

Retrospective Study



Perioperative Coagulation Profile with Thromboelastography in Aspirin-Treated Patients Undergoing Posterior Lumbar Fusion

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Disclaimer: Xiaoming Li, Jinhui Wu, Shuhan Zhang, Shu Liu, and Jiabin Yuan contributed equally to this work. There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-09-2019
Revised manuscript received: 04-04-2020
Accepted for publication: 04-16-2020

Free full manuscript: www.painphysicianjournal.com

Background: It has been generally recommended that platelet function may recover after the recommended 5-day discontinuation period prior to operation. The technique of thromboelastography has been demonstrated to monitor intraoperative platelet function in liver transplantation and coronary bypass surgery. However, there is a dearth of literature that addresses the utility of thromboelastography in aspirin-treated patients undergoing fusion.

Objectives: To introduce a functional method of monitoring coagulation and validate the effectiveness of thromboelastography perioperatively in assessing aspirin-treated patients undergoing posterior lumbar fusion.

Study Design: This research used a retrospective study design.

Setting: Orthopedic Department of Changhai Hospital, Shanghai, China and Orthopedic and Anesthesia Department of Changzheng Hospital.

Methods: Eighty patients were divided into aspirin-naïve and aspirin-treated groups in this study. They had equally undergone lumbar fusion surgery for at least one or more segments between January and June 2018. They matched for age, gender, number of fused segments, and surgical procedures. The coagulation profile, including the reaction time (R), kinetics (K), maximal amplitude (MA), α -angle, and coagulation index (CI), platelet inhibition ratio (PIR) was analyzed by thromboelastogram (TEG) prior to operation and on preoperative days 1, 3, and 5. Correlation analysis included parameters such as waiting time, intraoperative blood loss, and postoperative drainage.

Results: Perioperatively, the TEG values including R, K, MA, α -angle, and CI, PIR, and correlation analysis showed no significant difference between the 2 groups, respectively ($P > 0.05$).

Limitations: First, the relatively small number of patients recruited limits control over other factors; larger studies may need to confirm our findings. Second, the patients were objectively less healthy with more medication treatment, which may result in a variance in the amount of blood loss. Randomized controlled studies are needed to further confirm these results.

Conclusions: TEG may be a helpful method to monitor perioperative platelet function in aspirin-treated patients undergoing fusion. It may be comparatively safe to relax the restriction of the aspirin-discontinued therapeutic window to approximately 2 to 3 days prior to surgery.

Key words: Coagulation profile, platelet function, lumbar fusion surgery, TEG value

Pain Physician 2020; 23:E619-E628

Treatment with acetylsalicylic acid (ASA) is a well-established strategy in the primary and secondary prevention of ischemic events in patients with high-risk coronary artery disease (CAD), including myocardial infarction, unstable angina, stroke, or transient ischemic attacks. The most

commonly used antiplatelet agent is low-dose aspirin for preoperative pain control and antiplatelet effect (1,2).

However, low-dose ASA irreversibly disturbs the platelet cyclooxygenase enzyme system and inhibits platelet function, particularly in patients undergoing

coronary artery bypass graft surgery, ultimately significantly increasing the risk of postoperative bleeding (3,4). The perioperative complication that is of concern and that is associated with aspirin withdrawal syndrome is characterized by a rebound of primary hemostasis, leading to a clinical prothrombotic state (5,6).

Low-dose aspirin is generally discontinued prior to surgery to decrease perioperative bleeding complications. The lifespan of a normal platelet cell is 7 to 10 days. Approximately 7 to 10 days are required to metabolize the acetylated platelets. Approximately 4 to 5 days after withdrawing aspirin, 50% of the circulating platelets are replaced by new ones (7,8). Therefore it has been generally recommended that the bleeding tendency may be normalized, and that platelet function may recover after the recommended 5-day discontinuation period prior to the date of planned operation (5,9,10).

In patients undergoing lumbar decompression and posterolateral fusion, the major concern is postoperative bleeding, resultant epidural hematoma, and neurologic dysfunction, leading to deterioration of patients' general health, prolonged hospitalizations, and higher surgery-related costs (11-14). Only a few studies have researched the risk of bleeding in aspirin-treated patients undergoing spine surgery. A survey by neurosurgeons showed that aspirin was associated with

increased bleeding and hemorrhagic complications in lumbar spinal surgery (3,15). Some studies have shown that aspirin-treated patients had no definite increase in the amount of bleeding and do not necessarily require discontinuation of aspirin to prevent excessive bleeding (16-18). Therefore the assertion that there is increased risk of perioperative bleeding and in the scheduling of the operation in aspirin-treated patients undergoing spine surgery is under much debate and lacks extensive evidence in support of that assertion.

