

Comparative Analysis of Topical Versus Intravenous Administration of Epsilon-Aminocaproic Acid on Blood Management in Total Knee Arthroplasty

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ABSTRACT

Introduction. Although the use of antifibrinolytics to reduce perioperative blood loss during total knee arthroplasty (TKA) has shown unequivocal benefit in regard to blood conservation, the best route of administration remains in question. This study tested the hypothesis that topical delivery of epsilon-aminocaproic acid (EACA) was superior to intravenous (IV) administration in the setting of primary TKA.

Methods. This cross-sectional study included a six-year retrospective chart review of TKA patients done by a single surgeon. Post-operative hemoglobin levels and the incidence of blood transfusions were compared among three patient subgroups: no EACA, topical EACA, or IV EACA. Key outcome measures included post-operative hemoglobin, need for post-operative transfusion, and length of hospital stay.

Results. Of the 668 patients included in this study, 351 (52.5%) received IV EACA, 298 (44.6%) received topical EACA, and 19 (2.8%) received no EACA. For the three-way comparisons, significant differences were observed for post-operative mean hemoglobin on day one ($p < 0.001$), day two ($p < 0.001$), and day three ($p = 0.004$), with consistently higher means for participants in the topical group. Eight patients required transfusions in the IV EACA group, but none were needed in the topical EACA group ($p = 0.027$). Length of stay was shortest for patients in the topical group, with 66% hospitalized for two days, while 84% of the IV group remained hospitalized for three days ($p < 0.001$).

Conclusions. The topical delivery of EACA is superior to IV administration with respect to blood conservation for patients undergoing primary TKA. *Kans J Med* 2022;15:73-77

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most common orthopaedic surgery procedures performed today in the United States. The number of arthroplasties is expected to increase by 85%, to 1.26 million procedures, by 2030.¹ Historically, the reported rate of blood

transfusion after TKA has been as high as 40%.² However, recent blood conservation efforts markedly have decreased this transfusion rate and the associated complications and costs.

The mainstay of blood conservation treatment in the setting of TKA is the administration of antifibrinolytics, such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). The mechanism of action of these medications is through the inhibition of fibrinolysis by blocking the lysine-binding sites of plasmin and plasminogen to fibrin. This prevents the premature dissolution of clots, thereby decreasing perioperative bleeding and the need for blood transfusion. Multiple studies have confirmed the efficacy and safety of these medications in TKA patients.³⁻⁷ Although TXA historically has been used more widely, it has not been shown to be superior to EACA for TKA.⁸ Moreover, EACA is more affordable than TXA.⁹ For example, Churchill et al.¹⁰ determined that the average cost of EACA for each procedure is \$2.23 compared to \$39.58 for TXA.

The optimal method of EACA administration has not been determined. Antifibrinolytics may be administered orally, intravenously, topically by intra-articular placement during surgery, or by a combination of these means. Recent studies have shown that topical administration of TXA was associated with more effective blood conservation than intravenous (IV) administration during TKA.^{2,11} To the best of our knowledge, no similar study has been done on the more affordable antifibrinolytic alternative EACA.

This study compared topical vs. IV EACA administration, assessing key outcome measures, including post-operative hemoglobin (Hgb), the need for post-operative transfusion, the number of blood units required, and the length of hospital stay after primary TKA. Adverse events such as deep venous thromboses (DVT), pulmonary emboli (PE), or bleeding were recorded. We hypothesized that topical administration of EACA results in higher post-operative hemoglobin levels and fewer blood units transfused compared to intravenous administration. We also expected that fewer adverse events occurred in the topical EACA group compared to the group in which the drug was administered systemically.

METHODS

A retrospective chart review was performed on patients who had primary TKA by one fellowship-trained orthopaedist at a single institution from 2011 to 2016. This study was approved by the local institutional review board. Since this was a retrospective review of medical records, informed consent was waived.

