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Original Article

A randomized comparative study of topical versus intravenous tranexamic acid administration in enhanced recovery after surgery (ERAS) total knee replacement

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ABSTRACT

Background: The aim of this study was to compare the topical to IV tranexamic acid (TXA) administration of the same dose, given at the same time in patients who underwent TKR using an enhanced recovery after surgery (ERAS) regime.
Methods: Ninety patients were randomized in control group, and IV and topical application groups received 1 g TXA.
Results: Blood loss and transfusion requirements in control group were statistically higher compared to both TXA groups ($p < 0.05$). Length of stay was the same in all groups.
Conclusions: TXA reduced significantly the blood loss and the need for transfusion in ERAS primary unilateral TKR.

1. Introduction

Total knee replacement is a common procedure associated with substantial blood loss and often allogeneic blood transfusion (ABT) is required. The estimated blood loss, although varies, has been estimated around 1500 ml,[1,2] and the reported blood transfusion rate after unilateral TKR is ranging between 11% and around 50% using standard practice.[2,3]

In order to avoid allogeneic blood transfusion (ABT) and the associated significant complications,[2,4] different strategies have been described in order to reduce the need for ABT including the use of tranexamic acid.[5,6]

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent and several clinical studies, including randomized controlled trials, systematic reviews, and meta-analysis, have shown that both intravenous[7–9] and topical[10–12] TXA administration are effective in reducing blood loss and transfusion requirements after TKR, and safe as far as the possible complications are concerned.[13,14]

Despite the evidence from these reports as well as the studies comparing the topical to IV administration (Table 2), there is still no firm conclusion as far as the most effective route, dose, and timing regarding the TXA use in TKR.[14]

The aim of our study was to compare the topical to IV TXA administration with the same dose, given at the same time in patients, who underwent primary TKR performed using an enhanced recovery after surgery (ERAS) regime.

2. Material and methods

This is a prospective randomized clinical study including 90 patients who underwent unilateral TKR for knee osteoarthritis using an enhanced recovery after surgery (ERAS) regime. The patients had no history of thromboembolic episode or a high risk of

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venous thromboembolism, no hepatic/cardiorespiratory/renal insufficiency, and no congenital or acquired coagulopathy.

The study was authorized by the local ethical committee (Hospital's Ethics Committee) and was performed in accordance with the Ethical standards of the 1964 Declaration of Helsinki, as revised in 2008; an informed consent was obtained from all individual participants included in the study.

2.1. Design of the study and randomization

The patients were randomized using the technique of stratified randomization by minimization[15,16] and were assigned to three groups according to a stratified and blocked randomization based on three parameters: gender, age, and body mass index (BMI). These groups were a control group (Group C) with no treatment, the intravenous group (Group IV), and the topical group (Group T) of TXA administration.

The TXA was administered in both treatment groups at the same time, at the start of the wound suturing. Patients in the IV group received 1 g TXA intravenously, and in group T, 1 g TXA in 30 ml normal saline (a solution of 40 ml) was applied topically.

2.2. Operative technique and post-operative care

All operations were performed under spinal anesthesia, using a pneumatic tourniquet and a hybrid posterior cruciate retaining prosthesis was implanted through a standard midline skin incision and a medial parapatellar approach in all patients.

Antibiotic prophylaxis, anticoagulation regime and the rest of the post-operative regime were the same for all patients. The drains were opened immediately after the surgery and removed at 24 h post-operatively and all patients followed an enhanced recovery after surgery (ERAS) regime with mobilization the morning following the operation day, aiming to be discharged the fourth post-operative day.

The same allogeneic blood transfusions (ABT) regime was followed for all patients. ABT was allowed only for the patients whose hemoglobin level was less than 10.0 g/dl or those with intolerable anemic symptoms or any anemia-related organ dysfunctions the day of the operation.

Blood samples were taken pre-operatively and post-operatively at days 1, 2, and 4.

2.3. Outcome measures

Patients demographics (age, gender, BMI), tourniquet time, pre-operative and post-operative Ht and Hb, units of ABT, the discharged day, and complications were prospectively collected.

