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Original article

No additive effect of fibrin sealants to tranexamic acid in perioperative blood conservation in total knee arthroplasty

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Abstract. *Background:* Total knee arthroplasty (TKA) is associated with significant blood loss and reducing allogenic blood transfusions remains a challenge for orthopaedic surgeons. Between the various methods of blood conservation, the most appropriate solution is to minimize blood loss during and after surgery. *Materials and methods:* This prospective, randomized, standard treatment-controlled trial is based on the evaluation of the haemostatic efficacy of fibrin tissue sealant in association with tranexamic acid (TXA) in patients undergoing TKA. Sixty patients were scheduled to receive a TKA and randomly divided into two groups: a control group (30 patients), in which the standard means of haemostasis were applied, including the intraoperative intravenous administration of 1 g of TXA, and a treatment group (30 patients), in which the same standard method to control bleeding was used and, in addition to the TXA administration, a fibrin tissue adhesive was sprayed locally during the operation. *Results:* The main outcome of the study was the evaluation of postoperative levels of haemoglobin (Hb), red blood cells (RBC), and haematocrit (Ht) at 3 hours and on the first, the third and the sixth days after surgery. We found a slight decrease in Hb, RBC and Ht levels in the treatment group, but the difference was not statistically significant. The recovery of the knee range of motion on the first and the third postoperative day was lower in the treatment group, although this difference was not significant. No substantial difference in the grade of postoperative pain was recorded. In no case allogenic blood transfusions were necessary. No major adverse events were registered in our series. *Conclusions:* The use of fibrin sealant (FS) did not produce significant benefits compared to the isolated use of TXA. (www.actabiomedica.it)

Key words: fibrin tissue adhesive, total knee arthroplasty, blood loss, tranexamic acid, blood conservation

Introduction

Total knee arthroplasty (TKA) is associated with significant perioperative blood loss, putting patients at risk for allogeneic blood transfusions. The amount of blood loss is calculated in a range between 700 and 2100 ml and the decreased level of the haemoglobin is from 2.24 to 3.85 g/dL (1,2). Therefore, perioperative blood transfusion was needed in up to 38% of patients undergoing TKA (3). Reducing perioperative blood loss could potentially have a positive impact on patient morbidity, length of hospitalization, rehabilitation process and costs involved by eliminating the need for transfusion, which can be associated with adverse immunological reactions, disease transmission, intravascular haemolysis, transfusion-induced coagulopathy, renal impairment or failure and increased mortality (4-6). Various strategies have been

