The effect of application of topical tranexamic acid versus hydrogen peroxide on postoperative hemostasis in elective spine surgeries: a randomized controlled trial

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Abstract

Background: Spine surgery is usually associated with excessive blood loss that may necessitate a blood transfusion.

Objectives: to evaluate the topical application of tranexamic acid versus hydrogen peroxide for hemostasis in patients undergoing elective spine surgeries under general anesthesia.

Patients and Methods: One hundred twenty patients aged 20 to 60 participated in this prospective, randomized, single-blinded study. They were randomly allocated into three equal groups. Patients either receive topical tranexamic acid 2gm (Group T), 3% hydrogen peroxide (Group H), or normal saline in the control group (Group C), all in 100 mL volume, applied via irrigation before wound closure for 3 minutes. The primary endpoint was the estimation of postoperative blood loss within the first 48 hours. Secondary outcomes included: hemoglobin and hematocrit values, frequency of blood transfusion, and length of hospital stay.

Results: There were differences in postoperative blood loss at the first and second 24 hours in group T (194.1 ml and 98.1 ml) compared to group H (328.2 ml and 199.5 ml) and groups C (367.5 ml and 227.5 ml) with a p-value of 0.001. Postoperative hemoglobin and hematocrit levels after 48 hours were best in group T (11.2 gm/dl) compared to the H and C groups (10.97 and 10.52 gm/dl, respectively) with a p-value of 0.041. Incidences of postoperative blood loss > 500 ml, blood transfusion, and the length of hospital stay in days were the least in group T, with a p-value of 0.001.

Conclusion: The present study proves that topical tranexamic acid is superior to hydrogen peroxide in reducing postoperative blood loss and preserving hemoglobin and hematocrit. It also shortened the period of hospital stay.

Keywords: Hydrogen peroxide; Postoperative; Spine surgery; Topical; Tranexamic acid.

DOI: 10.21608/svuijm.2022.178705.1463

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Received: 6 December, 2022.

Revised: 19 December, 2022

Accepted: 20 December, 2022.

Published: 7 June, 2023

Cite this article as: Sarah M. Omar Mousa, Amany Khairy Abo El Hussien, Nehal Kamal Mohamed, Waleed Zidan Nanous. (2023). The effect of application of topical tranexamic acid versus hydrogen peroxide on postoperative hemostasis in elective spine surgeries: a randomized controlled trial. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 389-398 .

Introduction

Spine surgeries are the most performed neurosurgeries worldwide. Blood loss in these surgeries remains a challenge during spinal surgery. (Yuan et al., 2019) Medical adjuvants, including antifibrinolytics such as tranexamic acid (TXA) and chemicals such as hydrogen peroxide (H_2O_2), have been applied intraoperatively to reduce blood loss and possibly avoid the need to put a drain (**Chen et al., 2014**) .

Tranexamic acid is a synthetic analog of lysine (an amino acid). It reduces the conversion of plasminogen to plasmin and prevents fibrin degradation (**Xiong et al., 2020**) . It can provide a direct and local high drug concentration at the bleeding site and avoid systemic exposure to TXA. It can effectively decrease postoperative transfusion requirements and reduce postoperative blood loss (**Sudprasert et al., 2019**) .

Hydrogen peroxide is an inexpensive option with natural hemostatic and antiseptic properties (**Kambagi et al., 2020**). It is an oxidizing agent easily degraded by tissue catalase to form oxygen and water (**Hsien et al., 2021**) .

In this prospective single-blinded randomized controlled study, we evaluated the effect of the application of topical tranexamic acid versus hydrogen peroxide on postoperative blood loss as a primary goal. The difference between hemoglobin and hematocrit values pre- and postoperatively, the amount of blood transfusion, and the length of hospital stay as secondary goals.

Patients and Methods

Eligibility of the study

The study was approved by the ethical committee of the faculty of Medicine, El Minia University (no. 679-9/2020). The study was registered at clinicaltrial.gov, and the clinical trial registration number was (NCT05152186). This prospective randomized single-blinded study was conducted on 120 patients scheduled for elective spinal surgery from June 2021 to November 2021. Informed consent was obtained from all our patients. Patients aged 20- 60 years with in-place spinal trauma, thoracic or lumbar degenerative disease, or degenerative scoliosis were included in the study.

