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Plasma D-dimer and FDP are promising biomarkers to predict perioperative fibrinolysis and bleeding following primary total joint arthroplasty

A STROBE compliant article

Yan Wang, MD[a], Jinwei Xie, MD PhD[b,*], Fuxing Pei, MD[b]

Abstract

Perioperative bleeding is associated with postoperative hyperfibrinolysis caused by surgical trauma in the setting of total hip and knee arthroplasty (THA/ TKA). The study aimed to clarify the dynamics of postoperative fibrinolytic activity and the values of fibrin degeneration products and thromboelastography (TEG) to guide precisive antifibrinolytic therapy.

Forty three patients undergoing primary unilateral THAs and 40 TKAs were included to the prospective observational cohort study. Venous blood sample at different time points (preoperative, intraoperative, postoperative 6 hours, 12 hours, 24 hours, 48 hours) were drawn to test D-dimer, fibrin (-ogen) degradation products (FDP) and TEG.

The TEG parameters associated with coagulation (R, K, α, MA, and CI) and fibrinolysis (estimate percent lysis and Ly30) were all in normal range although had a higher level than preoperative time ($P < .05$). The postoperative levels of D-dimer and FDP were higher than preoperative level ($P < .05$). The dynamics of D-dimer and FDP presented a bimodal pattern, which peaked at 6 hours postoperatively, then remained and decreased until 24 hours, but would rebound at 48 hours postoperatively with smaller amplitude. Moreover, FDP_{6h} ($P = .028$), $D\text{-}Dimer_{6h}$ ($P = .044$), FDP_{12h} ($P = .009$), $D\text{-}dimer_{12h}$ ($P = .007$), and FDP_{48h} ($P = .016$) were all correlated with total blood loss on POD3.

FDP and D-dimer were effective and practical markers for prediction of acute postoperative fibrinolytic activity, which peaked at 6 hours after end of surgery and would maintain for at least 24 hours.

Abbreviations: EPL = estimate percent lysis, FDP = fibrin (-ogen) degradation products, MA = maximal amplitude, TEG = thromboelastography, TJA = total joint arthroplasty, TKA = total knee arthroplasty, THA = total hip arthroplasty, TXA = tranexamic acid.

Keywords: antifibrinolytic therapy, biomarker, fibrinolysis, thrombosis, total joint arthroplasty

1. Introduction

Total joint arthroplasty (TJA), as one of the most common surgeries in orthopedics, it can effectively alleviate pain, ameliorate function and improve the quality of patients' life. With the development of aging population, the demand of TJA is increasing. According to the projection in the United States, the demand for primary total hip arthroplasties is estimated to grow by 174% to 572000 by 2030; and the demand for primary total knee arthroplasties is projected to grow 673% to 3.48 million procedures.[1] Years ago, TJA was accompanied by significant

Editor: Bo Liu.

This research was supported by the Postdoctoral Research Program of West China Hospital, Sichuan University (2018HXBH073); the National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z2018B11); and the National Health and Family Planning Commission of the People's Republic of China (201302007).

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Core Facility of West China Hospital, [b] Department of Orthopaedic Surgery, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China.

[*] Correspondence: Jinwei Xie, Department of Orthopaedic Surgery, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, No. 37 Guoxue Road, Chengdu 610041, Sichuan Province, People's Republic of China (e-mail: rain_xjw@yeah.net).

How to cite this article: Wang Y, Xie J, Pei F. Plasma D-dimer and FDP are promising biomarkers to predict perioperative fibrinolysis and bleeding following primary total joint arthroplasty: a STROBE compliant article. Medicine 2021;100:20(e26058).

Received: 19 November 2020 / Received in final form: 8 April 2021 / Accepted: 30 April 2021

http://dx.doi.org/10.1097/MD.0000000000026058

blood loss, especially hidden blood loss and allogenic red blood cell transfusion.[2,3] The reason for the massive hidden blood loss and high transfusion rate was hyperfibrinolysis caused by surgical trauma and tourniquet use.[4]

In the past decades, patients' blood management has been put into the spotlight and achieved extraordinarily promising results, since 1 study suggested that transfusion rate since 2010 has fallen to 9%.[5] Of all the measures, antifibrinolytic agents have played a vital role in reducing blood loss and transfusion. Tranexamic acid (TXA) is a synthetic lysine analogue, which can inhibit the activation of plasminogen by blocking the lysing binding sites. Up to now, TXA has been applied by numerous surgeons in orthopedics surgeries, especially in joint arthroplasties.[6]

Although the efficacy and safety profile of TXA in primary total hip or knee arthroplasty has been confirmed by a lot of Level I evidence,[7–9] the optimal route, timing and dosage were in debate. Recently published research[10] found topical TXA use was associated with greater early postoperative pain and opioid consumption in primary THA patients, and this indicated the advantage of intravenous TXA. Meanwhile, the second important question is the optimal course of antifibrinolytic therapy. The answer for this question is to clarify the longitudinal dynamics of perioperative fibrinolytic activity, because it is vital to decide the rationality of postoperative multiple boluses of TXA.

