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Effect of Topical Administration of Tranexamic Acid on Intraoperative and Postoperative Blood Loss during Posterior Cervical Laminectomy and Fusion Surgery: A Retrospective Study

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ABSTRACT

AIM: To assess the role of topical administration of tranexamic acid (TXA) on intraoperative and postoperative blood loss of patients undergoing posterior cervical laminectomy and lateral mass screw fixation (PCLF) compared to a control group.

MATERIAL and METHODS: The data of 88 patients that underwent PCLF surgery, including 41 females and 47 males, were included in this retrospective study. Data elements including intraoperative blood loss (IBL), postoperative blood loss (PBL), amount of blood transfusion, surgical time, use of hemostatic agents, length of hospital stay, and time to return to work were extracted from medical records and compared between those who received topical TXA during surgery (irrigation of the surgical field with a solution of 3 g TXA in 100 ml normal saline) and an age- and sex-matched control group.

RESULTS: There were 48 patients in the TXA group and 40 patients in the control group. There were no significant differences in the baseline measurements and the level of operation between the two groups. The results showed that IBL and PBL were significantly lower in the TXA group compared to the control group ($p=0.03$ and $p<0.01$, respectively). There were no significant differences in the need for blood transfusion, surgical time, and hospital stay between the two groups ($p>0.05$). Moreover, the use of hemostatic materials during surgery and the time to return to work were significantly lower in the topical TXA group ($p=0.04$ and $p<0.01$, respectively).

CONCLUSION: Topical TXA efficiently reduces intraoperative and postoperative bleeding in patients undergoing posterior cervical laminectomy and PCLF surgery. These results need further investigation in future studies to draw a definite conclusion.

KEYWORDS: Posterior cervical laminectomy, Fusion surgery, Blood loss, Topical tranexamic acid

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ABBREVIATIONS: TXA: Tranexamic acid, **PCLF:** Posterior cervical laminectomy and fusion surgery, **IBL:** Intraoperative blood loss, **PBL:** Postoperative blood loss, **NSAIDs:** Nonsteroidal anti-ınflammatory drugs, **RTW:** Return to work, **SD:** Standard deviations, **VTE:** Venous thromboembolism, **IV:** Intravenous

INTRODUCTION

Open spinal surgery may cause massive bleeding as this lengthy surgery with a large incision involves richly supplied cancellous bone and soft tissues (2). In case of severe bleeding, the patients usually need blood transfusion during or shortly after the operation. However, blood transfusion is associated with a risk of infections, immunomodulation, hemolytic transfusion reactions, and transfusion-related acute lung injuries (3). Moreover, the hypovolemia caused by bleeding may be a risk factor for complications like hypotension, end-organ damage, and coagulopathy (15). Several blood conservative strategies have been developed to address and minimize intraoperative bleeding and thereby decrease the risk of postoperative complications of blood transfusion (24).

Standard guidelines recommend discontinuation of nonsteroid anti-inflammatory drugs (NSAIDs), antiplatelet agents, and anticoagulants preoperatively as a precaution to decrease intraoperative bleeding (5,29,47). Moreover, studies have shown that preventive erythropoietin injection can also reduce blood loss. As for the intraoperative management, the patient's position, normothermia, surgical approach, use of electrocautery, and the anesthesiologist's role in providing hypotensive anesthesia are prominent (1,8,35,40). Furthermore, many medications, including antifibrinolytics, ε-aminocaproic Acid, and Tranexamic acid are also used to control blood loss (10,42).

Tranexamic acid (TXA) has been used for blood loss control in different surgeries, including orthopedic surgery (e.g., hip and knee replacement) (19), cardiac surgery (e.g., coronary artery bypass) (11), and obstetric operations (e.g., postpartum hemorrhage) (28). It is an antifibrinolytic lysine analog that competitively inhibits plasminogen, plasmin, and tissue plasminogen activator at lysine binding sites (17). Over the past decade, many studies have evaluated the effect of systemic administration of tranexamic acid (TXA) on blood loss reduction during spinal surgery and reported its effectiveness in decreasing intraoperative and postoperative blood loss (16,26,36). TXA is usually administrated intravenously (38); however, the safety and efficacy of its topical application have shown in different studies (33). It is also hypothesized that using the topical form of TXA might prevent the occurrence of rare but serious adverse effects of the systemic use of the drug, including thromboembolic events, myocardial infarction, and seizure (4).

