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Topical co-delivery of platelet rich fibrin and tranexamic acid does not decrease blood loss in primary total knee arthroplasty compared to the standard of care: a prospective, randomized, controlled trial

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Abstract

Purpose The purpose of this study was to evaluate the efficacy of intra-operative co-administration of tranexamic acid (TA) and platelet rich fibrin (PRF) using a proprietary co-delivery system on the amount of blood loss, early functional outcomes and wound complications after primary total knee arthroplasty (TKA). The intervention was compared to the standard of care (combined intravenous & topical TA) in a prospective, randomized, blinded setting.

Methods 80 patients undergoing primary cemented TKA without tourniquet were prospectively randomized into control (combined intravenous and topical TA) and PRF (intra-venous TA and co-delivery of topical PRF and TA) groups after informed consent. Total blood loss, drainage blood loss, knee range of motion, VAS pain scores, length of stay and wound complications were analysed. Data collection was performed in a double blind manner on days 1, 3 and 21.

Results There was no statistically significant difference in drainage blood loss (550 ml vs. 525 ml, $p=0.643$), calculated total blood loss on day 1 (401 ml vs. 407 ml, $p=0.722$), day 3 (467 ml vs 471 ml, $p=0.471$) and day 21 (265 ml vs. 219 ml, $p=0.082$) between the PRF and control groups respectively. The PRF group had a small but statistically significant increase in median knee extension in the early post-operative period, however this difference evened out at 3 weeks. No significant difference could be demonstrated between the PRF and control groups in length of stay, VAS pain scores, narcotic usage, wound complications and knee flexion at all time points.

Conclusions The topical co-delivery of PRF and TA does not significantly decrease blood loss in primary TKA compared to the standard of care. Slightly better active knee extension in the first 3 postoperative days can be achieved, however this benefit is not clinically relevant.

Level of evidence I, Therapeutic study.

Keywords Platelet rich fibrin · Tranexamic acid · Total knee arthroplasty · Blood loss

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Abbreviations

ASA	Acetyl salicylic acid
DVT	Deep vein thrombosis
Hb	Haemoglobin
Hct	Haematocrit
iv	Intravenous
PDGF	Platelet derived growth factor
PRF	Platelet rich fibrin
sc	Subcutaneous
TA	Tranexamic acid
TGF-β	Transforming growth factor beta
TKA	Total knee arthroplasty
VEGF	Vascular endothelial growth factor

Introduction

Total knee arthroplasty (TKA) results in a significant amount of blood loss due to exposed cancellous surfaces and the soft tissue dissection during surgery. The amount of blood loss after primary TKA has been reported to be between 200 and 1500 ml [23]. Bleeding leads to well-known systemic and local adverse events that may affect the outcome of TKA. Allogenic transfusions to correct blood loss carry the risk of transfusion reactions, immune suppression and possibly increased risk of infection [4].

Tranexamic acid (TA), an anti-fibrinolytic agent either in intravenous, topical or combined form has been shown to significantly reduce blood loss and transfusion rates in TKA in recent years [30, 32]. TA is safe, readily available and has become the standard of care, with no increase in thrombotic complications [21]. Fibrin sealants have also been used to decrease blood loss in joint replacement. A recent meta-analysis has shown that intra-operative use of fibrin sealants during TKA can reduce total blood loss by 162 ml, reduce the need for transfusion (RR = 0.67) and reduce the length of hospital stay (RR = 0.98) without increasing the risk of infection [16].

The Vivostat® system (Vivostat, Alleroed, Denmark) used to produce platelet rich fibrin (PRF) in this study is a sterile, closed system; which concentrates the platelets and fibrin up to 7–10 times the level of donor blood. PRF is sprayed on to the exposed bone and soft tissues using an applicator pen that co-delivers TA and PRF. Unlike other fibrin sealants, PRF contains autologous platelets embedded in a fibrin matrix. In addition to its haemostatic effect, a prolonged release of growth factors and cytokines has been shown to occur up to 7–10 days in vitro studies, possibly resulting in anti-inflammatory and regenerative effects [20]. Musculo-skeletal applications include its use as a biological augmentation to repair of massive rotator cuff tears [2], cartilage regeneration in osteochondral lesions of the talus [5], and treatment of aseptic non-unions [8]. This is the first prospective randomized study to investigate its effectiveness in total knee arthroplasty.

The aim of this study was to evaluate the efficacy of intra-operative co-administration of tranexamic acid and platelet rich fibrin using a proprietary co-delivery system on the amount of blood loss, early functional outcomes and wound complications after primary TKA. The intervention was compared to the standard of care (combined intravenous and topical TA) in a prospective, randomized double blind setting. The primary outcome measure was total blood loss. Secondary outcome measures were drainage blood loss, early post-operative pain, knee range of motion, length of stay and wound complications. It was hypothesized that the co-delivery of PRF and TA would reduce total blood loss, thereby facilitating early rehabilitation by decreasing pain, increasing knee range of motion and reducing wound drainage and finally reducing length of stay.

Materials and Methods

Study design

All consecutive patients fulfilling the inclusion criteria undergoing unilateral cemented total knee arthroplasty (TKA) in a single centre were prospectively enrolled in the study. Patients with primary osteoarthritis over 50 years of age requiring TKA were eligible for inclusion in the study. No upper age limit was set to better investigate the efficacy of PRF on all eligible patients without significant co-morbidities undergoing TKA. The details of the exclusion criteria are described in Table 1. In brief, patients with malignant disease, coagulation disorders, renal and hepatic disease, previous open knee surgery, inflammatory arthritis, bilateral and revision TKA were excluded.

