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## Primary Arthroplasty

# Process Improvement Project Using Tranexamic Acid Is Cost-Effective in Reducing Blood Loss and Transfusions After Total Hip and Total Knee Arthroplasty



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## ABSTRACT

**Background:** Tranexamic acid (TXA) has been associated with decreased blood loss and transfusion after total hip arthroplasty (THA) and total knee arthroplasty (TKA). The purpose of this study was to examine both transfusion utilization and the economic impact of a Process Improvement Project implementing TXA for THA and TKA.

**Methods:** After standardization of TXA administration in THA and TKA patients, retrospective data were compared from 12 consecutive months before (group A, n = 336 procedures) and after (group B, n = 436 procedures) project initiation.

**Results:** TXA administration increased with project implementation (group A = 3.57%, group B = 86.01%) and was associated with reductions in perioperative hemoglobin decrement (20.2%), patients transfused (45%), and number of units transfused per patient (61.9%). Cost savings were notable per patient (\$128) and annually program wide (\$55,884) with the primary THA subgroup contributing the most to the savings. No increase in adverse effects was observed.

**Conclusion:** Standardized administration of TXA is an effective and economically favorable blood-reduction strategy for patients undergoing elective THA or TKA. Although reduction in transfusions with TXA may be greater after TKA, the economic and clinical impact of transfusion reduction is more substantial in THA patients.

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Perioperative surgical bleeding is a serious concern in many types of surgery, including total joint arthroplasty (TJA). Intraoperative bleeding and post-surgical hemorrhage can lead to detrimental consequences and complications such as acute blood loss anemia, increased length of stay, delayed recovery, hematoma, infection, and death in rare circumstances. Transfusion of packed red blood cells (PRBC) is advantageous in restoring oxygen-carrying capacity and replacing intravascular volume but is associated with

the risks of transfusion reactions, antigen exposure, disease transmission, immunosuppression, and infection [1–3]. In addition to patients' risk, bleeding and subsequent transfusion are associated with increased health care costs attributed to blood product acquisition and increased level of care [4–6].

Blood conservation and transfusion reduction strategies have been widely used in TJA to improve the quality of care and reduce the costs associated with these increasingly popular procedures. Preoperative strategies include cessation of medications associated with bleeding along with assessment and treatment of preoperative anemia. Intraoperative strategies include the use of a tourniquet when appropriate, hypotensive anesthesia, regional anesthesia, avoidance of hypothermia, blood salvage, meticulous hemostasis, and hemostatic agents. Postoperative measures include reduced phlebotomy, use of compressive dressings and reinfusion drains, cautious chemoprophylaxis for venous thrombosis, and alteration of transfusion triggers. More recently,

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intravenous antifibrinolytic agents have been used to reduce blood loss and transfusions without a significant increase in perioperative complications.

Tranexamic acid (TXA) is a synthetic analog of the amino acid, lysine. It exhibits antifibrinolytic activity by reversibly blocking the lysine-binding site on plasminogen, thus, competitively inhibiting plasminogen or plasmin binding to lysine residues on fibrin. This prevents the degradation of fibrin and stabilizes blood clots [7–11]. TXA was first used in cardiothoracic surgery 40 years ago and has since been described in other high blood loss scenarios, including acute trauma and gynecologic hemorrhage [7,12,13]. In addition, the efficacy and safety of TXA for TJA have been evaluated in several recent studies and meta-analyses [14–31]. In general, the drug is administered through either a topical or intravenous (IV) route during TJA procedures.

Published data indicate that the use of TXA in TJA is effective in reducing blood loss and transfusion requirements [14–23,30,32–36]. However, comparisons have not been made among the different types of TJA, that is, total hip arthroplasty (THA) vs total knee arthroplasty (TKA), and primary vs revision surgeries. Furthermore, past research has focused on patient well-being with limited evaluation on the economic impact to patients and hospitals. The present study (1) evaluates standardization of TXA administration in TJA patients through a hospital-initiated Process Improvement (PI) Project, (2) compares the efficacy and cost effectiveness of TXA utilization, and (3) aids in developing a strategy for implementing TXA use in TJA. We hypothesize that a PI Project using IV TXA in a standardized protocol improves the frequency of medication administration in TJA patients and is associated with reduced blood loss, fewer transfusions, and decreased hospital costs.