A recent systematic review and meta-analysis found that topical TXA might be beneficial in reducing bleeding in spinal surgery. However, as the authors mentioned, further studies are still needed to confirm the role of topical TXA in controlling hemorrhage in spinal surgery (44). In addition, the existing literature mostly focuses on lumbar spine surgery, and there are limited reports on the efficacy of topical TXA in cervical spine surgery. Therefore, we decided to retrospectively review the effect of topical TXA on intra/postoperative bleeding and the duration of hospitalization of the patients who underwent posterior cervical laminectomy and fusion surgery at our center. We compared the results with an age- and sex-matched control group with no use of TXA in our center.

MATERIAL and METHODS

Study Population and Sampling

This retrospective cohort study included 88 patients (41 females and 47 males) who underwent posterior cervical laminectomy and lateral mass screw fixation (PCLF). The data of all PLCF surgeries conducted at our university hospital between 2018 and 2020 were extracted. A senior attending spine surgeon determined the indications for surgery, including neurological deficits, myelopathic cervical cord change, gait disturbance, or any other signs or symptoms of hyperreflexia and intolerable pain that were intractable to eight weeks of conservative management. Our institutional ethical committee approved this study. All the participants provided written informed consent for using their data in medical research as a routine practice in our center.

The Inclusion and exclusion criteria were used to include the patients' data in the study analysis. The inclusion criteria were aged 18 to 85 years and a diagnosis of cervical cord myelopathy or cervical canal stenosis that was non-responsive to at least eight weeks of conservative therapy. The patients with a history of any coagulopathy or medicines that might influence coagulation cascade (e.g., aspirin, warfarin, etc.) were excluded from the study. Moreover, subjects with recent trauma were excluded from the study due to possible disturbances in coagulation lab results. The use of TXA is relatively contraindicated in subjects with liver/kidney dysfunction and those with a history of seizure. Therefore, the data of the subjects with any of the mentioned conditions was excluded from analysis.

Study Design and Intervention

A senior attending spine surgeon performed all of the surgeries at our hospital. The anesthesiology team and the anesthesia protocol were the same for all the patients, ruling out any confounding influence. A solution of three g TXA in 100 ml normal saline was prepared for use in some of the subjects. This solution was used during the operation for routine irrigation of the wound, bipolar electrocoagulation, and moistening of sterile gauze for packing. In addition, at the end of the surgery, the wound was irrigated with the solution, and a vacuum drain was placed under the fascia for all the subjects. The data of this group were compared with the data of a group of 40 age and sex-matched patients who underwent PCLF

at our center during the same time without using TXA in the irrigation solution.

The surgical procedure for all the patients was the same. A midline incision was made after proper prone positioning on Mayfield, and a bilateral subperiosteal dissection was done using electrocautery. Bony elements were completely exposed, and bilateral laminectomy was achieved using high-speed burr, bone rongeur, and Kerrison punch instruments. Lateral mass screws were inserted according to the standard techniques (23). All of the procedures as well as the surgical site levels were guided by C-Arm.

Outcome Measurement

Intraoperative blood loss (IBL) and postoperative blood loss (PBL) were measured and documented in milliliters. To measure the IBL, all fluids were collected in a suction bottle during the surgery, and the final volume was subtracted from the irrigation volume. To measure the PBL, the blood volume in the vacuum drain at the time of drain disconnection was measured. Drains were removed on the second postoperative day or earlier if the blood drainage was less than 100 ccs per day as per the routine protocol of our center. In addition, the surgical time and length of postoperative hospital stay were recorded in minutes and days, respectively. The coagulation laboratory tests and the need for blood transfusion were also recorded postoperatively and compared between the groups. All of the subjects were evaluated for possible systemic complications and they were followed for a minimum of 6 months for any delayed complications. The time to return to work (RTW) was also recorded for all subjects.

Statistical Analysis

Kolmogorov-Smirnov test was used to assess the normality of the variables. If applicable, outcome measures were compared between the two groups using the Chi-square, independent sample t-test, or Mann-Whitney test. The scores are presented as mean and standard deviation (SD). Analyses were conducted using the SPSS software version 26 (SPSS Inc., Chicago, Illinois, USA). P-values less than 0.05 were considered statistically significant.

RESULTS

The data of 88 subjects were included in this study. Topical TXA was administered intraoperatively in 48 patients, and data of the remaining 40 age- and sex-matched subjects was used as the control. The demographic findings and baseline characteristics of the subjects are shown in Table I. There was no difference in baseline measurements and the operation level (defined as the levels at which lateral mass screws were inserted) between the two groups.

