	Statistical value
	Clopidogrel (n = 20)	Control (n = 222)		
<b>Age (year)</b>	79.5 (4.0)	80.0 (10.0)	0.23	–
Hemi-hip replacement for femoral neck fracture	76.8 (5.3)	77.8 (6.6)	0.71	–
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin)	80.4 (5.8)	82.2 (6.2)	0.42	–
Internal fixation of femoral neck fracture with cannulated nails	73.0 (11.3)	76.6 (9.9)	0.62	–
<b>Female (cases)</b>	14 (70.0%)	168 (75.7%)	0.57	0.317
Hemi-hip replacement for femoral neck fracture	8 (72.7%)	66 (70.2%)	0.86	0.030
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin)	5 (71.4%)	77 (77.8%)	0.70	0.150
Internal fixation of femoral neck fracture with cannulated nails	1 (50.0%)	25 (86.2%)	0.72	0.124
<b>ASA score &gt; III (cases)</b>	12 (60.0%)	139 (62.6%)	0.82	0.053
Hemi-hip replacement for femoral neck fracture	6 (54.5%)	55 (58.5%)	0.80	0.064
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin)	4 (57.1%)	67 (67.7%)	0.88	0.025
Internal fixation of femoral neck fracture with cannulated nails	2 (100.0%)	17 (58.6%)	0.68	0.169
<b>General Anesthesia (cases)</b>	9 (45.0%)	41 (18.5%)	<b>0.01</b>	6.343
Hemi-hip replacement for femoral neck fracture	4 (36.4%)	9 (9.6%)	<b>0.04</b>	4.279
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin) (A1-2, short pin)	4 (57.1%)	31 (31.3%)	0.32	0.977
Internal fixation of femoral neck fracture with cannulated nails	1 (50.0%)	1 (3.4%)	0.27	1.219
<b>Hemoglobin value at admission (g/L)</b>	122.5 (15.0)	121.1 (16.1)	0.72	–0.365
Hemi-hip replacement for femoral neck fracture	122.2 (16.9)	126.8 (13.9)	0.32	1.013
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin)	122.6 (13.3)	114.6 (17.2)	0.23	–1.199
Internal fixation of femoral neck fracture with cannulated nails	124.0 (18.4)	125.1 (10.7)	0.90	0.132
<b>Time from admission to surgery (h)</b>	42.5 (12.0)	43.0 (33.0)	0.87	–
Hemi-hip replacement for femoral neck fracture	38.2 (11.4)	44.3 (20.0)	0.66	–
Internal fixation for intertrochanteric fracture of the femur (A1-2, short pin)	50.9 (25.3)	44.5 (20.2)	0.69	–
Internal fixation of femoral neck fracture with cannulated nails	43.5 (0.7)	44.9 (18.1)	0.84	–

The “Age” and “Time from admission to surgery (h)” variables were analyzed using independent-samples Mann–Whitney U test; the “Hemoglobin value at admission (g/L)” variable was analyzed using independent-samples Student’s t-test; the rest of variables were used the  $\chi^2$  or Fisher’s exact test. Data are presented as n (%) or mean (SD).  $P < 0.05$  was considered statistically significant in bold. ASA, American Society of Anesthesiologists.

including age, time from admission to surgery, hemoglobin value at admission, operation duration, and length of hospital stay, were summarized as mean (SD) or mean  $\pm$  SD. All statistical tests and corresponding  $P$  values were two-sided, and  $P < 0.05$  was considered statistically significant. All categorical variables were analyzed using the  $\chi^2$  or Fisher’s exact test, while the independent-samples Student’s t-test/Mann–Whitney U test was used for continuous variables when comparing the two groups in univariate analysis.