Exclusion criteria

Patients with a history of thromboembolic disease, coagulopathy, or allergy to TXA, patients on anticoagulants, antiplatelet drugs, and intravenous TXA were excluded from the study. Patients with spinal cord penetrating trauma or tumors were excluded. Associated head trauma, infection at the operative site, or revision surgeries were also excluded. A dural tear accompanied by cerebrospinal fluid leakage detected intraoperatively was an exclusion criterium.

Study design, randomization, and blinding

It was a prospective randomized controlled, single-blind study where patients were grouped into three equivalent groups of forty each based on a randomization computer-generated table using Microsoft Excel by a statistician who did not participate

in the patient's management. The grouping paper was put in a sealed opaque envelope to cover the allocation. For blinding, the study medications were prepared by the surgeon on the day of surgery.

The anesthetist who followed the patients up was blind to the study groups. After the study ended, it was revealed that the control group (where the incision was irrigated with 100 ml normal saline), group T (where patients received topical TXA 2gm in 100 mL saline solution via irrigation), and group H (in which the incision was irrigated with 100 mL of 3% H_2O_2 solution).

The technique of the study

All patients were admitted the night before surgery. Preoperatively, Laboratory (lab) investigations, serum hemoglobin (Hb), hematocrit (Hct) platelet count (PLT), Prothrombin concentration (PC), and international normalized ratio (INR) were recorded. Baseline vital signs such as heart rate, systolic, diastolic, mean blood pressure, and oxygen saturation were also recorded.

Patients received standardized general anesthesia. The patients were put in a prone position. The following monitors were applied to the patient pulse oximetry, electrocardiogram, and non-invasive blood pressure cuff to record hemodynamics after positioning and every 15 minutes intraoperatively till the end of the operation. Mean arterial blood pressure was maintained at 60- 80 mmHg till the end of the operation, then it was returned to baseline level to check for bleeding.

Operative data like type of operation, number of operating levels, and duration of operation were also recorded. Blood loss in the suction device, the number of gauzes and towels, and the amount of blood transfusion were reported. The gauze was calculated as containing 15 ml blood if thoroughly soaked, and the towel containing 150 ml if thoroughly soaked too.

Before wound closure, the study medications were prepared and applied by the surgeon topically as follows: group T patients received topical TXA (Kapron®, Amoun, Egypt) 2gm in 100 mL saline solution via irrigation for 3 minutes, patients' incisions in group H were irrigated with 100 mL of 3% H_2O_2 solution (30% sol. of Hydrogen peroxide 30ml volume, Luna, Egypt) for 3 minutes. The incision was irrigated with 100 ml of normal saline for patients in group C. Subfascial and subcutaneous suction drains were placed and maintained for 48 h postoperatively.

The blood volume in the drain (ml) in the first 24 hours and the second 24 hours were recorded. The laboratory investigations were recorded after 24 hours and after 48 hours (Hb, HCT, PLT, Pc, INR). The number of patients with blood loss >500 ml and those who needed blood transfusion were determined. The length of hospital stay (days) was also recorded.

Sample size calculation

Patients were categorized into three groups; the G power program version (3.1.9) was used to calculate the sample size for this study with priory analysis. F-tests (ANOVA: Fixed

effects, omnibus, one-way) were used to detect the difference between the 3 groups, considering blood loss as the primary outcome. Based on a previous study (**Chen et al., 2014**), assuming that the outcome is moderately affected, thus having moderate variance. The effect size was calculated at 0.3 (moderate effect size), an alpha error was 0.05, and a power of 0.80 was used. The resulting sample size was 120 patients. Each group had 40 patients randomly classified into three equal groups of 40 patients.

Statistical analysis

The collected study data were coded, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA program software version 24). Descriptive statistics were done for parametric quantitative data by mean and standard deviation, while they were done for categorical data by number and percentage.