Therefore, the authors conducted the prospective observational cohort study, in order to clarify the following issues:

1. the dynamics of perioperative fibrinolysis in primary unilateral total hip and knee arthroplasty;
2. the value of fibrin degeneration products and thromboelastography in predicting perioperative bleeding.

2. Materials and methods

2.1. Study design

This prospective observational study was an additional analysis of the previous randomized controlled study, which was performed in accordance with the provisions of the Declaration of Helsinki as revised in 2013. The study protocol was approved by the ethical committee (West China biomedical ethics committee, 2012–268) and registered in the Chinese Clinical Trial Registry (ChiCTR-INR-16009288). Before patient's inclusion, written informed consent and research authorizations were obtained from all the participants.

2.2. Patients cohort

From September 2016 to February 2017, a total of 40 patients who were scheduled to take primary unilateral total knee arthroplasty and 43 patients undergoing primary unilateral total hip arthroplasty were involved in the longitudinal laboratory cohort study. The indications for primary THA included primary or secondary osteoarthritis, osteonecrosis of femoral head (stage of Fict III or IV), dysplasia development of hip with severe pain or joint dysfunction. The indications for primary TKA included primary or secondary osteoarthritis, or other inflammatory arthritis with severe pain or joint dysfunction. The patients with following conditions were also excluded: age $<$18years or $>$80 years, flexion deformity $\geq$30°, Varus/valgus deformity $\geq$30°, preoperative fibrin (-ogen) degradation products (FDP) $>$ 5 mg/L, preoperative hepatic or renal dysfunction, cerebrovascular or cardiac problems taking oral anticoagulation or antiplatelet therapy, presentation of deep venous thrombosis, congenital or acquired clotting disorders.

2.3. Surgical procedure

All the surgical procedures were performed by 1 senior surgeon under general anesthesia. And standard medial parapatellar arthrotomy was applied for total knee arthroplasty without tourniquet, and the posterolateral approach was used for total hip arthroplasty. A cemented posteriorly stabilized prothesis was implanted in all total knee arthroplasty patients, and cementless acetabular and femoral components were implanted in total hip arthroplasty patients. An intra-articular drain was placed and remained clamped for 30 minutes, and removed on the postoperative first day morning. No vacuum wound drainage and blood salvage system were used.

2.4. Patients' blood management protocol

As to patients' blood management, erythropoiesis therapy was use for the preoperative anemia patients. Furthermore, controlled hypotensive blood pressure techniques were adopted by the anesthesia team to remain 90–110 mm Hg/60–70 mm Hg throughout the procedures. Considering the ethical injustice of high risk of bleeding and the definite efficacy of antifibrinolytic therapy, all the patients received a single bolus of 20 mg/kg tranexamic acid 10 minutes prior to incision.

2.5. Postoperative care protocol

In order to reduce postoperative hidden bleeding, cold pack was used for all the patients on the surgical site for 12 hours. And iron supplements and erythropoietin were administered to the postoperative anemic patients according to the WHO criteria and blood management guideline.[11] Allogenic red blood cell transfusion trigger was set as 7 g/dL in accordance with the guideline by the National Ministry of Health.

Chemical and physical prophylaxis were adopted against venous thromboembolism. Intermittent foot slope pump system was used before walking as mechanical prophylaxis in addition to the quadriceps muscle strength exercise. Rivaroxaban (10 mg) was initiated 6 hours postoperatively and repeated at 24-hour intervals for14 days at least.

2.6. Outcome measurements

The primary outcomes were level fibrinolysis parameters (D-dimer and FDP), and secondary outcomes were thromboelastography (TEG) parameters. Patients' demographical and surgical characteristics were obtained before arthroplasty. Coagulation, renal function, and liver function were routinely examined. Complete blood counts were examined preoperatively and on the morning of postoperative day 1 to 3. Perioperative total blood loss was calculated according to Nadler and Gross formula[12,13] taking into account of the allogenic blood transfusion.

