

Is Combined Administration of Tranexamic Acid Better than Both Intravenous and Topical Regimes for Total Loss, Hidden Loss and Post-operative Swelling? A Randomized Control Trial

Abstract

Background: Bleeding is one of the unavoidable complications of total knee arthroplasty (TKA). Tranexamic acid (TXA) in last decade has emerged as an effective and safe way to decrease postoperative bleeding and transfusion rates. Although there is little doubt on the efficacy of the drug, the debate on ideal mode is more recent. We undertook this study to find out the most effective and yet safest way of TXA administration. **Materials and Methods:** A single institution - two hospital-based, double-blinded, prospective, randomized control trial was conducted from January 2015 to December 2015. One hundred and fifty patients were randomly divided in one of the three groups using computer-generated tables - intravenous (IV), intraarticular and combined. Evident loss through drain, total loss based on gross method and hemoglobin balance method, hidden blood losses, hemoglobin, and hematocrit drop, all possible complications related to TXA were evaluated and compared among groups. The analysis of variance and Tukey's *post hoc* were used for continuous outcome variables and Chi-square test for binary outcome variables. **Results:** Evident loss in combined group was 574.25 ± 209.8 ml, significantly less than IV (685.4 ± 289.9 ml) and intraarticular group (724.3 ± 246.8 ml). Total loss was similarly least for combined group (930.1 ± 262.2 ml) compared to IV (1208.3 ± 368.8 ml) and intraarticular group (1198.1 ± 356.8 ml). There were no transfusions in combined group compared to five in IV and four in intraarticular group. Combined group also had least hidden losses after surgery. No patients in any group developed symptomatic deep venous thrombosis. **Conclusion:** Combined administration of drug is most effective way to decrease postoperative bleeding and requirement of transfusion in unilateral TKA without increasing any risk of complications.

Keywords: Primary total knee arthroplasty, randomized control trial, tranexamic acid, intravenous, topical, combined

MeSH terms: Arthroplasty, knee replacement, intravenous, infusion, postoperative care, randomized controlled trials as topic

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Introduction

Total knee arthroplasty (TKA) is an effective procedure for end-stage osteoarthritis. However, blood loss is its unavoidable complication, which has shown to reach up to 1–2 l in various studies.^{1,2} 10%–38% of patients undergoing knee arthroplasty are known to require blood transfusion.^{3–5} The risks and additional costs incurred through transfusion together with difficulties in obtaining and maintaining blood products have aroused great interest in blood-conserving strategies.

Most knee arthroplasty is done using a pneumatic tourniquet. Tourniquet is effective in controlling intraoperative blood loss but causes local increase in tissue fibrinolysis soon after its release, resulting in larger postoperative losses.^{6,7} Further systemic increase in fibrinolytic activity as a result of

surgical insult adds to the blood loss and may take 24 h to subside naturally.^{8,9} Tranexamic acid (TXA), synthetic antagonist of plasminogen, reduces both local and systemic fibrinolysis, and results in decreasing perioperative loss up to 30%–40%.¹⁰ The effectiveness of TXA is well established in literature; however, the dose and routes of administration are debatable.^{11–16}

In the absence of uniform method of administration and different dosage used by various authors, comparison of various reports is not possible. To the best of our knowledge, none of the available reports in literature has compared all the three modes in a single study.

This study was therefore aimed at finding an ideal route of administration of TXA that would have maximum effectiveness with minimal complications. We hypothesized

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that combine method would be better than both topical and intravenous (IV) modes in reducing blood loss, transfusion requirements, and postoperative swelling without increase in complication rates.

Materials and Methods

Patient's selection

A prospective randomized control, double-blinded trial was conducted in a single institution. All patients from 50 to 85 years with the diagnosis of primary osteoarthritis of knee awaiting surgery from January 2015 to December 2015 were eligible for the trial. Exclusion criterion included patients with secondary osteoarthritis (rheumatoid and other inflammatory arthritis, posttraumatic arthritis), known allergies to TXA, major comorbidities (the American Society of Anesthesiologists Grade 4 and above), coagulopathies (international normalized ratio >1.4), history of previous deep venous thrombosis (DVT) or patients on antithrombotic treatment, previous history of stroke, or severe ischemic cardiomyopathy patients undergoing bilateral TKA. Patients with hemoglobin levels of <11 were deferred for surgery till hemoglobin levels increased over 11. As hospital strategy, these patients were managed on oral hematinic and/or subcutaneous injection of 40,000 IU of erythropoietin. A total of 200 patients were recruited in the trial during the study. These were divided into four groups: (i) IV group, (ii) topical group, (iii) combined group, and (iv) control group. Finally, a control group was excluded. Because, we believed that debarring patients from well-known benefits of TXA only for study purpose was unethical.