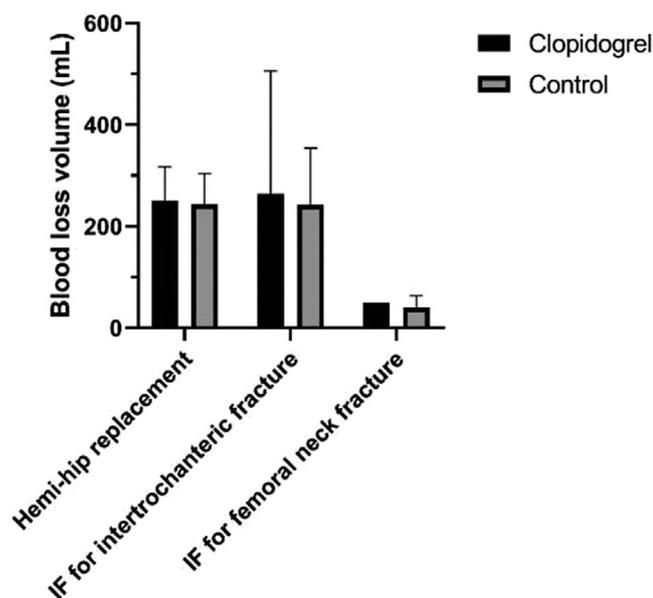
## Results

### General Results

#### Patients with Clopidogrel Administration

A total of 358 patients over 65 years old with newly developed hip fractures were admitted to our hospital.

All patients were of Han nationality. Among them, 20 patients were treated with clopidogrel anti-platelet therapy before the injury, discontinued clopidogrel at admission, and were operated on as early as possible (hemi-hip replacement for femoral neck fracture was performed in 11 patients, internal fixation for intertrochanteric fracture of the femur [A1-2, short pin] were performed in seven patients, and internal fixation of femoral neck fracture with cannulated nails were performed in two patients). All patients were hospitalized within 2 days after the injury and underwent surgery within 4 days. Among them, five patients were treated with aspirin as well (dual antiplatelet therapy). Reasons for taking clopidogrel included coronary heart disease (eight cases), coronary artery stent implantation (five cases), cerebral infarction (three cases), carotid artery stents (one case), and other causes (three cases).



**Fig 1** Comparison of the volume of blood loss in the clopidogrel group and control group in elderly patients undergoing early hip fracture surgery with/without receiving clopidogrel. IF: internal fixation. The volume of blood loss was also compared between different surgical methods for the patients.

#### Patients without Clopidogrel Administration

There were 338 patients without clopidogrel administration history. Among them, 76 patients were excluded from this study due to administration of other anticoagulant drugs, unqualified timing of admission or surgery, or having other severe co-morbidities. The remaining 262 patients were eligible for the control group.

#### Patient Grouping by Surgical Methods

The fracture/surgical type and clopidogrel medication status of the enrolled patients were shown in Table 1. Interestingly, there were only three surgical methods in the clopidogrel group, including semi-hip replacement for femoral neck fracture, internal fixation for intertrochanteric fracture (A1-2, short pin), and internal fixation for femoral neck fracture

with cannulated nail. As the other four surgical methods were not performed on patients taking clopidogrel (Table 1), we only compared and discussed the three major surgical methods mentioned above between the clopidogrel group and control group in this study.

#### Baseline Characteristics

There were 242 patients who performed the three main surgical methods, including 20 cases in clopidogrel group and 222 cases in control group. The baseline characteristics of both clopidogrel and control subgroups was summarized in Table 2. For all the three main surgical methods, the mean ages of patients in the clopidogrel group and control group are  $79.5 \pm 4.0$  and  $80.0 \pm 10.0$  years old, respectively ( $P = 0.23$ ). There were 14 female patients (70%) in the clopidogrel group; while in the control group, 75.7% of the patients were female ( $P = 0.77$ ). Meanwhile, 60% of the patients in the clopidogrel group were graded ASA III or above, while in the control group, 62.6% of the patients were graded ASA III or above ( $P = 0.97$ ). The hemoglobin levels at admission were  $122.5 \pm 15.0$  g/L and  $121.1 \pm 16.1$  g/L in the clopidogrel group and the control group, respectively ( $P = 0.72$ ). The mean time from admission to surgery was  $42.5 \pm 12.0$  h in the clopidogrel group,  $43.0 \pm 33.0$  h in the control group ( $P = 0.87$ ). Collectively, there were no significant differences between clopidogrel group and control group according to patients' age, gender, ASA score, hemoglobin level at admission, time from admission to surgery. However, the percentage of patients taking general anesthesia in the clopidogrel group (45%) was significantly higher than that in the control group (18.5%) ( $P = 0.01$ ). Particularly, under hemi-hip replacement for femoral neck fracture method, the proportion of general anesthesia in clopidogrel subgroup (36.4%) was also significantly higher than that in the control subgroup (9.6%) ( $P = 0.04$ ).