## Materials and Methods

A standardized protocol for administration of TXA in patients undergoing THA and TKA was initiated as a PI Project and implemented by a multidisciplinary Total Joint Quality and Process Improvement (TJ-QAPI) Committee at a single institution on November 1, 2013. The TJ-QAPI Committee consisted of representatives of several constituencies including orthopedic surgeons, anesthesiologists, perioperative nurses, pharmacists, managers, therapists, data analysts, and infection-control personnel. For ease of implementation, the PI protocol set the TXA dosage as 20 mg/kg, with a maximum of 2 g, via IV administration. TXA was administered by anesthesia personnel within 30 minutes of the anticipated surgical bleeding—before skin incision for THA and before tourniquet deflation for TKA. All TJA patients were candidates for TXA; however, TXA could be withheld if the surgeon or anesthesiologist determined an elevated risk of thromboembolic disease or coronary stent thrombosis.

Pooled patient data regarding the number of patients, the hospital length of stay, perioperative decline in hemoglobin, transfusion rates and units of blood transfused, compliance with transfusion guidelines, complications, and readmissions were monitored monthly by the TJ-QAPI Committee as a component of the PI Project. Prospective data from November 1, 2013, to October 31, 2014 (post-TXA, group B), were compared with data collected the previous year, November 1, 2012, to October 31, 2013, before standardized TXA implementation (pre-TXA, group A). No other blood management strategies and transfusion triggers were changed during the Project period. Four orthopedic surgeons participated in the program. Patient data were analyzed to compare variables from the year before Project initiation (group A) to the year after initiation (group B).

**Table 1**

Patient Demographics and Baseline Characteristics (Mean ± Standard Deviation) in Pre- and Post-TXA Protocol Patient Groups.

Demographics	Group A	Group B	P Value
Length of stay (d)	3.10 ± 1.68	3.13 ± 2.08	.87
Age (y)	61.99 ± 11.50	63.43 ± 10.75	.07
BMI (kg/m <sup>2</sup> )	32.64 ± 8.96	31.97 ± 7.69	.3
Gender (female), %	58	59	.93
Preop HgB (g/dL)	13.22 ± 1.59	13.03 ± 1.62	.1

BMI, body mass index; HgB, hemoglobin; Preop, preoperative; TXA, tranexamic acid.

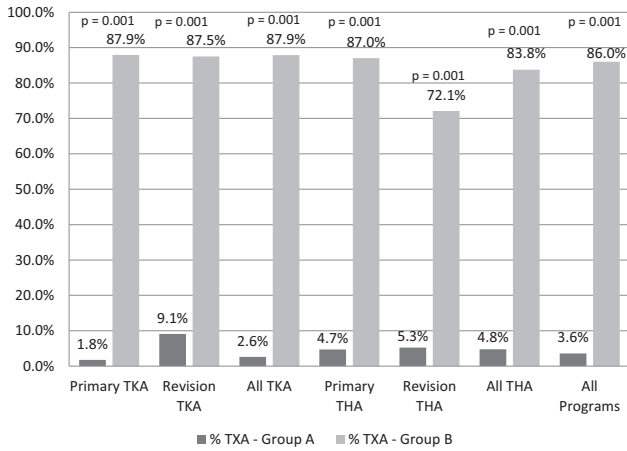
After completion of the PI Project and institutional review board approval, further data collection on individual patients (nonpooled) was initiated. Written, informed consent was waived by the institutional review board. Patient data were collected by a blinded third-party data analyst. Examined data included date of the surgery with respect to the initiation of the PI Project, the type of procedure, length of hospital stay, preoperative and postoperative hemoglobin levels, units of blood transfused, complications, readmissions, and demographic information (age, gender, weight, height, and body mass index). A power analysis was not necessary before the initiation of the review of individual outcomes because the prospectively collected pooled quality data indicated significant differences in most primary outcome measures. Moreover, expanding the study group would have introduced other variables including transfusion triggers, drain use, and additional surgesons.