The study proposed 1:1 randomization for each group. Each patient recruited in the study was assigned a unique identification number and was randomized using computer-generated tables by an independent orthopedic fellow in one of the three groups. The assigned group was kept in sealed envelope opened during surgery by nonscrubbing nurse. Drug [TXA 500 mg/5 ml amples—Trneas^R, Shin Poong, Korea] and placebo [normal saline] were prepared according to the envelope by Grade 1 resident not directly involved in surgery and administered by independent anesthetic. The volume and appearance of drug and placebo were identical, and both surgeons and patients were blinded to the assigned group throughout the study. Independent research fellow performed all data acquisition and analysis.

The study was approved by the Institutional Review Board and was conducted under the ethical norms laid down by the Declaration of Helsinki, 1964. Informed consent was sought from all participating patients.

Administration of tranexamic acid

Group 1 was planned for IV TXA transfusion. The drug was administered in dose 10 mg/kg 20 min before tourniquet

application as a preoperative dose, 10 mg/kg 15 min before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 h after the second dose as a postoperative dose. As placebo, the group received 50 ml of saline retrograde through drain after surgery.¹⁵

Group 2 was administered 1.5 g of TXA in 50 ml of saline retrograde through the drain after wound closure, and as placebo, it was given 5 cc of IV normal saline in doses similar to IV group.¹⁶

Group 3 was planned for combined administration. These patients received the preoperative and postoperative TXA injections of 10 mg/kg similar to IV group. The intraoperative dose was omitted. Instead, patients were given 1.5 g of TXA in 50 ml of saline retrograde through the drain after wound closure. As placebo, these patients received 5 ml of normal saline at the time of intraoperative dose.

Operative procedure and intraoperative management

All patients underwent a preanesthetic checkup as per institution policy. A routine prophylactic dose of 1 g cephalosporin was administered preoperatively. Similar multimodal analgesia regime starting preoperatively was used in all patients. Two senior authors performed all the surgeries. Surgeries were performed under tourniquet, with pressure of 280 mm of mercury for every patients. Standard midline incision with parapatellar approach was used in all cases. The femur was prepared using intramedullary alignment, and femoral canal was blocked with bone plug after femoral preparation. Tibia was prepared using extramedullary alignment. All patients received posterior stabilized type implant. Patellar resurfacing was not done for any patient. All patients received intraarticular drain. It was clamped only for 10 min in all patients. Previous experience had shown that clamping of drain for 30–60 min, as advised in various studies of intraarticular TXA, caused drains to be blocked by clotted blood and made them ineffective in postoperative period.^{12–14} Contact period of 10 min is shown effective for TXA, and further, clamping was found unnecessary.¹⁷ Tourniquets were released after closure before application of dressing. All patients received continuous femoral catheter for pain control, which was kept for 24 h.

A standard postoperative protocol was followed in all patients. All patients had postoperative hematocrit and hemoglobin measurements on day 0, 1, 2, 4, 7, and 14. As hospital policy, the transfusion was given only at hemoglobin levels of <8 gm%. The thigh (10 cm over suprapatellar border), suprapatellar, and calf girths (maximum calf circumference) were measured daily up to 7th postoperative days. The drains were emptied every day, and the amount of drained blood was measured. The drains were removed only when this amount was <100 ml for 24 h. On an average, drains were kept for 3 days (range 2–5 days). This has been our institution policy, as we have

observed that the removal of drains at one preselected time may not work in all cases. Some cases have collection for longer periods, and early removal in such cases may not only cause erroneous lower recordings of drained blood but also has a risk of hematoma formation. Foleys catheter and compression bandage were removed on day 1, and patients were encouraged for muscle strengthening exercises and walker assisted walking. Aggressive rehabilitation policy and inpatient physiotherapy were provided to all patients.