proposed to contain perioperative blood losses: before surgery, it is possible to get pre-donation of autologous blood units to use by reinfusion or stimulate patients' erythropoiesis with erythropoietin, iron and folic acid (7,8); between intraoperative procedures, the tourniquet use, the normovolemic haemodilution, the controlled hypotension induced by locoregional anaesthesia, the minimally invasive surgery, the cementation of the prosthetic components (which mechanically stanches the loss of blood), the intra-operative haemostasis with the electrocautery and the administration of various intravenous, intra-articular and oral medications can be included. In addition, both intraoperative and postoperative blood salvage devices (recovered from drainage containers) can be tools to reinfuse autologous blood. Compression bandages and local cryotherapy are common and simple after surgery adjuvants (9-13). As a pharmacological strategy, the antifibrinolytic activity of TXA is an optimal solution to enhance haemostasis and vessel sealing (14-18) but also other antihemorrhagic pharmacological aids, including FS or glues, are valid options (19,20). There is a substantial amount of literature on TXA use in these procedures (21) Consequently, organizations such as the American Association of Hip and Knee Surgeons (AAHKS), the American Academy of Orthopaedic Surgeons (AAOS), The Hip Society (THS), The Knee Society (TKS), and the American Society of Regional Anaesthesia and Pain Medicine (ASRA) have collaborated to create evidence-based guidelines for the use of TXA in primary total joint arthroplasty (TJA). These guidelines aim to enhance the treatment of orthopaedic surgical patients and minimize practice variability by advocating for a multidisciplinary, evidence-based approach to TXA usage (22). The recent fibrin glues are composed of two main components: fibrinogen and human thrombin that, mixed, mimic the last step of the coagulation cascade: thrombin activates fibrinogen to polymerize to an unstable clot, and factor XIII, which is present in the fibrinogen concentrate and is activated by thrombin (factor XIIIa), stabilizes the clot by catalysing cross-linking between the fibrin molecules. Factor XIIIa also cross-links between natural plasmin inhibitors and the fibrinogen mash to enhance clot resistance against fibrinolysis. The potential for viral transmission through fibrin sealants remains a concern, despite various virus reduction measures. Theoretical risks include the transmission of viruses such as hepatitis B, hepatitis C, HTLV-III/LAV, HIV-1, and other blood-borne pathogens like Epstein-Barr virus and cytomegalovirus, which might persist in commercial preparations after processing. Recently, cases of parvovirus B19 transmission have been linked to the use of fibrin sealants. While most adults possess antibodies to parvovirus B19, which typically results in mild infections, the risk is higher for pregnant women and neonates. In response, some manufacturers have implemented polymerase chain reaction testing to detect and reduce parvovirus B19 levels. The components of fibrin sealants, including fibrinogen and thrombin, undergo a series of treatments such as solvent-detergent treatment, vapor heat treatment, and nanofiltration to inactivate viruses. Despite the rigorous screening and treatment processes, no significant cases of viral transmission have been reported, likely due to the meticulous donor selection and plasma screening practices in place. However, the historical use of single-donor sourced fibrin sealants had a similar risk profile to blood transfusions, underlining the importance of ongoing vigilance in monitoring for potential viral transmission (23). Several studies in the literature have shown that application of FS without the use of other antihemorrhagic pharmacological aids, significantly reduces the rate of transfusion, blood loss, and HB levels drop; many studies also demonstrated superior efficacy of FS than procedures such as reinfusion of autologous blood deposited before surgery or recovered from post-operative losses (24,25). In addition, when compared with the isolated use of tranexamic acid, fibrin-based sealants show partially lower results in terms of transfusion rate and maintenance of haemoglobin levels, without however significant differences in the amount of total blood losses and in the prevalence of adverse events, such as superficial infections or deep vein thrombosis (26). To our knowledge, no study in literature compares the isolated use of TXA to the association of FS with TXA: the aim of this study was to evaluate if this co-administration of FS and TXA could enhance the beneficial effects of TXA in reducing blood loss in TKA.

Methods

This monocentric, prospective, standard-treatment-controlled, randomized, and single-blind study includes 60 patients. The investigation was approved by ethics committee at local Review Board (n° 21/2020 IRB Università degli Studi dell'Aquila). All patients gave informed written consent. Inclusion criteria were male and female, aged from 60 to 85 years, affected by advanced knee osteoarthritis with primary total knee replacement surgery indication, without previous operations on the affected knee, (excluding meniscectomy), and preoperative haemoglobin value ≥ 11 g/dl for women and ≥ 13 g/dl for men. The exclusion criteria in this study were: patients with ASA (American Society of Anaesthesiologists) risk grade ≥IV, known allergies or contraindications to fibrin sealants (FS) and/or tranexamic acid, congenital or acquired coagulation disorders, cancer, bilateral prosthetic replacement in a single session, and TKA revision surgery. The randomization was conducted by selecting patients for total knee arthroplasty (TKA) using a sealed envelope system, drawn from a waiting list. Thirty patients were randomized to receive the standard treatment of haemostasis, including 1g i.v. of tranexamic acid (Control Group); thirty patients were randomized to be managed with the same control patient's method plus 2 ml of local FS (Treatment Group), applied during surgery and used according to the manufacturer's instructions and recommendations. The fibrin tissue adhesive used consisted of two human plasma-derived components, contained in separate vials: one consisting of fibrinogen and human fibronectin (55-85mg/dl), the other consisting of human thrombin (800-1200 IU/ml). The constituents were mixed by connecting the two vials to a single lumen, through which the glue was ejected as a high-pressure spray. The patients were blinded treated, and the surgeons for practical reasons couldn't be blinded. The antalgic protocol used in each patient was paracetamol three times for days for a total of five days. For each patient at the time of admission, the day before the intervention, two units of allogenic blood were required to have them available after surgery.

