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ORIGINAL RESEARCH

Tranexamic Acid Demonstrated a Trend Toward Decreased Perioperative Blood Loss in Posterior Decompression Surgery of Patient with Metastatic Spinal Tumor

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Background: To explore the effect of tranexamic acid (TXA) on perioperative blood loss in posterior decompression surgery of patient with metastatic spinal tumor.

Methods: Three hundred sixty-eight consecutive patients between May 2011 and Aug 2022 were retrospectively reviewed. One hundred eighty patients (182 surgeries) met the criteria and were included in the study. Sixty-two surgeries received preoperative intravenous TXA (TXA group), and 120 did not (non-TXA group). The primary outcome was total blood loss. *T*-test, Mann–Whitney U, and chi-square tests were used to evaluate the difference in baseline data, total blood loss, and other outcome measures between the two groups.

Results: Patients with hyper vascular tumors had significantly more blood loss compared with non-hyper vascular tumors (2002 (1531,2792) mL vs 1469(1036,1962) mL, p=0.001). There was no significant different in the postoperative venous thromboembolism of the lower limb between the two groups. For patients with non-hyper vascular tumors, the blood loss (1216(827, 1709) mL vs 1561 (1146, 2019) mL, p = 0.012) and postoperative drainage (1-day post-operation: 240(150,290) mL vs 280(150,395) mL, p=0.040; 3-days post-operation: 450(348,630) mL vs 613(398,799) mL, p=0.025) of TXA group were significantly less compared with that of the non-TXA group. Meanwhile, the TXA group had significantly less postoperative hospitalization compared with the non-TXA group (11.0(9.0, 13.3) days vs 12.5(9.0, 16.3) days, p=0.023). For patients with hyper vascular tumors, there were no significant differences in the blood loss and amount of postoperative drainage between the two groups.

Conclusion: Preoperative intravenous TXA demonstrated a trend toward decreased perioperative blood loss in posterior decompression surgery of spinal metastases with non-hyper vascular tumors.

Keywords: tranexamic acid, spinal metastases, blood loss, transfusion, blood supply

Background

Due to population growth and prolonged survival, there has been a significant increase in patients with spinal metastases.[1] The stubborn pain and neurological dysfunction caused by spinal metastases seriously affect patients' quality of life, causing significant social and economic burdens. Surgical decompression and stabilization followed by postoperative radiotherapy is one of the most effective methods for patients with metastatic spinal cord compression.[2,3] Although surgery can improve quality of life, perioperative blood loss remains a significant issue.[4] A Meta-analysis by Chen et al showed that the average intraoperative blood loss in patients with spinal metastasis was 2180 milliliters.[5] It has been proven that blood loss and allogeneic blood transfusion are closely related to perioperative complications in patients with spinal metastasis.[6] Reducing perioperative blood loss in patients with spinal metastasis remains a severe challenge.

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Hyperfibrinolysis is an essential cause of hemorrhage in spinal surgery. Tranexamic Acid (TXA) is an artificially synthesized lysine analog that can act on plasminogen and plasmin. TXA can inhibit fibrinolysis caused by plasmin, achieving hemostasis. TXA is widely used in patients with spinal degenerative diseases undergoing surgical treatment, including venous and local TXA. Preoperative intravenous infusion including the loading dose and the maintenance dose, is the most common method. The dose of TXA used preoperatively varies among different institutions.[7] In order to simplify clinical dosing, K Ker et al conducted a meta-analysis, which showed that for most patients, a loading dose of 1 g tranexamic acid given preoperatively, without considering maintenance dosing, resulted in better clinical efficacy, and that increasing the dose of tranexamic acid did not improve efficacy.[8]

TXA can reduce perioperative blood loss, allogeneic transfusion, occurrence of blood loss-related complication, and accelerate postoperative recovery.[9–12] Few studies evaluate the efficacy and safety of TXA in patients with spinal metastases. These studies show that TXA cannot effectively reduce perioperative blood loss in patients with spinal metastases.[13–16] For metastatic spinal surgery, the blood loss is significantly based on the blood supply of the primary tumor.[17] Previous studies do not differentiate the blood supply of the primary tumor. In addition, assessing only dominant blood loss while ignoring recessive blood loss may bias the results of the previous study. Patients with spinal metastases are predominantly middle-aged and elderly, with poor general conditions. Reducing intraoperative blood loss has always been a complex problem for spinal tumor surgeons. The amount of surgical blood loss is closely related to the probability of perioperative complications in patients.[18]

It is significant to confirm the efficacy of intravenous TXA in metastatic spinal tumors.

