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# Withholding clopidogrel for 3 to 6 versus 7 days or more before surgery in hip fracture patients

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## ABSTRACT

**Purpose.** To compare morbidity and mortality after hip fracture surgery in patients withholding clopidogrel for 3 to 6 days versus ≥7 days.
**Methods.** Records of 16 men and 31 women aged 49 to 92 (mean, 80.2) years who underwent hip fracture surgery after withholding clopidogrel for 3 to 6 days (n=24) versus ≥7 days (n=23) were compared. The patients were taking clopidogrel owing to ischaemic heart disease (n=37), cerebrovascular disease (n=7), and intolerance to aspirin (n=3). Patient demographics, American Society of Anesthesiologists status, preoperative delay, length of hospital stay, perioperative haemoglobin reduction, receipt of blood and platelet transfusions, morbidity, and mortality were recorded.
**Results.** Respectively in the early-surgery and delayed-surgery groups, the mean surgical delay was 4.2 and 8.0 days, the mean length of hospital stay was 21.1 and 28.7 days, the mean peri-operative haemoglobin reduction was 1.5 and 1.1 g/dl, the mean units of blood transfusion per patient was 0.8 and 0.7. No severe intra-operative bleeding or wound haematoma was encountered in either group. Two patients in each group died within one month, and 2 more in the delayed-surgery group died within 3 months. The main cause of death was cardiovascular.
**Conclusion.** Withholding clopidogrel for <7 days before surgery conferred no increased risk in hip fracture patients.

***Key words:*** *blood platelets; clopidogrel; femoral neck fractures; hip fractures; platelet aggregation inhibitors*

## INTRODUCTION

Clopidogrel is a thienpyridine derivative, which inhibits platelet aggregation and thrombus formation by irreversibly binding to adenosine diphosphonate receptors on platelets.[1,2] Release of adenosine-5'-diphosphate from activated platelets is one of the primary mediators of platelet aggregation, leading to a sustained response via activation of P2Y12 receptors. Inhibition of platelet aggregation is an important

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strategy to prevent ischaemic events.[3] Clopidogrel is not active *in vitro*, and a biotransformation by the hepatic cytochrome P450–1A is necessary to enable the expression of its anti-aggregating activity.[1,2] Therefore, Clopidogrel can be considered as a pro-drug for an active metabolite. The half-life of the circulating active metabolite is 8 hours,[4] but the exposed platelets remain irreversibly inactive for the rest of their lives until replaced by new platelets 7 days after the last dose.[5]

There is no consensus regarding the optimal waiting period for patients receiving clopidogrel to undergo surgery for hip fractures. The British National Formulary recommends withholding clopidogrel for 7 days for elective procedures, but no recommendations for emergency procedures are given.[6] The British Orthopaedic Association recommends operation within 48 hours of admission for medically fit patients, and during normal working hours.[7] However, there are increased risks of surgical bleeding and spinal haematoma after spinal or epidural anaesthesia.[8–10] Premature cessation of antiplatelet therapy is the strongest predictor of stent thrombosis.[11,12] The risk of developing a new myocardial infarction is 50% and mortality was 20%.[13] The American College of Chest Physicians guideline recommends stopping antiplatelet drugs for a minimum of 5 days before elective surgery,[14] For emergency surgery, there should be no delay and platelet transfusion should be performed only in the event of excessive surgical bleeding.[14] The Scottish Intercollegiate Guidelines Network recommends operation with no delay, but neither spinal nor epidural anaesthesia is mentioned.[15] Only a few studies have reported withholding clopidogrel for ≤3 days in hip fracture patients.[16,17] The current study compared morbidity and mortality after hip fracture surgery in patients withholding clopidogrel for 3 to 6 days versus ≥7 days.

## MATERIALS AND METHODS

Strengthening the Reporting of Observational Studies in Epidemiology guidelines[18] were followed. Approval was obtained from the regional ethics committee. Between May 2008 and April 2010, 793 patients were admitted to our hospital with a hip fracture. Of whom, 16 men and 31 women aged 49 to 92 (mean, 80.2; standard deviation, 8.4) years were taking clopidogrel owing to ischaemic heart disease (n=37), cerebrovascular disease (n=7), and intolerance to aspirin (n=3).