Operative procedure

All surgeries were performed by the same senior knee-expert surgeon, using the same prosthetic model (CR Vanguard, Zimmer Biomet), a posterior cruciate-retaining implant type with the same technique (27). All the operations were performed by medial parapatellar approach, under hypotensive spinal-epidural anaesthesia, in a bloodless field with the use of a pneumatic tourniquet, until prosthesis insertion. Bone cuts both femoral and tibial were made with extramedullary guides, reducing further blood loss from the bone. In the treatment group, after the preparation of the femur and the tibia, the operative field was washed of any debris and accurately dried; local periarticular analgesic infiltration was performed (28); then the FS (about half of the total volume of 2 ml) was applied in the popliteal fossa by locally spraying the product with use of the double-syringe device. After prosthesis insertion, a residual 1 ml of fibrin glue was sprayed on the exposed cancellous surfaces of the femur and tibia not covered by the metallic implant and over soft tissues of medial and lateral joint recesses and of the prepatellar bursa (Figure 1).

After the tourniquet was deflated, meticulous haemostasis of major bleeding vessels of deep and subcutaneous tissues was performed by using electrocautery (29). One drainage was placed inside the knee joint and connected to a high vacuum suction drain container and, at the time of suturing the muscle fascia, both in the treatment group and in the control group, 1 g of TXA was administered intravenously (iv). A femoral-podalic compression bandage was placed at the end of the operation. No recovery devices were used. For thromboprophylaxis, each patient received a subcutaneous injection of 40 mg of low-molecular-weight heparin (Enoxaparin) approximately 12 hours postoperatively and then it was continued each 24 hours for 30 days. The patients stayed in an anti-declive position with the operated leg during bed rest and utilized cryotherapy. At about 24 hours after surgery, the drainage was removed, and the compression bandage was replaced with a single-pantyhose elastic stocking. At the same time, every patient started physiotherapy with manual passive and active knee mobilization;

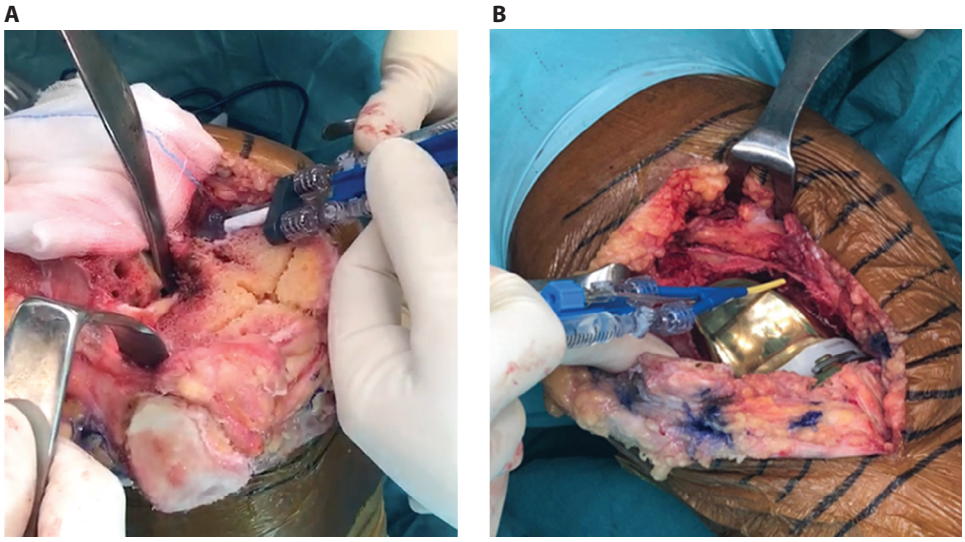

Figure 1. Fibrin glue placement in the posterior capsular recess (a) and in the exposed cancellous bone surface adjacent to the prosthetic components (b).

