

Rethinking universal anti-fibrinolysis: a randomized controlled trial on divergent fibrinolytic phenotypes in total knee arthroplasty

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Orthopedic surgeries, such as total knee arthroplasty (TKA), often involve extensive soft tissue dissection and osteotomy, a traumatic process that frequently leads to obvious bleeding. Of particular note is postoperative hidden blood loss (HBL), which is secondary to an overactivated fibrinolytic system and accounts for two-thirds of total perioperative bleeding [1]. Hence, anti-fibrinolysis treatment has been widely recognized for effectively reducing postoperative HBL by inhibiting surgery-induced hyperfibrinolysis, and it is now recommended in clinical guidelines for all patients undergoing major orthopedic procedures (Figure S1) [2, 3]. However, recent studies have identified distinct fibrinolytic phenotypes after trauma, with nearly half of patients exhibiting fibrinolysis shutdown (SD) [4]. This is a special phenotype representing a group of patients whose inherent fibrinolytic level is low, and thus anti-fibrinolysis treatment not only fails to reduce bleeding among these patients, but may increase their risks of complications such as venous thromboembolism (VTE), disseminated intravascular coagulation (DIC), and mortality [5]. Therefore, all emerging evidence emphasizes the importance of tailoring anti-fibrinolysis treatment (TAT) to specific fibrinolytic phenotypes.

LY30 has been suggested as a marker for identifying fibrinolytic phenotypes in trauma patients [4], but its effectiveness in TKA remains unclear. It is also uncertain whether the recommended universal anti-fibrinolysis treatment benefits patients with different fibrinolytic phenotypes after TKA. To address these gaps, we designed a prospective randomized controlled trial (RCT) to: (i) evaluate the effectiveness of

LY30 in distinguishing postoperative fibrinolytic phenotypes in TKA patients, and (ii) determine whether all phenotypes benefit from universal anti-fibrinolysis treatment.

A prospective, double-blind RCT was rigorously designed. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (ethical approval number: 2019–015), and registered on the International Clinical Trial Registry (registration number: ChiCTR2200057886). Patients hospitalized in our orthopedics department with a diagnosis of knee osteoarthritis were assessed for eligibility in this trial. The specific inclusion and exclusion criteria are listed in Table S1. Patients deemed eligible after assessment were informed by the authorized doctors about the associated risks and benefits of participation. All enrolled patients signed an informed consent form before enrollment.

Randomization was performed using computer-generated numbers. Patients were randomly assigned (1:1) to the control group [postoperative normal saline (NS)] or the anti-fibrinolysis group [postoperative tranexamic acid (TXA)]. To ensure blinding, TXA (1.5 g diluted in 100 mL NS) and NS solutions appeared identical. All patients, healthcare workers, and data collectors were blinded until data analysis, except for the nurse administering the medication. All patients received 1.5 g intravenous TXA 30 min before surgery and 1.0 g local TXA into the joint before suturing. Postoperatively, the control group received 100 mL NS intravenously every 12 h until postoperative day 3 (POD3), while the anti-fibrinolysis group received 1.5 g TXA intravenously at the same intervals.

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Table 1. The specific data of the different subgroups.