Parametric quantitative data between the three groups were analyzed using the One-Way ANOVA test followed by Post Hoc Tukey correction between every two groups. Analyses were done for parametric quantitative data within each group using paired sample t-tests. Analyses were done for qualitative data using the chi-squared test. The level of significance was taken at (P-value < 0.05).

Results

The current study included 120 patients in the final analysis from 127 patients initially assessed for eligibility, as shown in the CONSORT flow chart of enrollment (**Fig.1**).

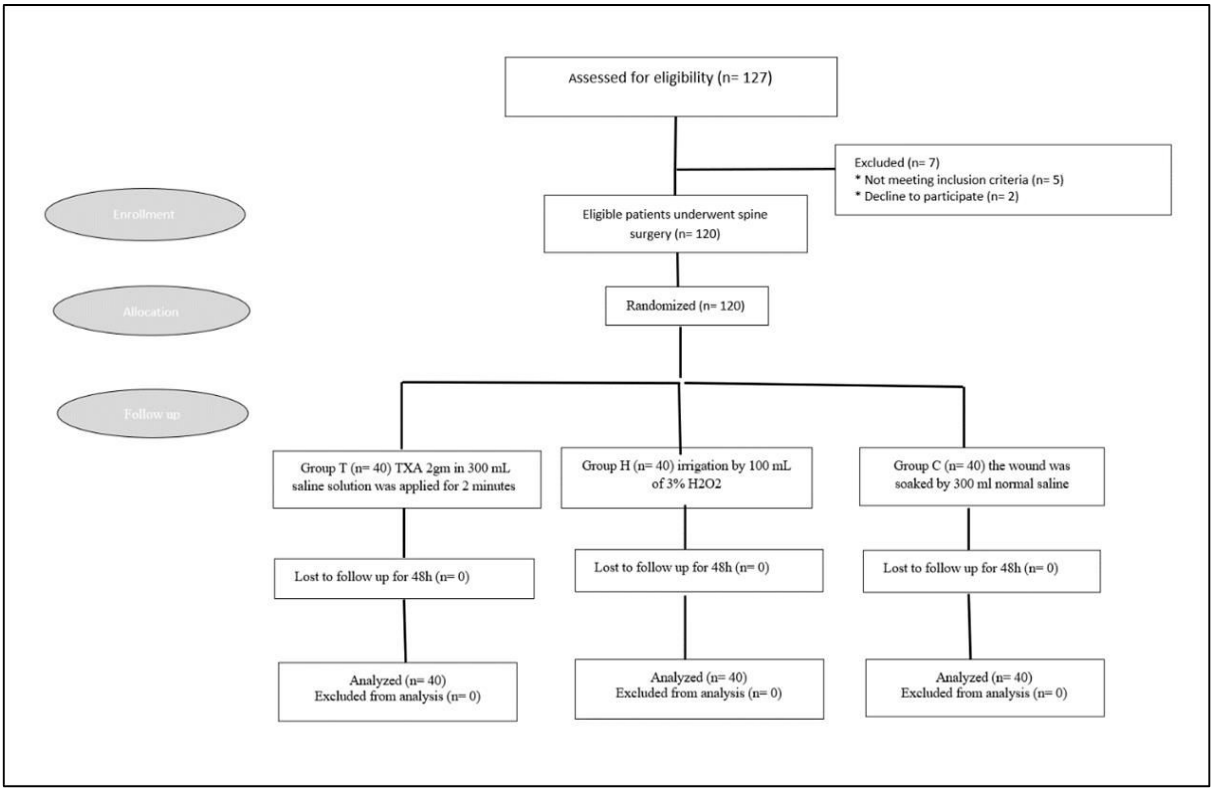

Fig.1.The CONSORT flowchart of the study

There were no statistically significant differences between the three groups as regards the demographic data (age, sex, and body mass index BMI) as well as the operative data (duration of surgery, number of levels, and the type of operation), as shown in (**Table.1**). The hemodynamics as heart rate, blood pressure (systolic, diastolic, and mean), and oxygen saturation showed statistically insignificant changes throughout the study period.