they were allowed to get out the bed on the second day after the operation and they started walking rehabilitation with tolerance load on the operated limb with aids, under the supervision of a physiotherapist. The primary endpoint of this study was to assess the effectiveness of the association of the FS with tranexamic acid, evaluating laboratory data with the complete blood count on the days following the surgery. Levels of haemoglobin (HB), haematocrit (HCT), and the number of erythrocytes (RBC) were collected preoperatively (the day before the surgery), on the day of surgery (3 hours later the dismission from the theatre) and then on the first, third and sixth postoperative days. The duration of the interventions, the tourniquet time and the need for blood transfusions were documented. The loss of blood at the end of the operation was recorded by measuring the volume in the aspiration system, without washing solutions. The apparent postoperative blood loss was registered by measuring the volume collected in the suction-drain containers upon removal. The degree of pain, valued with the VAS (Visual Analogue Scale), and the articular range of motion (ROM), measured as the maximum knee extension flexion grade by the use of a goniometer, were also registered in the preoperative phase and at the discharge; the length of hospital stays on the first and third postoperative days, to evaluate the possible correlation with clinical symptoms and rehabilitation path, was evaluated. In addition, for each patient, the presence of arterial hypertension under treatment and/or the use of oral antiplatelets or anticoagulant drugs was recorded; generally, anti-platelets drugs were suspended five days before surgery and anticoagulants seven days before. The safety of the fibrin tissue adhesive was assessed by monitoring adverse events, vital signs and laboratory findings.

Statistical methods

The study was based on an estimated sample of 60 subjects with a 1:1 ratio for the two types of treatment, which was calculated to be adequate to obtain a power greater than 95%, to verify an Effect Size of 0.25 and an α of 0.05 on the values of the variables between the two treatment groups. Statistical power was calculated using G * POWER Version 3.1.9.2. The Wilcoxon rank sum test was used to compare the two groups for both continuous variables during the time. The χ^2 test was used to examine categorical variables, such as differences in arterial hypertension (AHT) and use of antiplatelet/anticoagulant therapy between two groups; the variable sex was instead evaluated with

Fisher's exact test. Differences were considered significant when p ≤ 0.05. All statistical analyses were performed using SAS software (version 9.2, 2002-2008; SAS Institute, Inc., Cary, NC). A two-factor analysis of variance (ANOVA) for repeated measures, after logarithmic transformation of variables (Hb, Hct, Gr, ROM and VAS) in the event of non-normality of data, was performed to assess differences between groups using the MedCalc statistical software version 13.3.1 (MedCalc software bvba, Ostend, Belgium). P-values ≤ 0.05 were taken as statistically significant.

Results

The treatment and control groups were comparable in terms of demographic characteristics of the patients; no significant differences were found in terms of preoperative levels of haemoglobin (*p* = 0.281), haematocrit, red blood cells, and in terms of hypertension and antiplatelets or anticoagulants treatments (Table 1).

The surgical time and the relative tourniquet time were found to be similar in control and treatment groups with no statistically significant difference (*p-value*> 0.05) (Table 2).

The intraoperative blood loss was similar between the two groups, with a mean of 447.6±82.9 ml in the control group and 464.3±74.4 ml in the treatment group (*p-value* = 0.841).

The apparent postoperative blood loss was represented by an average drainage volume of 367.3±115.7 ml in the control group, with a minimum of 200ml and a maximum of 700ml, and 237±77.6 ml in the treatment group, with a minimum of 150ml and a maximum of 460ml, with a *p-value* = 0.043 (Table 2).