Data analysis was performed with IBM SPSS Statistics for Windows, version 23 (Armonk, NY). Data normality was assessed with the Shapiro-Wilk test. Independent *t* test analyses were performed for pre-TXA protocol vs post-TXA protocol for (1) all TJA combined, (2) primary and revision TKAs, (3) primary TKA, (4) revision TKA, (5) primary and revision THAs, (6) primary THA, and (7) revision THA. The following were evaluated for each of the major hypotheses tested: (1) administration of TXA, (2) hemoglobin loss, (3) transfusion rate/units of PRBC, and (4) complications/readmissions. Dichotomous variables were compared with the chi-square test. Alpha was originally set at  $P \leq .05$ ; however, because there were 4 distinct major hypotheses tested, the original alpha was divided by 4 to reduce the risk of type I statistical error (Bonferroni); therefore, alpha was set at 0.0125.

## Results

There were 336 patients in group A and 436 patients in group B. Cases examined included 48% primary TKA, 36% primary THA, 8% revision THA, and 8% revision TKA. There were no statistically significant differences in patient age, gender, body mass index, preoperative hemoglobin, or length of stay between the 2 groups ( $P > .0125$ ). Demographic information is summarized in Table 1. In both groups combined, length of stay was increased for patients requiring a blood transfusion, by an average of 2.28 days (transfused, 5.11 days; nontransfused, 2.83 days;  $P \leq .001$ ).

Administration of IV TXA in TJA patients increased from 3.57% to 86.01% after implementation of the protocol ( $P = .001$ ; Fig. 1). Overall perioperative hemoglobin decline was reduced by 20.2% (group A, 3.08 g/dL; group B, 2.46 g/dL;  $P = .001$ ); this improvement was statistically significant in all groups except revision THA (Fig. 2) and translated into a 45% reduction in the number of patients requiring a blood transfusion (16.67% vs 9.17%;  $P = .002$ ; Fig. 3). Subgroup analysis revealed a significant reduction in transfusion rate for primary TKA (7.7% vs 1.0%;  $P = .012$ ), all TKA (7.4% vs 2.1%;  $P = .008$ ), and primary THA (25.2% vs 12.3%;  $P = .005$ ). Revision THA ( $P = .028$ ) and all THA ( $P = .016$ ) subgroups did not reach statistical significance after Bonferroni correction of the *P* value. In aggregate,

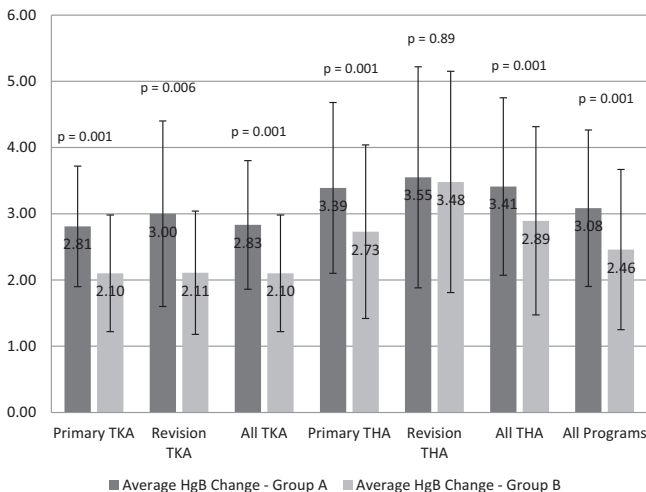


**Fig. 1.** Percent of patients receiving tranexamic acid (TXA) in each surgical group. TXA administration was increased in group B for all comparisons. TKA, total knee arthroplasty; THA, total hip arthroplasty.

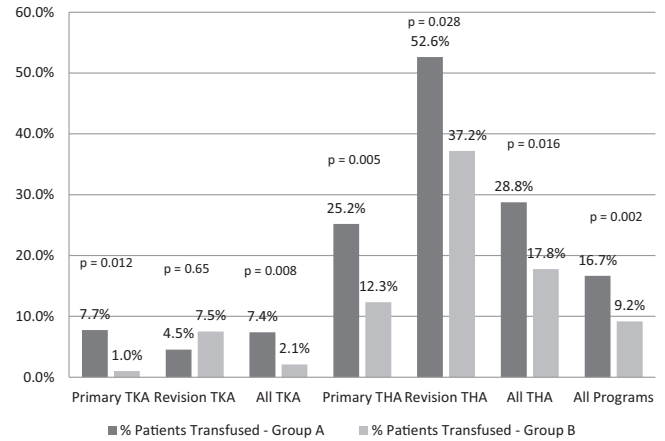
the number of units transfused per patient was reduced by 61.9% (0.48 vs 0.21;  $P = .001$ ; Fig. 4); all subgroups reached statistical significance except the revision TKA ( $P = .091$ ) and all TKA ( $P = .037$ ).