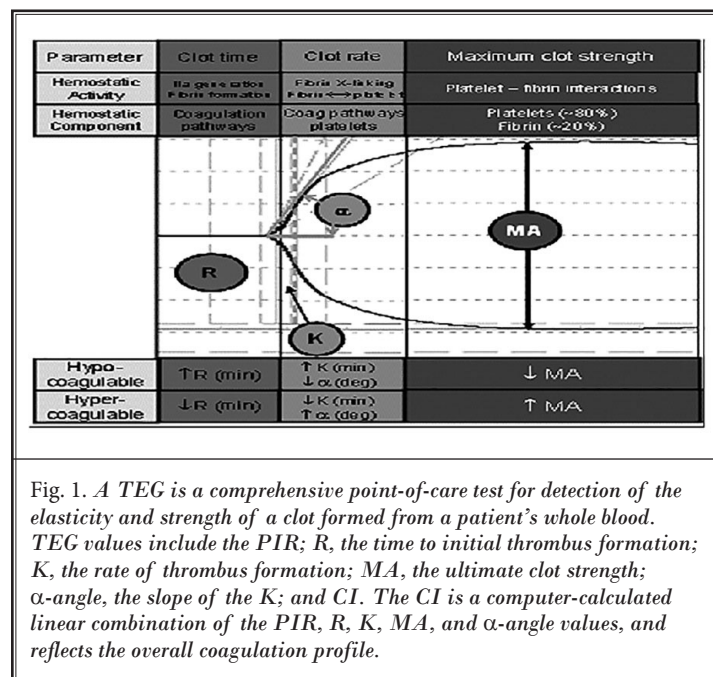
Thromboelastography is a point-of-care test for evaluation of hemostasis and thromboprophylaxis for liver transplantation and coronary bypass surgery and it is used as an intraoperative hemostatic monitoring device. A thromboelastogram (TEG) measures the dynamic process of blood coagulation, with defined parameters reflecting the integrity of specific hemostatic components, especially platelet function (Fig. 1) (19,20). However, there is a dearth of literature that directly addresses the utility of coagulation tests in the field of spinal surgery. To obtain a better understanding of hemostasis in aspirin-treated patients undergoing spine surgery, we assess the perioperative coagulation status and enable accurate risk stratification, utilizing a thromboelastograph and standard measures of coagulation, from the time of admission to the hospital until 1 week following surgery.

METHODS

Patients

This study was conducted prospectively and approved prior to initiation of enrollment by the institutional review board. Eighty consecutive patients undergoing posterior spinal instrumented fusion procedures were investigated between January and June 2018. The Pfirrmann grading system and algorithm were utilized to identify the inclusion criteria for 80 patients with lactate dehydrogenase (LDH). Informed consent was preoperatively obtained from each patient at the Orthopedic Department of Changhai Hospital.

Patients were not administered antifibrinolytics or other procoagulant medications. The coagulation functions of all patients were normal prior to the operation. None of the patients had a history of coagulation defects or renal insufficiency (glomerular filtration rate < 70 mL/min). Patients were



recommended to discontinue ASA at a preoperative visit to the outpatient clinic. ASA was designated as a confounding variable as it confounds the analysis of the difference in perioperative blood loss by its administration. In group 1 (aspirin-treated, 39 cases), aspirin therapy was not discontinued 2.94 ± 0.75 days preoperatively, whereas in group 2 (aspirin-naïve, 41 cases) operations were performed 2.06 ± 0.72 days after admission.

All patients in both groups underwent a laminectomy, posterolateral fusion, and pedicle screw instrumentation. All lumbar fusion surgeries were performed by the same fellowship-trained group of surgeons in a standard fashion. The procedures were carried out under general anesthesia. The anesthesiologist and surgeons were blinded to the coagulation profile during the operation. The EXPEDIUM system (DePuy, Shanghai, China) was used in the spinal internal fixation operations.

Statistical data were gathered from the medical records, including demographic data and surgical factors such as operation time, the number of levels fused, and the amount of autotransfusion or allogeneic blood products transfused, and the waiting time and length of stay. Intraoperative blood loss was calculated by summation of the total amount suctioned (minus the amount of washing saline solution), the weight of gauze (minus the weight of dry gauze), and the surgeon's estimation. Postoperative blood loss was measured by the amount of blood drained through a drainage tube, maintained until the drainage was reduced to less than 60 mL per day.