The mean of HB levels at 3 hours after the surgical procedure was 13.05±1.05 g/dl in the control group compared with 13.01±1.05 g/dl in the treatment group; then on the first postoperative day, on the third day and the sixth day, it was respectively 11.98±0.89 g/dl vs 12.02±0.90 g/dl, 11.09±0.99 g/dl vs 11.27±1.14 g/dl and 11.14±0.84 g/dl vs 11.17±1.09 g/dl (complete data on each variable are reported in Tables 3 and 4). No statistical differences were found between both groups for all variables considered (*p-value* = 0.212) (Figure 2).

The average HB decrease from preoperative value was 3.16±0.85 g/dl in the control group compared with 3.12±1.11 in the treatment group (*p-value* = 0.994) (Figure 2).

The trend in the levels of RBC and HCT was also not significant in any of the repeated comparisons (p-value> 0.05). In no case, neither in the control group nor in the treatment group, blood transfusions were required. Only one measurement of HB level for the control group and one for the treatment group reached a value inferior to 8,5 g/dl but considering the absence of clinical signs related to hypoxia and since these patients were not suffering from cardiovascular diseases,

Table 1. Mean preoperative values (min-max)

	CONTROL GROUP (TXA)	TREATMENT GROUP (TXA+EVICEL)	p Value
Sex (M:F)	10:20	11:19	1.223
Age	73.06 (61 – 86)	72.73 (60 – 85)	0.378
BMI	31.22 (24.20 – 38.60)	30.31 (23.30 – 39.80)	0.970
ASA	2.13 (1.00 - 3.00)	2.33 (1 – 3)	0.194
ROM preop. (max flexion)	107.17 (90 -120)	103.50 (90 -130)	0.441
HB preop. g/dl	14.07 (12.20 – 16.90)	13.99 (12.40 – 17.20)	0.281
HCT preop. %	43.16 (38.20 – 50.70)	42.56 (34.60 – 49.00)	0.470
RBC preop. (mil/mmc)	4.83 (4.23 – 5.67)	4.74 (3.78 – 5.37)	0.470
AHT %	73.3	76.6	0.480
Antiplatelet/anticoagulant TX %	50	43.3	0.330

Table 2. Intra-operative records

	CONTROL GROUP (TXA)			TREATMENT GROUP (TXA+EVICEL)		
	Surgical time (min)	**Tourniquet time (min)**	**DRAINAGE VOLUME (ml) CONTROL GROUP (TXA)**	**Surgical time (min)**	**Tourniquet time (min)**	**DRAINAGE VOLUME (ml) TREATMENT GROUP (TXA + EVICEL)**
Mean	89.17	74.73	367.3	87.50	72.10	237
Median	90	73	350	87.50	72.50	204
SD	8.91	9.14	115.7	9.44	8.92	77.6

Abbreviation: SD = Standard Deviation.