In order to longitudinally evaluate the dynamics of perioperative coagulation and fibrinolysis, venous blood samples were collected before surgery (pre-op), 30 minutes after incision (intra-op), at 6 hours (post-op 6 hours), 12 hours (post-op 12 hours), 24 hours (post-op 24 hours) and 48 hours (post-op 48 hours) after surgery. The levels of plasma D-dimer and plasma FDP were measured by immunoturbidimetry method (FDP kits, Biolinks Co., Ltd., Tokyo, Japan, reference: $<$5 mg/L; D-dimer kits,

Siemens Healthcare GmbH, Erlangen, Germany, references: <0.55 mg/L FEU) using automated blood coagulation analyzer CS-5100 (SYSMEX Co. JAPAN). Blood for TEG analysis was drawn into a 2 mL citrated vacutainer. TEG samples were processed within 2 hours of blood draw at 37°C using a TEG analyzer (CFMS LEPU-8800, Beijing Lepu Medical Technology Co., LTD, China). Citrated venous blood (1 mL) was added to 1 vial of kaolin, and after gentle mixing by inversion, 340 μL of this solution was added to the TEG cup along with 20 μL 0.2 M calcium chloride. Then thromboelastography was initiated and parameters of coagulation markers: R (the time to onset of clot formation), K (interval from R to a fixed level of clot firmness), α (the slope of TEG tracing), MA (maximum amplitude, measures the strength of the clot), clotting index (composite score of coagulation); and fibrinolysis markers: LY30 (percent lysis at 30 minutes after MA), EPL (estimate percent lysis, predicted percent lysis at 30 minutes after MA) were recorded from tracings (Fig. 1).

2.7. Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM, Chicago, IL). Descriptive statistics are presented as mean (standard deviation, SD) for normally distributed continuous variables or median (interquartile range, IQR) for non-normally distributed data, and frequency (percentage) for categorical variables.

The prespecified primary analysis assessed the change in the outcomes of interest over time. Due to the known dynamic nature of the biomarkers, one-way repeated measures ANOVA with post hoc Bonferroni correction was adopted to analyze the normally distributed biomarkers at different time points. And related-sample Friedman test two-way analysis of variance with post hoc Bonferroni correction for multiple tests was adopted to compare the non-normally distributed biomarkers at different time points.

The prespecified secondary analysis evaluated the correlation between biomarkers and bleeding outcomes. Pearson or Spearman correlations were calculated between biomarkers and total blood loss on postoperative day 1 and 3. In addition to univariate analysis, generalized linear model was performed to test the association between biomarkers and bleeding outcomes with covariate adjustment of age, BMI, preoperative hematocrit level and operation time. Furthermore, post hoc power analysis was performed using F test (repeated measures ANOVA within factors) with G Power software 3.1. In all cases a *P* value less than .05 was considered to be statistically significant.

3. Results

A total of 83 patients were finally analyzed, consisting of 40 primary TKA and 43 primary THA. The baseline characteristics were presented in Table 1. All the coagulation profiles of the patients were in the normal range.

The perioperative bleeding outcomes were shown in Table 2. The total blood loss on POD 3 was about 877.99 mL in primary unilateral TKA, and 1031.71 mL in primary unilateral THA, which was about twice that on POD 1. Only 1 patient received allogenic red blood cell transfusion in the subgroup of primary TKA.

The TEG outcomes were presented in Table 3. During all the evaluation period, the TEG parameters associated with coagulation (R, K, α, MA, and CI) tended to increase intraoperatively, and decrease at 6 hours postoperatively, although all the parameters were within normal range. And the differences of R, K, α, MA, and CI between different time points were statistically significance ($P < .05$). In terms of parameters associated with fibrinolysis (Ly30 and EPL), they had the same trend with statistically significance between different time point ($P < .001$). The Ly30 and EPL continued to increase from intraoperative time to postoperative 48 hours although the values were all within normal range.