Patients were reviewed by the anaesthesia and cardiology teams regarding withholding the clopidogrel. Clopidogrel was withheld from the time of admission, and a pool of platelets was prepared. According to the hospital guidelines, surgeries were performed at least 3 days after stopping the clopidogrel. Second-generation cephalosporin was administered as prophylaxis for infection. General anaesthesia was used. Clopidogrel was commenced within 48 hours post surgery. The orthogeriatric team was consulted to optimise the patients' health during hospitalisation and rehabilitation.

Patient demographics, American Society of Anesthesiologists (ASA) status, preoperative delay, length of hospital stay, perioperative haemoglobin reduction, receipt of blood and platelet transfusions, morbidity, and mortality were recorded.

Patients who underwent surgery after withholding clopidogrel for 3 to 6 days (n=24) and ≥7 days (n=23) were compared using the independent *t*-test or Mann-Whitney test for continuous variables. The Chi-squared test was used for categorical data.

## RESULTS

The mean surgical delay in patients who underwent surgery after withholding clopidogrel for 3 to 6 days versus ≥7 days was significantly different (mean difference, 3.8; 95% confidence interval [CI], 3.2–4.4 days). Group allocation was independently predictive of surgical delay when adjusting for the type of fracture and ASA status ($p<0.001$). Patients withholding clopidogrel for 3 to 6 days had a shorter length of hospital stay (mean difference, 7.6; 95% CI, 0.8–16.0 days), but this trend was not significant, as were the mean peri-operative haemoglobin reduction (1.5 vs. 1.1 g/dl) and the mean units of blood transfusion per patient (0.8 vs. 0.7) [Table].

Both groups were similar in terms of co-morbidities, perioperative blood transfusions received, and intra-operative bleeding/wound haematomas encountered. In the early-surgery group, one patient presented with chronic anaemia and received 3 units of blood preoperatively for optimisation, whereas 2 others received platelet transfusions (1 unit per patient) intra-operatively. Neither the type of fracture ($p>0.52$) nor the ASA status ($p>0.93$) was independently predictive of haemoglobin reduction during surgery ($p>0.51$) or receipt of blood transfusions ($p>0.49$).

No severe intra-operative bleeding or wound haematoma was encountered in either group. Two patients in the delayed-surgery group developed

**Table**
**Comparison of patients in the early-surgery and delayed-surgery groups**

| Parameter | Early surgery (withholding clopidogrel for 3–6 days) | Delayed surgery (withholding clopidogrel for ≥7 days) |
|---|---|---|
| No. of males:females | 10:14 | 6:17 |
| Mean±SD (range) age (years) | 80.9±6.8 (62–92) | 79.7±9.8 (49–91) |
| Indication for clopidogrel (no. of patients) | | |
| Ischaemic heart disease | 19 | 18 |
| Cerebrovascular disease | 3 | 4 |
| Intolerance to aspirin | 2 | 1 |
| Mean±SD American Society of Anesthesiologists score | 2.7±0.6 | 2.8±0.6 |
| Type of fracture (no. of patients) | | |
| Intra-articular | 14 | 11 |
| Extra-articular | 9 | 10 |
| Others | 1 | 2 |
| Type of surgery (no. of patients) | | |
| Hemiarthroplasty | 14 | 9 |
| Dynamic hip screw fixation | 7 | 9 |
| Cephalomedullary nailing | 2 | 2 |
| Total hip replacement | 0 | 1 |
| No surgery | 1 | 2 |
| Mean±SD surgical delay (days) | 4.2±1.0 | 8.0±1.0 |
| Mean±SD (range) length of hospital stay (days) | 21.1±11.9 (3–61) | 28.7±16.4 (8–64) |
| Blood transfusion (no. of patients) | 6 | 8 |
| Blood transfusion (no. of units) | 19 | 16 |
| Mean±SD blood transfusion (units/patient) | 0.8±1.6 | 0.7±1.1 |
| Complication (no. of patients) | | |
| Non-ST segment elevation myocardial infarction | 0 | 1 |
| Atrial fibrillation | 0 | 1 |
| Lower respiratory tract infection | 2 | 1 |
| Methicillin-resistant *Staphylococcus aureus* infection | 1 | 0 |
| *Clostridium difficile* infection | 0 | 1 |
| Viral gastroenteritis | 0 | 1 |
| Urinary tract infection and urine retention | 2 | 0 |
| Acute confusion | 2 | 1 |
| Conjunctivitis | 1 | 0 |
| Haematuria | 0 | 1 |
| Upper gastrointestinal bleeding | 0 | 1 |
| Fall & re-fracture | 0 | 1 |