Patient Population. All patients in this cross-sectional study underwent a unilateral cemented TKA through a medial parapatellar approach under tourniquet control. The wound was not drained following surgery. Post-operative pharmacologic DVT prophylaxis varied during the study period, according to the surgeon's preference, which changed over time. Fondaparinux was used in 2011, rivaroxaban from 2012 to 2014, and aspirin from 2015 to 2016. Patients who were on warfarin prophylaxis pre-operatively were bridged to warfarin post-operatively using low-molecular-weight heparins as bridging agents.

Patients were excluded from antifibrinolytic treatment if they had allergy to EACA, disseminated intravascular coagulation, coronary stenting (drug-eluting stent within one year of placement or bare-metal stent within two months of implantation), heart valve replacement,

atrial fibrillation, current anticoagulation therapy, or documented personal history of DVT, PE, or hematuria.

Treatment Cohorts. Three patient groups were compared. The control group included patients who did not receive antifibrinolytic therapy at any point in the perioperative period during the TKA. The EACA treatment group included patients who received epsilon-aminocaproic acid either intravenously or topically during the TKA. The method of EACA administration varied according to surgeon preference, which evolved during the study period.

In the IV group, the EACA dosing regimen included a loading dose of 5 g intravenously over 30 minutes, followed by a maintenance dose of 10 g over five hours by intravenous infusion. The loading dose was started in the operating room at the beginning of the procedure. Patients in the topical group received an intra-articular administration of EACA after the TKA. A single 5 g dose of EACA in 20 cc of saline was injected into the knee joint after capsular closure and before the tourniquet was deflated.

Outcome Measures. Patient demographic data collected during chart review included age, gender, and body mass index. Key clinical outcome data included the dosage and route of EACA administration, pre-operative hemoglobin level, hemoglobin values on the first three days after TKA, the requirement for blood transfusion, the number of blood units transfused, the length of hospital stay (LOHS), and occurrence of DVT, PE, and post-operative bleeding. The indication for a blood transfusion was any post-operative patient with a Hgb < 8 g/dL. Post-operative hemoglobin values on days one, two, and three served as estimates for operative blood loss.

Statistical Analysis. A power analysis was conducted in a web calculator using data from Wang et al.² Results comparing two proportions, IV (81%) vs. topical (71%), showed that 267 patients per group, or 534 total patients, would have 80% power to detect a significant difference between the two groups using an alpha level of 0.05.

Descriptive statistics were used to summarize the data. Continuous data were assessed for normality using the Kolmogorov-Smirnov test. Where the normality assumption was valid, continuous data were reported as means and standard deviations (SD). Otherwise, medians, minimums (min), and maximums (max) were used to characterize the data. Categorical data were summarized as frequencies and percentages.

Bivariable comparisons by groups were conducted using Pearson Chi-square test, Fisher exact test, Mann-Whitney exact test, ANOVA, Tamhane T2 test (equal variances not assumed), or Kruskal-Wallis exact test. Exact tests were used to accommodate sparse data. Generalized Estimating Equation was conducted to assess hemoglobin measures over time by EACA route. Wilcoxon signed-rank test was used for analyzing pre-operative and post-operative paired ordinal data. All statistical tests were two-sided and conducted with IBM® SPSS Statistics, version 26.

RESULTS

The total number of patients receiving TKA during the study period was 748. Eighty patients who did not have unilateral primary TKA were excluded. Of the remaining 668 patients comprising the study cohort,

351 (52.5%) received IV EACA, 298 (44.6%) received topical EACA, and 19 (2.8%) received no EACA (Figure 1). The mean age of those studied was 63.8 years with a SD of 10.8, mean BMI was 34.2 (7.2), and LOHS ranged from one to five days. There were 427 (63.9%) women in the study group.