Owing to low incidence of DVT in Asian population, routine chemoprophylaxis was not warranted.¹⁸ Pneumatic calf pumps were used in all patients until they started ambulation. Chemical prophylaxis using low-molecular-weight heparin was given only in high-risk patients screened preoperatively. Routine deep vein thrombosis was not done for asymptomatic patients. Symptomatic patients were screened for DVT using Doppler ultrasonography and computed tomography (CT) angiography of deep veins of leg and for chest. As our institution policy, all patients were discharged after suture removal at 2 weeks.

Outcome assessment

The primary outcome variables were transfusion incidence, drain output, postoperative hemoglobin and hematocrit drop, calculated perioperative blood loss through gross formula¹⁹ and hemoglobin balance method,¹⁷ and postoperative increment in lower limb girth measurement. Blood volume was estimated using Nadler's formula,²⁰ and perioperative loss was calculated as described in the previous studies. The secondary outcome measurements were the incidence of symptomatic DVT and pulmonary embolism within 30 days of surgery, duration of surgery, wound-related complications, including excessive oozing and skin ecchymosis and skin blisters.

Statistical analysis

Sample size estimation was done based on total blood loss calculated in the previous studies¹⁻⁵ (D value: 0.52). A reduction of blood loss of 200 ml, half of allogenic blood transfusion unit, was considered significant. Mean losses were taken from the average of previous studies;¹⁻⁵