This study involves a retrospective analysis of consecutive patients diagnosed with spinal metastases who underwent decompression surgery in our department. The aim of this study was to explore the effect of tranexamic acid (TXA) on perioperative blood loss in posterior decompression surgery of patient with metastatic spinal tumor.

Methods

Study Design and Selection Criteria

This was a single-centered, respectively, nested case–control study. Consecutive patients with spinal metastases who underwent decompression surgery in our department from May 2011 to Aug 2022 were reviewed. Surgical indications were intractable pain due to myelopathy or radiculopathy, those not responding to conservative treatment such as radiation and chemotherapy. The surgical option was determined by multidisciplinary cooperation, composed of a neuro-radiologist, spinal tumor surgeon, and oncologist. Patients with the following conditions were excluded from this study.

Exclusion Criteria

(1) Missing of laboratory tests;
(2) Missing of weight;
(2) Sacral metastases;
(3) En-bloc resection;
(4) Without internal fixation;
(5) Anterior decompression surgery;
(6) 0.5g intravenously of TXA;
(7) 1g intravenously of TXA intraoperative: The application of TXA intraoperative may indicate that patients have already experienced significant bleeding before using tranexamic acid. Inclusion of these patients may have biased the results.

After the screening, surgeries were divided into two groups according to the intravenous use of TXA. TXA group: 1g intravenous of TXA bolus pre-operation; non-TXA group: did not use. The use of TXA during surgery was determined by the anesthesiologist. TXA was used after anesthesia induction, and before cutting the skin with the surgical knife.

Data Collection

Patients' characteristics, including the data of general, cancer, operation, laboratory, and perioperative venous thrombosis of the lower limb, were extracted from their electronic medical records. Metastases from renal, liver, and thyroid tumors were assigned to hyper vascular tumors.[19] General data included age, gender, ASA (American Society of Anesthesiologists Physical Status Classification System), and the application of anticoagulant or antiplatelet drugs (These drugs were discontinued seven days before surgery). Cancer-related data included pathological type and systemic treatment, including chemotherapy, targeted therapy, and immunotherapy. Laboratory data included preoperative Hemoglobin (Hgb), hematocrit (Hct), platelet (Plt), Prothrombin time (PT), activated partial thromboplastin time (APTT), and postoperative Hct. Operation-related data included the location and number of decompression levels, type of operation, operative time, blood transfusion on the operative day, drainage amount, and postoperative hospitalization.

All surgeries were performed by an experienced spinal tumor surgeon under general anesthesia. Circum-spinal decompression was achieved. The conventional surgery was performed via the median posterior approach with a standard incision. The deep fascia was cut longitudinal along the incision. Sacrospinalis muscles were stripped from the bone surface to expose the lamina and facet joints. Minimally invasive surgery was performed through a posterior mini-open approach or an expandable tubular retractor system via a transmuscular approach. Pedicle screws were percutaneously placed under fluoroscopy. For the transmuscular approach, a 4 cm skin incision was made 2 cm or more lateral from the lesion pedicle's skin projection, depending on the degree of obesity.[20] For the small incision approach, a small skin incision was performed posteriorly only at the decompression segment.[21]

Outcome Measurement

The primary outcome was total blood loss. The Gross formula calculated the total blood loss.[22]

Gross formula: total perioperative blood loss = theoretical total blood loss + allogeneic blood transfusion. (Patients in this study did not use autologous blood transfusions during and after surgery).

Theoretical total blood loss = estimated blood volume × (preoperative Hct-postoperative Hct) / Hct average.

Hct average = (preoperative Hct + postoperative Hct) / 2.

Postoperative HCT was examined on the first morning after the operation.