#### Bleeding Outcomes

##### Intraoperative Blood Loss

The bleeding outcomes of 242 patients who performed the three main surgical methods are summarized in Fig. 1 and Table 3. In each fracture/surgery group, there was no

**TABLE 3** Blood transfusion rate in the clopidogrel group and control group

Blood transfusion rate (cases)	Patient groups		P value
	Clopidogrel	Control	
Hemi-hip replacement for femoral neck fractures	1 (9.1%)	21 (22.3%)	0.53
Internal fixation for intertrochanteric fractures of the femur (A1-2, short pin)	3 (42.9%)	65 (65.7%)	0.42
Internal fixation of femoral neck fracture with cannulated nails	0 (0.0%)	1 (3.4%)	1.00

Data are presented as n (%).

**TABLE 4 Secondary outcomes**

	Patient groups		P value
	Clopidogrel	Control	
Operation duration (h)			
Hemi-hip replacement for femoral neck fractures	74.5 (21.5)	75.2 (14.9)	0.49
Internal fixation for intertrochanteric fractures of the femur (A1-2, short pin)	56.1 (7.7)	62.9 (24.3)	0.68
Internal fixation of femoral neck fracture with cannulated nails	42.5 (24.8)	52.2 (17.6)	0.52
Length of hospital stay (days)			
Hemi-hip replacement for femoral neck fractures	4.45 (0.69)	5.06 (2.55)	0.49
Internal fixation for intertrochanteric fractures of the femur (A1-2, short pin)	4.86 (1.21)	4.79 (1.62)	0.72
Internal fixation of femoral neck fracture with cannulated nails	3.50 (0.71)	4.21 (1.08)	0.39

Data are presented as mean (SD).

statistically significant difference of intraoperative blood loss and transfusion rate between the clopidogrel and control subgroups. The intraoperative blood loss in patients during hemi-hip replacement for femoral neck fracture was  $250.0 \pm 67.1$  mL and  $243.1 \pm 60.7$  mL in clopidogrel and control subgroups, respectively ( $P = 0.73$ ). Similarly, intraoperative blood loss during internal fixation for intertrochanteric fracture of the femur (A1-2, short pin) was observed with no significant difference in the two subgroups ( $264.3 \pm 94.5$  mL for the clopidogrel subgroup and  $241.6 \pm 112.3$  mL for the control subgroup,  $P = 0.33$ ). For the internal fixation of femoral neck fracture with cannulated nails, considering the procedure was performed on patients, the intraoperative blood loss was significantly less,  $50.0 \pm 0.0$  mL for the clopidogrel subgroup and  $40.3 \pm 22.9$  mL for the control subgroup.