TEG was performed on the day of operation and on postoperative days 1, 3, and 5. The motion was detected as previous method (21). The composite signal tracing was displayed on a computerized thromboelastograph coagulation analyzer (TEG model 5000; Haemoscope Corporation, Niles, IL). As the thromboelastograph monitors shear elasticity, which is a physical property, it is sensitive to all the coagulation and fibrinolytic activity of the blood sample. TEG values include the platelet inhibition ratio (PIR); the reaction time (R), the time to initial thrombus formation; kinetics (K), the rate of thrombus formation; maximal amplitude (MA), the ultimate clot strength; α -angle, the slope of the K; coagulation index (CI); and PIR. The CI is a computer-calculated linear combination of the PIR, R, K, MA, and α -angle values, and reflects the overall coagulation profile (Fig. 1).

Data Analyses

Results were presented as mean \pm SEM, deviation for continuous variables with normal distribution, and n (%) for category variables. A Student t-test was utilized to compare the means of continuous variable with normal distribution, and the χ^2 test was used to compare the proportion of category variable between the 2 groups. All statistical analyses were conducted with SPSS Version 13.0 (SPSS Inc., Chicago, IL). In all the cases, $P < 0.05$ was regarded as statistically significant.

RESULTS

Characteristics of Patients

Eighty consecutive patients were strictly screened by preoperative evaluations, including detailed medical histories, physical examinations, and laboratory testing. The demographic data of the patients before the operation are summarized in Table 1. The mean age of patients was 60.88 ± 9.14 and 57.37 ± 8.84 years for groups 1 and 2, respectively ($P = 0.906$). The percentage of male and female patients and means of body mass index showed no significant difference among the 2 groups ($P > 0.05$). The groups were well-matched overall. The number of patients with a history of hypertension and diabetes was 30 (76.9%) and 9 (23.1%) versus 24 (58.5%) and 6 (14.6%), respectively, in groups 1 and 2. One patient had a history of right iliac artery aneurysm embolization with 100 mg/d aspirin therapy 15 years ago. These underlying diseases among the groups showed no significance ($P = 0.068$ and 0.054).

Aspirin Withdrawal in the Perioperative Period

All patients underwent early operative therapy, usually on the day after rigorous preoperative evaluations. Patients with a history of blood coagulation disorders, such as aplastic anemia and hypohepatia, were excluded preoperatively. The aspirin-treated patients discontinued aspirin on the morning of admission, without subcutaneous injection of low-molecular weight heparin unless there were foreseeable severe complications. This was continued for 7 days or until discharge. Postoperative mobilization was strongly encouraged by instructing patients on functional exercises for the limbs, training sessions with the physiotherapist to perform activities of daily living, and performing mental care sitting following surgery. The mean number of patients with 100 to 300 mg/d aspirin dose was

26 (66.7%), 10 (25.6%), and 3 (7.69%) in group 1 (Table 1). It was discontinued with a mean waiting time of 2.06 ± 0.73 days prior to surgery, showing no significant differences in the 2 groups ($P = 0.484$) (Fig. 2).

Operation, Hospitalization Time, and Fused Number

Surgical variables associated with excessive bleeding included operation time and an increased number of surgically fused posterior levels. The mean number of levels fused was 1.56 ± 0.71 in group 1 and 1.66 ± 0.67 in group 2, respectively ($P = 0.557$), showing no significant differences. The average operation time was 3.55 ± 0.54 and 3.04 ± 0.73 hours, respectively, showing no statistical difference ($P = 0.143$) (Table 2). The mean hospitalization time was 8.47 ± 1.01 and 12.72 ± 1.27 days, respectively, showing no statistical difference either ($P = 0.035$) (Fig. 2).

Intraoperative Blood Loss and Postoperative Drainage

Average estimated blood loss intraoperatively was 378.87 ± 36.88 mL versus 302.6 ± 68.59 mL in groups 1 and 2, respectively ($P = 0.076$). The results revealed no

statistical difference (Table 2). The mean postoperative drainage was 245.5 ± 23.6 mL, 138.8 ± 20.8 mL, and 57.1 ± 8.0 mL versus 234.8 ± 18.5 mL, 110.4 ± 12.7 mL, and 54.8 ± 12.6 mL, respectively, on preop, day 1, and day 2, showing no statistical difference ($P = 0.198, 0.069, 0.052$). Drainage was significantly higher on postop and day 1 versus day 2 in both groups ($P = 0.008^{**}, 0.03^{*}$) (Fig. 3) ($^{**}P < 0.01, ^{*}P < 0.05$).