The FDP levels at intraoperative time point and postoperative time point were all higher than preoperative level ($P < .05$ for all, Table 3). The level of FDP peaked at 6 hours postoperatively, and

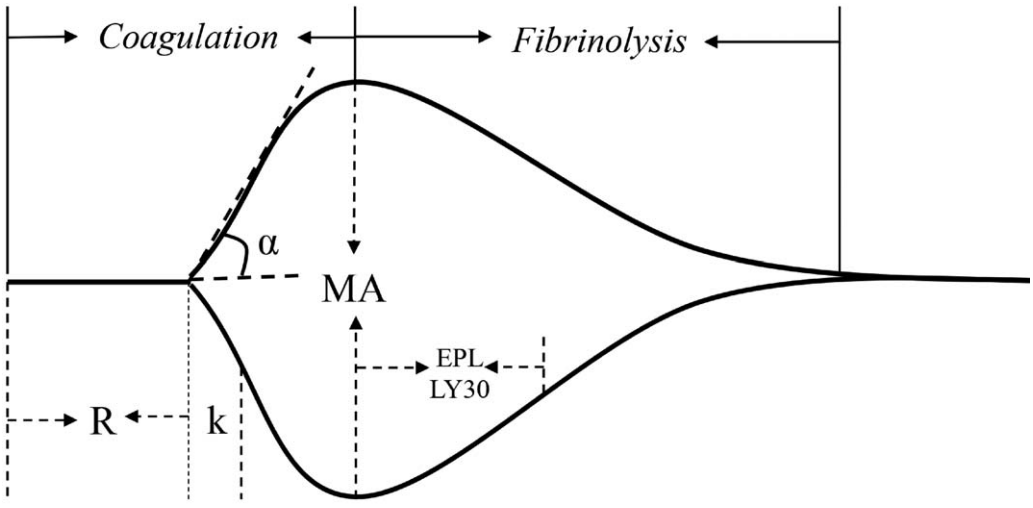

Figure 1. Schematic example of thromboelastography tracing. The *R* value, or reaction time represents the time to onset of clot formation. Clot formation time, *K*, is the interval from *r* time to a fixed level of clot firmness, the point that the amplitude of the tracing reaches 20 mm. Alpha angle, is the slope of the TEG tracing and demonstrates the rate of clot formation. Maximum amplitude, MA, is maximum amplitude and measures the strength of the clot. The clotting index (CI) is a composite score of coagulation taking into account all of the above values. LY30, percent lysis at 30 minutes after MA. Estimate percent lysis (EPL) value is the predicted percent lysis at 30 minutes after MA.

Table 1

The demographic and surgical parameters of involved patients.

	TKA (n = 40)	THA (n = 43)	Total (n = 83)
Age (year)	65.97 ± 8.60	54.05 ± 12.58	59.80 ± 12.34
Gender (male /female)	8/32	17/26	25/58
Height (m)	1.57 ± 0.07	1.60 ± 0.06	1.59 ± 0.07
Weight (kg)	61.30 ± 9.31	63.27 ± 10.84	62.32 ± 10.12
BMI (kg/m^2)	24.68 ± 3.10	24.56 ± 3.74	24.62 ± 3.42
ASA score	1.95 ± 0.22	2.00 ± 0.01	1.98 ± 0.15
OA (n, %)	39 (97.5%)	28 (65.11%)	67 (80.72%)
Range of Motion (°)	97.50 ± 14.19	84.30 ± 23.26	90.66 ± 20.42
HSS / Harris score	47.78 ± 10.22	40.42 ± 10.76	43.96 ± 11.07
PLT (*10^9/L)	182.78 ± 62.19	190.51 ± 54.08	186.78 ± 57.90
PT (s)	11.64 ± 0.61	11.57 ± 0.75	11.61 ± 0.68
APTT (s)	30.10 ± 4.25	30.70 ± 4.13	30.41 ± 4.18
INR	1.01 ± 0.05	1.00 ± 0.05	1.01 ± 0.05
Hb (g/L)	127.53 ± 11.34	135.56 ± 13.87	131.69 ± 13.27
Hct	0.39 ± 0.03	0.41 ± 0.04	0.40 ± 0.03
PBV (mL)	3693.33 ± 542.16	3911.27 ± 629.98	3806.24 ± 595.89

The data were presented with mean ± standard deviation or frequency (percentage).
BMI = body mass index; HSS = hospital of special surgery, ASA = American society of Anesthesiologist; PLT = platelet, PT = prothrombin time, APTT = activated partial thromboplastin time, INR = International normalized ratio, Hb = Hemoglobin, Hct = haematocrit, PBV = patient blood volume.

would last for 24 hours. Similarly, the levels of D-dimer at intraoperative time, postoperative 6 hours, 12 hours and 24 hours were higher than preoperative level ($P < .05$ for all, Table 3). The D-dimer also peaked at 6 hours postoperatively, and lasted for 24 hours. Moreover, the levels of FDP and D-dimer were higher in patients undergoing TKA (Fig. 2, Tables S1 and S2, Supplemental Digital Content http://links.lww.com/MD/G161, http://links.lww.com/MD/G162).