The primary outcome measures were the calculated blood loss and the need for allogeneic blood transfusion. The calculated blood loss was estimated according to Sehat et al.[17] as the sum of the change in blood volume plus the volume of transfused blood. The change in blood volume was calculated using the formula of Bourke and Smith[18] while the patients' blood volume was calculated using the formula of Nadler et al.[19]

The secondary outcome measures were complications such as symptomatic deep vein thrombosis (DVT), pulmonary embolism, or any other thromboembolic event, superficial and deep infections and any deterioration of hepatic or renal function during the first 30 post-operative days.

2.4. Statistical analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM). The normality of quantitative variables was tested by Kolmogorov–Smirnov test. To assess differences of demographic and clinical characteristics between the three groups of patients, one-way analysis of variance ANOVA (age, BMI, tourniquet time, Hb and Ht levels) and chi square test (gender) were used. Between groups, differences of blood loss, transfusion rates and used number of units were assessed by ANOVA, chi-square test, and Kruskal–Wallis test, respectively. Post hoc analysis was performed using Tukey's test (blood loss) and Mann–Whitney *U*-test (transfusion quantity). Odds ratios (OR) with their 95% confidence intervals (CI) were estimated by means of logistic regression models as the measure of association between transfusion and different groups of patients. All tests were two tailed and statistical significance was considered for p values less than 0.05.

Table 1
Statistical analysis of the patients' demographics, clinical data and results.

	Control (C)	IV (IV)	Topical (T)	*p*
Number	30	30	30	
Age (years)	71.77 ± 6.50	69.27 ± 7.21	71.10 ± 6.32	0.329[a]
Gender				
Male/female	6 (20.0)/24 (80.0)	6 (20.0)/24 (80.0)	6 (20.0)/24 (80.0)	1.000[b]
BMI	32.63 ± 4.37	32.79 ± 5.04	33.38 ± 6.08	0.843[a]
Tourniquet time	94.83 ± 15.64	89.67 ± 16.97	90.57 ± 15.13	0.410[a]
Hb pre-operatively	14.13 ± 4.21	13.63 ± 1.32	14.49 ± 5.61	0.713[a]
Hb post-operative (day 4)	10.49 ± 0.83	11.19 ± 1.12	11.10 ± 1.08	0.017[a]
Ht pre-operatively	39.64 ± 6.47	41.03 ± 3.58	40.10 ± 5.80	0.605[a]
Ht post-operative (day 4)	31.45 ± 2.34	32.41 ± 5.20	33.19 ± 2.97	0.197[a]
Blood loss				
Mean ± SD	1342.49 ± 363.04	1123.42 ± 216.58	1048.15 ± 214.49	<**0.001**[a]
Median	1246.78	1073.97	1017.01	
IQR	1128.90–1454.51	998.79–1217.82	929.42–1190.20	
Transfusion rate				
Number (%)	18 (60.0)	4 (13.3)	3 (10.0)	<**0.001**[b]
Transfusion quantity (number of units)				
Median (range)	1.00 (0.00–3.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	<**0.001**[c]
Mean ± SD	0.97 ± 0.99	0.13 ± 0.34	0.10 ± 0.30	

[a] ANOVA.
[b] Chi square test.
[c] Kruskal–Wallis test.
Blood loss: C versus IV, $p = 0.007$/C versus T, $p < 0.001$/IV versus T, $p = 0.538$ [Tukey test].
Transfusion quantity: C versus IV, $p < 0.001$/C versus T, $p < 0.001$/IV versus T, $p = 0.690$ [Mann–Whitney test].
OR (IV versus C) = 0.10 (0.03–0.37), $p < 0.001$/OR (IV versus T) = 0.07 (0.02–0.30), $p < 0.001$.

Table 2
Comparative studies between topical and IV TXA administration regimes.

