

Safety of early surgery for geriatric hip fracture patients taking clopidogrel: a retrospective case-control study of 120 patients in China

Ming-Hui Yang¹, Bo Li¹, Dong-Chen Yao¹, Yan Zhou², Wen-Chao Zhang², Geng Wang², Ping Zhang³, Shi-Wen Zhu¹, Xin-Bao Wu¹

¹Department of Orthopedics and Traumatology, Beijing Jishuitan Hospital, Peking University Fourth School of Clinical Medicine, Beijing 100035, China;

²Department of Anesthesiology, Beijing Jishuitan Hospital, Peking University Fourth School of Clinical Medicine, Beijing 100035, China;

³Department of Geriatric Medicine, Beijing Jishuitan Hospital, Peking University Fourth School of Clinical Medicine, Beijing 100035, China.

Abstract

Background: Geriatric hip fracture patients receiving clopidogrel are a surgical challenge. In China, most of these patients undergo delayed surgical treatment after clopidogrel withdrawal for at least 5 to 7 days. However, delayed surgery is associated with increased complications and mortality in the older adults. This retrospective paralleled comparison study investigated the safety of early surgery for geriatric hip fracture patients within 5 days of clopidogrel withdrawal.

Methods: Acute hip fracture patients (≥ 65 years) who were hospitalized in the orthogeriatric co-management ward of Beijing Jishuitan Hospital between November 2016 and April 2018 were retrospectively reviewed. Sixty patients taking clopidogrel before injury and discontinued < 5 days before surgery constituted the clopidogrel group. The control group constituted 60 patients not taking antiplatelet or anticoagulant drugs and matched 1:1 with the clopidogrel group for sex, fracture type, operative procedure, and time from injury to operation (± 10 h). The primary outcome was perioperative blood loss and the secondary outcomes were transfusion requirement, complications, and mortality. The Student's *t* test or Wilcoxon signed rank sum test was used for continuous variables and the Chi-square test was used for categorical variables.

Results: Age, body mass index, American Society of Anesthesiologists score, and percentage undergoing general anesthesia were comparable between the groups ($P > 0.050$). The percentages of patients with coronary heart disease (61.7% *vs.* 18.3%; $P < 0.001$) and cerebrovascular disease (45.0% *vs.* 15.0%; $P < 0.010$) were significantly higher in the clopidogrel *vs.* control groups, respectively. The median clopidogrel discontinuation time before operation was 73.0 (range: 3.0–120.0) h. There was no significant difference in the estimated perioperative blood loss between the clopidogrel group (median: 745 mL) and control group (median: 772 mL) ($P = 0.866$). The intra-operative transfusion rate was higher in the clopidogrel group (22/60, 36.7%) than that in the control group (12/60, 20.0%) ($P < 0.050$). However, there was no significant difference in the blood transfusion rate during the entire perioperative period (26/60, 43.3% *vs.* 20/60, 33.3%; clopidogrel group *vs.* control group, respectively; $P > 0.050$). There was no significant difference in perioperative complications, and 30-day and 1-year mortality rates between the groups.

Conclusions: Early hip fracture surgery is safe for elderly patients within 5 days of clopidogrel withdrawal, without increased perioperative blood loss, transfusion requirement, complications, and mortality compared with patients not taking antiplatelet drugs.

Keywords: Hip fracture; Clopidogrel; Blood loss; Blood transfusion; Complication; Mortality

Background

Geriatric hip fractures are the most severe type of fragility fractures, with high morbidity^[1] and mortality.^[2,3] With aging populations, the incidence of hip fractures has also increased, with approximately 6.26 million hip fractures estimated to occur annually by 2050.^[4] Early surgery is

recommended for geriatric hip fractures in several guidelines^[5-7]; however, approximately one-third of these patients take oral antiplatelet or anticoagulant drugs owing to various comorbidities,^[8] which might influence the timing of surgery. Clopidogrel is one of the most commonly used antiplatelet drugs, and this drug inhibits platelet activation and aggregation throughout the lifespan

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Correspondence to: Dr. Shi-Wen Zhu, Department of Orthopedics and Traumatology, Beijing Jishuitan Hospital, Peking University Fourth School of Clinical Medicine, No. 31 Xijiekou East Street, Xicheng District, Beijing 100035, China
E-Mail: zhusw1207@sina.com