Following a priori power analysis, the study was designed to include 40 patients each in the PRF and control groups and was terminated when a total of 80 patients were enrolled. One hundred and thirteen patients underwent TKA during the study period. All patients consenting to participate in the study who met the inclusion and exclusion criteria were randomized into intervention and control groups (Fig. 1). Randomization was performed with sealed envelopes containing cards with either "PRF-treatment group" or "conventional treatment group" in random order that were opened before the induction of anaesthesia. The patients were blinded to the intervention. An independent blinded examiner (MP) not involved in the surgery and primary care of the patient performed the measurements and data collection.

Operative procedure

All pre-operative work-up was done on an out-patient basis. Patients were hospitalized on the morning of surgery. Regional anaesthesia with 100 mg Bupivacaine and 200 µg Fentanyl was performed in all patients. Tenoxicam 20 mg *iv* was administered pre-emptively. All patients received a single *iv* dose of 1 g of tranexamic acid at the induction of anaesthesia. Cefazoline 2 g *iv* was used for antimicrobial prophylaxis. 100 ml of venous blood was drawn before administration of antibiotics in the PRF group and was used to prepare the PRF spray.

All patients received a cemented, posterior stabilized, fixed bearing total knee prosthesis (Smith and Nephew Genesis II) with routine patellar resurfacing that was performed through a standard medial parapatellar incision

Table 1 Exclusion criteria

Exclusion criteria
Malignant disease
Disturbed coagulation (APTT > 40 s, INR > 1.5); Platelet count < 100×10^9/L
Patients with a history of DVT or hypercoagulability
Coagulopathies or cardiac valve replacement patients requiring uninterrupted anti-thrombotic treatment
Impaired renal function (serum creatinine: > 150 mmol/L, serum urea: > 10 mmol/L), renal failure or patients on renal dialysis
Impaired liver function or chronic hepatic disease
Anti-platelet medication (ASA) within 10 days of surgery
Previous open knee surgery (arthroscopic surgery was not an exclusion criteria)
Inflammatory arthritis (Rheumatoid arthritis, Ankylosing spondylitis, Systemic Lupus Erythematosus etc.)
Revision TKA, bilateral simultaneous TKA
Patients not consenting to participate

APTT activated partial thromboplastin time, *INR* international normalised ratio, *DVT* deep vein thrombosis, *ASA* acetyl salicylic acid, *TKA* Total knee arthroplasty