Outcomes	Control (n = 96)			Anti-Fibrinolysis (n = 96)		
	Shutdown (n = 41)	Non-Shutdown (n = 55)	P-value	Shutdown (n = 36)	Non-Shutdown (n = 60)	P-value
HBL (mean $\pm$ SD, mL)						
POD1	310.89 $\pm$ 263.87	339.79 $\pm$ 302.57	0.670 ^a	347.80 $\pm$ 377.58	310.27 $\pm$ 218.58	0.543 ^a
POD3	623.51 $\pm$ 341.03	805.68 $\pm$ 399.95	0.045 ^{a,*}	623.94 $\pm$ 293.94	528.30 $\pm$ 314.21	0.149 ^a
Δ Hb (mean $\pm$ SD, g/L)						
POD1	12.84 $\pm$ 10.03	14.21 $\pm$ 9.54	0.551 ^a	13.88 $\pm$ 14.97	12.62 $\pm$ 8.31	0.595 ^a
POD3	23.18 $\pm$ 12.09	29.71 $\pm$ 13.93	0.035 ^{a,*}	23.00 $\pm$ 11.24	21.00 $\pm$ 11.40	0.399 ^a
PT (mean $\pm$ SD, s)						
Pre-OP	12.99 $\pm$ 0.87	13.06 $\pm$ 0.79	0.687 ^a	13.08 $\pm$ 0.54	13.14 $\pm$ 0.65	0.587 ^a
POD1	13.65 $\pm$ 0.89	13.53 $\pm$ 0.67	0.482 ^b	13.64 $\pm$ 0.43	13.76 $\pm$ 0.60	0.274 ^a
POD3	13.17 $\pm$ 0.60	13.15 $\pm$ 0.77	0.893 ^a	13.19 $\pm$ 0.47	13.15 $\pm$ 0.57	0.722 ^a
APTT (mean $\pm$ SD, s)						
Pre-OP	34.90 $\pm$ 3.33	34.22 $\pm$ 3.58	0.367 ^b	34.70 $\pm$ 2.70	34.83 $\pm$ 2.85	0.811 ^b
POD1	33.83 $\pm$ 5.60	32.52 $\pm$ 3.38	0.180 ^a	33.07 $\pm$ 2.38	33.03 $\pm$ 3.08	0.941 ^a
POD3	33.45 $\pm$ 3.12	32.83 $\pm$ 4.87	0.520 ^a	34.11 $\pm$ 2.74	33.88 $\pm$ 2.87	0.706 ^a
Outcomes	Shutdown (n = 77)			Non-Shutdown (n = 115)		
	Control (n = 41)	Anti-Fibrinolysis (n = 36)	P-value	Control (n = 55)	Anti-Fibrinolysis (n = 60)	P-value
HBL (mean $\pm$ SD, mL)						
POD1	310.89 $\pm$ 263.87	347.80 $\pm$ 377.58	0.637 ^a	339.79 $\pm$ 302.57	310.27 $\pm$ 218.58	0.583 ^a
POD3	623.51 $\pm$ 341.03	623.94 $\pm$ 293.94	0.996 ^a	805.68 $\pm$ 399.95	528.30 $\pm$ 314.21	0.000 ^{a,*}
Δ Hb (mean $\pm$ SD, g/L)						
POD1	12.84 $\pm$ 10.03	13.88 $\pm$ 14.97	0.915 ^a	14.21 $\pm$ 9.54	12.62 $\pm$ 8.31	0.906 ^a
POD3	23.18 $\pm$ 12.09	23.00 $\pm$ 11.24	0.949 ^a	29.71 $\pm$ 13.93	21.00 $\pm$ 11.40	0.001 ^{a,*}
PT (mean $\pm$ SD, s)						
Pre-OP	12.99 $\pm$ 0.87	13.08 $\pm$ 0.54	0.578 ^a	13.06 $\pm$ 0.79	13.14 $\pm$ 0.65	0.530 ^a
POD1	13.65 $\pm$ 0.89	13.64 $\pm$ 0.43	0.929 ^a	13.53 $\pm$ 0.67	13.76 $\pm$ 0.60	0.061 ^b
POD3	13.17 $\pm$ 0.60	13.19 $\pm$ 0.47	0.908 ^a	13.15 $\pm$ 0.77	13.15 $\pm$ 0.57	0.978 ^a
APTT (mean $\pm$ SD, s)						
Pre-OP	34.90 $\pm$ 3.33	34.70 $\pm$ 2.70	0.765 ^a	34.22 $\pm$ 3.58	34.83 $\pm$ 2.85	0.312 ^a
POD1	33.83 $\pm$ 5.60	33.07 $\pm$ 2.38	0.435 ^a	32.52 $\pm$ 3.38	33.03 $\pm$ 3.08	0.398 ^a
POD3	33.45 $\pm$ 3.12	34.11 $\pm$ 2.74	0.357 ^a	32.83 $\pm$ 4.87	33.88 $\pm$ 2.87	0.168 ^a