In order to evaluate the correlation between FDP, D-dimer and postoperative bleeding, generalized linear model was performed on the basis of spearman analysis (Table 4). The results showed FDP_{6h} ($P = .028$), $D\text{-}dimer_{6h}$ ($P = .044$), FDP_{12h} ($P = .009$), $D\text{-}dimer_{12h}$ ($P = .007$), FDP_{48h} ($P = .016$) were all correlated with total blood loss on POD3 after adjusting for age, BMI, operation time and preoperative Hct level. Moreover, these trends were identified in both TKA and THA procedures (Tables S3 and S4,

Table 2

Perioperative blood loss and transfusion requirement in each group.

	TKA (n = 40)	THA (n = 43)	Total (n = 83)
Operation time (min)	68.97 ± 12.30	73.49 ± 15.22	71.31 ± 13.99
Hb POD1 (g/L)	118.18 ± 10.80	117.40 ± 15.32	117.77 ± 13.26
Hb POD3 (g/L)	101.83 ± 11.57	103.47 ± 13.92	102.67 ± 12.79
TBL POD1 (ml)	349.60 ± 259.92	535.24 ± 298.67	445.78 ± 294.16
TBL POD3 (ml)	877.99 ± 438.47	1031.71 ± 403.38	957.63 ± 425.15
Drainage (ml)	168.75 ± 116.86	213.37 ± 114.75	191.87 ± 117.23
Transfusion (n, %)	1 (2.5%)	0	1 (1.2%)
VTE	0	0	0

The data were presented with mean ± standard deviation or number (percentage).
Hb = hemoglobin, TKA = total knee arthroplasty, THA = total hip arthroplasty, POD = postoperative day, TBL = total blood loss, VTE = venous thromboembolism.

Supplemental Digital Content http://links.lww.com/MD/G163, http://links.lww.com/MD/G164).

4. Discussion

The most important find of this study was that we have identified 2 useful biomarkers, D-dimer and FDP, for prediction of acute postoperative blood loss and fibrinolytic activity. Furthermore, we have clarified the duration and dynamics of postoperative fibrinolytic activity.

Total joint arthroplasty is associated with substantial blood loss, which is caused by the bone and soft tissues surface bleeding. Of this, the hidden blood loss is account for over 50% of total blood loss.[14] From the perspective of clinical experience, the hidden blood loss could aggravate postoperative knee swelling and pain, thus hindering the enhanced recovery after surgery. Therefore, it is more clinically significant to reduce hidden blood loss.

As well as known, the hidden blood loss results from perioperative hyperfibrinolysis which is caused by surgical trauma and enhanced by use of tourniquet.[15] And that is why the antifibrinolytic therapy could work. Given the higher antifibrinolytic activity of intravenous administration and potential harm to chondrocyte cell or neuron of topical administration,[10,16]

Table 3

The results of perioperative TEG parameters at each time point.