Patient's estimated blood volume = $k1 \times \text{height (m)}^3 + k2 \times \text{weight (kg)} + k3$[23]

Male patients k1=0.3669, k2=0.03219, k3=0.6041; Female patients k1=0.3561, k2=0.03308, k3=0.1833

Secondary outcomes included

- the amount of blood transfusion on the operative day,
- the amount and time of drainage,
- the length of postoperative hospitalization
- the occurrence of venous thrombosis of lower limbs during postoperative hospitalization.

The indication for transfusion was Hgb less than 80 g/L in general or 90 g/L for patients with coronary heart disease.

Statistical Analysis

Shapiro–Wilk was used to check whether the continuous variables conform to the normal distribution. Continuous variables were presented as mean ± SE in the normal distribution and median (25% quantile, 75% quantile) when they were not. Categorical variables were expressed as numbers. Independent sample *t*-test and Mann–Whitney *U*-test was used to detect the difference among continuous variables. The differences among the categorical variables were analyzed using the chi-square test. For the 2×2 contingency table, when $n \geq 40$ and $T \geq 5$, the Pearson chi-square test was used; when $n \geq 40$ and $1 \leq T \leq 5$, continuity adjusted Pearson chi-square test was used; when $n < 40$, or $T < 1$, Fisher's Exact Test was used. All tests were 2-sides. A p-value < 0.05 was considered statistically significant. Data were analyzed using SPSS 27.0 statistical software (IBM Corporation, Armonk, NY).

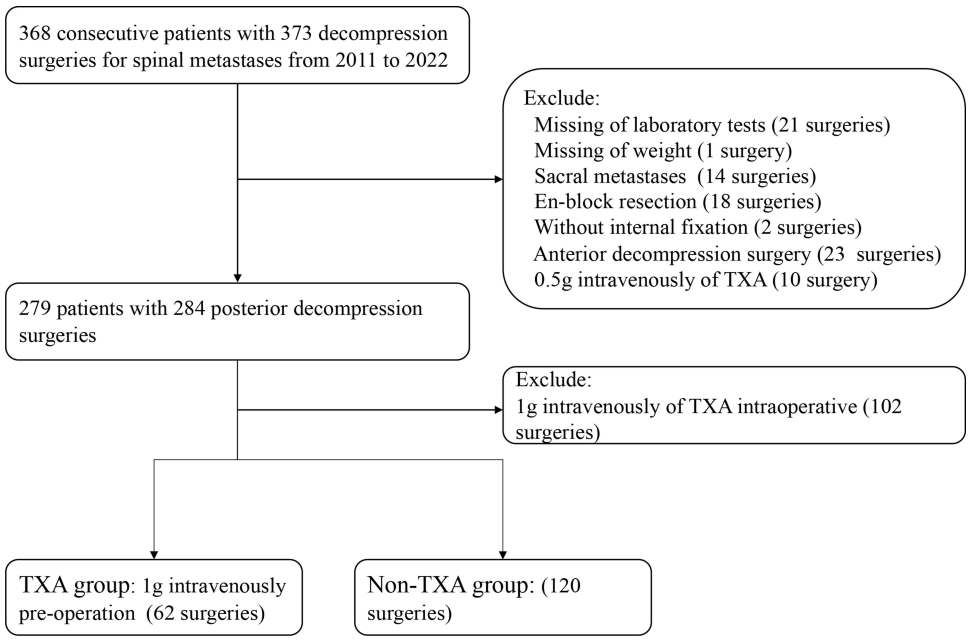

Figure 1 The flowchart of patient enrolment.

Results

Patient Reviewed

Three hundred sixty-eight consecutive patients with 373 surgeries were reviewed. We excluded those surgeries that are missing laboratory tests (21 surgeries), missing weight (1 surgery), sacral decompression (14 surgeries), en-bloc resection (18 surgeries), without internal fixation (2 surgeries), anterior decompression surgery (23 surgeries), 0.5g intravenously of TXA (10 surgeries), 1g intravenous of TXA after the surgery start (102 surgery).

At last, 180 patients with 182 surgeries were included in this study. Sixty-two surgeries received 1g intravenous of TXA pre-operation (TXA group), and 120 surgeries did not receive TXA (non-TXA group). The flow of patient enrolment is shown in Figure 1.