HBL hidden blood loss, SD standard deviation, POD postoperative day, Δ Hb decline of hemoglobin level, PT Prothrombin time, Pre-OP pre-operative, APTT activated partial thromboplastin time. ^aIndependent-samples t-tests. ^bMann–Whitney U-test. *Statistically significant difference in mean values between groups.

All surgeries were performed under general anesthesia with a medial parapatellar incision. A pneumatic tourniquet (30 kPa) was applied during surgery, limited to 60 min at a time, with breaks to prevent ischemic injury. No postoperative drainage tubes were used. All patients received the same prosthesis (NexGen[®] system, Zimmer Biomet) to minimize bias. All the TKA procedures of the enrolled patients were executed by the same team of surgeons, complemented by a standardized protocol encompassing perioperative medical care, anesthesia, surgical practices, post-surgical rehabilitation, pain management, infection and VTE prevention, which maintained throughout the duration of the trial.

The primary outcomes were HBL and hemoglobin drop (Δ Hb), with HBL calculated using the Gross and Nadler formula [6]. Secondary outcomes included prothrombin time (PT), activated partial thromboplastin time (APTT), surgical indicators (e.g. operation time, intraoperative blood loss), and perioperative complications [e.g. allogeneic blood transfusion (ABT), VTE, length of stay (LOS)]. LY30 levels were measured on POD1 to classify patients into fibrinolysis shutdown (SD, LY30 < 0.8%) or non-shutdown (NSD, LY30 $\geq$ 0.8%) groups. Sample size calculations based on prior data required 36 patients per group to detect a 200 mL difference in HBL with 95% power and a 5% dropout rate [7]. Data were analyzed

using SPSS 24.0, with categorical variables assessed by chi-square or Fisher's exact tests and continuous variables by t-tests or Mann–Whitney U tests, depending on normality ($P < 0.05$ considered significant).

From April 2022 to July 2023, 271 patients were screened, with 192 eligible participants randomized 1:1 into control and anti-fibrinolysis groups (Figure S2). Based on POD1 LY30 levels, patients were further stratified into SD and NSD subgroups for analysis. The specific data of the monitored outcomes were listed in Table 1. Baseline characteristics were balanced across subgroups (Table S2), and no significant differences were observed in LOS, ABT rates, or VTE incidence across subgroups in any analysis (Table S3).

In the control group, NSD patients had significantly higher HBL and Δ Hb than SD patients on POD3, while no significant differences were observed on POD1 (Figure 1a and b). Coagulation parameters (PT, APTT) were consistent across subgroups (Figure 1c and d). In the anti-fibrinolysis group, NSD patients showed lower HBL and Δ Hb than SD patients, but differences were not statistically significant on POD1 or POD3 (Figure 1e and f). Coagulation parameters were also similar across subgroups (Figure 1g and h).

Among SD patients, anti-fibrinolysis treatment did not significantly reduce HBL or Δ Hb, nor did it affect PT and