Hemoglobinometry and Intraoperative Blood Transfusion

The mean hemoglobin level decreased from 110.1 ± 14.91 and 116.0 ± 16 g/L preoperatively to 83.01 ± 5.98 and 75.2 ± 5.19 g/L intraoperatively in groups 1 and 2, respectively ($P = 0.337, 0.412$). The intraoperative hemoglobin was significantly decreased in both groups ($P = 0.02^{*}$) ($^{*}P < 0.05$). Intraoperative transfusion requirements, including autotransfusion of red blood cells (RBCs), allogeneic RBCs, and fresh frozen plasma were 28 (2.81 ± 0.49 units), 13 (3.38 ± 0.92 units), and 10 (5.13 ± 1.81 units) versus 33 (2.49 ± 0.37 units), 11 (2.75 ± 0.71 units), and 9 (4.88 ± 1.46 units), respectively, in groups 1 and 2. There was little difference between the groups with regard to laboratory parameters, ($P = 0.211, 0.489, 0.643$). In all cases, patients with longer operation time and greater number of levels fused had relatively greater estimated blood loss and needed extra blood transfusion. The reason for postoperative blood transfusion was the development of symptoms and signs of insufficiency

Table 1. The baseline characteristics of patients before operation.

	Total Patients (n = 80)	Aspirin-treated (n = 39)	Aspirin-naïve (n = 41)	P Value
Age, (y)	59.19 ± 9.11	60.88 ± 9.14	57.37 ± 8.84	0.906
Gender, (% male)	53 (66.3%)	27 (65.9%)	26 (66.7%)	0.633
BMI	23.95 ± 3.22	24.05 ± 3.02	23.83 ± 3.46	0.121
Underlying diseases				
Hypertension, n (%)	54 (67.5%)	30 (76.9%)	24 (58.5%)	0.068
Post-op of IAH, n (%)	1 (1.25%)	1 (2.56%)	0	1
Diabetes, n (%)	15 (18.8%)	9 (23.1%)	6 (14.6%)	0.5054
Aspirin dose, n (%)				
(mg/d) 100	26 (32.5%)	26 (66.7%)	0	
200	10 (12.2%)	10 (25.6%)	0	
300	3 (3.75%)	3 (7.69%)	0	

Values are Mean \pm SD and median in parenthesis or n (%) where applicable. IAH: iliac artery aneurysm embolization. BMI: body mass index

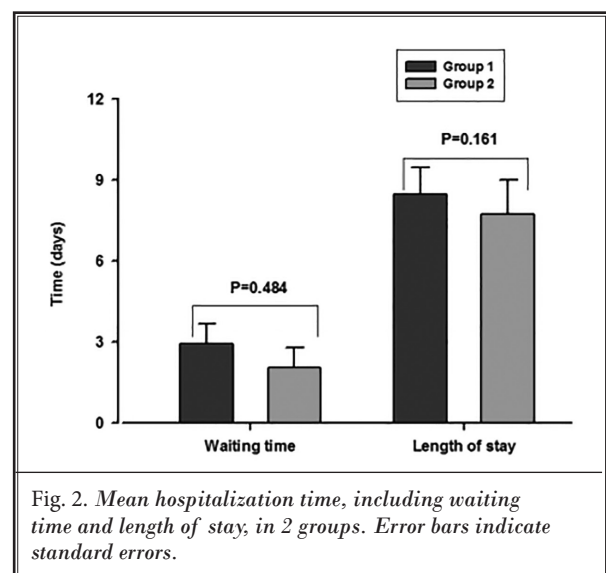


Fig. 2. Mean hospitalization time, including waiting time and length of stay, in 2 groups. Error bars indicate standard errors.

Table 2. Perioperative variables between 2 groups at different time points.