#### Blood Transfusion Rate

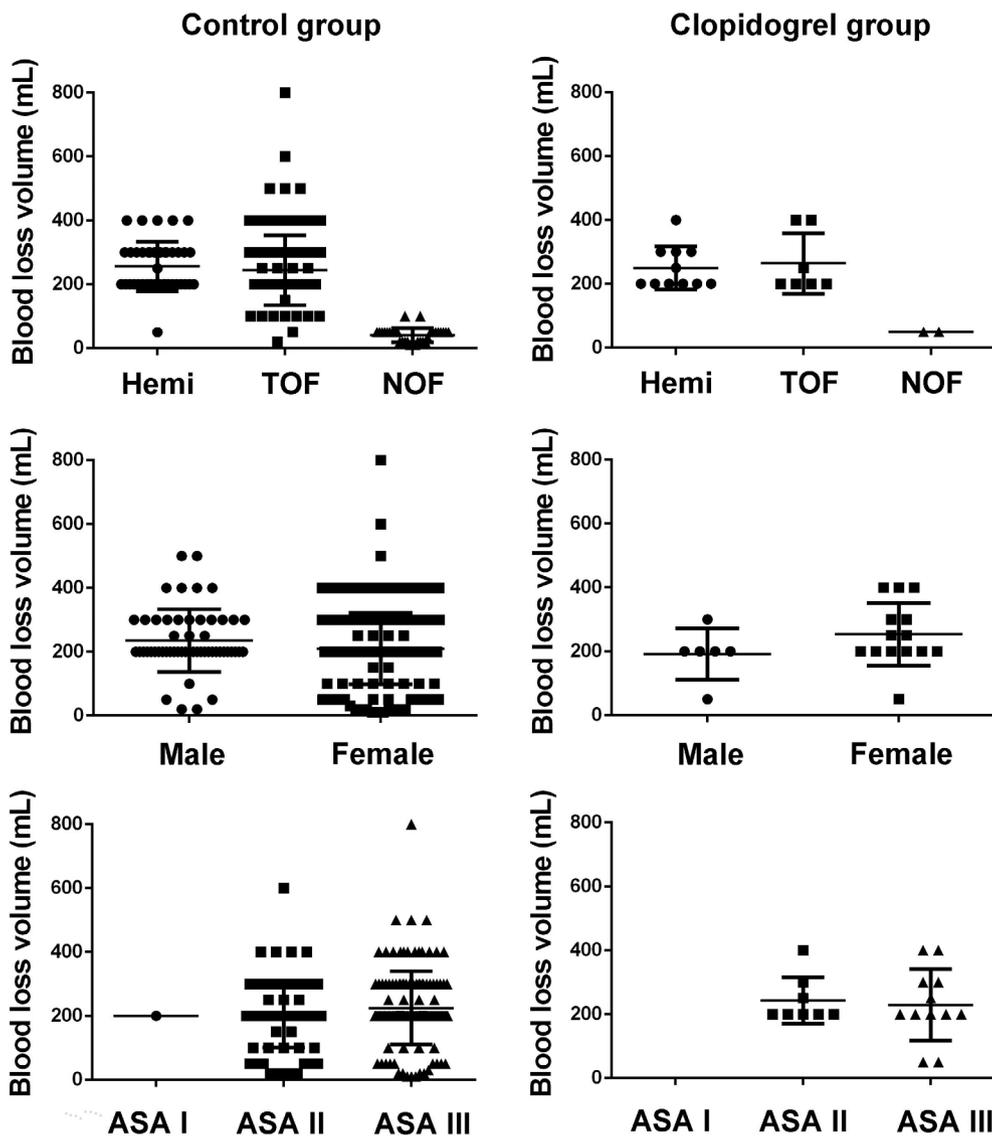
The blood transfusion rate on patients during hemi-hip replacement for femoral neck fracture was 9.1% and 22.3% for clopidogrel and control subgroups, respectively ( $P = 0.53$ ); while the transfusion rate during internal fixation for intertrochanteric fracture of the femur (A1-2, short pin) was relatively higher (42.9% for the clopidogrel subgroup and 65.7% for the control subgroup,  $P = 0.42$ ). For the internal fixation of femoral neck fracture with cannulated nails, the transfusion rate was quite low, as only one patient in the control subgroup had the blood transfusion (Table 3).

#### Secondary Outcomes

As shown in Table 4, none of the differences in the operation duration and length of hospital stay between the clopidogrel subgroup and the control subgroup showed statistically significant difference in each fracture/surgery group ( $P > 0.05$ ).