Table 1. The demographic and operative data of the study groups

Variables	Group T (n= 40)	Group H (n= 40)	Group C (n= 40)	P-value
Age (yr) mean ±SD	44.9±14.0	40.55±15.9	44.1±12.6	0.341
Sex (n %):				0.351
Males	20(50%)	21(52.5%)	26(65%)	
Females	20(50%)	19(47.5%)	14(35%)	
BMI (kg/L2)	26.6±1.3	26.5±1.8	26.6±1.6	0.969
Duration of surgery (min) mean±SD	113.2±16.2	111.3±20.0	108.8±16.4	0.533
The number of operated levels (n%):				0.317
One	3(7.5%)	0(0%)	0(0%)	
Two	22(55%)	25(62.5%)	22(55%)	
Three	12(30%)	12(30%)	13(32.5%)	
Four	3(7.5%)	3(7.5%)	5(12.5%)	
Type of operation (n %):				0.693
Laminectomy	12(30%)	12(30%)	11(27.5%)	
Discectomy	14(35%)	11(27.5%)	9(22.5%)	
Fixation	14(35%)	17(42.5%)	20(50%)	

Min: minutes, Yrs: years, kg: kilogram, L: liter. BMI: body mass index SD: standard deviation, n: number. The quantitative data are displayed as mean and SD, and qualitative data are displayed as number and percent.

The postoperative blood loss in the first 24 and second 24 hours showed a statistically significant difference between the three groups (p-value of 0.001). The comparison between every two groups revealed a lower mean volume of blood loss (ml) at both the first and the second 24 hours postoperative in the TXA group (200.1 ml and 98.1 ml, respectively) compared to the H_2O_2 group (328.2 ml and 199.5 ml, respectively) and the control groups (367.5 ml and 227.5 ml respectively) with p-value 0.001. Group H showed significantly lower drain volumes at the first and second 24 hours compared to group C, with p values 0.024 and 0.014, respectively, as in table (2) and figure (2). The intraoperative blood loss was comparable between the three study groups T, H, and C (358.5±134.4, 411.2±139.3, 422.5±148.4 ml, respectively) with a p value> 0.05.

Table 2. The postoperative blood loss at the first and second 24 hours in the study groups

Variable	Group T (n=40)	Group H (n=40)	Group C (n=40)	P-value			
				ALL	T&H	T&C	H&C
Drain in the first 24 hr mean±SD	200.1±95.5	328.2±59.6	367.5±76.4	0.001	0.001	0.001	0.024
Drain in the second 24 hr mean±SD	98.1±48.7	199.5±42.7	227.5±57.6	0.001	0.001	0.001	0.014

Hr: hours, SD: standard deviation. The data are displayed as mean and SD.

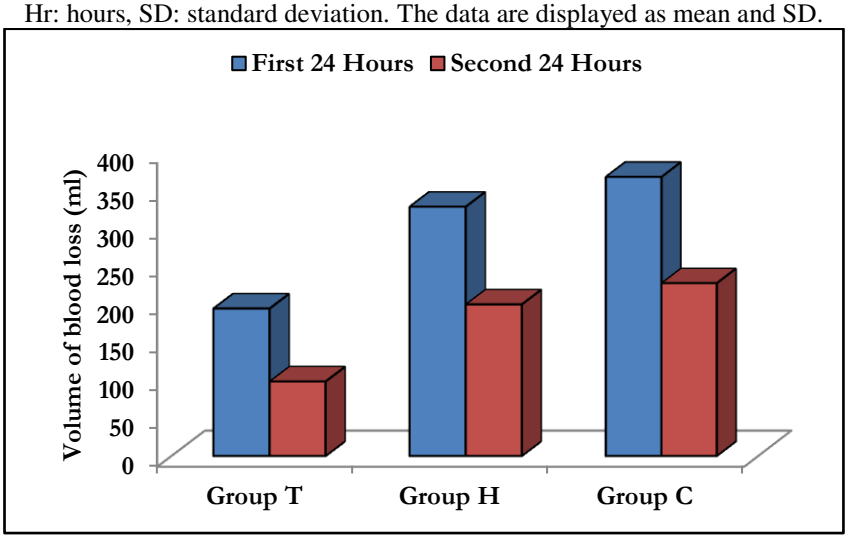

Fig.2. The postoperative blood loss at the first and second 24 hours

The hemoglobin and hematocrit baseline values were comparable between the three study groups. Also, their 24 hours postoperative values showed insignificant differences. In the second 24 hours, the Hb values showed statistically significant differences between the study groups' p-value of 0.041. Group T showed the highest mean Hb value after 48 hours (11.2 gm/dl) when compared to both group H and group C (10.97 gm/dl and 10.52 gm/dl, respectively) with a p-value < 0.05.