As shown in Table II, IBL and PBL were significantly lower in the TXA group compared to the control group (p value=0.3 and 0.01, respectively). There was no significant difference in surgical time and blood transfusion rate between the two groups (p=0.18 and p=0.15, respectively). We followed the

Table I: Comparison of Baseline Variables Between the Groups

Variable	Topical TXA group n=48	Control group n=40	p
Age (years old)	51.1 (11.0)	53.5 (13.7)	0.38
Gender (M/F)	25/23	22/18	0.78
BMI (kg/cm²)	28.3 (5.3)	28.6 (5.7)	0.83
Diagnosis (level)	C4-C5: 5 C4-C6: 11 C3-C6: 17 C3-C5: 14 C5-C6: 1	C4-C5: 3 C4-C6: 9 C3-C6: 14 C3-C5: 11 C5-C6: 3	0.78
AST (U/L)	26.3 (6.9)	24.6 (5.1)	0.18
ALT (IU/L)	30.6 (5.5)	31.4 (4.7)	0.47
ALK-P (U/L)	75.7 (28.3)	83.3 (16.4)	0.12
BUN (mg/dl)	25.1 (6.5)	24.3 (3.7)	0.51
Cr (mg/dl)	1.02 (0.24)	1.08 (0.21)	0.25
Preoperative PT (Sec)	13.1 (0.75)	13.2 (0.49)	0.33
Preoperative PTT (Sec)	30.3 (3.0)	29.3 (2.8)	0.12
Preoperative INR (Index)	1.01 (0.05)	1.02 (0.03)	0.33

M: *Male,* ***F:*** *Female,* ***U:*** *Units,* ***L:*** *Liter,* ***IU:*** *International units,* ***mg/dl:*** *Milligrams pre deciliters,* ***Sec:*** *Seconds,* ***BUN:*** *Blood Urea Nitrogen,* ***Cr:*** *Creatinine,* ***BMI:*** *Body mass index.*

Table II: Comparison of Intra and Post-Operative Variable

Variable	Topical TXA group n=48	Control group n=40	p
Intraoperative Blood Loss (ml)	215.9 (167.2)	292.2 (155.8)	**0.03***
Postoperative Blood loss (in Drain, ml)	70.8 (64.9)	113.7 (75.4)	**<0.01***
Blood Transfusion (Yes/No)	2/46	5/35	0.15
Operation time (min)	116.5 (20.0)	121.3 (12.9)	0.18
Hemostatic materials (N/OC/BW/GS)	34/12/1/1	17/17/4/2	**0.04***
Postoperative PT (Sec)	13.2 (1.5)	13.3 (0.9)	0.85
Postoperative PTT (Sec)	31.7 (3.6)	29.8 (3.9)	**0.02***
Postoperative INR (Index)	1.02 (0.11)	1.03 (0.07)	0.85
Hospital stay (days)	1.50 (0.65)	1.45 (0.55)	0.70
Return to work (days)	31.79 (8.49)	39.95 (16.94)	**<0.01***

ml: *Milliliters,* ***min:*** *Minutes,* ***Sec:*** *Seconds,* ***N:*** *No hemostatic material,* ***OC:*** *Oxidized cellulose polymers,* ***BW:*** *Bone wax,* ***GS:*** *Gelatin sponge* ****:*** *Statistically significant.*

patients in the TXA group for potential systemic and local adverse effects of topical TXA administration. In this regard, the results showed no cases of wound infection, thrombotic events, myocardial infarction, or systemic nervous system toxicity.

DISCUSSION

Bleeding is an unavoidable part of any spinal surgery. It has been reported that PCLF surgery may result in a blood loss with a volume ranging between 225 and 480 mL (9,13,34). Moreover, blood loss can result in the physiologic fluid shift, coagulopathy, and antibiotic dilution (18). On the other hand, blood transfusion can lead to a significant burden on patients and the health care system. Therefore, many clinical researchers have investigated the possible strategies to prevent severe blood loss during surgery and in the postoperative period over the past decades (2,31,41). Preoperative use of erythropoietin, administration of autologous blood through cell salvage system, intraoperative induced hypotension, and the use of antifibrinolytic drugs are some of the suggested strategies to control and manage bleeding (2,24). A possible mechanism for significant blood loss during surgery is a sudden rise in the rate of fibrinolysis. The activation of fibrinolysis is triggered by several enzyme activations. Theoretically, TXA inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator (30). As fibrinolysis is a continuous mechanism that lasts for several hours after surgery, the TXA could effectively reduce blood loss both during and after surgery theoretically (22).

The safety and efficacy of intravenous administration of TXA in reducing blood loss during spine and other general surgeries have been widely investigated over the past years. According to pharmacological studies, it has been suggested that a loading dose of 10-15 mg/kg TXA followed by a maintenance dose of 1 mg/kg/hour provides an efficient and safe reduction in blood loss with minimum adverse effects (43,45). However, the dose-efficacy relationship for intraoperative systemic administration of TXA is not fully studied and the possible complications related to this type of drug administration need to be further assessed (21). It is reported that in the case of IV administration of TXA, up to 10% of drug molecules cross the blood-brain barrier and concentrate in the cerebrospinal fluid (21,32). Therefore, in patients that are prone to seizures, TXA administration (with neurotoxic potentials due to its interference with GABA and glycine receptors) should be used with caution (20). Venous thromboembolism (VTE), impairment of visual perception, and necrosis of the renal cortex are other possible adverse effects of systemic TXA administration during surgery (6,25,27).