Based on a pharmacy cost of \$25 per gram, the average cost of TXA was \$43 per patient. The cost of 1 unit of PRBC at our institution was estimated at \$500 per unit, not including costs associated with administration, complications, or associated increased length of stay. The net direct cost savings from the decrease in number of transfusions, minus the cost of the TXA, resulted in a savings of \$128 per patient or \$55,884 program wide for the year (Figs. 5 and 6). Despite a 72% reduction in the number of patients transfused after primary and revision TKAs, this group demonstrated the smallest cost benefit (−\$5 per patient). The largest cost savings per patient was noted after revision THA (\$606 per patient), and the largest overall savings was realized in the primary THA group (>\$30,000).

Evaluation of 30-day readmissions to our facility did not yield any statistically significant differences ( $P > .0125$ ) in any of the groups. There were 11 readmissions in group A (3.27%) with 6 readmissions related to the surgical procedure (1.79%) compared with 14 readmissions (3.21%) with 7 related readmissions (1.60%) in group B.



**Fig. 2.** Mean perioperative hemoglobin (Hgb; g/dL) decrease for each surgical group. Mean Hgb decrease was lower in group B for all comparisons except revision THA.

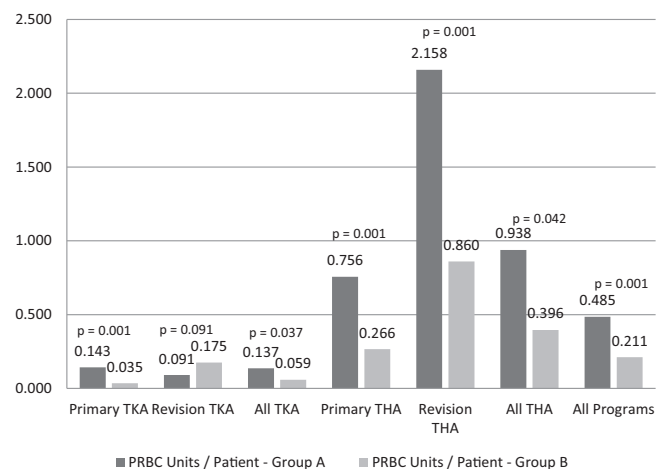


**Fig. 3.** Percent of patients requiring packed red blood cells (PRBC) transfusion in each surgical group. Transfusion rates were reduced in group B for primary TKA, all TKA, and primary THA but not other subgroups after Bonferroni correction of the  $P$  value.

Eight in-house complications were noted in group A (2.38%), including 2 cases of postoperative shock, 1 hemorrhage, and 1 respiratory failure. The complication rate of the 12 patients receiving TXA before the initiation of the protocol was 16.7% (1 hemorrhage and 1 gastrointestinal bleed) compared with 1.85% in those not receiving TXA (6 complications in 324 patients;  $P = .0009$ ). There were 15 complications in group B (3.44%;  $P = .39$ ), including 1 myocardial infarction, 1 postoperative shock, 3 cases of respiratory failure, and 2 thromboembolic events. The complication rate of the patients receiving TXA after the initiation of the protocol was 3.2% (12 of 375) compared with 4.9% (3 of 61;  $P = .497$ ) in those not receiving TXA. Across both groups A and B, the complication rate of patients receiving TXA was 3.61% and those not receiving TXA was 2.34% ( $P = .299$ ). Patients in group A receiving TXA before the protocol had a higher complication rate than those in group B receiving TXA after the protocol (16.67% vs 3.2%;  $P = .014$ ).

### Discussion

Despite the growing number of publications describing TXA as an effective transfusion-reduction strategy for TJA patients, implementation of a TXA protocol may be challenging. Institutional



**Fig. 4.** Mean PRBC units transfused per patient in each surgical group. Units transfused were decreased for group B in all comparisons except revision TKA and all TKA with the Bonferroni correction of the  $P$  value.