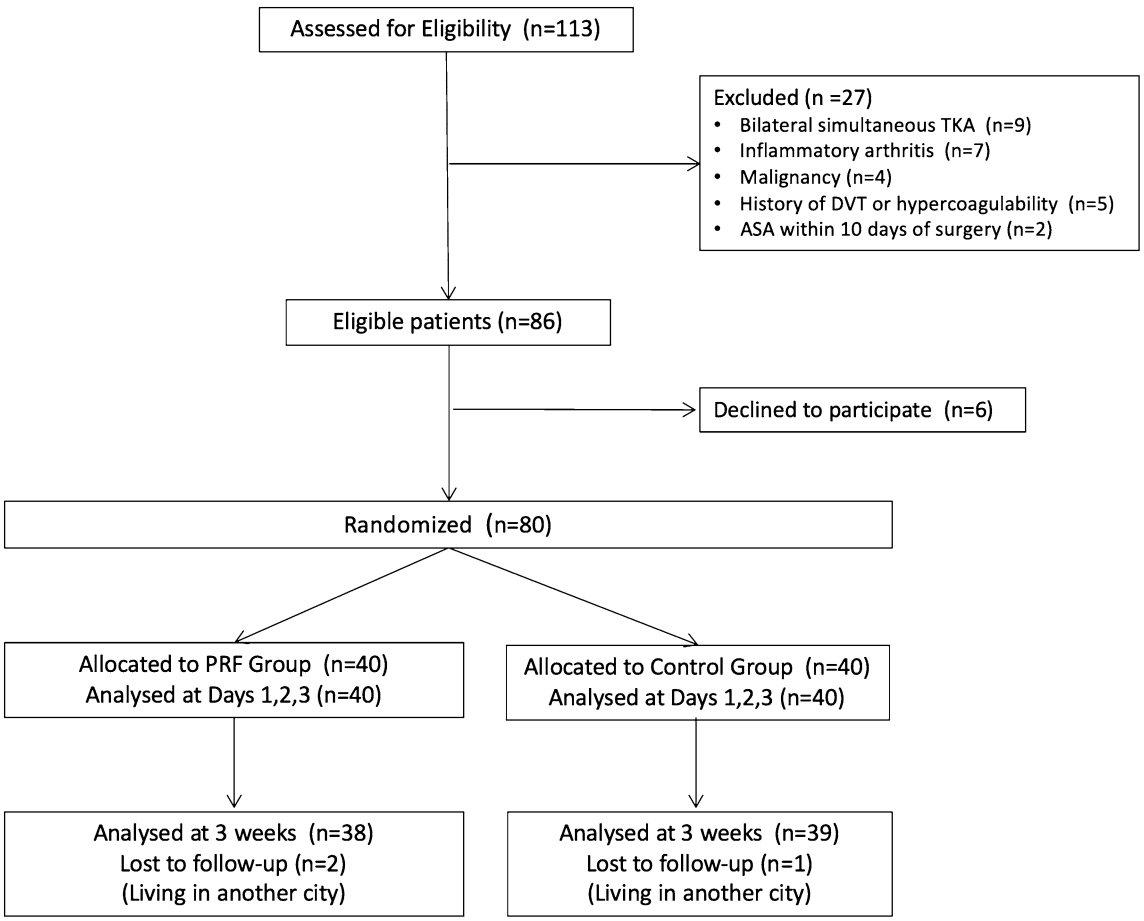

Fig. 1 The CONSORT [22] flow diagram of the study (*ASA* acetyl salicylic acid, *DVT* deep vein thrombosis)

without a tourniquet under hypotensive regional anaesthesia. Two surgeons (RNT and AK) who had performed more than 2000 TKA's with the same implant performed the surgery using identical techniques. Local infiltration anaesthesia was performed with injection of 60 ml of 100 mg dilute bupivacaine to the posterior capsule, synovium and the arthrotomy site. Haemostasis was obtained with the use of electrocautery and the entire operative field

was thoroughly dried with gauzes before the application of the PRF and/or TA.

PRF preparation and application

The collected venous blood was processed with the Vivostat Processor Unit, which is an automated and sterile closed system. The device concentrates platelets to approximately seven times the platelet level of the donor's blood. This high number of platelets are combined with a concentrate of fibrin approximately 7–10 times of the baseline value. The process takes about 30 min. The PRF was then transferred to the PRF Application Unit in the operating theatre. A vial of 10% 500 mg tranexamic acid was drawn into the co-delivery syringe and this was combined with the PRF produced by the Vivostat system. The final product was a 4–6 ml of clear solution that could be delivered to the tissues using a spray pen. The sterile spray pen was connected directly to the Applicator Unit and activated using a foot pedal. The PRF solution polymerises and forms a gel immediately upon application by a simple pH-change at the tip of the spray pen. 1–2 ml PRF was sprayed to the posterior capsule before implantation of the components. The remaining 4–5 ml PRF was sprayed over the exposed bone surfaces, synovium and arthrotomy incisions after implantation of the prosthesis (Fig. 2). Wound closure in layers was performed after insertion of a drain.

Patients in the control group received 500 mg topical tranexamic acid after implantation of the components. Wound closure and drain placement were similar to the PRF group. The total tranexamic acid dose was 1500 mg (1000 mg *iv* plus 500 mg topical) for all patients in the PRF and control groups.

Patients and the independent examiner for data collection were blinded to the treatment.

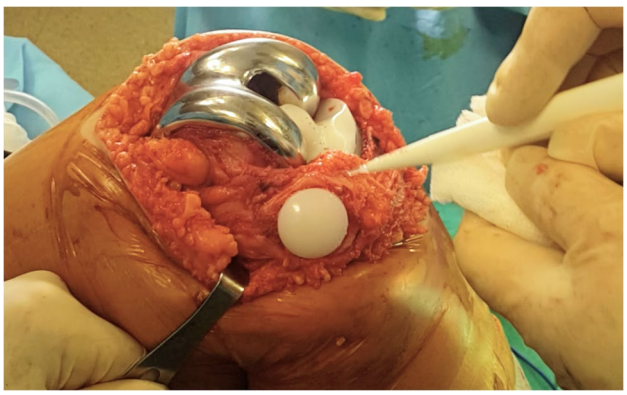

Fig. 2 Application of PRF and TA onto the periprosthetic synovial tissue and exposed bone using the dedicated spray pen

Postoperative management

An enhanced recovery protocol consisting of pre-operative education, multi-modal analgesia and early mobilization was employed in all patients. Post-operative pain management was performed with a standardized protocol using oral paracetamol 4 × 1 g, pregabalin 2 × 75, diclofenac 2 × 75 mg with narcotic analgesics as rescue medicine. Enoxaparin 0.4 ml *sc* was used for DVT prophylaxis for 10 days. All drains were removed at 24 h. Antimicrobial prophylaxis with *iv* cefazoline 3 × 2 g was terminated at 24 h. The patients were mobilized in the afternoon of surgery and received the same inpatient physiotherapy with full weight bearing, continuous passive motion device and active assisted exercises.

Transfusion trigger was set at Haemoglobin < 8 g/dl for symptomatic patients. Erythrocyte suspension was used for transfusion if needed. Discharge criteria were as follows:

1. Independent ambulation was possible with a walking aid
2. Active knee flexion while sitting on the side of the bed was 90° or more
3. Pain was controlled with multi-drug, non-narcotic oral medication
4. There was no drainage from the wound or the drain exit site
5. No in-hospital treatment was necessary for medical co-morbidities

Data collection

Data collection was performed by an independent examiner blinded to the treatment on the pre-op visit, days 0, 1, 3 and at 3 weeks (21–23 days to account for week-ends). A separate form was filled for the relevant data and stored until final data analysis. These data were not visible in the patient's electronic medical records.