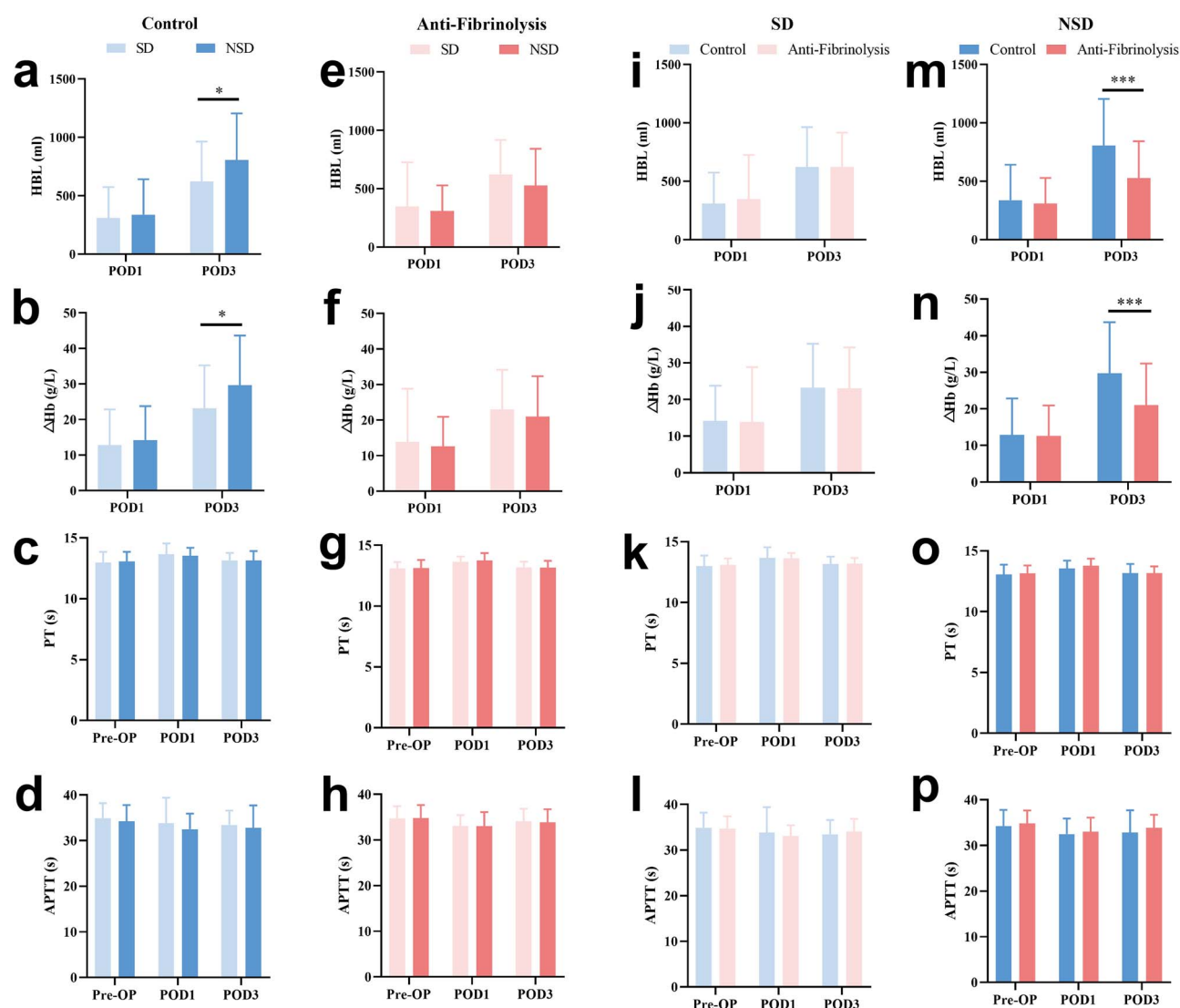


Figure 1. The perioperative HBL (a), Δ Hb (b), PT (c), and APTT (d) in the control group, and the perioperative HBL (e), Δ Hb (f), PT (g), and APTT (h) in the anti-fibrinolysis group. The perioperative HBL (i), Δ Hb (j), PT (k), and APTT (l) in the SD patients, and the perioperative HBL (m), Δ Hb (n), PT (o), and APTT (p) in the NSD patients. SD shutdown, NSD non-shutdown, HBL hidden blood loss, POD1 postoperative day 1, Δ Hb hemoglobin drop, PT prothrombin time, Pre-OP preoperative, APTT activated partial thromboplastin time. *, $P < 0.05$. ***, $P < 0.001$.