	Total patients (n = 80)	Aspirin-treated (n = 39)	Aspirin-naïve (n = 41)	P Value
No. of levels fused	1.61 ± 0.69	1.56 ± 0.71	1.66 ± 0.67	0.557
Operation time, (h)	3.24 ± 0.70	3.55 ± 0.54	3.04 ± 0.73	0.143
Hemoglobin, (g/l)				
Pre-op	113.1 ± 15.30	110.1 ± 14.91	116.0 ± 16.11	0.337
Intra-op	78.67 ± 6.74	83.01 ± 5.98	75.2 ± 5.19	0.412
Platelet count				
(10 ³ /mm ³) pre-op	216.39 ± 42.69	227.87 ± 30.96	207.2 ± 49.87	0.061
Day 1	169.11 ± 43.84	178.50 ± 35.79	161.60 ± 49.92	0.067
Day 3	187.83 ± 43.84	201.51 ± 33.89	176.91 ± 50.51	0.051
Day 5	204.89 ± 42.02	215.52 ± 31.32	196.41 ± 48.90	0.054
Blood product (n/unit)				
Autotransfusion RBC	61 (2.66 ± 0.46)	28 (2.81 ± 0.49)	33 (2.49 ± 0.37)	0.211
Allogeneic RBC	24 (3.06 ± 0.85)	13 (3.38 ± 0.92)	11 (2.75 ± 0.71)	0.489
Fresh frozen plasma	28 (5.01 ± 1.59)	10 (5.13 ± 1.81)	9 (4.88 ± 1.46)	0.643
Platelets	0	0	0	0
Intraoperative blood loss, (mL)	340.75 ± 66.19	378.87 ± 36.88	302.6 ± 68.59	0.076
Cardiovascular events	1 (1.3%)	1 (2.6%)	1 (2.4%)	1
Mortality	0	0	0	0

Data are reported as mean ± SD, RBC: red blood cell, INR: international normalized ratio. PT: prothrombin time. aPTT: activated partial thromboplastin time. PIR: platelet inhibition ratio

of arterial hypoperfusion (arrhythmia, hypotension, oliguria, hypothermia) accompanied by a decrease in hemoglobin perioperatively (Table 2).

Hematologic Findings

The mean platelet count decreased from 227.87 ± 30.96 versus 207.2 ± 49.87 10³/mm³ preoperatively to 178.50 ± 35.79 versus 161.60 ± 49.92, 201.51 ± 33.89 versus 176.91 ± 50.52, and 215.52 ± 31.32 versus 196.41 ± 48.90 10³/mm³ postoperatively between the 2 groups on postoperative days 1, 3, and 5, respectively. The intraoperative international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), PIR were 1.12 ± 0.34 versus 1.32 ± 0.45, 13.6 ± 1.63 versus 14.3 ± 1.47 seconds, 35.8 ± 6.788 versus 36.8 ± 5.88 seconds, 42.7% ± 7.92% versus 38.7% ± 8.01% showed no difference in the 2 groups ($P > 0.05$) (Table 2). A change in TEG values of PIR, R, K, MA, α -angle, and CI between the 2 groups showed no significant difference before operation and on postoperative days 1, 3, and 5. The range of PIR (30%–50%) in patients with aspirin may be a helpful index for guiding safety therapeutic window and timing of operation.