Haemoglobin (Hb) and Haematocrit (Hct) levels were measured pre-operatively, and then on post-operative days 1, 3 and 21. The type and volume of blood transfusions were recorded. Drainage blood volume was measured in ml as the total amount of blood collected in the drain at the end of 24 h after surgery. Total blood loss was calculated using the modified Gross formula for days 1, 3 and 21 [11, 13]. The total blood volume was calculated as follows:

$$\mathrm{BV} = k_1 \times H^3 + k_2 \times W + k_3$$

BV: blood volume before surgery, H(m): height, W(kg): weight, for males, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$, for females, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$.

The total blood loss was calculated using the following formula:

$$V_{\text{loss total}} = \text{BV} \times \left(\text{Hct}_{\text{preop}} - \text{Hct}_{\text{postop}}\right)$$

$V_{\text{loss total}}$: total blood volume loss, Hct: hematocrit.

The percentage of blood loss was found using the ratio below:

$$\%\ \text{Blood loss} = \frac{\text{Total calculated blood loss} \times 100}{\text{Total blood volume}}$$

All patients were included in the analysis of total calculated blood loss for day 1. Patients who received blood transfusions were excluded from the total blood loss analysis for the succeeding timepoints since Hb and Hct values had been altered. Two separate calculations were performed for total blood loss. In the first calculation, 100 ml venous blood drawn for the preparation of PRF was subtracted from the total blood loss volume, to observe the direct effect of PRF on the blood lost from the knee joint. These calculations showed a statistically significant reduction of blood loss in the PRF group (not reported in the results). The second set of calculations were performed without subtracting the blood drawn for the preparation of PRF to observe the overall effect of PRF, and these are reported in the results section.

Pain was measured using the Visual Analogue Scale (VAS) on a scale of 0 to 10; 0 being no pain and 10 being the worst possible pain. VAS was measured 4 times a day on days 1, 2, 3, and the mean value was used in the analysis to account for breakout pain during physiotherapy or exercise. Knee range of motion (ROM) was measured on days 1, 2, 3 and 21 using a long arm manual goniometer with an accuracy of 1°.

A major bleeding event was described as fatal bleeding or bleeding requiring re-operation for hematoma drainage or debridement. Extended wound drainage was described as drainage requiring dressing change more than 48 h postoperative or extended hospitalization. All secondary surgical procedures such as debridement, lavage for haematoma or drainage were recorded. Acute periprosthetic infection was defined using the Musculoskeletal Infection Society (MSIS) revised criteria [24].

Length of stay (LOS) was measured as the number of nights spent in the hospital after surgery. All discharges were performed before 9.00 A.M. All periods longer than three nights were considered extended LOS.

Adverse events and medical complications were recorded on the patient data form.

Ethical aspects

Ethical approval was obtained from Halic University, Istanbul, Clinical Studies Ethical Board (29.12.2016, no. 30). The study was conducted in conformance with the Declaration of Helsinki, the laws and regulations of Turkey and hospital requirements, whichever affords the greater protection to the patient. Written informed consent was obtained from all patients.

Statistical analysis

Descriptive statistics were used to report patient population characteristics, intra-operative and post-operative data. The clinically significant difference in blood loss was set at 100 ml (SD ± 150 ml). A priori power analysis indicated that a sample size for the PRF and control groups should be a minimum of 39 patients each to achieve 90% power at 0.05 significance level. Normal distribution assumption of numerical variables was assessed by using Shapiro–Wilk test. For categorical variables, frequencies and percentages were used in the statistics. Mean ± standard deviation or median (min–max) values were given as descriptive statistics for numerical variables. The effect of PRF treatment vs. control was compared using Student's unpaired *t*-test and Mann Whitney *U* test for normally and non-normally distributed numerical variables, respectively. For categorical data, the effect of PRF treatment was analysed using Fisher's exact test. A p value < 0.05 was regarded as statistically significant.

Results

The age, sex, BMI and preoperative Hb values of the patients were comparable in the PRF and control groups (Table 2). All patients had complete data for days 0 to 3. Two patients in the PRF and 1 patient in the control group had missing data at 3 weeks due to patients living in another city and were excluded from the analysis for parameters at 3 weeks.

The data for blood loss values are given in Table 3 and supplementary material Appendix 1. There was no statistically significant difference in drainage blood loss between the PRF and control groups (550 ml vs. 525 ml) at 24 h. We first performed the statistical analysis for calculated blood loss values by subtracting the 100 ml blood drawn for the production of PRF to see its effect on the knee; this demonstrated a statistically significant decrease in blood loss.

Table 2 Patient demographics

	Control	PRF	*p* value
Age (year)	70 ± 7	68 ± 7	0.395
BMI	31.39 ± 5.06	30.77 ± 3.73	0.536
Pre-op Hb (g/dl)	13.1 ± 1.2	12.8 ± 1.1	0.240
Gender			
Male	4 (10%)	5 (12.5%)	1.000
Female	36 (90%)	35 (87.5)	

Table 3 Blood loss values

	Control	PRF	*p* value
D1 drain (ml)	525 (100–1400)	550 (250–1200)	0.643
D1 blood loss (ml)	407 (138–1081)	401 (150–682)	0.722
% of total blood	9.74 ± 2.73	9.39 ± 2.57	0.555
D3 blood loss (ml)	471 (262–1421)	467 (183–786)	0.471
% of total blood	11.73 ± 3.37	10.89 ± 3.04	0.205
W3 blood loss (ml)	219 (45–525)	265 (121–550)	0.082
W3% blood loss	5.22 ± 2.40	6.23 ± 2.415	0.079

D day, *W* week

However, when the 100 ml used for the production of PRF was not subtracted from the calculated total blood loss, no statistically significant reduction in blood loss could be demonstrated. Calculated total blood loss values for PRF vs. control groups were 401 ml vs. 407 ml for day 1; 467 ml vs. 472 ml for day 3 and 265 ml vs. 219 ml for 3 weeks, respectively. Similarly, no difference in the percentage of blood loss to the patient's total blood volume could be found. This refuted our hypothesis that the co-delivery of PRF and TA would result in clinically significant decrease in blood loss after TKA.