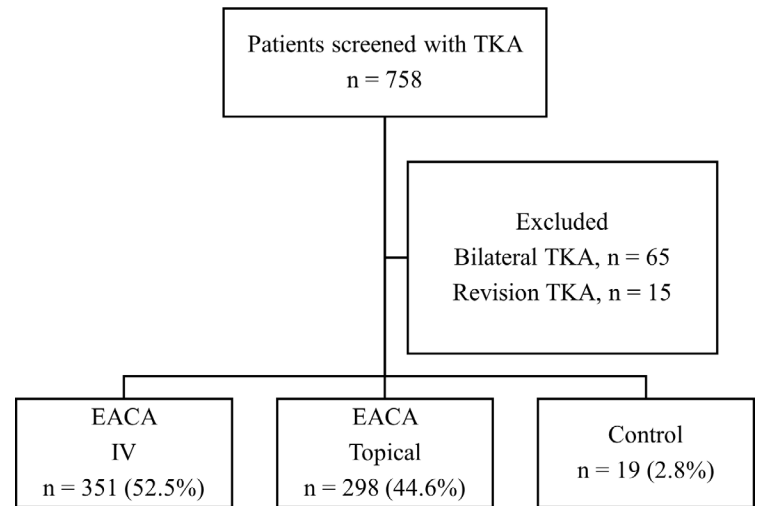


Figure 1. Study population.

Table 1 shows participant comparisons by EACA route of administration: IV, topical, and control. The table shows two sets of p values: the first compared all three groups, while the second compared IV vs. topical. For the three-way comparisons, significant differences were observed for post-operative mean hemoglobin days one, two, and three ($p < 0.001$, $p < 0.001$, and $p = 0.004$, respectively) with consistently higher means for participants in the topical group. The number of transfusions also differed significantly by group ($p = 0.027$), although most patients did not receive one. Regarding the number of blood units transfused, five participants received one unit and three received two units. All transfusions were in the IV group ($p = 0.026$). LOHS was shortest for patients in the topical group, most (66%) incurred two hospital days, while almost all (84%) of the IV group were hospitalized for three days ($p < 0.001$). Apart from mean hemoglobin day three, all results were significant for the two-way comparisons.

Paired comparisons were conducted between mean pre- and post-operative day one hemoglobin measures for all groups (Table 1). All differences were statistically significant ($p < 0.001$). The greatest mean reduction observed over time was in the control group, 13.7 g/dL vs. 10.5 g/dL on day one, followed by the IV group, 14.0 g/dL vs. 11.6 g/dL on day one.

Results from Generalized Estimating Equations showed that mean hemoglobin changes in both IV and topical groups differed significantly as compared to perioperative hemoglobin differences in the control group ($p < 0.001$) as shown in Figure 2. Within group differences by day were also significant as compared to pre-operative hemoglobin ($p < 0.001$ for each comparison).

Table I. Comparison of participant characteristics by group.

Description	N	IV n = 351 (52.5%)	Topical n = 298 (44.6%)	Control n = 19 (2.8%)	p*	p**
Gender; n (%)	668					
Male		134 (38.2)	104 (34.9)	3 (15.8)	0.115	0.414
Female		217 (61.8)	194 (65.1)	16 (84.2)		
Median age; y (min, max)	649	65 (25, 88)	65 (28, 87)	--	0.519	
Median BMI (min, max)	649	33 (17.2, 73.0)	33.5 (19.2, 54.8)	--	0.344	
Operation side; n (%)	667				0.410	0.375
Left		186 (53.0)	147 (49.5)	12 (63.2)		
Right		165 (47.0)	150 (50.5)	7 (36.8)		
Mean preop hemoglobin; g/dL	668	14.0 ± 1.1 ^a	14.0 ± 1.2 ^a	13.7 ± 1.1 ^a	0.425	--
Mean postop hemoglobin, day 1; g/dL	668	11.6 ± 1.4 ^a	12.1 ± 1.3 ^b	10.5 ± 1.3 ^c	< 0.001	--
Mean postop hemoglobin day 2; g/dL	477	10.8 ± 1.5 ^a	11.3 ± 1.5 ^b	9.8 ± 1.3 ^c	< 0.001	--
Mean postop hemoglobin day 3; g/dL	263	10.1 ± 1.4 ^a	10.7 ± 1.4 ^a	9.0 ± 10.9 ^b	0.004	--
Transfusion number; n (%)	668				0.027	0.009
None		343 (97.7)	298 (100.0)	18 (94.7)		
One		8 (2.3)	0 (0.0)	1 (5.3)		
Blood unit number; n (%)	668				0.026	0.009
None		343 (97.7)	298 (100.0)	18 (94.7)		
One		5 (1.4)	0 (0.0)	0 (0.0)		
Two		3 (0.9)	0 (0.0)	1 (5.3)		
Length of hospital stay in days; n (%)	668				< 0.001	< 0.001
One		0 (0.0)	15 (5.0)	0 (0.0)		
Two		25 (7.1)	197 (66.1)	4 (21.1)		
Three		295 (84.0)	77 (25.8)	12 (63.2)		
Four		29 (8.3)	8 (2.7)	2 (10.5)		
Five		2 (0.6)	1 (0.3)	1 (5.3)		