There were statistically insignificant differences between groups H and C. The mean Hct values after 48 hours were the same as the Hb values. Group T (35.8%) showed the best Hct values when compared with both group H (32.8%) and group C (31.9%) with p-value < 0.05. Comparison between H_2O_2 and the control group revealed a statistically insignificant difference. Within-group comparison of Hb and Hct values throughout the study period compared to the baseline value showed a statistically insignificant change in the TXA group. In contrast, both H_2O_2 and the control group showed a statistically significant within-group drop in both Hb and Hct values compared to the baseline value of each group. The other lab investigations, such as platelet count, prothrombin concentration, and INR, showed statistically insignificant changes throughout the study period (**Table.3**).

Table 3. The hemoglobin and the hematocrit variation

Variable	Group T (n= 40)	Group H (n= 40)	Group C (n= 40)	P-value			
				ALL	T&H	T&C	H&C
Baseline hemoglobin (gm/dL) mean±SD	12.27±1.7	13.13±1.8	13.07±1.4	0.286	0.402	0.435	0.119
Hb after 24 hrs (gm/dL) mean±SD	11.79±1.4	11.52±1.5***	11.41±1.1***	0.439	0.371	0.726	0.214
Hb after 48 hrs (gm/dL) mean±SD	11.20±1.3	10.97±1.5***	10.52±1.0***	0.041	0.024	0.035	0.140
Baseline HTC (%) mean±SD	38.8±5.1	39.5±5.5	40.0±4.5	0.176	0.349	0.063	0.350
HTC after 24 hrs (%) mean±SD	36.5±4.2	35.3±4.4**	34.5±3.5***	0.638	0.439	0.931	0.390
HCT after 48 hrs (%) mean±SD	35.6±4.0	32.8±4.6**	31.9±3.4***	0.010	0.016	0.005	0.350

gm/dl: gram per deciliter, SD: standard deviation. Hrs: hours. The data are displayed as mean and SD. ***: intragroup significance at <0.001 **: intragroup significance at <0.01 *: intragroup significance at <0.05

The incidence of postoperative blood loss of more than 500 ml was statistically different between the three groups. Group T showed the least number of patients (7 patients only) compared to group H (25 patients) and group C (35 patients) with a p-value of 0.001. The comparison between groups H and C showed a statistically significant difference p-value of 0.001. The number of patients who received postoperative blood transfusion showed statistically significant differences between the three groups. Group T showed the fewest number of patients who received transfusion (7 patients only) compared to group H (17 patients) and group C (33 patients) with a p-value of 0.001, the comparison between group H and C showed a statistically significant difference with a p-value of 0.001. As regards the length of hospital stay, the TXA group showed the shortest duration (2.18 days) compared to both H_2O_2 and the control group (3.55 and 3.73 days, respectively), with a p-value of 0.001 for both groups. In contrast, a comparison between groups H and C revealed statistically insignificant differences with a p-value of 0.084, as shown in (**Table.4**).

Table 4. The postoperative complications and the length of hospital stay

Variable	Group T (n= 40)	Group H (n= 40)	Group C (n= 40)	P-value			
				ALL	T&H	T&C	H&C
Blood loss >500ml (n %)	7(17.5%)	25(62.5%)	35(87.5%)	0.001	0.001	0.001	0.001
Blood transfusion (n %)	7(17.5%)	17(42.5%)	33(82.5%)	0.001	0.001	0.001	0.001
Length of hospital stay (days) **mean±SD**	2.18±0.3	3.55±0.5	3.73±0.45	0.001	0.001	0.001	0.084

N: number, SD: standard deviation, n: number. The quantitative data are displayed as mean and SD, and the qualitative data is displayed as number and percent

Discussion

The most important finding of the present study is that the topical TXA or H_2O_2 wash reduces postoperative bleeding after spine surgeries compared to the control group. The TXA is superior to the H_2O_2 in reducing postoperative blood loss.