These complications and some dark aspects of the systemic administration of TXA have urged the researchers to investigate the efficacy of the topical use of TXA (with minimum side effects) to reduce bleeding during surgery. There are controversial reports regarding the role of topical TXA in spine surgery. While many researchers have reported that topical administration of TXA ca favorably reduce postoperative blood loss and hospital stay in patients undergoing spine surgery (44), a recent meta-analysis showed that topical TXA administration did not significantly reduce intraoperative and postoperative blood loss (12). This inconsistency in the results is due to the lack of well-controlled prospective data in subjects with similar pathologies. The unequal administration dose of topical TXA and surgical technique diversity are other issues that make studies incomparable (12,44). Indeed, the included studies were mostly conducted on patients who underwent lumbar surgery, and a few studies were conducted in subjects with cervical spinal complaints. To address this problem, the data of the present retrospective study were collected. The

results showed that intraoperative blood loss, postoperative blood loss, use of hemostatic materials, and time to return to work were significantly lower in patients who received topical TXA during posterior cervical fusion and laminectomy surgery versus controls in the same center.

Regarding the cervical surgery, Yu et al. measured the effect of systemic TXA administration on intraoperative, postoperative, and total blood loss in patients undergoing PCLF surgery (46). According to their findings, patients who received TXA had less bleeding during and after surgery. Ho and Wong also assessed the role of intravenous TXA in patients with cervical surgery due to cervical myelopathy (14). Their results showed that the intraoperative and postoperative blood loss and drop in the blood hemoglobin level were significantly lower in those who received TXA during surgery compared to controls. Tsutsumimoto et al. investigated the role of 15 mg/kg intravenous injection of TXA in reducing blood loss during "French-door" cervical laminoplasty from C3 to C6 (39). They reported that postoperative and total blood loss were significantly lower in the TXA group compared to the controls. However, the intraoperative blood loss showed no significant difference between the two groups. These findings are mostly from studies that administered TXA through the intravenous route. The results of the present study showed that topical administration of TXA might have significant effects on the reduction of blood loss during and after posterior cervical laminectomy and fusion surgery. None of patients that received topical TXA during surgery developed local or systemic adverse effects of the systemic administration of TXA (such as seizure, cardiac infarct, and venous thromboembolism). These findings might help the patients with systemic comorbidities and those who are at risk of VTE and seizure to undergo major spinal surgeries with topical administration of TXA instead of IV drug delivery. Our findings are parallel with a study conducted by Sudprasert et al. that showed that topical administration of TXA during thoracolumbar long-segment instrumentation surgery reduced the postoperative bleeding volume, length of hospital stays, and time of drain removal in patients with traumatic spinal fracture (37). Similarly, El-Sharkawi et al. assessed the efficacy of topical TXA in patients with lumbar deformities who underwent osteotomy and posterior spinal fusion (7). They reported that the volume of blood loss and number of blood transfusion units were significantly lower in patients who received topical TXA. Ren et al. also showed that topical TXA reduced the postoperative blood loss and the length of postoperative hospital stay in patients who underwent posterior lumbar spinal fusion due to lumbar canal stenosis (33).

The retrospective design and a small sample size were the major limitations of the present study. Accordingly, future studies need to be carried out with a prospective blind design and recruitment of more participants. In addition, a comparison of IV and topical administration of TXA could be targeted by researchers in the future. Another limitation of the present study was the lack of viscoelastometric assessment of the patients' blood samples. This method can be used to register and quantify the systemic effects of topical administration of TXA.

CONCLUSION

According to the present study, topical TXA is efficient in reducing post and intraoperative bleeding in patients undergoing posterior cervical laminectomy and lateral mass screw fixation (PCLF) surgery. The findings need to be further investigated in future studies to draw a definite conclusion.

AUTHORSHIP CONTRIBUTION

Study conception and design: MK, MR, RK
Data collection: SS, MM, HA
Analysis and interpretation of results: ME, MFJ
Draft manuscript preparation: SS, NM
Critical revision of the article: MK, MR, MS
Other (study supervision, fundings, materials, etc...): MZ, AB, AJ
All authors (MK, SS, NM, MZ, MM, HA, AJ, AB, MS, ME, MFJ, RK, MR) reviewed the results and approved the final version of the manuscript.

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