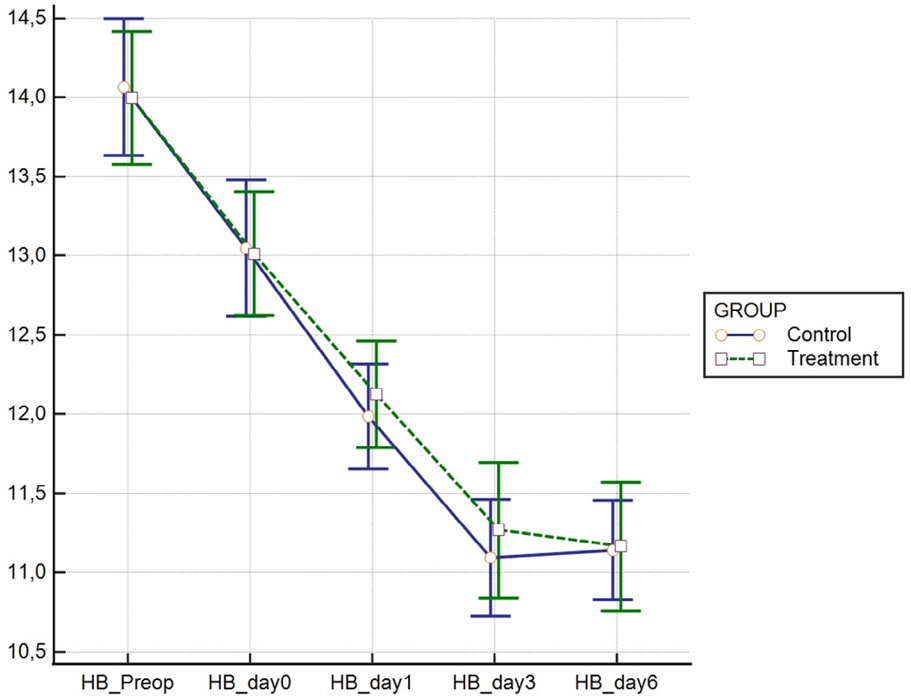

Figure 2. HB level variation.

they did not need transfusions. Regarding the clinical postoperative outcomes, the ROM measurements with the goniometer on the first and third days after surgery were comparable in the two groups (Table 3 and Table 4).

At discharge time there was the largest variation in the ROM: a mean of 81.3±5.8 degrees in the control group compared to 77.8±7 degrees in the treatment group, but the difference was not statistically significative. The postoperative VAS levels were similar for both groups with no significative differences. Also, the length of hospital stay did not demonstrate significant differences in the two groups, with a common average of seven days, including the day before surgery for hospital admission. During the study, we recorded no major complications such as pulmonary embolism, deep-vein thrombosis, superficial or deep infections, wound dehiscence, or prolonged drainage

Table 3. Control Group (TXA) findings

Variables	Patients N	Mean	Std Dev	Median	Minimum	Maximum
ROM preop.	30	107.17	7.03	110.00	90.00	120.00
ROM 1st day	30	56.67	7.91	60.00	40.00	65.00
ROM 3rd day	30	81.33	5.86	81.12	70.00	90.00
HB preop.	30	14.07	1.16	14.05	12.20	16.90
HB surgery day	30	13.05	1.15	13.05	10.70	15.40
HB 1st day	30	11.98	0.89	11.95	10.30	14.10
HB 3rd day	30	11.09	0.99	11.20	9.10	13.20
HB 6th day	30	11.14	0.84	11.35	9.30	12.50
RBC preop.	30	4.83	0.32	4.82	4.23	5.67
RBC Surg. Day	30	4.42	0.30	4.45	3.65	5.03
RBC 1st day	30	4.07	0.25	4.08	3.45	4.51
RBC 3rd day	30	3.75	0.28	3.74	3.11	4.37
RBC 6th day	30	3.84	0.34	3.79	3.17	4.62
HCT preop.	30	43.16	3.17	42.75	38.20	50.70
HCT Surg. Day	30	39.55	3.00	39.55	33.00	45.20
HCT 1st day	30	36.42	2.59	36.65	31.30	40.80
HCT 3rd day	30	33.64	2.66	33.90	27.80	38.80
HCT 6th day	30	34.24	2.59	34.10	28.50	38.80

Abbreviation: ROM= maximum flexion degree.

Table 4. Treatment Group (TXA + INN-human fibrinogen/human thrombin) findings

Variables	Patients N	Mean	Std Dev	Median	Minimum	Maximum
ROM preop.	30	103.50	8.32	100.00	90.00	130.00
ROM 1st day	30	57.50	4.87	60.00	45.00	65.00
ROM 3rd day	30	77.83	7.03	78.69	55.00	90.00
HB preop.	30	14.00	1.13	14.00	11.80	17.20
HB surgery day	30	13.01	1.05	13.15	10.70	15.80
HB 1st day	30	12.12	0.90	12.20	10.40	13.60
HB 3rd day	30	11.27	1.14	11.60	8.50	13.00
HB 6th day	30	11.17	1.09	11.20	8.40	13.00
RBC preop.	30	4.74	0.37	4.81	3.78	5.37
RBC Surg. Day	30	4.35	0.37	4.38	3.54	5.00
RBC 1st day	30	4.06	0.34	4.18	3.22	4.67
RBC 3rd day	30	3.78	0.42	3.86	2.89	4.65
RBC 6th day	30	3.82	0.41	3.86	2.76	4.69
HCT preop.	30	42.56	3.19	42.70	34.60	49.00
HCT Surg. Day	30	38.92	2.88	39.30	32.50	44.00
HCT 1st day	30	36.36	2.69	37.00	30.70	40.50
HCT 3rd day	30	33.80	3.60	34.50	25.20	39.50
HCT 6th day	30	33.98	3.27	33.50	24.40	39.40