#### Factors that Affect Intraoperative Blood Loss

The factors that affect intraoperative blood loss, including patients' age, gender, surgical methods, ASA score, operation duration, as well as PLT levels before the surgery, were analyzed in clopidogrel group and control group. As shown in Figs 2 and 3, there were no significant differences of intraoperative blood loss between clopidogrel group and control group according to the surgical methods ( $273 \pm 70$ ,  $242 \pm 112$ , and  $40 \pm 23$  mL for Hemi, TOF, and NOF in control group,  $250 \pm 67$ ,  $264 \pm 94$ , and  $50 \pm 0$  mL for Hemi, TOF, and NOF in clopidogrel group), patients' gender ( $235 \pm 98$  and  $210 \pm 112$  mL for male and female in control group, while  $192 \pm 80$  and  $254 \pm 5$  mL for male and female in clopidogrel group), ASA score ( $200 \pm 0$ ,  $201 \pm 99$ , and  $225 \pm 114$  mL for ASA I, II, and III in control group,  $0 \pm 0$ ,  $244 \pm 73$ , and  $229 \pm 112$  mL for ASA I, II, and III in clopidogrel group), patients' age (subgrouped into  $<70$ ,  $70-80$ ,  $80-90$ ,  $>90$  years for each group, the specific blood loss volume for each subgroup is shown in Fig. 3), operation duration (subgrouped into  $<60$ ,  $60-90$ ,  $90-120$ ,  $>120$  min for each group, the specific blood loss volume for each subgroup is shown in Fig. 3), and PLT level (subgrouped into  $<100$ ,  $100-200$ ,  $200-300$ ,  $>300 \times 10^9/L$  for each group, the specific blood loss volume for each subgroup is shown in Fig. 3) before the surgery. However, according to the regression analysis, the surgical methods were in correlation with the volume of blood loss in the control group (Table 5,  $P = 0.000$ ), while they were not in the clopidogrel group (Table 6,  $P = 0.244$ ), even though the blood loss volume in each surgical method showed no significant difference in the control group and clopidogrel group (Fig. 1). This may be due to the small sample size of the clopidogrel group ( $n = 20$ ) analyzed in this study. The other factors were not significantly associated with blood loss volume both in the control group and clopidogrel group (Tables 5 and 6).



**Fig 2** Comparison of the surgical methods, patients' gender, and ASA scores that may be associated with volume of blood loss between the control group (n = 222) and the clopidogrel group (n = 20). Hemi: Hemi-hip replacement for femoral neck fracture; TOF: internal fixation for intertrochanteric fracture of the femur (fracture type A1-2, short pin); NOF: Internal fixation of femoral neck fracture with cannulated nails; ASA: American Society of Anesthesiologists.