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of platelets. For urgent operations with an intermediate hemorrhagic risk, such as geriatric hip fracture, discontinuing clopidogrel is recommended 5 days before surgery for patients with low thrombotic risk.^[9] As delayed surgery is associated with increased complications and mortality among elderly patients with hip fractures,^[10] some studies have found that early surgery after clopidogrel discontinuation was safe.^[11,12]

The timing of surgery for geriatric hip fractures in patients receiving clopidogrel is controversial because of the limited evidence.^[7] Similarly, there is minimal evidence from China, and most of these patients still undergo delayed surgical treatment after clopidogrel withdrawal for at least 5 to 7 days. Based on orthogeriatric co-management model, our center began to investigate the safety of early surgery for hip fracture patients receiving clopidogrel according to results in previous studies. Because of the ethical difficulties associated with performing prospective randomized controlled studies in these patients, we conducted a retrospective cohort study with matched cases to improve the scientific quality of this study. This paralleled comparison study investigated the safety of early surgery for geriatric hip fractures in a Chinese population.

Methods

Ethical approval

This study was approved by the Ethics Committee of the Beijing Jishuitan Hospital (BJH) (No. 201901-16).

Study design

This is a single site, retrospective paralleled comparison study, comparing geriatric hip fracture patients receiving clopidogrel with those not taking antiplatelet or anticoagulant drugs. This study was conducted in BJH, affiliated with Peking University, which is a leading orthopedic hospital in China with approximately 40,000 orthopedic operations per year. Elderly patients (≥ 65 years of age) with acute hip fractures have been admitted to our orthogeriatric co-management unit and managed with a multidisciplinary approach since May 2015.^[13]

Participants and intervention

Hip fracture patients who were hospitalized between November 2016 and April 2018 were identified. The inclusion criteria were as follows: (1) age ≥ 65 years; (2) X-ray-confirmed hip fracture; and (3) undergoing operative treatment. The exclusion criteria were: (1) pathological fracture owing to tumor; (2) periprosthetic fracture; (3) multiple injuries; (4) coagulopathy, thrombocytopenia, or bleeding disorders; (5) taking antiplatelet or anticoagulant drugs other than clopidogrel; and (6) chronic peptic ulcer, chronic liver disease, or end-stage renal disease.

Clopidogrel was stopped at emergency department, except in those patients with a high risk of catastrophic thrombosis, such as patients who recently underwent coronary stenting. A prophylactic dose of low-molecular weight heparin was administered to all patients perioper-

atively, and clopidogrel was restarted post-operatively (PO). The operative procedure was determined according to the fracture type: cannulated compression screws for stable femoral neck fractures (FNFs), joint replacement for unstable FNFs,^[14] and intramedullary nail or dynamic hip screw fixation for intertrochanteric fractures (ITFs). The indication for blood transfusion was hemoglobin (HB) < 80 g/L or corresponding anemia symptoms.

Sixty patients taking clopidogrel before injury and discontinued < 5 days before surgery constituted the clopidogrel group. During the study period, 749 hip fracture patients were not taking antiplatelet or anticoagulant drugs. To control the differences, 60 patients from these 749 cases were matched 1:1 with patients of clopidogrel group using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA). The matched factors were sex, fracture type, operative procedure, and time from injury to operation (± 10 h).

Data collection

The medical record system, geriatric hip fracture database, and medical imaging system of our institute were reviewed to collect the relevant data for the patients' sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, fracture type, operative procedure, time from injury to operation, time from admission to operation, operation duration, type of anesthesia, length of hospital stay, comorbidities and age-adjusted Charlson comorbidity index (CCI),^[15] HB concentration at specific time points, blood transfusion amount, complications, and mortality. After patients were discharged, we conducted regular outpatient visits and telephonic follow-up interviews.

Outcomes

The primary outcome was perioperative blood loss and the secondary outcomes were transfusion requirement, complications, and mortality. Perioperative estimated blood loss (PEBL) was defined as the calculated blood loss from admission to the emergency department to discharge, assuming that the patient's total blood volume (TBV) remained constant during this period. The volume was calculated using the following formula^[16]:

$$\text{PEBL (mL)} = (\text{HB loss}/\text{HB ini}) \times 1000$$

$$\text{HB loss (g)} = \text{TBV} \times (\text{HB ini} - \text{HB fin}) + \text{HB trans}$$

PEBL: Perioperative estimated blood loss (mL), HB loss: Hemoglobin loss (g), HB ini: Initial hemoglobin (g/L), HB fin: final hemoglobin (g/L), TBV: Total blood volume (L), HB trans: Transfusion hemoglobin (g). One unit of transfused blood was considered to contain 52 g of HB.