	Preoperative	Intra-OP	Post-OP 6h	Post-OP 12h	Post-OP 24h	Post-OP 48h	*P* value
R (5-10 min)[§]	5.71 ± 1.01	6.78 ± 1.20[*]	4.48 ± 0.90[*,¶]	4.87 ± 1.57[*,¶]	4.93 ± 0.89[*,¶]	5.37 ± 1.43[¶,†]	<.001
K (1-3min)[§]	1.88 ± 0.55	2.16 ± 0.63[*]	1.63 ± 0.49[*,¶]	2.07 ± 1.99	1.76 ± 0.54[¶]	1.68 ± 0.62[¶]	.021
α (55-78°)[§]	63.94 ± 5.56	70.33 ± 6.11[*]	66.81 ± 5.45[*,¶]	65.38 ± 7.02[¶]	65.66 ± 5.29[¶]	66.53 ± 6.33[*,¶]	<.001
MA (51-55mm)[§]	55.73 ± 5.32	59.78 ± 7.78[*]	56.56 ± 5.84[¶]	53.42 ± 10.52[¶]	56.04 ± 4.55[¶]	57.09 ± 8.12	<.001
CI (-3~+3)[£]	-0.30 (−1.40 to 0.70)	0.59 (−0.20 to 1.20)	1.00 (−0.50 to 2.00)[*]	0.50 (−1.00 to 1.00)	0.40 (−0.30 to 1.20)	0.40 (−0.80 to 1.40)	<.001
EPL (0-15%)[£]	0.10 (0.00–1.00)	0.11 (0.00–0.32)	0.20 (0.00–0.60)	0.30 (0.00–1.40)[¶]	0.40 (0.00–0.90)	0.80 (0.20–1.90)[*,¶,#]	<.001
Ly30 (0-8%)[£]	0.10 (0.00–1.00)	0.10 (0.00–0.30)	0.20 (0.00–0.60)[¶]	0.30 (0.00–1.50)[¶]	0.40 (0.00–0.90)	0.70 (0.10–1.70)[*,¶,#]	<.001
FDP[£]	1.55 (1.00–3.08)	4.82 (2.66–6.97)[*]	15.00 (8.90–23.60)[*,¶]	11.50 (5.60–17.00)[*,¶,†]	12.40 (6.40–21.30)[*,¶]	4.90 (3.50–6.10)[*,†,‡,#]	<.001
D-Dimer[£]	0.46 (0.30–0.85)	1.80 (1.07–2.63)[*]	5.63 (3.34–8.23)[*,¶]	4.28 (2.35–6.17)[*,¶,†]	4.03 (2.14–6.28)[*,¶]	1.27 (0.80–1.80)[†,‡]	<.001

The data were presented with mean ± standard deviation or median (interquartile range, IQR).
[§]*P* values were analyzed using one-way repeated measures ANOVA with post hoc Bonferroni correction.
[£]*P* values were analyzed using related-sample Friedman's test two-way analysis of variance with post hoc Bonferroni correction for multiple tests.
[*]$P < .05$ when compared with preoperative level.
[¶]$P < .05$ when compared with intraoperative level.
[†]$P < .05$ when compared with post-op 6 h.
[‡]$P < .05$ when compared with post-op 12 h;# $P < .05$ when compared with post-op 24 h.
TEG = thromboelastogram. R-time = reaction time. K = time from R to a fixed level of clot firmness (20 mm). a = alpha angle. MA = maximal amplitude. Ly30 = percent lysis at 30 min after MA. EPL = estimate percent lysis.

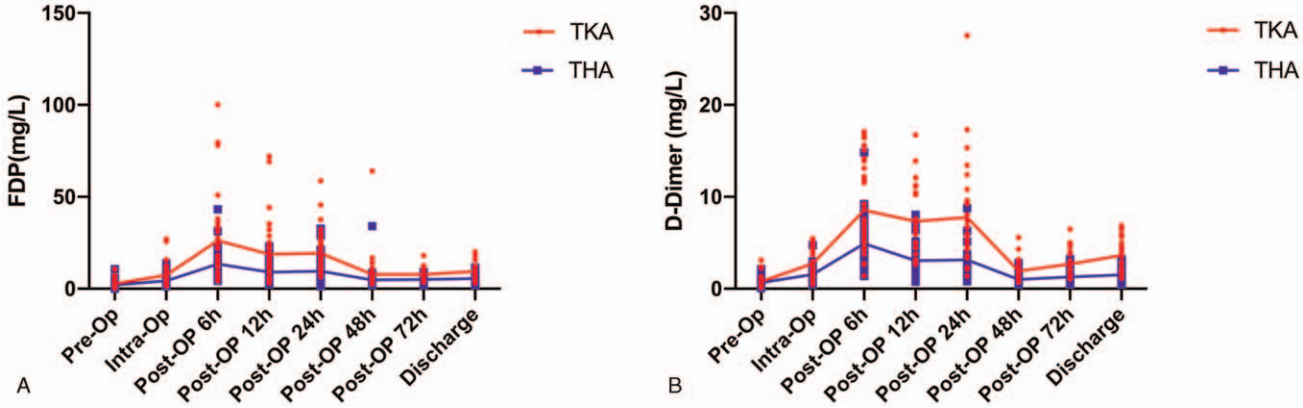

Figure 2. The dynamic trend of FDP (A) and D-dimer (B) following primary total hip and knee arthroplasty.

intravenous route is preferred. However, up to now, the optimal antifibrinolytic duration in primary total hip or knee arthroplasty is still controversial. Mukherjee[17] found single dose intravenous TXA may not be adequate to reduce blood loss and transfusion in patients undergoing single stage bilateral TKA. Tzatzairis and his colleagues[18] also found 3 doses of intravenous TXA (about 12 hours for antifibrinolytic therapy) was more effective to reduce blood loss and transfusion in patients undergoing TKA without tourniquet. While the randomized controlled trial by Tsukada [19] found postoperative intravenous TXA had no additive effect in reducing blood loss when compared with intraoperative TXA administration. But the study has not evaluated the outcomes regarding hidden blood loss, inflammatory marker or limb swelling. Considering the half-life of TXA (about 3 hours), in our opinion, it is vital to identify the duration and dynamics of perioperative fibrinolysis to guide the precise antifibrinolytic treatment following THA and TKA.