* Three group comparisons: IV vs. Topical vs. Control

** Two group comparisons: IV vs. Topical

^{a,b,c} Tamhane's T² (equal variances not assumed); letter change indicates significant differences between groups.

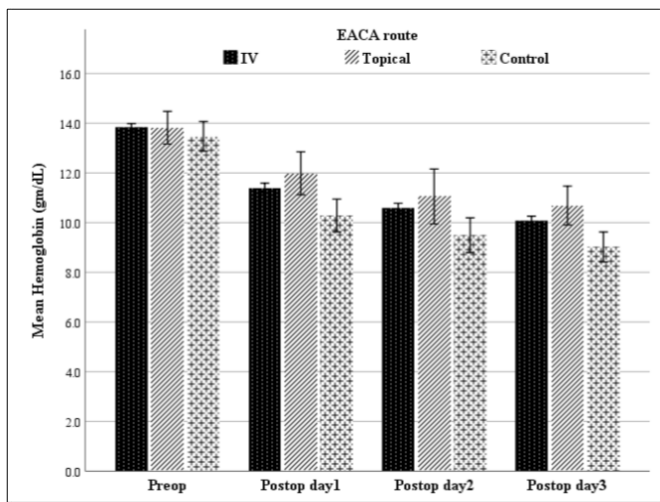


Figure 2. Results from Generalized Estimating Equations. Mean hemoglobin changes in both IV and topical groups differed significantly as compared to perioperative hemoglobin differences in the control group ($p < 0.001$). Within group differences by day were also significant as compared to pre-operative hemoglobin ($p < 0.001$ for each comparison).

Pre- and post-operative day one hemoglobin was measured by gender within each subgroup as hemoglobin tends to differ for males and females (Figure 3). No other time differences were evaluated because data were sparse, and males were absent in the control group for day three hemoglobin. All such comparisons revealed statistically significant differences for both men and women ($p < 0.001$). While post-operative hemoglobin measures were below average ranges for both genders, differences were smallest for those in the topical group at 2.1 g/dL for both males (14.7 vs. 12.6) and females (13.7 vs. 11.6).

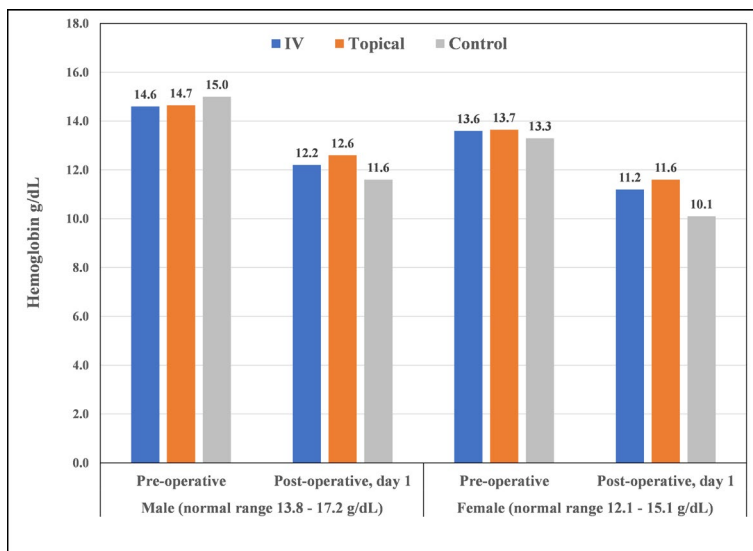


Figure 3. Comparing pre- and post-operative hemoglobin measures (g/dL) by group and gender. Wilcoxon signed-rank tests showed all pre- and post-operative differences were significant ($p < 0.001$).