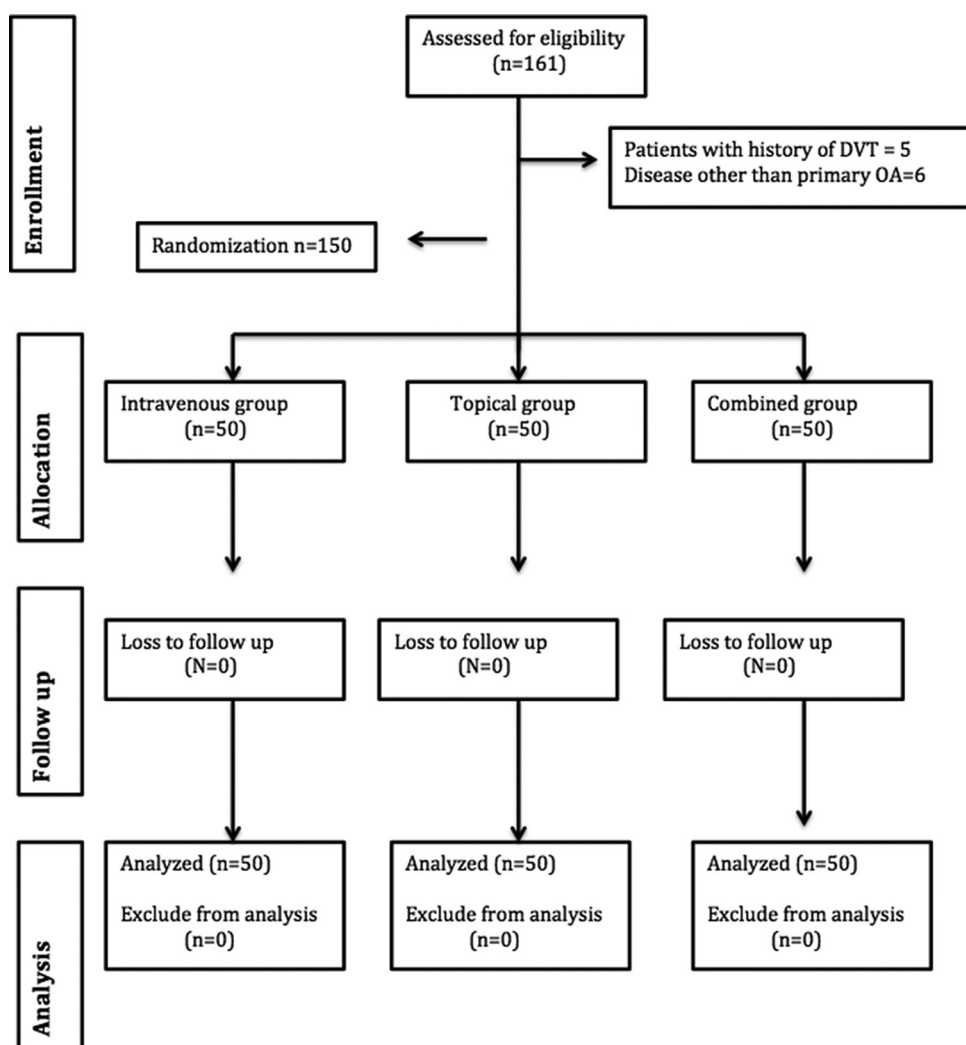


Figure 1: CONSORT chart for the study

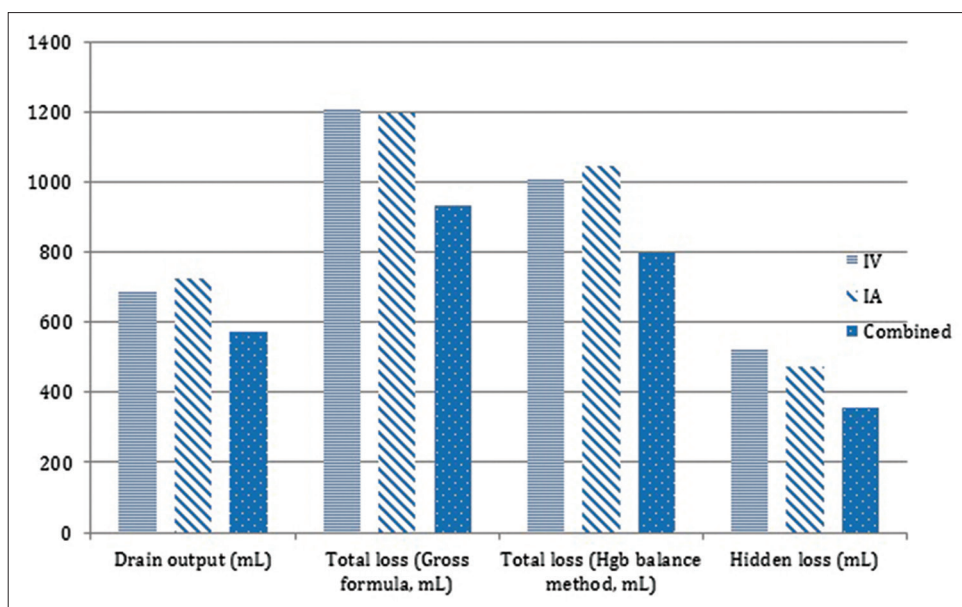


Figure 2: A bar diagram showing comparison of three groups about drain output, total blood loss (gross formula), total blood loss (hemoglobin balance method), and hidden blood loss. Combined group had significantly better outcome in all measurements compared to intravenous and intraarticular group

Table 1: Clinical details of all 3 groups of patients

Subjects	IV	Intraarticular	Combined
Age	69.2±6.4	69.8±6.8	70.8±6.8
Gender (male/female)	6/44	8/42	7/43
BMI*	26.52±3.3	26.96±4.2	27.47±4.8
Preoperative hemoglobin	12.35±1.3	12.65±1.2	12.16±1.5
Preoperative hematocrit	37.02±3.5	38.06±3.9	36.4±3.9
Preoperative varus deformity (°)	9.2±3.2	9.8±2.9	9.1±2.9
Operative time (min)	81±13.9	79.8±10.1	78.9±10.3

*BMI=Body mass index, IV=Intravenous

Table 2: Comparison of postoperative outcomes of all 3 group

Maximum girth increment (cm)	IV* group (A)	Topical group (B)	Combined group (C)
Thigh	2.1	1.4	1.3
Supra-patellar	2.8	2.1	1.8
Calf	0.01	0.01	0.01
Transfusions (pint)	4	5	0

*IV=Intravenous

the alpha error was kept at 0.05 with power of analysis to discern a difference of 200 ml of 90%. After that, we estimated the total sample size as 116 patients. A sample of 150 was, therefore, deemed appropriate.