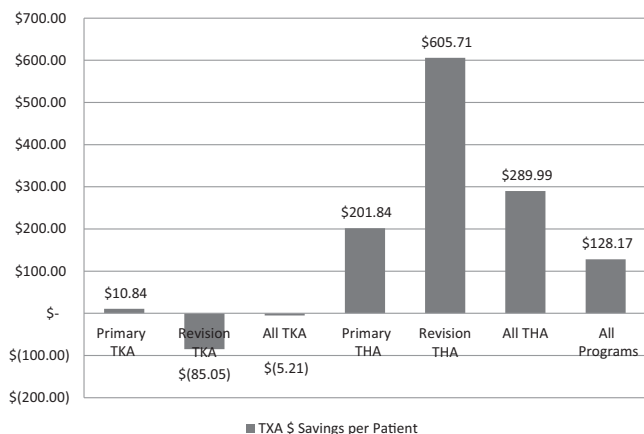


Fig. 5. Cost savings per patient with the use of TXA in each surgical group.

barriers may include concerns about safety, cost, optimal dosage, route, anticipated physician noncompliance, and specific concerns about thromboembolic event risk. In addition, national shortages of all medications, including TXA, present their own challenges. At our institution, each of these barriers delayed widespread use of TXA in TJA patients. In the year before this PI Project, TXA was used only in highly selective cases, often when significant blood losses had already occurred. This selective use of TXA in group A was associated with an in-house complication rate of 16.67%.

In establishing a multidisciplinary PI Project, there was input from all stakeholders in developing a protocol that proved to be highly successful. Consequently, TXA utilization increased from 3.6% to 86% in TJA patients. Without changing any other blood conservation measures or transfusion triggers, the patients' hemoglobin decline decreased by 20%, the transfusion rate by 45%, and the units of PRBC per patient by 61.9%. This led to an annual program direct cost savings of nearly \$56,000, exclusive of other transfusion-associated costs such as the 2.28-day increased length of stay in transfused patients, without a significant increase in complications. Overall, the complication rate of group A (2.38%) did not differ from that of group B (3.44%;  $P = .39$ ). The complication rate associated with TXA administration decreased from 16.67% in group A to 3.2% in group B, indicating that the standardized protocol improved safety.

Although it was anticipated that the procedures with the most blood loss would likely have the greatest clinical benefit from

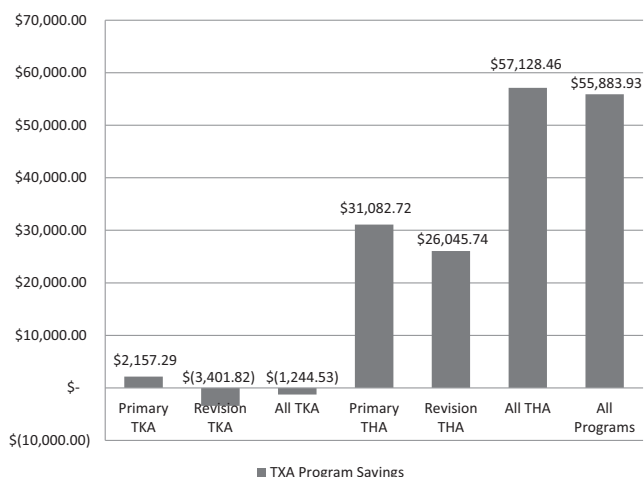


Fig. 6. Total cost savings with the use of TXA in each surgical group.