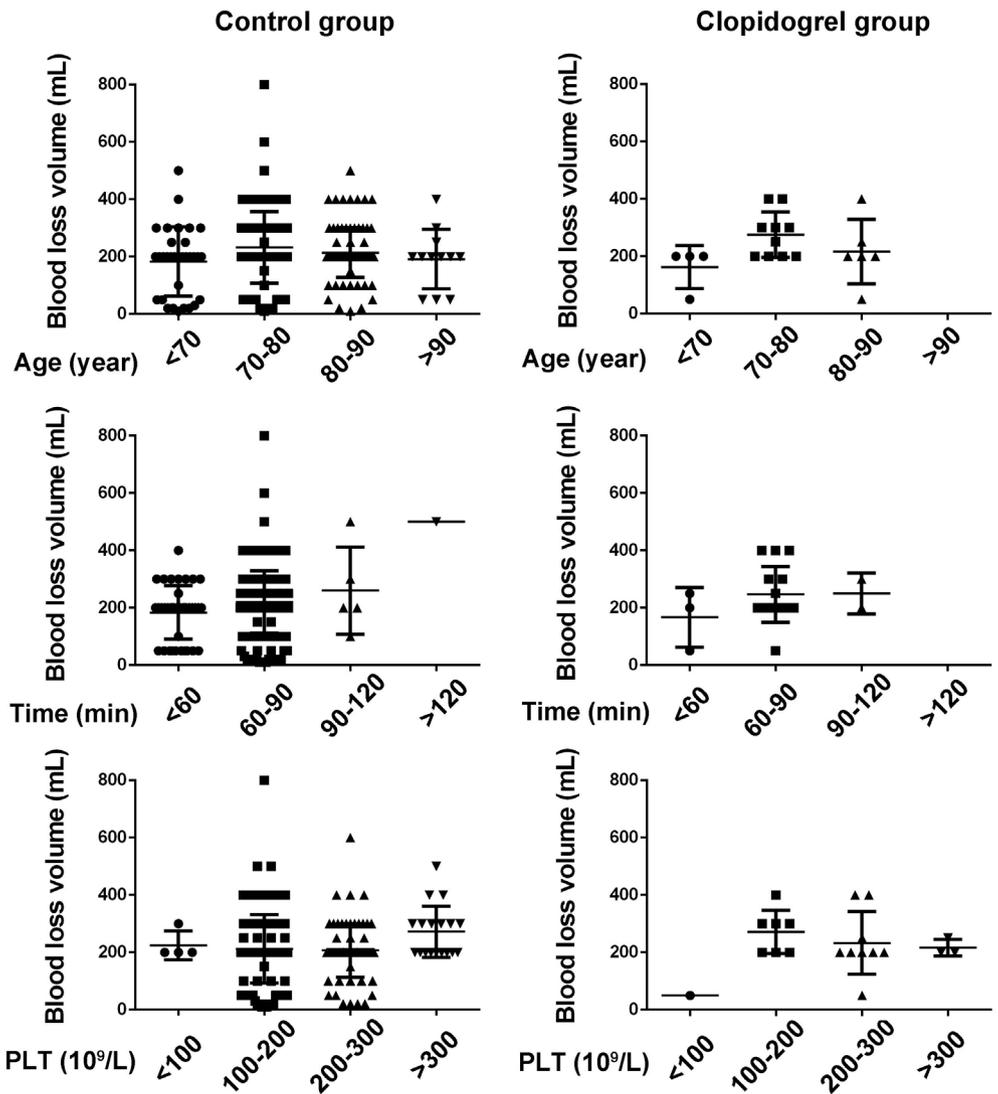
## Discussion

Within each of the above three fracture/surgery groups, there were no statistically significant differences in intraoperative blood loss, blood transfusion rate, operation duration, and length of hospital stay between the clopidogrel subgroup and the control subgroup. Our study has shown that early surgical intervention for hip fracture of senior patients receiving clopidogrel does not increase the risk of bleeding compared with patients without clopidogrel administration. Therefore, it could be concluded that early surgical intervention could be relatively safe.

Our baseline characteristic data showed that the mean age of the patients with fresh hip fracture in our hospital was around 80 years, and the majority of the patients were females. This may be due to the high risk of postmenopausal osteoporosis in females, and this disease could lead to increased risk of fracture. These patients had higher ASA

scores. Around 60% of the patients were graded ASA III or above. The elderly patients are relatively fragile physically and vulnerable to pneumonia, stress ulcers, pressure ulcers, etc. The anesthesia for elderly patients could be still challenging due to not only the coexisting morbidities but also aging-related metabolism. Apart from age, their coexisting morbidities can be quite severe and complicated. The most common coexisting morbidities are coronary heart disease, stroke, COPD, etc., which means we must have thorough understanding of these sort of diseases to provide appropriate peri-operative management.