APTT levels (Figure 1i–l). In NSD patients, anti-fibrinolysis treatment significantly reduced HBL and Δ Hb on POD3 but not on POD1 (Figure 1m and n). PT and APTT levels remained similar between groups (Figure 1o and p).

Recent studies have highlighted LY30 as a valuable marker for real-time differentiation of fibrinolysis levels in trauma patients due to its simplicity and rapid detection [4]. Similarly, in this study, we observed that LY30 can aid orthopedic surgeons in real-time differentiation of patients with different fibrinolytic activities. Following the reported methods, we successfully classified patients into two subgroups (SD and NSD) after TKA, and significant differences in postoperative blood loss were identified between the two subgroups. This suggests that patients classified by LY30 indeed represent subgroups with distinct fibrinolytic activities, and the NSD subgroup exhibits significantly higher level of fibrinolysis and correspondingly more postoperative bleeding.

In this study, SD phenotype was observed in 42.71% of TKA patients, aligning with the 46% reported in trauma cases [4]. Consistent with previous findings, NSD patients

exhibited more active fibrinolysis, leading to greater HBL and Δ Hb on POD3 in the control group (Figure 1a and b). This observation suggested that NSD patients may belong to a subset with an increased postoperative fibrinolytic activity, leading to more substantial secondary HBL induced by this active fibrinolytic response. However, in the anti-fibrinolysis group, the NSD and SD patients demonstrated comparable postoperative HBL and Δ Hb (Figure 1e and f). This could be attributed to anti-fibrinolysis treatment mitigating the typically heightened fibrinolytic activity in NSD patients to levels akin to SD patients, which resulted in reduced fibrinolysis-associated HBL. Therefore, in alignment with published evidence, the findings of this study once again confirm that not all patients exhibit activation of the fibrinolysis system after injury [8]. This further supports the correctness and necessity of selectively choosing antifibrinolytic treatments based on the fibrinolytic phenotype of the patients.

In addition, our results showed that anti-fibrinolysis treatment significantly reduced HBL and Δ Hb on POD3 in NSD patients (Figure 1m and n), supporting its role in limiting

excessive fibrinolysis and reducing blood loss [1]. In contrast, this treatment had no effect on postoperative bleeding in SD patients (Figure 1i and j). This is likely due to the inherently subdued postoperative fibrinolytic activity in SD patients, where the HBL induced by hyperfibrinolysis was already minimal (Figure 1a and b). These findings reinforce the recommendation to selectively use anti-fibrinolysis treatment for NSD patients, as it provides limited benefit in SD patients and may hinder clot dissolution, potentially increasing VTE risk [9, 10]. This stance stems from the recognition that in SD patients with already suppressed fibrinolysis, anti-fibrinolysis treatment is unlikely to reduce HBL stemming from premature clot breakdown and may, in fact, hinder clot dissolution, elevating the risk of VTE (Figure S1) [5, 9].

Although some concerns exist about anti-fibrinolysis treatment in SD patients, this study found no evidence of increased postoperative complications, including extended LOS, ABT rates, or VTE rates, in either SD or NSD patients (Table S3). However, this result should be interpreted with caution, as the incidence of VTE in TKA patients is already very low under standard anticoagulation therapy. Detecting differences in such a low-incidence event would require a much larger sample size, estimated at over 2000 patients per group. Larger-scale prospective multicenter studies are needed to further assess this potential risk.

In conclusion, LY30 is an effective tool to identify postoperative fibrinolytic phenotypes and guide selective anti-fibrinolysis treatment following TKA. 42.71% of TKA patients presented with SD phenotype, which exhibited significantly lower fibrinolytic activity and less HBL when compared with the NSD patients. Anti-fibrinolysis treatment could effectively reduce postoperative HBL only in the NSD patients, and thus TAT rather than universal anti-fibrinolysis treatment should be advocated.

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Author contributions

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Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

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