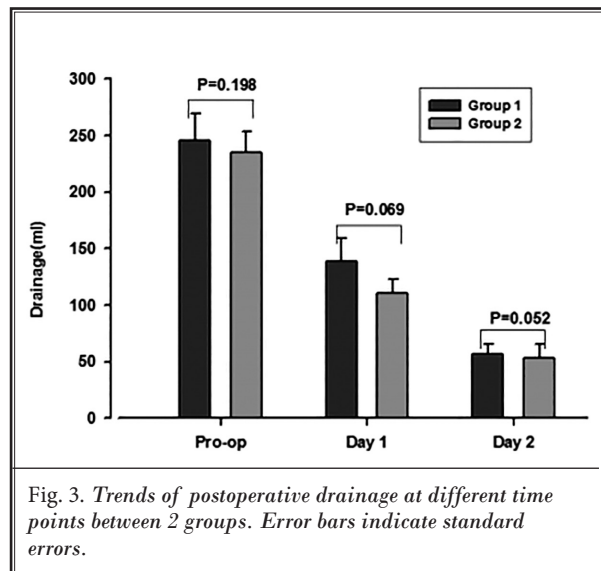
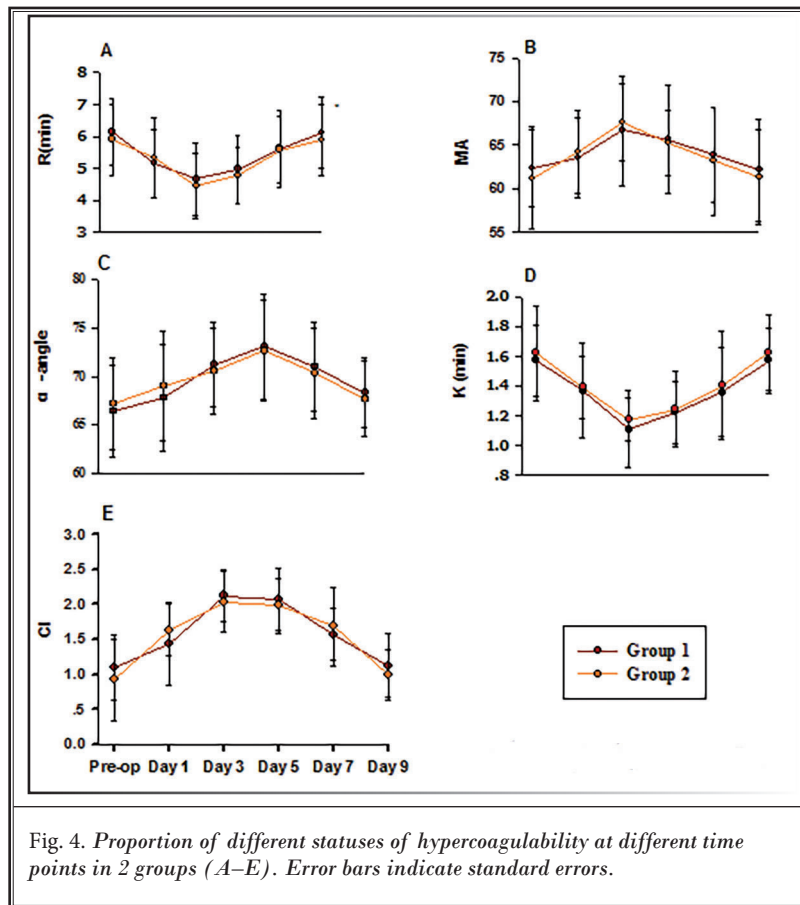


Fig. 3. Trends of postoperative drainage at different time points between 2 groups. Error bars indicate standard errors.

However, a relative decrease in the intraoperative platelet count and change trend of K, MA, α -angle, and CI values was observed in both groups postoperatively (Fig. 4). The intraoperative INR, PT,



and aPTT levels were consistent with the change in TEG values. Analysis of the individual components of the thromboelastographic profile of both groups showed that altered coagulability was identified with a short-lived period of significant hypercoagulability and enhanced fibrinolysis occurring after fused surgery and persisting until postoperative day 5. This hypercoagulability may highlight the use of low-molecular weight heparin for chemical prophylaxis.

Morbidity and Mortality

In group 1, one patient had stable angina pectoris (2.6%), whereas one patient in group 2 developed atrial fibrillation in addition (2.4%). The mortality rate in both groups was 0%. The morbidity of cardiovascular complications and mortality rate in both groups showed no statistical difference ($P = 1$) (Table 2).

Case Report

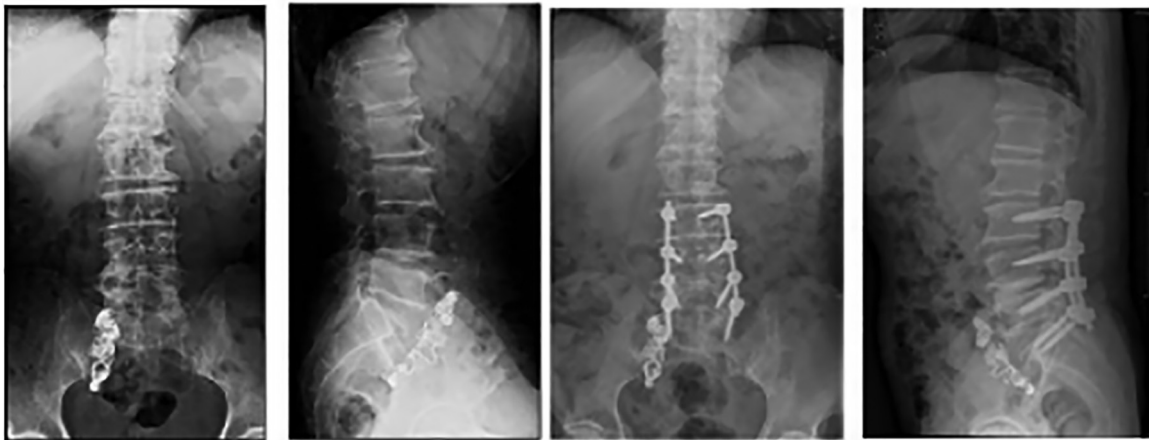
One patient had no visible hematoma on postoperative day 3 with regard to the operative field