Statistical analysis was performed using SPSS for Mac (version 20.0; IBM, Chicago, IL, USA) and statistical significance was defined as $P < 0.05$. The quantitative variables were expressed in terms of means \pm standard deviation. Analysis of variance and Tukey's *post hoc* were used for continuous outcome variables (blood loss, drop in hemoglobin, lower limb girth measurements, or age) and

Chi-square test for binary outcome variables (sex, side of surgery, requirement of blood transfusion, or presence or absence of complications).

Results

The CONSORT flow diagram presented outline of the study [Figure 1]. A total of 150 patients with fifty patients in each group participated in the trial. The patients did not differ significantly in basic demographic details and preoperative variables [Table 1].

Results of primary output variables are detailed in Figure 2. There was no statistical difference among intraarticular and IV group among all above variables except thigh girth swelling. Thigh girth swelling was significantly less in intraarticular group.

Combined group had significantly lower drain output, hemoglobin, hematocrit fall, calculated blood loss, and blood transfusion compared to IV and topical group. However, thigh circumference was less than IV, it was similar to topical group [Table 2].

Other interesting finding was hidden loss calculated as a difference of drain output from total calculated loss. It was significantly less in combined group compared to all other groups.

In addition, we found losses calculated on hematocrit fall (gross formula) were higher than those based on hemoglobin fall (hemoglobin balance method).

No patients in any group developed symptomatic DVT or pulmonary embolism 0.3 patients from IV group, two from control and combined group, and one patient from topical group had clinical suspicion of DVT based on calf

swelling and tenderness. However, ultrasound and CT angiography showed no evidence of DVT in any patient. Two patients each from combined and intraarticular group developed skin ecchymosis in calf and posterior knee area but were not statistically significant. One patient from IV group developed wound gaping at eighth postoperative day and required resuturing of the wound. One patient from IV group developed an eschar in lower part of incision site, which healed with time. No case of surgical site infection was noted in the series drains of 5 patients in intraarticular group, and four patients in the combined group became nonfunctional on first postoperative day which was statistically significant. These patients were excluded from drain output calculation as it would lead to erroneous lower drain output results in this group.

Discussion

The main findings of the study are that the combined group administration results in minimal bleeding following unilateral TKA assessed either through evident losses in drain or calculated losses based on hemoglobin drop or hematocrit fall. In addition, combined administration causes least hidden losses than any other group, and probably, therefore, is the cause of least postoperative thigh swelling following arthroplasty. Further, all modes of administration were found safe with no complications occurred in any group due to drug administration.

Surgical trauma after arthroplasty results in a hyperfibrinolytic state.^{6,7} This is further augmented by increased fibrinolysis following tourniquet release.^{8,9} Since early postoperative bleeding is the result of shift in hemostatic mechanism toward fibrinolysis, the antifibrinolytic drugs such as TXA are very effective to control this bleeding. Literature confirms this point, and there is little controversy regarding the effectiveness of drug.¹⁰⁻¹⁷ The recent debate is regarding the mode of administration of the drug.^{14,17} IV, topical, or combined administration are most commonly used modes in orthopedic practice. However, to the best of our knowledge, no randomized control trial has yet compared the three modes in a single study.

The regimen proposed in the study was based on review of literature and our experience. The combination of preoperative, intraoperative, and postoperative doses for IV group has been shown to be most effective by study of Maniar *et al.*¹⁵ The strength of 10 mg/kg has been shown to be effective to produce antifibrinolytic effect in various studies.²¹⁻²³ This formed the basis of IV regime as we tried to keep total dose to be minimal. Intraarticular dosages have varied from 1.5 g to 3 g in various studies; however, none of them has measured serum tranexamic levels.^{11-14,16} Animal studies have shown low systemic absorption of the drug, yet limited clinical results are available on the topic.²⁴ Further Wong *et al.* have shown 1.5 g to be equally

effective as 3-g dose.¹⁶ In view of equal efficacy and limited results on systemic absorption of drugs in humans, we chose the least effective dose of 1.5 g for topical group.