Generally, systemic fibrinolytic activity was evaluated with a series of biomarkers, including plasmin-anti-plasmin complex (PAP), tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1) D-dimer or euglobulin lysis time (ELT). In these cases, it will take approximately 60 minutes to test ELT. And the other biomarkers such as PAP, tPA, PAI-1 are not routine testing items and expensive. All these disadvantages have limited the value of routine practice.

TEG is a blood test developed in 1950s, which provides a snapshot of patients' coagulation and fibrinolysis profile by evaluating clot formation and lysis. Recently, TEG has been applied to assess traumatic coagulopathy and explore the feasibility of individualized anticoagulation following TKA.[20–22] Few studies have evaluated perioperative systemic fibrinolytic activity with use of TEG in the setting of primary unilateral THA and TKA. In our study, intraoperative coagulation parameters (R, K, alpha angle, MA) significantly increased from the baseline (Table 3 and $P < .05$ for all). And the coagulation index (CI) peaked 6 hours postoperatively and then decreased with statistical significance (Table 3, $P < .05$). These results indicated a hypercoagulable state, which were consistent with the other studies.[23] The state may owe to the surgical trauma and use of TXA, which also indicated the importance of early initiation of anticoagulation against venous occlusive events.

On the other hand, we tried to assess the systemic fibrinolytic activity with the use of TEG. Unfortunately, the fibrinolysis parameters, namely EPL and Ly30, were all in normal range at each time point although absolute increase was observed (Table 3). The following factors may contribute to the phenomenon. The blood sample was drawn from upper limb instead of wound. Benoni[24] compared the difference in markers for coagulation and fibrinolysis in peripheral venous blood with blood from the wounds. And they found the activation of fibrinolysis was significantly higher in blood from the wounds than in peripheral venous blood. Secondly, the threshold for hyperfibrinolysis (Ly30 > 15%) was too critical. In the study by Raza,[25] the authors found only 5% of trauma patients have hyperfibrinolysis on TEG. Similarly, Ives[22] also found approximately 10% of trauma patients had hyperfibrinolysis based on the TEG threshold (Ly30 > 15%). If the cut-point of Ly30 was set as 3%, the hyperfibrinolysis was 24% and associated with higher mortality among pediatric trauma patients (OR = 6.2).[26] Therefore, we also held the opinion that TEG is an insensitive measure of endogenous fibrinolytic activity.

Coagulation and fibrinolysis system keep balance to remain physiological clearance of vessels. After surgical trauma, intravascular fibrin deposition is vital to prevent life-threatening bleeding. Nevertheless, this process is relatively short-lived, and

Table 4

Association of D-Dimer, FDP and TEG parameter with post-operative bleeding.

Outcome variable	Biomarker	Parameter estimate (Std. Error)	*P* value[¶]
Total blood loss on POD1	EPL_{pre}	90.71 (26.92)	.001
	$LY30_{pre}$	−94.99 (27.67)	.001
	R_{0}	−90.96 (29.08)	.002
	FDP_{24h}	5.79 (2.77)	.036
Total blood loss on POD3	K_{pre}	709.91 (246.98)	.004
	MA_{pre}	−37.57 (11.15)	.001
	EPL_{pre}	129.77 (39.33)	.001
	CI_{pre}	211.56 (64.66)	.001
	$LY30_{pre}$	−79.53 (40.42)	.049
	FDP_{6h}	10.16 (4.62)	.028
	$D\text{-}Dimer_{6h}$	13.69 (7.89)	.044
	R_{12h}	−133.35 (62.87)	.031
	FDP_{12h}	7.59 (4.61)	.009
	$D\text{-}Dimer_{12h}$	9.75 (5.28)	.007
	FDP_{48h}	27.89 (11.55)	.016

[¶] Only significant covariables in the model were presented, and the model was adjusted for age, body mass index, patients' blood volume, preoperative Hct level and operation time. POD, postoperative day.