(Fig. 5B). Patient 61 was a 62-year-old man with a history of right iliac artery aneurysm embolization with 100 mg/d aspirin therapy 15 years ago. He presented with bilateral lower limb pain and intermittent claudication. He discontinued aspirin 3 days prior to the operation and restarted aspirin 2 weeks after the surgery. The L3-S1 fixation and L4-L5 fusion were accomplished in 3 hours (Fig. 5A). Total intraoperative blood loss was 650 mL. His hemoglobin decreased from 12.3 to 8.7 g/dL and platelet count decreased to 76,000/mL postoperatively. Wound drainage totaled 450 mL and the drain was removed on postoperative day 2. He received 2 units of autotransfusion and allogeneic RBC and 3 units of fresh frozen plasma during the case. He had no history of bleeding issues and had normal coagulation testing with TEG on the day prior to the surgery and on postoperative day 3 (PIR = 45%, R = 7.1 vs. 4.4 min, K = 1.7 vs. 1.2 min, MA = 56.4 vs. 68.3, α-angle = 66.3 vs. 70.4, and CI = 1 vs. 2). He was discharged home on postoperative day 7 (Fig. 6).

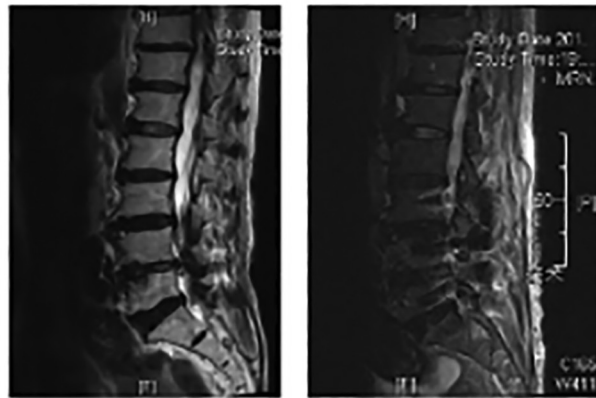
DISCUSSION

Previous metaanalysis of randomized trials have demonstrated that antiplatelet therapy effectively prevented serious cardiovascular events, arteriolar occlusion, and deep venous thromboembolism, and significantly reduced morbidity and mortality among a wide range of patients who are at high risk of occlusive vascular events (22-24). Aspirin is an effective antiplatelet agent for the primary (first occurrence of disease) and secondary (recurrence of disease) prevention of CAD. A large meta-analysis of approximately 200 randomized trials demonstrated an approximately 25% reduction in mortality with aspirin versus placebo in patients with a history of CAD (25,26).

A single oral dose of aspirin 150 mg inhibited platelet aggregation in vitro, and aspirin 650 mg significantly lengthened the bleeding time in normal human patients by approximately 3 to 7 days (4,27). The irreversible platelet inhibition associated with aspirin therapy can lead to an increased risk of periopera-



A. Preoperative and postoperative standing front and lateral radiographs of Patient 61



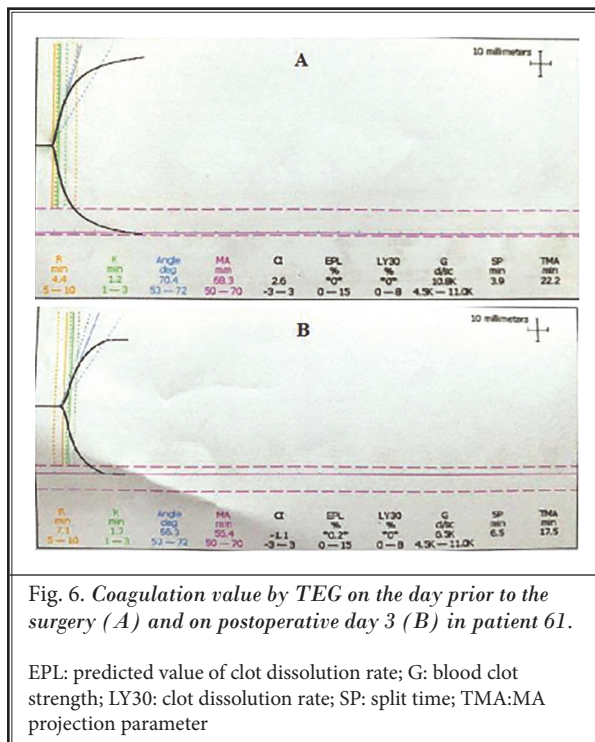
B. Perioperative standing MRI of Patient 61 (showed no visible hematoma after surgery)