Study	Control	Topical	IV pre	IV intra	IV multiple	Results
Topical versus IV intra						
[1] *N*: 150	*N*: 50 • 100 ml NS	*N*: 50 • 1.5 g TXA in 100 ml NS • While suturing		*N*: 50 • 1.5 g TXA in 100 ml NS • After closing surgical sites		Topical more effective
[2] *N*: 89	No	*N*: 47 • 2.0 g TXA in 100 ml NS • 2 min before tourniquet release		*N*: 42 • 10 mg/kg TXA • 10 min before tourniquet release		Topical and IV equally effective
[3] *N*: 200	*N*: 50 • No treatment	*N*: 50 • 3 g TXA in 100 ml NS • Before suturing, clamp drain 1 h, then fully open *N*: 50 • 1.5 g TXA in 100 ml NS • Injected through the drain after wound closure		*N*: 50 • 500 mg TXA in 100 ml NS • After closing the wound immediately		• TXA: statistical significant effect • IV TXA much more effective
[4] *N*: 571		*N*: 198 • 3 g TXA in 100 ml NS • After capsular closure		*N*: 373 • 1.5 g TXA at time of incision		Both routes are safe and effective
Topical versus IV pre						
[5] *N*: 90 Simultaneous bilateral computer assisted TKR – no drain	*N*: 30 • 10 ml NS IV • 20 min before tourniquet inflation	*N*: 30 • 1 g TXA in each knee • After wound closure	*N*: 30 • 1 g TXA • 20 min before tourniquet inflation			• TXA: significant benefit • Local versus IV: no difference
Topical versus IV multiple						
[6] *N*: 78		*N*: 39 • 3 g TXA in 100 ml NS • After capsular closure			*N*: 39 • IV intra, 15 mg/kg in 100 ml NS before tourniquet deflation and • IV post, 10 mg/kg TXA, 3 h after surgery	Similar results
[7] *N*: 60		*N*: 30 • 3 g TXA in 100 ml NS • At least 5 min before tourniquet deflation			*N*: 30 • IV pre, 10 mg/kg TXA, 20 min before tourniquet inflation and • IV intra, 10 mg/kg TXA, 15 min before tourniquet deflation and • IV post, 10 mg/kg TXA, 3 h after intra dose	Topical TXA is equally effective as 3 doses of IV regimen
[8] *N*: 150	*N*: 50 • Routine hemostasis	*N*: 50 • 3 g TXA in 100 ml NS • After capsular closure			*N*: 50 • IV pre, 1 g TXA before tourniquet inflation and • IV post, 1 g TXA after tourniquet removal	• Both regimens are more effective than routine hemostasis • No significant difference between the two TXA groups
[9] *N*: 240	*N*: 40 • No treatment	Group 5, *N*: 40 • 2.0 g TXA in 100 ml NS • At least 5 min before tourniquet release		Group 1, *N*: 40 • 10 mg/kg TXA • 15 min before tourniquet deflation	Group 2, *N*: 40 • IV pre, 10 mg/kg TXA, 20 min before tourniquet inflation and • IV intra, 10 mg/kg TXA, 15 min before tourniquet deflation Group 3, *N*: 40 • IV intra, 10 mg/kg, TXA, 15 min before tourniquet deflation and • IV post, 10 mg/kg TXA, 3 h after first dose Group 4, *N*: 40 • IV pre, 10 mg/kg TXA, 20 min before tourniquet inflation and • IV intra, 10 mg/kg TXA, 15 min before tourniquet deflation • IV post, 10 mg/kg TXA, 3 h after first dose	• Single dose: not effective • Two dose: the least amount necessary for effective results • Three dose: the maximum effective

IV: intra-venous; pre: pre-operative; intra: intra-operative; post: post-operative; *N*: number of patients; NS: normal saline; min: minutes.

3. Results

There were no statistically significant differences in age ($p = 0.329$), gender ($p = 1.000$), BMI ($p = 0.843$), pre-operative hemoglobin (Hb) ($p = 0.713$), pre-operative hematocrit (Ht) ($p = 0.605$) and post-operative Ht ($p = 0.197$) between the three groups of patients (Table 1). The post-operative Hb in control group was significantly lower ($p = 0.017$) compared to the other two groups despite the fact the patients in this group received more ABT units.

The mean tourniquet time was similar in the three groups ($p = 0.410$), with a mean value of 94.83 ± 15.64 min (median time, 90 min) for control group, a mean value of 89.67 ± 16.97 min (median time, 90 min) for group IV and a mean value of 90.57 ± 15.13 min (median time, 90 min) for group T.