TBV was calculated using Nadler method^[17] according to gender, height, and body weight:

$$\text{TBV (L)} = k1 \times \text{height (m)}^3 + k2 \times \text{weight (kg)} + k3$$

Table 1: Baseline data of the geriatric hip fracture patients in the clopidogrel and control groups.

Parameters	Clopidogrel group (n = 60)	Control group (n = 60)	P
Female*, n (%)	45 (75.0)	45 (75.0)	–
Age (years), median (IQR 25–75)	80.0 (76.0, 84.0)	81.0 (77.3, 86.0)	0.337
BMI, mean ± SD	23.2 ± 3.1	22.9 ± 3.5	0.690
ASA score, n (%)			0.059
II	21 (35.0)	25 (41.7)	
III	37 (61.7)	34 (56.7)	
IV	2 (3.3)	1 (1.7)	
Fracture pattern*, n (%)			–
FNF G I/II	12 (20.0)	12 (20.0)	
FNF G III/IV	25 (41.7)	25 (41.7)	
ITF A1/A2	21 (35.0)	21 (35.0)	
ITF A3	2 (3.3)	2 (3.3)	
Type of surgery*, n (%)			–
Screw fixation	11 (18.3)	11 (18.3)	
Joint replacement	26 (43.3)	26 (43.3)	
Dynamic hip screw	2 (3.3)	2 (3.3)	
Intramedullary nail	21 (35.0)	21 (35.0)	
Time from injury to operation* (h), median (IQR 25–75)	68.5 (49.0, 85.0)	68.0 (51.0, 86.0)	0.401
Surgery within 48 h after admission, n (%)	53 (88.3)	46 (76.7)	0.092
Operation duration (min), median (IQR 25–75)	60.0 (50.0, 60.0)	60.0 (40.0, 73.8)	0.832
General anesthesia, n (%)	16 (26.7)	13 (21.7)	0.664
Length of hospital stay (days), median (IQR 25–75)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	0.965

* Matched factors. ASA: American Society of Anesthesiologists; BMI: Body mass index; FNF: Femoral neck fracture; G: Garden classification; ITF: Intertrochanteric fracture; IQR: Interquartile range; SD: Standard deviation.

Table 2: Comorbidities and age-adjusted CCI of the geriatric hip fracture patients in the clopidogrel and control groups.

Parameters	Clopidogrel group (n = 60)	Control group (n = 60)	P
Comorbidities, n (%)			
Hypertension	49 (81.7)	40 (66.7)	0.078
Atrial fibrillation	4 (6.7)	3 (5.0)	1.000
Diabetes mellitus	18 (30.0)	13 (21.7)	0.332
Coronary heart disease	37 (61.7)	11 (18.3)	0.000*
Cerebrovascular disease	27 (45.0)	9 (15.0)	0.002*
Peripheral artery disease	3 (5.0)	2 (3.3)	1.000
Cardiac insufficiency	5 (8.3)	2 (3.3)	0.453
Renal insufficiency	10 (16.7)	7 (11.7)	0.581
Respiratory disease	11 (18.3)	9 (15.0)	0.815
Malignant tumor	4 (6.7)	8 (13.3)	0.289
Autoimmune disease	1 (1.7)	3 (5.0)	0.625
Dementia	4 (6.7)	2 (3.3)	0.688
CCI, median (IQR 25–75)	2 (1, 3)	1 (0, 3)	0.002*

* P < 0.05. CCI: Charlson comorbidity index; IQR: Interquartile range.

where k_1 , k_2 , and k_3 are constants, as follows: for women: $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$; for men: $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$.

Statistical analysis

SPSS 24.0 (IBM Corp.) was used for the statistical analysis. Clinical data were compared between the clopidogrel and control groups using Student's *t* test or Wilcoxon signed

rank sum test for continuous variables and the Chi-square test for categorical variables. A *P* value < 0.050 was considered statistically significant.

Results

Patient population

There were 60 matched patients in the clopidogrel and control groups, respectively. Sex, fracture type, and operative procedure were same between the two groups after matching. Age, BMI, ASA score, time from injury to operation, surgical rate within 48 h after admission, operation duration, the rate of general anesthesia, and length of hospital stay were comparable between the groups [Table 1]. In the clopidogrel group, the median time from injury to operation was 68.5 h. In 88.3% of the patients, operation was performed within 48 h of admission.