The preoperative dose has been described as most important dosage in any IV regime.¹⁵ This deactivates fibrinolysis as soon as it starts.²⁵ In addition, fibrinolysis is best inhibited at early stages, and this can be achieved by preoperative dose.²⁶ Hence, this dose was chosen to be the part of combined regime. The intraarticular dose was same as topical group as it was most effective. This also replaced the intraoperative dose which served to decrease overall systemic load of drug without compromising results. Most of the intraarticular drug has shown to maintain biological half-life of 3 h.¹⁴ However, fibrinolytic response after surgical trauma is known to be biphasic with an increased activity during the first 3 h, followed by a shutdown that peaks at about 24 h.^{25,27} Hence, a postoperative dose was considered important for the second peak. TXA is known to enter extravascular space and accumulates in tissues for 17 h.²⁷ This formed the basis of our combined regime.

Similar to most authors, our results also showed combined administration to be most effective regime.^{25,28} IV and intraarticular regimes were found to be equally effective.¹¹⁻¹⁴ However, drain losses and calculated losses were higher in our study than few papers in literature. This is because drains in most series have been removed at fixed point of time – 24–48 h.^{11-14,25,28} On the other hand, we continued drains till output was <100 ml/24 h and on average kept drains for 3 days (range 2–5 days). Similarly, most calculated losses were based on fixed day hemoglobin value in most series (2nd or 4th day).^{11-14,25,28} However, since fixed day value may not be lowest for all patients, we chose lowest value over first 7 days for this calculation. We believe fixed day drain output or hemoglobin value are underestimation of actual losses and our method is a better approximation of true blood loss.

Hidden losses are shown to be around 40%–50% of true losses.^{29,30} This was true in our series for IV group (43.2% of total loss) and control group. The hidden losses for topical group were 39.4% and 38.2% for combined group. This showed that the intraarticular administration was effective in reducing hidden losses. These hidden losses are thought to be due to bleeding from tissues and hemolysis. It seems that direct high concentration of drug in tissues may have decreased this part of bleeding resulting in lower hidden losses. This tissue swelling and bleeding are the cause of postoperative swelling. A decrease in hidden losses also resulted in decrease postoperative swelling in above groups. Although the hidden losses and swelling have not been directly compared in all groups, there have been few isolated reports supporting our finding. Good *et al.* showed that IV TXA in two doses of 10 mg/kg reduces external blood loss but not hidden loss.⁴ In another study by Ishida *et al.* showed intraarticular administration

reduces postoperative swelling probably by reducing hidden loss. This study has for the first time compared hidden losses and swelling in all three modes.³¹

As concluded by most authors, we also found that the use of TXA is safe over described drug dosages.¹⁰⁻¹⁴ No report of DVT was found in any group despite no use of routine prophylaxis. The intraarticular administration was not sought with any wound-related complications.

The strength of our study is a large number of patients and description of all modes in a single study. Different authors use different dosages and calculation methods for total losses. This makes comparison among various reports difficult. This study not only describes all modes of administration of drug but also uses various methods of blood loss calculation to be able to compare with available data. In addition, method of calculations used in this study appears more accurate as hemoglobin and hematocrit trends were followed for 2 weeks, and lowest 7-day values were taken for calculation instead of a fixed day value for all patients. Similarly, drains were maintained for longer periods to give more accurate idea of evident losses. The number of patients is large and to the best of our knowledge has not been superseded in any previous study. The study of hidden loss and postoperative swelling has also not been done in the past.

There are some limitations of this study. First, two different surgeons performed surgeries; the surgical technique by itself might be a confounding factor in assessing the blood loss. Second, we also did not include patients who underwent simultaneous bilateral TKA in the present study, and therefore, our conclusions may not apply to these patients. Third, no blood studies have been carried out to estimate serum TXA levels following TKA, and thus, no information regarding the toxicity related to TXA can be retrieved. Last, the present study has not addressed the subjective knee function score of the patients after TKA, as the main purpose of this study was to evaluate the ideal mode of administration of drug.

Conclusion

Combined administration of the drug is most effective way to decrease postoperative bleeding and requirement of transfusion in unilateral TKA without increasing any risk of complications. Further, combined method is most effective in decreasing postoperative hidden losses and thigh swelling.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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None

Conflicts of interest

There are no conflicts of interest.

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