No statistically significant differences were observed between the PRF and control groups in length of stay, narcotic usage, wound complications and knee flexion at all time points (Tables 4, 5). VAS pain scores were similar for both PRF and control groups at all time periods, with no clinically important difference (Table 4). The PRF group had a significantly better median knee extension in the early post-operative period, however, this difference evened out at 3 weeks, with both groups achieving similar knee extension (Table 4).

Table 4 Post-operative outcomes

	Control	PRF	*p* value
Pain			
D0 VAS	1.5 (0.5–4)	1.25 (1–3.25)	0.509
D1 VAS	1 (0.5–2.5)	1.25 (0.75–2.5)	0.064
D2 VAS	1 (0.25–2.25)	1 (0.5–2.5)	0.545
D3 VAS	1 (1–1)	1.38 (1–2.5)	**0.029**
Range of motion (°)			
D1 extension	10 (5–18)	7 (5–18)	**< 0.001**
D1 flexion	84 ± 14	87 ± 13	0.265
D2 extension	9 (5–15)	7 (4–15)	**0.001**
D2 flexion	91 ± 12	95 ± 11	0.096
D3 extension	8 (5–13)	7 (4–15)	**0.010**
D3 flexion	95 (73–111)	97 (72–120)	0.102
D4 extension	10 (6–12)	9 (6–11)	0.618
D4 flexion	97 (90–110)	108 (84–120)	0.623
W3 extension	3 ± 2	3 ± 2	0.892
W3 flexion	120 (107–130)	123 (95–136)	0.648
Length of stay (days)	3 (2–4)	3 (2–7)	0.490

LOS length of stay, *VAS* visual analogue scale, *D* day, *W* week

Table 5 Comparison of early post-operative parameters

Group					
	Control		PRF		*p* value
	n	%	*n*	%	
Narcotic use					
D0	27	67.5	27	67.5	0.534
D1	7	17.5	10	25.0	
D2	4	10.0	1	2.5	
D3	2	5.0	2	5.0	
Extended wound drainage					
No	38	97.5	36	90.0	1.000
Yes	1	2.5	2	5.0	
Complication					
No	38	95.0	38	95.0	1.000
Yes	2	5.0	2	5.0	
Blood transfusion					
No	36	90.0	39	97.5	0.359
Yes	4	10.0	1	2.5	

D day

The number of patients requiring narcotic analgesics were same for both groups on the day of surgery, with 67.5% of the patients requiring narcotics despite multimodal analgesia (Table 5). This number decreased rapidly throughout days 1 to 3, with 5% of the patients still needing narcotics at day 3 in both groups. Although there was a trend for less blood transfusions in the PRF group (1 patient in the PRF group vs. 4 patients in the control group), this difference did not reach statistical significance (Table 5).

Extended wound drainage occurred in 2 patients in the PRF group and 1 patient in the control group (Table 5) ($p = 1.00$). One resolved with dressing changes; while one patient in each group required debridement and wound revision with retention of the implants and uneventful healing. There were no infections in either group using the MSIS criteria. No major bleeding events occurred.

The median length of stay was 3 days for both groups, with only one patient in the PRF group requiring hospitalization for medical co-morbidities. We could demonstrate no beneficial effect of PRF on the length of stay.

There were no adverse effects related to the use of PRF. One patient in the control group had a traumatic patellar dislocation after a fall on the operated knee at 2 weeks and had to undergo repair of the disrupted arthrotomy incision without revision of implants.

Discussion

The most important finding of this study was that the intraoperative co-delivery of PRF and TA during primary total knee arthroplasty did not significantly reduce blood loss compared to the standard of care, refuting our primary hypothesis. PRF treatment resulted in slightly better knee extension during the early post-operative period, however this benefit was not clinically relevant and evened out at 3 weeks.

Several strategies have emerged in recent years to reduce blood loss during and after TKA. Although hypotensive anaesthesia, modifications of surgical technique that do not breach the medullary canal (patient specific instrumentation or computer assisted surgery) have shown a beneficial effect [19, 28], the most dramatic effect has occurred with the use of tranexamic acid (TA). Tranexamic acid administration during total knee arthroplasty has been shown to decrease blood loss and has become the standard of care in most centres. Oral, topical and intravenous administration are equally effective, and have led to significant decreases in transfusion rates without an increase in thromboembolic events [7, 30]. In a recent meta-analysis of 1495 patients, the combination of topical and intravenous TA was shown to be superior to the administration of intravenous or topical TA alone [17]. However, even with the use of combined intravenous and topical TA, a significant amount of blood loss occurs during the perioperative period. Our study has shown that, despite topical and intravenous administration of TA, 400–500 ml blood occurs during the perioperative period, which corresponds to 9–11% of total blood volume of the patient. This is especially important for elderly patients with lower preoperative haemoglobin levels. A recent study has shown that a preoperative Hb level less than 12.5 g/dl is an independent risk factor for transfusion despite the use of antifibrinolytic agents such as TA [26]. Therefore, further methods to decrease blood loss are needed, especially in elderly patients with anaemia. We designed our study to see if co-administration of PRF with TA would further decrease total blood loss in this population of patients, however no clinically significant reduction in blood loss could be observed with this treatment.