adding TXA, it is interesting that revision THA was the only subgroup to not have a significant decrease in the perioperative hemoglobin change. When grouped along with the primary THA patients, the benefit of TXA on this measure of blood loss was statistically significant, although not as large as in the TKA patients. Nonetheless, the revision THAs had a 29% decreased rate of transfusion and a notable 60% reduction in the number of units transfused per patient (2.158-0.860 units) after TXA implementation. Conversely, the primary TKA group had the largest percentage reduction in blood product utilization with an 87% decrease in overall transfusion rates (7.7%-1%) and a 75% reduction in the number of PRBC units transfused per patient (0.143-0.035 units). However, since the percentage of all-TKA patients receiving a transfusion before the TXA project was relatively small (7.4%), compared with the all-THA group (28.8%), the TKA group had many more patients that likely would not have needed a transfusion, even without TXA. Thus, the TKA patients benefited more from TXA in regard to decreasing blood loss, but the amount of blood lost in these patients was unlikely to require a transfusion—even before the TXA protocol. The THA patients had larger hemoglobin declines, both before and after the protocol, and benefitted more from TXA administration as it relates to transfusion reduction. The effectiveness of TXA in decreasing blood loss and transfusion requirements in both THA and TKA patients was clearly demonstrated in this study.

THA patients also demonstrated greater economic benefits from TXA. Since TXA cost was approximately the same for all patients and the benefits of transfusion reduction were observed more often in the THA patients, the economic impact was dramatic in both revision and primary THA patients. The revision THA patients, despite their minimal improvement in hemoglobin change, had the highest per-patient cost savings of \$605. Despite a smaller savings, per patient, of \$202 for the primary THA patients, the larger sample size led this group to have the largest program savings at \$31,000 per year. In contrast, cost savings were negligible in the TKA patients.

Thus, the determination as to which subgroup benefited the most from the administration of TXA depends on the metric and surrogate chosen for that discussion. Although the TKA patients seem to have the biggest improvement in blood loss and percentage of transfusion reduction, the initial transfusion rate was so small that this reduction is not as clinically or economically meaningful as the reductions observed in THA patients. Conversely, as THA patients were more likely than TKA patients to receive a transfusion before our TXA protocol, the observed reduction in transfusion and number of PRBCs received per patient had a much larger economic impact in the THA population.

The strength of the present study is the comparison of specific cost savings in each surgical subgroup of TJA patients and the benefits of implementing TXA as a standardized hospital-based PI Program. Previously published studies have largely compared reduction in combined pharmacy and transfusion costs or cost of hospital stay per patient [14,29,37–45]. As in other studies, this study showed TXA to be beneficial in reducing blood loss, transfusions, and costs, without an increase in complications. This study demonstrates the differences in each of these outcomes, based on surgical subgroup. Importantly, this study also demonstrates the efficacy of a collaborative, multidisciplinary, standardized protocol regarding TXA which increased TXA administration from 3.6% to 86% in TJA patients and decreased complications in patients receiving TXA from 16.67% to 3.2%.

There are several limitations to this study. First, it is a retrospective review of prospectively collected data regarding a PI Project that was not designed for scientific study. The PI Project was not blinded or randomized and compared clinicians' subjective determination of need for transfusion across 2 different calendar



years. It should be noted, however, that there was little change to our team members or decision-making processes and no additional change in blood management strategies or transfusion triggers. A second limitation is the ability to analyze complications that occurred after the index hospitalization. This information was recorded only if the patients returned to our hospital for readmission. The blinded nature of this retrospective study did not allow for unique patient identifiers, so an in-depth analysis of post-hospitalization complications could not be completed. Theoretical complications related to TXA, such as thromboembolic disease or cardiac events, are rare events, requiring a much larger sample size to demonstrate significant differences. However, our findings are consistent with previously published data on the safety of TXA use [16–19,21–28,30,35–37,40,41,43,45–58]. Similarly, this study was underpowered to show any secondary TXA benefits, including reduction in infections and avoidance of hematomas requiring additional surgery. Post hoc analyses of the secondary outcome variables with G\*Power (2016, Heinrich-Heine-Universität Düsseldorf) using a 2-sample z test for group proportions, using an alpha of 0.05, and a beta of 0.8 yielded exceedingly high numbers to demonstrate statistical significance; 46,888 procedures would need to be reviewed to demonstrate a significant difference in pooled TXA-related complications or benefits including thromboembolic disease, cardiac complications, infections, postoperative shock, and hemorrhage. The numbers required for individual complications were much higher. What can be reasonably concluded is there are likely no statistical differences between groups A and B for readmissions, related readmissions, and complications.

## Conclusion

Through a multidisciplinary PI Project, a standardized approach to TXA administration greatly increased the use of this important blood-management strategy and created value by concurrently increasing quality and decreasing costs with no demonstrable increase in adverse effects.

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