subsequent fibrinolysis will dissolve the clots to prevent thrombosis and thromboembolic complications. Thus, the breakdown of fibrin or fibrinogen would lead to the formation of FDP and D-dimer. D-dimer was utilized to predict VTE although the results remained controversial. In the study by An,[27] the authors characterized the longitudinal resolution of D-dimer after primary THA and TKA over a 6-week period, and found 92% of THA and 100% of TKA patients had a positive test of serum D-dimer (higher than threshold) without any symptomatic DVTs. In the current study, we also found the level of D-dimer did not fall back to the normal range before discharge, and no DVTs were detected (Table 2 and Fig. 2). Thus, D-dimer is an ineffective screening test for the diagnosis of symptomatic DVTs in the acute postoperative period after THA and TKA.

On the contrary, it was of significantly clinical utility to assess the postoperative fibrinolytic activity.[25,28,29] After comprehensively review of literature, only 1 study described the dynamics of system fibrinolytic activity in the postoperative 24 hours period.[29] And no studies have evaluated the clinical utility of FDP in the prediction of fibrinolysis. In our study, we found the fibrinolytic activity peaked at postoperative 6 hours, then started to decrease, and would last for at least 24 hours, no matter of D-dimer or FDP. And this trend was similar with the results from Blanié,[29] which indicated the hyperfibrinolysis would maintain 18 h as evidenced by an increase in D-dimer. Moreover, our study also found the significant correlation between peak level of D-$dimer_{6h}$, FDP_{6h} and total blood loss on POD3, which provided robust evidence for the clinical value of D-dimer, FDP in the prediction of hyperfibrinolysis and antifibrinolytic therapy.

More interestingly, the level of D-dimer and FDP rebounded at postoperative 48 hours, although the amplitude was much smaller. Our recent study also found the D-dimer and FDP would remain a higher level until postoperative 90 days.[30] The main reason may be related to wound healing and inflammation, because the deposition and subsequent clearance of fibrin from the extravascular space have been proven to be essential element of tissue remodeling.[27,31,32] Moreover, plasminogen or plasmin via fibrinolysis play a vital role in the inflammation. Plasmin exhibits a broad spectrum of proinflammatory responses by binding and activating monocytes, neutrophils, platelets, and endothelial cells, and complement-releasing lipid mediators and cytokines.[33] Our previous study also indicated a higher D-dimer and FDP in the patients of periprosthetic joint infection.[34] Thus, we should pay close attention to the potential risk of infection after discharge.

There are several limitations that should be taken into consideration when interpreting our findings. Firstly, only TEG, D-dimer and FDP were tested to observe the systemic fibrinolytic activity. D-dimer and FDP are the routine items for coagulation function in patients undergoing THA and TKA, while PAP, tPA, or PAI-1 were not carried out routinely in most hospitals. Therefore, maybe further studies are warranted to confirm our results with other markers. Secondly, the patients in the study received a single dose of 20 mg/kg TXA, which would reduce the amplitude but not change the pattern of the postoperative fibrinolysis, especially during the first postoperative 24 hours. However, as mentioned above, we need to keep it in mind that the level of fibrinolytic activity after postoperative 48 hours may lower in normal circumstance, because a newly published study[35] has found that the blood loss tended to be greater in the TXA group after postoperative 48 hours. And the paradoxical blood loss may be explained by the hypothesis that inactivated plasmin can demonstrate a delayed fibrinolytic function when the TXA reversibly bound to the plasmin was removed. Therefore, further studies were warranted to explore and confirm the dynamics of postoperative fibrinolytic activity without TXA administration. Finally, sample size was not large enough with a power of 0.86. And further study with larger sample size was needed.

5. Conclusion

FDP and D-dimer were effective and practical markers for prediction of acute postoperative fibrinolytic activity, which peaked at 6 hours after end of surgery and would maintain for at least 24 hours. And TEG, as a measure of endogenous fibrinolytic activity was of limited value.

Author contributions

Conceptualization: Jinwei Xie, Fuxing Pei.
Data curation: Yan Wang, Jinwei Xie.
Formal analysis: Yan Wang, Jinwei Xie.
Funding acquisition: Jinwei Xie, Fuxing Pei.
Investigation: Yan Wang.
Methodology: Jinwei Xie.
Supervision: Fuxing Pei.
Writing – original draft: Jinwei Xie.
Writing – review & editing: Jinwei Xie, Fuxing Pei.

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