The exact volume of clinically relevant blood loss is not known. Different parameters such as 1 g/dl drop in Hb level [10], Hb level below 8 g/dl [9] have been proposed. However, the Hb level may be affected by haemodilution due to fluid replacement during the early post-operative period and is unreliable. In a study comparing the dosing regimen of TA in revision TKA, as little as 53 ml difference in calculated blood loss has been reported to be significant [1], while a meta-analysis of 10 studies comparing topical and intravenous TA in TKA considered a 51 ml difference in calculated blood loss not clinically significant [27]. Since no previous guideline was available on the amount of clinically significant blood loss, we chose to set our value at 100 ml for this study and performed the power analysis accordingly.

Although the preoperative Hb values were comparable, a smaller number of patients in the PRF group required transfusions compared to controls (1 vs. 4 patients). However, this difference was not statistically significant, and our study might have been underpowered to detect such a difference. Further analysis with a larger number of patients may be justified to clarify this issue.

The drainage volume was greater than the calculated blood loss values at 24 h. This discrepancy might be explained by the fact that the fluid collected in drain is a mix of blood, increased secretion of synovial fluid and residual irrigation solution.

The relative benefits and deleterious effects of tourniquet use in TKA are still being debated. A recent randomized controlled trial confirmed that multiple doses of intravenous and topical TA without a tourniquet resulted in less hidden blood loss, lower ratio of postoperative knee swelling, less postoperative knee pain and better outcomes than those treated with a tourniquet [14]. A meta-analysis of 18 studies in 1279 TKA's demonstrated that tourniquet use resulted in more post-operative pain, deep vein thrombosis and worse knee range of motion in the early post-operative period [15]. These findings were corroborated in the systematic review of 46 randomized controlled trials by Liu [18]. In contrast, a recent double blind randomized trial of 200 TKA's demonstrated no deleterious effects of tourniquet on function and pain; with less calculated blood loss and better functional tests in the tourniquet group [12]. Similarly, in a recent meta-analysis of 11 randomized controlled trials, Cai et al. [6] have shown that usage of tourniquet in TKA decreases intraoperative blood loss, calculated blood loss, and operation time but does not significantly decrease the rate of transfusion or the rate of DVT in TKA. Our study demonstrated slightly better active knee extension in the first 3 post-operative days in the PRF group compared to controls. Since no tourniquet were used in both groups, this difference cannot be attributed to avoidance of muscle ischemia and pain due to tourniquet. Less bleeding and anti-inflammatory effects of PRF might have contributed to this difference. The difference in active knee extension evened out at 3 weeks; with both PRF and control groups achieving similar knee range of motion. Although statistically significant, 2°–3° gain in mean extension in the PRF group is not clinically relevant. Knee range of motion was measured with a manual goniometer with an accuracy of 1° by the same blinded examiner in all patients. Although a standard technique was utilized, measurement error cannot be ruled out. With the

use of local infiltration anaesthesia techniques, avoidance of tourniquet and multi-modal analgesia, most patients are expected recover early active knee extension regardless of bleeding control methods. The additional benefit of PRF was minimal in our series.

Topical fibrin sealants are composed of allogenic fibrinogen, thrombin and tranexamic acid and have been used to decrease blood loss in TKA. However, these formulations do not contain autologous platelets that are a part of PRF. A recent meta-analysis of 19 clinical trials involving 1489 patients has shown that fibrin sealants can effectively reduce the need for transfusion, total blood loss and the volume of drainage without increasing the rate of infection [16]. In this meta-analysis, length of hospital stay was shorter, but no difference in wound infection rate was observed. The haemostatic effect seems to be dose dependent; with studies using 2 ml of fibrin sealant reporting inferior results [33]. The effect of fibrin sealants on functional outcomes after TKA is controversial, with one study reporting better range of motion in 144 patients [31], versus a recent multi-centre trial with 466 patients showing no significant effect [29]. In contrast, the PRF used in this study has a high concentration of autologous platelets in addition to fibrin that is 7–10 times the baseline blood level. Therefore, PRF involves direct application of concentrated platelets using fibrin as a delivery media to ensure a controlled and prolonged release of platelet growth factors. The high concentration of fibrin binds and protects several growth factors from proteolytic degradation and protects the product from an early fibrinolysis [20]. Platelet growth factors, especially PDGF, TGF-β and VEGF, have favourable effects on the augmentation of the wound healing cascade [25]. TA also prolongs the fibrinolytic degradation of the fibrin scaffold in PRF, thereby extending the total release time of growth factors from the matrix. The use of PRF has shown an enhanced effect on fibroblast proliferation in vitro as well as in vivo, this effect is not present in other commercial fibrin sealants [20]. It has been demonstrated in vitro that the expression of the highly potent antimicrobial peptide human beta-defensin-2 (hBD-2) in keratinocytes is directly related to platelet released growth factors from PRF in a concentration- and time-dependent manner [3]. This anti-bacterial peptide might also aid in the prevention of peri-prosthetic infection. With these positive effects on wound healing and prevention of infection in mind, we hypothesized that the combination treatment of PRF and TA would synergistically reduce the LOS, amount and duration of wound leakage and the incidence of wound healing disturbances. However, we could demonstrate no significant difference in the above mentioned parameters with combined PRF-TA treatment compared to controls. Since the incidence of wound problems was small, our study was probably underpowered to detect such a difference.