For senior patients with hip fracture, early surgical treatment was highly recommended due to surgery delay-related complications, including increased risk of hypostatic pneumonia, pressure ulcers, deep vein thrombosis, and gastrointestinal dysfunction. Some elderly patients may have exacerbation of coexisting morbidities while awaiting



**Fig 3** Comparison of patients' age, operation duration, and PLT levels before the surgery that may be associated with volume of blood loss between the control group (n = 222) and the clopidogrel group (n = 20). PLT: Platelet.

surgery. For patients with heart disease, the pain caused by the hip fracture can increase the burden on the heart. Patients with pre-existing lung disease, such as COPD, are

more likely to develop pneumonia. Nutritional status could deteriorate due to hip fracture-related pain. Prolonged bed rest can also lead to urinary tract infections. In addition, the

**TABLE 5** Correlation between patients' gender, age, ASA score, PLT levels before the surgery, surgical methods, and operation duration with volume of blood loss in the control group (n = 222)

Model	Unstandardized Coefficients		Standardized Coefficients $\beta$	t	P value	95% Confidence Interval	
	B	SD				Lower Bound	Upper Bound
Gender	-6.977	15.822	-0.028	-0.441	0.660	-38.162	24.209
Age (year)	-0.108	0.916	-0.007	-0.117	0.907	-1.912	1.697
ASA score	23.822	13.428	0.110	1.774	0.077	-2.645	50.288
Platelet level	0.071	0.109	0.040	0.651	0.516	-0.143	0.285
Surgical Methods	-67.077	10.305	-0.422	-6.509	<b>0.000</b>	-87.390	-46.765
Operation duration	0.481	0.329	0.095	1.461	0.145	-0.168	1.130

P < 0.05 was considered statistically significant in bold. ASA, American Society of Anesthesiologists.

**TABLE 6 Correlation between patients' gender, age, ASA score, PLT levels before the surgery, surgical methods, and operation duration with volume of blood loss in the clopidogrel group (n = 20)**

Model	Unstandardized Coefficients		Standardized Coefficients $\beta$	t	P value	95% Confidence Interval	
	B	SD				Lower Bound	Upper Bound
Gender	52.248	51.075	0.256	1.023	0.325	-58.093	162.589
Age (year)	3.729	3.742	0.239	0.996	0.337	-4.355	11.812
ASA score	15.991	47.336	0.084	0.338	0.741	-86.272	118.254
Platelet level	-0.035	0.264	-0.032	-0.134	0.895	-0.606	0.535
Surgical Methods	-49.618	40.644	-0.354	-1.221	0.244	-137.425	38.188
Operation duration	0.552	1.329	0.119	0.416	0.685	-2.319	3.424

ASA, American Society of Anesthesiologists.

fracture site may become more complex than the fresh fracture after long-term waiting, which may increase the difficulty of surgery and intraoperative blood loss. Zuckerman *et al.* prospectively illustrated operative delay beyond 2 calendar days doubled the risk of death within the first postoperative year<sup>8</sup>. In 2004, a meta-analysis by Orosz *et al.* involving 16 observational studies, showed that a delay of 48 h or more for surgical repair was associated with increased 30-day and 1-year mortality; similarly, early surgery allowed reduction in pain and length of hospital stay<sup>9</sup>. In 2010, a meta-analysis by Simunovic *et al.* of five prospective observational studies showed that lower mortality was found in those undergoing early surgery (within 72 h after admission) than in those undergoing delayed surgery<sup>10</sup>.

There is a general consensus that early surgery should be performed for hip fractures in senior patients. However, as for patients taking clopidogrel, there is still lack of evidence for proving appropriate operative timing. Clopidogrel is a thienopyridine derivative, which inhibits platelet aggregation and thrombus formation by irreversibly binding to adenosine diphosphonate receptors on platelets<sup>11,12</sup>. It is superior to aspirin in secondary prevention of ischemic stroke, myocardial infarction, or vascular death<sup>12</sup>, with dual anti-platelet therapy using clopidogrel and aspirin being most effective in the management of vascular events particularly in patients following coronary stenting<sup>23,24</sup>. Therefore, clopidogrel is widely used in elderly patients. The half-life of the circulating active metabolite is 8 h, but the exposed platelets remain irreversibly inactive for the rest of their lives until replaced by new platelets<sup>11</sup>. Thus, most guidelines recommend withholding clopidogrel for 5–7 days for elective surgeries<sup>13–15</sup>. But for emergency surgery, there should be no delay and platelet transfusion should be performed only in the event of excessive surgical bleeding<sup>13</sup>.