The age-adjusted CCI was significantly higher in the clopidogrel group, and there were more patients with coronary heart disease and cerebrovascular disease in the clopidogrel group compared with the control group [Table 2]. The median withdrawal time of clopidogrel before operation was 73.0 (range: 3.0–120.0)h. All operations were performed within 5 days of clopidogrel withdrawal.

Perioperative blood loss and blood transfusion

HB levels were routinely checked in the emergency department, after surgery, on the first PO day, and before

Table 3: Perioperative blood loss and blood transfusion data of the geriatric hip fracture patients in the clopidogrel and control groups.

Parameters	Clopidogrel group (n = 60)	Control group (n = 60)	P
Estimated perioperative blood loss (mL), median (IQR 25–75)	745 (435, 1201)	772 (486, 1245)	0.866
HB Level, mean ± SD			
Emergency HB (g/L)	118.6 ± 17.2	123.3 ± 15.4	0.086
PO HB (g/L)	107.8 ± 15.6	107.1 ± 14.3	0.783
POD1 HB (g/L)	108.2 ± 15.5	109.1 ± 14.0	0.490
Discharge HB (g/L)	101.6 ± 9.2	102.1 ± 11.8	0.783
Intra-operative transfusion, n (%)	22 (36.7)	12 (20.0)	0.041*
Perioperative transfusion, n (%)	26 (43.3)	20 (33.3)	0.327
Screw fixation of FNF	2/11 (18.2)	0/11 (0)	0.500
Joint replacement of FNF	9/26 (34.6)	8/26 (30.8)	1.000
Fixation of ITF	15/23 (65.2)	12/23 (52.2)	0.549

* $P < 0.050$. FNF: Femoral neck fracture; HB: Hemoglobin; ITF: Intertrochanteric fracture; IQR: Interquartile range; PO: Post-operative; POD1: Post-operative day 1; SD: Standard deviation.

Table 4: Perioperative complications and mortality of the geriatric hip fracture patients in the clopidogrel and control groups.

Parameters	Clopidogrel group (n = 60)	Control group (n = 60)	P
Perioperative complications, n (%)			
Cerebral infarction	1 (1.7)	0	1.000
Acute coronary syndrome	0	1 (1.7)	1.000
DVT	9 (15.0)	5 (8.3)	0.424
Chest infection	5 (8.3)	6 (10.0)	0.774
Urinary tract infection	6 (10.0)	5 (8.3)	1.000
Decubitus	0	1 (1.7)	1.000
Acute upper gastrointestinal hemorrhage or stress ulcer	2 (3.3)	1 (1.7)	1.000
ICU admission, n (%)	7 (11.7)	6 (10.0)	0.774
In-hospital mortality, n (%)	0	0	–
30-day mortality, n (%)	0	1 (1.7)	1.000
One-year mortality, n/N (%)	6/50 (12.0)	6/48 (12.5)	0.940

DVT: Deep vein thrombosis; ICU: Intensive care unit.

discharge. Results showed HB concentrations at these time points were comparable between the two groups [Table 3]. There was no significant difference in estimated perioperative blood loss between the clopidogrel group (median: 745 mL) and control group (median: 772 mL) ($P = 0.866$). There was also no significant difference in blood transfusion rates between the groups during the entire perioperative period ($P > 0.050$); however, the intraoperative transfusion rate was higher in the clopidogrel group ($P < 0.050$). In a subgroup analysis of different surgical procedures, transfusion rates were comparable between the two groups [Table 3]. Only one patient in the clopidogrel group received platelet transfusion just after intramedullary nailing for an ITF because the surgeon considered that the intra-operative blood loss was huge.

Complications and mortality

There were no significant differences in perioperative complications, nor in-hospital and 30-day mortality between the two groups. Only 98 patients (50 in the clopidogrel group and 48 in the control group) could be followed to assess 1-year mortality. Six patients in each

group died in the first year after surgery, and all of these patients died after discharge. The causes of death were lung infection, heart failure, acute cardiac arrest, tumor, and other causes [Table 4].