An enhanced recovery protocol was utilized in all patients; therefore, the LOS was 2 days less than the national average of 5 days. We could demonstrate no additional benefit of PRF treatment on LOS and most patients were discharged on day 3. We tried to eliminate confounding factors for length of stay by excluding patients with severe co-morbidities using a standardized pain control and rehabilitation programme and establishing clear discharge criteria, however, the decision to discharge the patient from the hospital still remains a multifactorial one.

Our study has several strengths; this is a single centre, prospective, randomized, blinded study with an adequate number of comparable patients, selected using clear inclusion and exclusion criteria. The same implant was used in all cases, with two surgeons using identical techniques. The perioperative management protocols were standardized for all patients to decrease the effect of confounding factors and to make study and control groups homogenous.

Our study has several limitations. Although power analysis was performed for blood loss, the study was underpowered to analyse the effect of PRF on infection. The current rate of infection for primary TKA in our centre is 0.5%, therefore a much larger number of patients are needed to confirm the possible beneficial effect of PRF on wound healing & infection. The cost effectiveness of PRF treatment compared to the standard of care was not examined, since this was a pilot study to prove efficacy and safety. We did not perform a synovial fluid analysis for the increased presence of growth factors, and the anti-inflammatory and regenerative effects of PRF were based on previous in vitro studies. Performing an arthrocentesis in a recently operated arthroplasty patient would have introduced the risk of infection and was not deemed ethical. Only patients undergoing unilateral TKA for osteoarthritis were included, and the efficacy of PRF in other types of arthritis and revision TKA were not analysed. Indeed, PRF treatment may be more beneficial in complex cases such as bilateral TKA, revision TKA and inflammatory arthritis where more bleeding is expected to occur. Finally, patients with significant co-morbidities that might have affected blood loss were excluded, however, we did not investigate the effect of BMI or other factors on blood loss since this was a study to prove efficacy in the general arthroplasty population.

Conclusions

The topical co-delivery of PRF with TA does not significantly decrease blood loss in primary TKA compared to the standard of care. Slightly better active knee extension in the first 3 postoperative days can be achieved, however this benefit is not clinically relevant. No beneficial effect of

PRF on pain scores, allogenic transfusion rate, narcotic use, wound problems and length of stay could be demonstrated.

Author contributions RNT: co-designed the study, conceived the protocols, performed the surgical operations, contributed to data analysis and interpretation, wrote the manuscript. MP: performed all measurements and collected patient outcomes data, contributed in the writing of the article. TB: co-designed the study, contributed to data analysis and interpretation and critically reviewed the paper. EK: selected and performed the appropriate statistics and critically reviewed the final manuscript. AK: performed surgeries, critically reviewed the final manuscript. KY: contributed in the design and reviewed the final manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Reha N. Tandogan is a consultant for Smith & Nephew, and has received honoraria from Abdi İbrahim, Ibrahim Etem, Glaxo-Smith Kline and Santa Farma Pharmaceuticals. Tahsin Beyzadeoglu is a consultant for Vivostat and has received honoraria from Abdi Ibrahim and Santa Farma Pharmaceuticals. Asim Kayaalp has received honoraria from Abdi İbrahim, Ibrahim Etem, Glaxo-Smith Kline and Santa Farma Pharmaceuticals. Metin Polat, Kerem Yildirim and Erdem Karabulut declare that they have no competing interests.

Ethical approval Ethical approval was obtained from Halic University Clinical Studies Ethical Board (29.12.2016, no. 30). The study was conducted in conformance with the Declaration of Helsinki, the laws and regulations of Turkey and hospital requirements, whichever affords the greater protection to the patient.

Informed consent A written informed consent was obtained from all patients.