DISCUSSION

The results of this study indicated the blood conservation effects of EACA were superior when the drug is administered topically rather than intravenously during primary unilateral TKA. The topical EACA group had a statistically higher post-operative day one hemoglobin value compared to both the IV EACA group and the control group. Statistical significance also was observed in the post-operative day two hemoglobin comparison. Furthermore, no patients in the topical group received blood transfusions compared to the IV group in which 14% of patients received one unit of blood product and 0.9% received

two units. This difference also was statistically significant. Interestingly, the pre-operative hemoglobin values between male and female participants were significantly different, but the efficacy of EACA showed no gender bias regarding its effects on blood conservation.

This study demonstrated a statistically significant shorter LOHS in the topical EACA group. Of the 298 patients in the topical group, 197 (66.1%) were discharged from the hospital on post-operative day two compared to 25 of the 351 patients (7.1%) in the IV group. The majority of patients (84%) in the IV group was discharged from the hospital on post-operative day three.

To the authors' knowledge, there is no published literature comparing outcomes of intravenous EACA to topical administration. However, this comparison has been made for patients treated with TXA in the setting of unilateral primary TKA. For example, Goyal et al.¹² in a randomized trial of 83 patients treated with intra-articular TXA and 85 receiving IV TXA, found that topical administration of TXA was not inferior to intravenous administration. The investigators concluded that a single dose of topical TXA was preferable to IV administration secondary to the ease of administration.

In another randomized trial, Wang et al.² analyzed 150 unilateral primary TKA patients evenly divided into three study groups: topical TXA, IV TXA, and no TXA. Their study showed topical administration of TXA significantly reduced total blood loss and drainage volume to a greater degree than IV administration. In a third study, Chen et al.¹¹ randomized 50 patients to receive IV TXA and 50 patients to receive topical TXA in the setting of primary unilateral TKA. They found no difference in peri-operative blood loss or post-operative lower limb swelling between the two groups. Notably, these two trials utilized intra-articular drains post-operatively which can complicate data comparisons.

A recent meta-analysis showed EACA and TXA to be equally efficacious for blood conservation after TKA,¹³ which is consistent with established literature. Comparing the data from similar studies to our own results suggested that topical TXA and topical EACA were both effective means of blood conservation in unilateral primary TKA. Moreover, EACA is the more cost-effective alternative of the two options. Comparable studies evaluating IV and topical TXA have not reported on LOHS.

There were several limitations to our study. First, as is typical in retrospective chart reviews, some data were missing resulting in an incomplete demographic database. Second, all procedures were performed at a specialty hospital without a critical care unit, thus introducing a bias towards patients with fewer comorbid conditions. Third, since patients in the study were not classified according to American Society of Anesthesiology grade, we could not determine if there were significant differences in co-morbidities among the cohorts. Fourth, we did not control for peri-operative anticoagulation, which varied over time according to the surgeon's preference and was a confounding variable. Fifth, EACA was administered intravenously from 2011 to 2014

and topically later in the study to limit the potential adverse effects of systemic administration. Furthermore, this transition period occurred during a trend toward enhanced recovery protocol (ERP) for TKA which incorporates a standardized pre-operative education program, regional anesthesia, post-operative multimodal pain management, and early rehabilitation. Since ERP usually results in earlier hospital discharge, this was also a confounding variable in the study and our LOHS data must be interpreted accordingly.

Strengths of this study included the relatively large number of patients analyzed and the fact that the procedures were all performed by a single surgeon. This large patient population (668) permitted detection of statistical significance among the study groups. However, due to the low incidence of adverse reactions, a larger cohort of patients would be required to detect a significant difference in regard to thromboembolic events. Future research should use randomized controlled methods to delineate the optimum administration of EACA.

CONCLUSIONS

Our results showed that topical administration of EACA outperforms IV treatment. Participants in the topical group required no transfusions and had higher post-operative hemoglobin levels. Furthermore, a single intra-articular introduction of EACA was easier than multiple intravenous dosing and is our preferred method of administration.

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