Mean values of blood loss, transfusion rates, and used number of units are also shown in Table 1. One-way ANOVA showed statistically significant differences in blood loss between the three groups of patients ($F(2, 87) = 9.365$, $p < 0.001$). In pairwise comparisons using Tukey's test, groups IV and T demonstrated significantly lower blood loss compared to control group by 16.3% ($p = 0.007$) and 21.9% ($p < 0.001$), respectively; no statistically significant difference was found between groups IV and T ($p = 0.538$). Transfusion rates were significantly lower ($\chi^2 = 23.372$, df = 2, $p < 0.001$) in groups IV (13.3%) and T (10.0%) compared to control group (60.0%). In particular, the likelihood of transfusion was 90% lower in group IV (OR = 0.10, 95% CI = 0.03–0.37, $p < 0.001$), and 93% lower in group T (OR = 0.07, 95% CI = 0.02–0.30, $p < 0.001$), compared to control group. Finally, Kruskal–Wallis test showed statistically significant differences in transfusion quantity between the three groups of patients ($\chi^2 = 25.544$, df = 2, $p < 0.001$). Post hoc analysis using Mann–Whitney test revealed that the number of units used in groups IV and T were significantly lower compared to control group (both $p < 0.001$); no statistically significant difference was found between groups IV and T ($p = 0.690$).

All patients were discharged as planned on the fourth post-operative day.

3.1. Complications

There were no thromboembolic complications in any patient of all the three groups. There were also no deep infections, while 2 superficial infections (one in the control group and one in the IV group) were managed successfully with antibiotics.

4. Discussion

The calculated blood loss and the need for ABT were significantly lower in both groups of patients where the TXA was used, either IV or topically compared to the control group, with no significant difference in complications between the three groups. No significant difference in blood loss and the need for blood transfusion was found between the IV and topical TXA groups. No patient was required to stay in the hospital beyond the fourth post-operative day.

The findings of this study are in agreement with the existing literature that supports the efficacy of TXA in reducing the blood loss and safety regarding the possible complications in TKR after either IV[7–9] or topical[10–12] administration. However, as already mentioned, it is not clear yet which regime (route, doses, and timing) is more effective.[14]

4.1. Route of TXA administration (topical versus IV)

Although several studies have confirmed the safety regarding the possible complications of the IV TXA use in TKR,[7–9,13,14,20] there is still a concern about the use in patients with history or at risk for thromboembolic events.

The local application is easy to administer, providing maximum local application of the drug at the site where needed – the bleeding site, and inhibits the fibrin clot dissolution in the affected area, and inducing partial microvascular hemostasis.[13] Furthermore, the systematic absorption after local application is significantly lower compared to IV administration.[21]

Therefore, the topical TXA may be a safe alternative to the IV use and, at least theoretically, can avoid or reduce the risk of potential complications related to the IV TXA in patients that are in high risk for developing thromboembolic disease, and in patient with a cardiovascular disease or renal dysfunction.[14]

Thus, and according to the results of our study, we propose the topical application of TXA in TKR the time of starting the wound suturing.

4.2. Dose and timing

In the comparative studies between IV and topical TXA use, different dose and timing have been reported (Table 1), and furthermore, it seems that the effects of TXA are influenced by doses and timings of administration.[14]

There is evidence suggesting that two-dose regimens and in particular those giving TXA one dose before and one dose during surgery are more efficacious than other regimens, i.e. one-dose regimens giving TXA before or during surgery or even two-dose regimens giving TXA during and after surgery.[22,23] On the other hand, one dose of locally applied TXA (3 g TXA in 100 ml NS) was found to be equally effective as three doses of IV regimen (before, during and 3 h after the surgery).[24] There is also evidence that smaller doses of 1.5 g or even 1 g, either IV or topical, are effective in reducing blood loss and transfusion requirement (Table 2). Therefore, it is not clear what regime concerning the dose/s and timing is more effective.[14]

The dose used in our study is the lowest one; a new study comparing this dose to a higher dose but the same concentration is underway.

4.3. Transfusion rate and quantity

It is known the transfusion quantity and rate depends on many factors, including the transfusion trigger. In our department, this trigger is relatively high and this probably explains the high transfusion rate in the control group. We believe that this also makes the difference between the TXA groups and the control group more pronounced.

5. Conclusion

The results of this study are in accordance to the available evidence; TXA given either IV or topically in the same dose of 1 g reduced significantly the blood loss and the need for transfusion with no increased risk of complications in patients who underwent unilateral TKR. Using an enhanced recovery after surgery regime, with a planned four-day length of stay, there was no difference between the treatment and control groups.

Conflict of interest

The authors declare that they have no conflict of interest.

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