Hip fracture surgery in elderly patients should not be strictly classified as elective surgery or emergency surgery. For elderly patients with hip fractures who receive clopidogrel, we should fully assess the risks of delayed surgery against the risk of bleeding from early surgery. Somehow, there was still no consensus about risk of bleeding in elderly patients undergoing hip fracture surgery with/without

clopidogrel administration. In 2008, Lavelle *et al.* demonstrated the feasibility of hip fracture surgery performed without delay, but there was an increased need for transfusions for the patients on clopidogrel before the injury<sup>25</sup>. Feely *et al.* found no evidence that prompt surgical treatment of hip fracture in patients on clopidogrel compromised perioperative outcomes. They found no difference in perioperative bleeding between the groups<sup>19</sup>. In the same year, the study by Wallace *et al.* examined the impact clopidogrel had on blood loss and transfusion rates in early (less than 2-day) operative treatment of elderly hip fractures. There was no statistical difference in intraoperative blood loss or preoperative transfusion rates; however, there was a statistical difference in postoperative transfusion rates ( $P = 0.012$ )<sup>26</sup>. In 2015, a study by Purushothaman *et al.* showed that hip fracture patients on clopidogrel could be safely operated on early. In their study, the bleeding risk was only slightly higher in patients on aspirin and clopidogrel who received surgery within 2 days, compared with patients with delayed surgery for the same condition<sup>27</sup>.

In this study, we did not find any difference in intraoperative blood loss, blood transfusion rate, operation duration, and length of hospital stay between the clopidogrel group and the control group in each fracture/surgery subgroup. Clopidogrel has a half-life of 8 h. Platelets are replaced at a rate of 10%–15% each day, and only 20% of circulating platelets is needed to be functional to achieve haemostasis<sup>28</sup>. Thus, theoretically, these patients can be operated on after withholding clopidogrel for 48 h. Our patients took a relatively long time from admission to surgery, with an average of 42–43 h. It was speculated that the time between the patient taking the last clopidogrel and the surgery was longer. It was not excluded that the newborn platelets from this period of time supported the patient's coagulation function. In 2015, Clareus *et al.* measured the response to clopidogrel in hip fracture patients who were on long-term clopidogrel anti-platelet therapy<sup>29</sup>. The results showed that one-third of these patients did not respond to clopidogrel. There was no point in postponing surgery for such patients. This may also be one of the potential reasons why the difference in intraoperative blood loss between the clopidogrel and control

subgroups could not be observed in our study. It also reminds us of the importance of individualized treatment. The function of platelets can be detected by means of multiple electrode aggregometry to avoid the unnecessary delay of surgery, and to avoid the real risk of increased bleeding from anti-platelet drugs.

The limitation of this study lies in the limited sample size. We did not consider dual anti-platelet therapy (aspirin and clopidogrel) separately. And we also lack the data of the bleeding outcomes of the total hip arthroplasty, which has the highest bleeding risk among all the surgical methods. The timing of hip fracture surgery in senior patients should be carefully decided, fully weighing the risks of delayed surgery against the risk of bleeding from early surgery. The focus of this study was relatively simple, focusing only on intraoperative bleeding and blood transfusion rate, without comparing postoperative complications, long-term and short-term survival rate, etc. In particular, no cardiovascular events were recorded after the discontinuation of clopidogrel.

All of these are what we should consider in our further research.

### Conclusion

Compared with patients who do not have a history of clopidogrel administration, senior patients with hip fractures who receive clopidogrel as long-term anti-platelet therapy are relatively safe for surgery in less than 5–7 days after discontinuation of clopidogrel. In the three most common surgical methods of geriatric hip fracture, no increase in intraoperative blood loss or blood transfusion rate was observed in our study, and there was no statistically significant difference in the operation duration or the length of hospital stay between the clopidogrel and control subgroups. Considering the risk of the delay of the surgery, early surgery is recommended. However, we still lack the data of the bleeding outcome of total hip arthroplasty, which has the highest bleeding risk among all the surgical methods involved.

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