Discussion

Geriatric hip fractures have become a global health challenge because of the high incidence, and disability and mortality rates. Many of these patients require oral clopidogrel treatment owing to chronic cardiovascular and cerebrovascular diseases before injury. This was consistent with our finding that the percentages of patients with coronary heart disease (61.7% vs. 18.3%; $P < 0.001$) and cerebrovascular disease (45.0% vs. 15.0%; $P < 0.010$) as comorbidities in the clopidogrel group were significantly higher than those in the matched control group, respectively. The CCI of the clopidogrel group was also higher than that of the control group ($P < 0.010$) [Table 2]. As a platelet P2Y₁₂-receptor antagonist, clopidogrel irreversibly inhibits platelet function^[18,19]; therefore, recovery of platelet function depends on the production of new platelets. Guidelines recommend a 5 to 7 day

withdrawal of clopidogrel before elective surgery to reduce the risk of blood loss. Because delayed surgical treatment leads to increased morbidity and mortality, geriatric hip fractures are considered an urgent surgery. Researchers have explored the feasibility of early surgery with a shorter clopidogrel withdrawal time or without withdrawal for geriatric hip fracture patients receiving clopidogrel, but the results are controversial.^[19-23] In China, most of these patients still undergo delayed surgery after clopidogrel withdrawal for >5 to 7 days, and related research data from our country are very scarce. Long-term discontinuation of clopidogrel also increases the risk of cardiovascular and cerebrovascular events.

This study was conducted to investigate the safety of early surgery for hip fracture patients on clopidogrel in Chinese population. Patients receiving clopidogrel were first evaluated and classified into high- and low-thrombosis risk groups. Clopidogrel could not be stopped for the former, and these patients were excluded.^[9] Patients with low thrombosis risk were included to investigate whether surgery within 5 days after clopidogrel withdrawal increased perioperative blood loss and transfusion rates. To minimize differences between the two groups, each patient from the clopidogrel group was matched with one patient from the control cases who were not taking anticoagulant or antiplatelet drugs. Patients were matched according to sex, fracture type, time from injury to operation, and surgical procedure. Age, BMI, ASA score, surgical rate within 48 h after admission, surgical time, and the rate of general anesthesia were comparable between the clopidogrel group and the control group.

Several studies have reported that early surgery for hip fracture patients receiving clopidogrel increased perioperative blood loss or resulted in greater HB decline^[24-26]; however, other studies showed that early operation did not increase perioperative blood loss.^[12,27,28] Mattesi *et al*^[22] conducted a systematic review and showed that early surgery did not lead to increased perioperative bleeding for hip fracture patients taking clopidogrel. Changes in HB levels were comparable between the two groups before and after surgery in our study. The estimated perioperative blood loss in the clopidogrel group also showed no significant difference compared with the control group, in our study (745 *vs.* 772 mL, respectively; $P > 0.050$). The intra-operative transfusion rate was significantly higher in our clopidogrel group (22, 36.7%) than that in the matched control group (12, 20.0%) ($P < 0.050$). However, there was no significant difference in the blood transfusion rate during the entire perioperative period. This was supported by the research of Nydick *et al*,^[19] which showed that a surgical delay of <5 days after clopidogrel withdrawal did not increase the transfusion rate compared with the control group not taking clopidogrel (18/28 *vs.* 13/29, respectively; $P > 0.050$). The increased intra-operative transfusion rate might be associated with surgeons' concerns regarding blood loss in patients taking clopidogrel. Previous studies reported that approximately 40% to 50% of patients were resistant to clopidogrel.^[12,29] Clareus *et al*^[30] indicated that almost one-third of hip fracture patients taking clopidogrel were non-responders to this antiplatelet therapy. This might

partially explain why the blood loss and blood transfusion rates in patients undergoing early surgery did not increase significantly.

The most common complications and causes of death after hip fractures are pulmonary, cardiac, and neurological complications.^[31-34] To further investigate the safety of early surgery, the current study compared the incidence of complications and the mortality rate between the two groups. Similar to findings in previous reports,^[8,19-21] the incidence of various perioperative complications, and 30-day and 1-year mortality rates were comparable between the clopidogrel group and the matched control group, in our study.

This study indicated that early surgery with clopidogrel withdrawal for <5 days was safe in terms of perioperative blood loss, blood transfusion rate, complications, and mortality rate for patients with low thrombotic risk. The limitations of the current study are the retrospective study design, single-center investigation, small sample size, and interference because of multiple surgical methods. Future studies should focus on prospective multi-center large sample-size investigations of the safety of early surgery within 48 h or without withholding clopidogrel.

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Conflicts of interest

None.

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