Fig. 5. Perioperative standing front and lateral radiographs (A) and standing MRI image (B) of patient 61 showed no visible hematoma after surgery.

tive bleeding, even when used in low doses. A meta-analysis of 474 studies showed that aspirin treatment increased perioperative bleeding by a factor of 1.5 (10,28). Perioperative bleeding raises the underlying risk of consequent complications, including acute coronary syndrome, neural compression, delayed wound healing, and prolonged hospitalization, as reported in cardiovascular surgery, orthopedic surgery, urologic surgery, and dentistry (29-31). Lewis and Pritchard (32) reported that antiplatelet administration, associated with repeated hematoma formation and platelet dysfunction caused by aspirin, can induce hemorrhage after spinal surgery. Therefore in view of the underlying

risk of perioperative bleeding and consequent complications, and the general acceptance that the bleeding tendency would normalize, routine surgical practice tends to temporarily discontinue aspirin therapy 7 to 10 days prior to noninstrumented lumbar spine surgery (9,33).

However, there is significant controversy as to whether aspirin therapy should be interrupted or maintained perioperatively, and the routine withdrawal of aspirin 7 to 10 days prior to surgery has been questioned (27,34). Aspirin withdrawal perioperatively is associated with a significantly increased risk of perioperative cardiovascular complications, whereas



perioperative myocardial infarction has an in-hospital mortality rate of 17% to 21% (35,36). Recent articles have reported that the cardiovascular mortality rate after cardiac surgery can increase even 7-fold in patients with abrupt cessation of aspirin for greater than 3 to 5 days (19). A meta-analysis by Burger and Chemtius (10) demonstrated that perioperative aspirin interruption raised the cardiovascular risk in 10.2% of the cases and resulted in lower limb ischemic complications in 6.1% of the cases (37). For this reason, it is highly recommended that patients with preexisting CAD should be administered aspirin indefinitely and without cessation. Therefore it appears likely that the benefits of thromboprophylaxis therapy will far outweigh the perioperative hazards, excluding the definite bleeding risks carried by hemodialysis patients or the negligible risk of vascular events in apparently healthy people. Consequently, routine aspirin therapy should be considered perioperative for all patients with a potential risk of occlusive vascular disease unless a definite contraindication exists (38,39).

In this prospective randomized aspirin-controlled multicenter study, we monitored perioperative coagulation profile with thromboelastography, which may

be an effective method to identify hypo- and hypercoagulability in aspirin-treated patients undergoing posterior lumbar fusion. TEG values may differentiate patients with clinical evidence of platelet function from those with normal coagulation function, especially in patients who are on aspirin therapy. We found that the aspirin-treated group seemed to have relatively higher intraoperative blood loss, postoperative drainage, et cetera, highlighting the necessity of aspirin withdrawal. Meanwhile, preoperative aspirin interruption (2.06 ± 0.73 days) showed no significant differences in the tendency for perioperative severe hemorrhage, intraoperative blood transfusion, morbidity and mortality rate, and coagulation profile with thromboelastography undergoing posterior lumbar fusion. Based on our results, we believe that it may be comparatively safe to relax the restriction of the aspirin therapeutic window to approximately 2 to 3 days prior to surgery based on the TEG result, unless there are foreseeable severe complications. Meanwhile, we routinely restarted aspirin 1 week after surgery and found that there was no recurrence or aggravation of cardiovascular events. Therefore the perioperative management of aspirin therapy, especially for the secondary prevention of CAD, should be given serious consideration, and meanwhile may regulate in a flexible manner with TEG.

Our study had some limitations. First, the relatively small number of patients recruited limits control over other factors; larger studies may need to confirm our findings. Second, the patients were objectively less healthy and with more medication treatment, which may result in a variance in the amount of blood loss. Randomized controlled studies are needed to further confirm these results. Despite these limitations, we hope that the study is meaningful and acts as reference material for perioperative aspirin management in the future during spinal surgeries.

CONCLUSIONS

In our small series, it may be comparatively safe to relax the restriction of the aspirin therapeutic window to approximately 2 to 3 days prior to surgery than what is recommended in current guidelines based on the TEG result. TEG may be a helpful method to monitor perioperative coagulation profile in aspirin-treated patients with LDH, offering a safety therapeutic window and timing of operation. Larger prospective studies would be helpful in further verification of our findings.

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