Abbreviation: ROM= maximum flexion degree.

from the wound. The most common adverse events were fever associated with the operation and hematoma. Fever was recorded in seven patients in the control group and in eight in the treatment group; it never exceeded 38.5 °C, never lasted more than three days and required the use of antibiotic therapy in no case. The presence of hematoma, accompanied by limb swelling, was more frequent in the treatment group with eight cases versus three cases in the control group.

Discussion

Many studies in the literature have compared fibrin-based sealants with placebo and TXA, but the data are conflicting. In a paper of 2014, the Authors examined a sample of 183 patients including 113 treated with fibrin-based sealants and 70 without any treatment, highlighting that there were no differences between the two groups in terms of reducing blood loss and the rate of transfusion supporting what we found in our study (30). On the contrary, a 2015 meta-analysis showed how patients undergoing TKA surgery can benefit from the use of fibrin-based sealants in terms of reducing transfusion rates while less evident results are in terms of reducing blood loss (31). Also, the differences in different experimental studies such as the amount of medication used [2, 5, 10, or 20 ml] (32), the use of tourniquet (release before or after the prosthetic implant) (11,12), insertion of the post-operative drainage (in suction or not, for 24 or 72 hours), makes it difficult to draw unambiguous conclusions about their influence on pharmacological blood loss strategies. The aim of our study was to test the association of TXA with the fibrin-based sealant to verify a possible sum effect. This is motivated by the implications that could have been in the clinical and economic aspects as well as by the fact that there are no studies in the literature that test the association of these two drugs. We found that administration of FS in association with TXA did not show a significant reduction in the decrease in levels of Hb (primary outcome of our choice), Hct, and Gr compared to TXA alone, as literature data shows (33). In terms of functional knee recovery, we did not register statistically significant differences but only a slightly better flexion on the third postoperative day in the control group. We speculated that this could be because a reduced loss of intraarticular blood in the postoperative phase had allowed a better bending of the knee. Consequently, the lower ROM in the treatment group may be due to a higher rate of hematoma and limb swelling caused by hidden postoperative bleeding. Because of the placement of the drain close to the fibrin glue application site, we hypothesize that the formation of early clots may have caused the drainage tube occlusion determining the accumulation of blood in the knee. The presence of conflicting data on intra- and perioperative strategies for primary total knee arthroplasty (TKA) underscores the need for further research in this area. While this study provides valuable insights, it is important to acknowledge several limitations that could affect the interpretation of its findings. Firstly, the study's sample size was relatively small, which may limit the statistical power and generalizability of the results. Small sample sizes can lead to insufficient representation of the diverse patient population typically encountered in clinical practice. Consequently, the findings may not fully capture the variability in outcomes across different patient subgroups or settings. Secondly, the study did not employ a double-blinded design. Without blinding, there is a risk of bias in both the administration of treatments and the assessment of outcomes. In addition, exclusion criteria could have significantly influenced the study's findings and generalizability in the following ways:

- ASA Risk Grade ≥IV: Excluding patients with higher ASA risk grades (≥IV) could skew the results towards a healthier cohort. These patients are typically at a higher risk of complications and may respond differently to treatment and interventions compared to those with lower ASA risk grades. Consequently, the outcomes observed in the study may not fully represent the experiences of patients with more severe systemic conditions.
- Allergies and Contraindications: Patients with allergies or contraindications to FS and/or tranexamic acid were excluded to avoid adverse reactions. This exclusion may limit the study's applicability to those who are sensitive or intolerant to these treatments. Thus, the study's results might not accurately reflect outcomes in the broader patient population, including those who could have different reactions to these medications.
- Coagulation Disorders and Cancer: Patients with coagulation disorders or cancer were excluded because their conditions could significantly impact bleeding and clotting processes, potentially skewing the study's results. Such exclusions ensure that the data reflects patients with more typical bleeding profiles, but

it also means the findings may not be applicable to individuals with these complex medical issues who might experience different bleeding patterns or require different management strategies.

- Bilateral Prosthetic Replacement and TKA Revision Surgery: Excluding patients undergoing bilateral procedures or revision surgeries is important as these cases often involve different surgical challenges and risks compared to primary, unilateral TKA. Bilateral replacements and revisions may have different blood loss profiles, recovery trajectories, and responses to interventions like FS and tranexamic acid. Thus, the study's conclusions may not be fully applicable to these more complex scenarios.

By excluding these patient groups, the study ensures a more homogeneous sample, which can help in isolating the effects of the interventions being studied. However, this also means that the findings may not be fully generalizable to the broader population of TKA patients, including those with more severe conditions or those undergoing more complex procedures. However, to reduce biases to standardize the treatment of patients as much as possible, we employed the following strategies in our study: 1) do not pre-deposit patients with autologous blood units to the blood bank; 2) do not re-inflate the blood inside the drains; 3) avoid local use of tranexamic acid; 4) use the same surgical technique and the same implant in all operated patients (34). We believe that sticking to these points can represent a first step to standardizing studies on the topic and obtaining the clearest possible results on the individual experimental factors tested to reduce blood loss (35). Furthermore, the study did not account for long-term outcomes beyond the immediate postoperative period. While early outcomes such as blood loss and transfusion rates are critical, understanding the long-term impact of intra- and perioperative strategies on functional recovery, prosthesis longevity, and patient satisfaction is equally important. Future research should aim to address these long-term effects to provide a more comprehensive assessment of the strategies under investigation. Finally, the discussion on the economic aspect assumes nowadays a particular value on the difficulties that the national health system is experiencing. As we know from Scardino et al (36) the use of FS can induce a reduction in resource consumption with an average cost-savings of €1.676 per patient. In our experience, the price of the FS product utilized is 90 euros per ml, compared to the 2 euros of the TXA. Since not supported by a sum effect the routinary use of FS is not recommended for primary TKA in all cases in which TXA is not contraindicated (37); as widely demonstrated in the literature, our study also confirms that tranexamic acid used in isolation allows excellent control of blood loss (38,39). It is implied that an accurate, standardized surgical technique with particular attention to haemostasis is essential to achieve positive results (40). In addition, all other operative and peri-operative strategies for blood loss management during TKA can influence blood loss-related outcomes (41).

Conclusions

The results of our study showed no significant advantages in using FS glues in association with TXA for blood loss management. The IV administration of 1 gr of TXA, associated with a meticulous operative technique, was sufficient to obtain excellent results in all patients, without ever needing to transfuse. We can conclude that the routinary use of FS products in primary TKA cannot be justified since its non-clinical superiority over the TXA: conversely, they represent an additional charge for a surgical procedure, the TKA, already burdened by large health costs (38). Since literature reported conflicting results on the use of FS like intraoperative strategy for blood loss management, we think that further studies are necessary to understand the best modality of application and minimum effective dose that could be used in case of TXA intolerance or contraindication.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: Conceptualization RG; Data curation & Formal analysis GGC, AP, MS, GP and LG; Methodology RG; Statistical Analysis SN; Validation GL; Writing original draft RG and GA; Writing review & editing GA; Supervision GL and RG.

Ethic Approval: Ethics committee at local Review Board (n° 21/2020 IRB Università degli Studi dell'Aquila)

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