This finding correlates with **Chen et al.(2014)** which included three groups: TXA, H_2O_2, and control groups (50 patients in each group). In this study, topical TXA wash reduced total blood loss during total knee arthroplasty (TKA), but H_2O_2 wash did not reduce the total blood loss compared to the control group

The drain volume after 24 and 48h was significantly lower in the study groups (TXA & H_2O_2) compared to the control group. TXA group showed the lowest drain volumes. These results agree with multiple studies as that of **Xu et al. (2020)** who conducted a randomized controlled trial on patients who underwent posterior lumbar interbody fusion to assess the efficacy and safety of TXA in reducing hidden blood loss compared to saline wash. There were statistically significant differences between topical TXA and control groups for drainage volumes.

Fatima et al. (2021) study aimed to evaluate the safety and efficacy of topical TXA compared to both placebo and IV TXA in patients who underwent spinal deformity surgery. It included a total of 609 patients from 8 studies. They found a statistically significant difference in postoperative drain output in patients treated with TXA, either IV or topical, compared to the control group.

In agreement with our results**, Shen et al.(2021),** involved 66 patients with acute thoracolumbar burst fractures. The enrolled patients were randomly assigned to the TXA and control groups, in which the wound surface was soaked with TXA or the same volume of normal saline for 5 min after the wound incision, respectively. In the TXA group, the postoperative blood loss was significantly less than in the control group. They reported that the topical TXA application has the advantages of the maximum concentration at the bleeding site and avoiding systemic complications of TXA.

As regards H_2O_2 wash, our findings correlate with **Chen et al. (2020)** who studied 2626 patients; 1345 patients in the control group (no H_2O_2irrigation) and 1281 patients in the experimental group (H_2O_2 irrigation); The postoperative drain collection was significantly lower in the experimental group compared to the control group.

Regarding postoperative blood transfusion, our study revealed a significant decrease in the incidence of blood transfusion in the TXA group compared to the H_2O_2 and control groups.

Sudprasert et al.(2019) studied 57 patients who were operated on with long-segment instrumented fusion without decompression. Patients either received a solution containing 1 g of TXA (20 mL) applied to the surgery site via a drain tube after the spinal fascia was closed or the same

volume of normal saline, and then the drain was clamped for 2 hours. The groups were compared for postoperative packed red cells (PRC) transfusion rate and drainage volume. The results of their study were like our study's results. The rate of postoperative transfusion was significantly lower in the topical TXA group than in the control group. The mean total drainage volume was significantly lower in the topical TXA group than in the control group.

The same results were recorded by **Shen et al. (2021)** who detected that the blood transfusion rate and volume were significantly lower in the TXA group. Topical TXA can decrease the bleeding from exposed bony surfaces by attenuating the fibrinolytic activity in spine surgery.

When comparing Hb and Hct levels between the three study groups, all groups were comparable in the baseline Hb level. After 24 and 48 hours postoperatively, we found that the TXA group preserved the postoperative Hb and Hct more than the control and H_2O_2 groups after 48 hours. **Shen et al. (2021)** study detected that Preoperative Hb was similar between the study & control groups. However, it was significantly higher in the TXA group on the first day without a significant difference on the third day postoperatively.

Our results were also like **Fatima et al.(2021)** who demonstrated that the administration of topical TXA significantly preserved the postoperative Hb compared to the patients in the control group. **Chen et al.(2014)** claimed that the most important findings of their study are that topical TXA wash reduced the drop in serum hemoglobin level during TKA compared to the H_2O_2 group.

In this study, the length of hospital stay was significantly shorter with the topical tranexamic acid application. **Sudprasert et al.(2019)** who used topical TXA in spine fusion surgery**,** got the same result.

Conclusion

We conclude that topical TXA is superior for H_2O_2 in decreasing postoperative blood loss and the incidence of transfusion and preserves Hb and Hct levels in spine surgeries.

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