References

1. Abdel MP, Chalmers BP, Taunton MJ, Pagnano MW, Trousdale RT et al (2018) Intravenous versus topical tranexamic acid in total knee arthroplasty: both effective in a randomized clinical trial of 640 patients. J Bone Joint Surg Am 100:1023–1029
2. Antuña S, Barco R, Martínez Diez JM, Sánchez Márquez JM (2013) Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: a prospective randomized pilot clinical trial. Acta Orthop Belg 79:25–30
3. Bayer A, Lammel J, Rademacher F, Groß J, Siggelkow M et al (2016) Platelet-released growth factors induce the antimicrobial peptide human beta-defensin-2 in primary keratinocytes. Exp Dermatol 25:460–465
4. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE et al (1999) An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 81:2–10
5. Buda R, Vannini F, Castagnini F, Cavallo M, Ruffilli A et al (2015) Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation. Int Orthop 39:893–900
6. Cai DF, Fan QH, Zhong HH, Peng S, Song H (2019) The effects of tourniquet use on blood loss in primary total knee arthroplasty for patients with osteoarthritis: a meta-analysis. J Orthop Surg Res 14:348
7. Chen TP, Chen YM, Jiao JB, Wang YF, Qian LG et al (2017) Comparison of the effectiveness and safety of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. J Orthop Surg Res 12:11
8. Dallari D, Rani N, Sabbioni G, Mazzotta A, Cenacchi A et al (2016) Radiological assessment of the PRF/BMSC efficacy in the treatment of aseptic nonunions: a retrospective study on 90 subjects. Injury 47:2544–2550
9. Dan M, Martos SM, Beller E, Jones P, Randle R et al (2015) Blood loss in primary total knee arthroplasty–body temperature is not a significant risk factor—a prospective, consecutive, observational cohort study. J Orthop Surg Res 10:97
10. Fillingham YA, Darrith B, Calkins TE, Abdel MP et al (2019) Hip society research group. 2019 mark coventry award: a multicentre randomized clinical trial of tranexamic acid in revision total knee arthroplasty: does the dosing regimen matter? Bone Joint J 101-B(7-Supple-C):10–16
11. Gao FQ, Li ZJ, Zhang K, Sun W, Zhang H (2015) Four methods for calculating blood-loss after total knee arthroplasty. Chin Med J 128:2856–2860
12. Goel R, Rondon AJ, Sydnor K, Blevins K, O'Malley M et al (2019) Tourniquet use does not affect functional outcomes or pain after total knee arthroplasty: a prospective, double-blinded, randomized controlled trial. J Bone Joint Surg Am 101:1821–1828
13. Gross JB (1983) Estimating allowable blood loss: corrected for dilution. Anesthesiology 58:277–280
14. Huang Z, Xie X, Li L, Huang Q, Ma J et al (2017) Intravenous and topical tranexamic acid alone are superior to tourniquet use for primary total knee arthroplasty: a prospective, randomized controlled trial. J Bone Joint Surg Am 99:2053–2061
15. Jawhar A, Skeirek D, Stetzelberger V, Obertacke U (2019) Influence of the tourniquet on pain and function in total knee arthroplasty: a systematic review and meta-analysis. Z Orthop Unfall. https://doi.org/10.1055/a-0983-3808
16. Li J, Li HB, Zhai XC, Qin-Lei JXQ et al (2016) Topical use of topical fibrin sealant can reduce the need for transfusion, total blood loss and the volume of drainage in total knee and hip arthroplasty: a systematic review and meta-analysis of 1489 patients. Int J Surg 36:127–137
17. Lin C, Qi Y, Jie L, Li HB, Zhao XC et al (2016) Is combined topical with intravenous tranexamic acid superior than topical, intravenous tranexamic acid alone and control groups for blood loss controlling after total knee arthroplasty: a meta-analysis. Medicine (Baltimore) 95:e5344
18. Liu Y, Si H, Zeng Y, Li M, Xie H et al (2019) More pain and slower functional recovery when a tourniquet is used during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. https://doi.org/10.1007/s00167-019-05617-w
19. Lu Q, Peng H, Zhou GJ, Yin D (2018) Perioperative blood management strategies for total knee arthroplasty. Orthop Surg 10:8–16
20. Lundquist R, Dziegiel MH, Agren MS (2008) Bioactivity and stability of endogenous fibrogenic factors in platelet-rich fibrin. Wound Repair Regen 16:356–363
21. Mi B, Liu G, Zhou W, Lv H, Liu Y et al (2017) Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg 137:997–1009
22. Moher D, Schulz KF, Altman D (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357:1191–1194

23. Park JH, Rasouli MR, Mortazavi SM, Tokarski AT, Maltenfort MG et al (2013) Predictors of perioperative blood loss in total joint arthroplasty. J Bone Joint Surg Am 95:1777–1783
24. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD et al (2011) New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res 469:2992–2994
25. Pierce GF, Mustoe TA, Altrock BW, Deuel TF, Thomason A (1991) Role of platelet-derived growth factors in wound healing. J Cell Biochem 45:319–326
26. Ryan SP, Klement MR, Green CL, Blizzard DJ, Wellman SS et al (2019) Preoperative hemoglobin predicts postoperative transfusion despite antifibrinolytics during total knee arthroplasty. Orthopedics 42:103–109
27. Shin YS, Yoon JR, Lee HN, Park SH, Lee DH (2017) Intravenous versus topical tranexamic acid administration in primary total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc 25:3585–3595
28. Themistoklis T, Theodosia V, Konstantinos K, Georgios D (2017) Perioperative blood management strategies for patients undergoing total knee replacement: where do we stand now? World J Orthop 8:441–454
29. Verra WC, van Hilten JA, Honohan Á, van Zwet EW, van der Bom JG et al (2018) The effect of a fibrin sealant on knee function after total knee replacement surgery. Results from the FIRST trial. A multicenter randomized controlled trial. PLoS ONE 13:e0200804
30. Wang F, Zhao KC, Zhao MM, Zhao DX (2018) The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: a meta-analysis. Medicine (Baltimore) 97:e12270
31. Wang H, Shan L, Zeng H, Sun M, Hua Y et al (2014) Is fibrin sealant effective and safe in total knee arthroplasty? A meta-analysis of randomized trials. J Orthop Surg Res 9:36
32. Xiong H, Liu Y, Zeng Y, Wu Y, Shen B (2018) The efficacy and safety of combined administration of intravenous and topical tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord 19:321
33. Yang TQ, Geng XL, Ding MC, Yang MX, Zhang Q (2015) The efficacy of fibrin sealant in knee surgery: a meta-analysis. Orthop Traumatol Surg Res 101:331–339