cardiac problems (myocardial infarction and atrial fibrillation) while waiting for surgery. Infection (of the lower respiratory and urinary tracts) was the main complication in the early-surgery group. Two patients in each group died within one month, and 2 more in the delayed-surgery group died within 3 months. The main cause of death was cardiovascular.

## DISCUSSION

In patients with hip fractures, delayed surgery is associated with increased mortality and morbidity.[19–31] The one-month mortality has been reported to be 5 to 37%.[24–27] In hip fracture patients on clopidogrel, mortality was also greater.[32,33] The one-month mortality was 2.5 fold higher in patients having delayed surgery owing to co-morbidities than in those who were fit for surgery.[19] The one-month and one-year mortality rates were significantly higher in hip fracture patients in whom surgery was delayed beyond 72 hours.[20] Early surgery (within 48 hours of admission) reduces the length of hospital stay and rates of complications and mortality.[34] Nonetheless, this might be due to multiple co-morbidities of the patients and deterioration of their condition.

Stress response to both trauma and surgery could lead to a state of hypercoaguablility compounded by patient immobility and a rebound increase in platelet function secondary to withholding antiplatelet medications.[35] This transient hypercoaguable state peaks at postoperative days 3 to 5,[36] and thus cardiac morbidity peaks at 4 to 8 days after stopping of clopidogrel.[37] Premature discontinuation of clopidogrel is associated with a 19- to 89-fold increase in the risk of stent thrombosis and is the most important risk factor for such an event.[11,12,38] Acute withholding of clopidogrel may cause adenosine-

5′-diphosphate concentrations to activate GPIIbIIIa receptors and cause an increase in platelet aggregation and even rebound platelet activity.

The cut-off point for the withholding clopidogrel for 3 instead of 7 days is based on the half-life of the circulating active metabolite, which is 8 hours.[4] This may increase to 20 to 50 hours in elderly patients.[39] Injection of platelets can rapidly restore normal haemostasis in the event of life-threatening bleeding. Platelets are replaced at a rate of 10 to 15% each day,[40] and only 20% of circulating platelets need to be functional to achieve haemostasis. Thus, these patients can be operated on after withholding clopidogrel for 48 hours. Blood transfusion received and haemoglobin levels within 4 days after surgery as well as mortality and morbidity were not significantly different in patients withholding clopidogrel for ≤5 days and controls not receiving any antiplatelet agents.[41,42] Nonetheless, in clopidogrel recipients operated on within 2 days, estimated blood loss and transfusion received are increased.[42]

Our findings were in agreement with those of the Scottish Intercollegiate Guidelines Network, which recommends stopping antiplatelet drugs for a minimum of 5 days before elective surgery and not to delay emergency surgery and transfusion of platelets only in the event of excessive surgical bleeding.[15]

Limitations of the current study were its retrospective nature and small sample size. Larger controlled prospective studies are necessary to assess the effect of clopidogrel on patients with hip fractures and when the cut-off point is lowered to 48 hours. Measurement of intra-operative blood loss is needed. Different treatment methods have different blood loss; randomisation of patients can adjust for this confounding factor.

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## DISCLOSURE

No conflicts of interest were declared by the authors.

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