Patient's Baseline Data

The preoperative data are shown in Table 1. There were no significant differences in the baseline data between the two groups. The surgical data are shown in Table 2. There were no significant differences in the surgical data between the two groups.

Table 1 Preoperative Data of 182 Surgeries

Characteristic	TXA Group (n=62)	Non-TXA Group (n=120)	*P*
Age (years, mean ± SE)	63.4±0.9	63.9±1.3	0.815
Gender			
Female	24(38.7%)	42(35.0%)	0.622
Male	38(61.3%)	78(65.0%)	

(*Continued*)

Table 1 (Continued).

Characteristic	TXA Group (n=62)	Non-TXA Group (n=120)	*P*
Pathology			
Lung	21(33.9%)	45(37.5%)	0.599
Prostate	11(17.7%)	33(27.5%)	
Colon or rectum	3(4.8%)	4(3.3%)	
Breast	8(12.9%)	15(12.5%)	
Esophagus	1(1.6%)	1(0.8%)	
Renal	13(21.0%)	13(10.8%)	
Thyroid	2(3.2%)	5(4.2%)	
Liver	3(4.8%)	4(3.3%)	
Systemic therapy (chemotherapy, or targeted therapy, or Immunotherapy)			
Yes	27(43.5%)	52(43.3%)	0.978
No	35(56.5%)	68(56.7%)	
Anticoagulants			
Yes	1 (1.6%)	3(2.5%)	1.000
No	61 (98.4%	117 (97.5%)	
Antiplatelet drugs			
Yes	9(14.5%)	8(6.7%)	0.085
No	53(85.5%)	112(93.3%)	
Preoperative venous thromboembolism of lower limb			
Yes	4(6.5%)	19(15.8%)	0.185
No	32(51.6%)	53(44.2%)	
Unknown	26(41.9%)	48(40.0%)	
Laboratory data			
Preoperative HGB (g/L)	131(112, 140)	132(113, 143)	0.216
Preoperative PLT (10^9/L)	252.5(171.8, 339.0)	231.0(190.3, 282.8)	0.334
Preoperative PT (s)	11.3(10.9, 11.9)	11.3(10.7, 12.2)	0.787
Preoperative APTT (s)	31.2(29.1, 33.8)	30.3(28.1, 32.2)	0.064

Abbreviations: HGB, haemoglobin; PLT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time.

Clinical Characteristics and Blood Loss

The mean blood loss was 1595 (1125, 2135) mL. The patient's characteristics-related blood loss is shown in Table 3. Blood loss was significantly different between primary tumors (p=0.034). Patients with hyper vascular tumors had significantly more blood loss compared with non-hyper vascular tumors (2002(1531,2792) mL vs 1469(1036,1962) mL, p=0.001). Patients with a history of antiplatelet drug application had significantly more blood loss compared with patients

Table 2 Surgical Data of 182 Surgeries

Characteristic	TXA Group (n=62)	Non-TXA Group (n=120)	*P*
ASA score			
I	1(1.6%)	0(0.0%)	0.345
II	30(48.4%)	70(58.3%)	
III	29(46.8%)	47(39.2%)	
IV	2(3.2%)	3(2.5%)	
Location of decompression levels			
Cervical	1(1.6%)	7(5.8%)	0.147
Thoracic	42(67.7%)	60(50.0%)	
Lumbar	15(24.2%)	36(30.0%)	
Cervical + Thoracic	1(1.6%)	7(5.8%)	
Thoracic + Lumbar	3(4.8%)	10(8.3%)	
Type of surgery			
Conventional	58(93.5%)	107(89.2%)	0.336
Mis-invasive	4(6.5%)	13(10.8%)	
Decompression levels involved			
1 level	34(54.8%)	72(60.0%)	0.226
2 levels	19(30.6%)	40(33.3%)	
3 or more than 3 levels	9(14.5%)	8(6.7%)	
Surgical exposure segment	6(5, 7)	6(5, 7)	0.207
Operation time (min)	250.5(211.5, 315.3)	258.0(220.3, 299.0)	0.784

Abbreviation: ASA, American Society of Anesthesiologists Physical Status Classification System.

with no history of antiplatelet drug application (2004(1610,2411) mL vs 1517(1033,2086) mL, p=0.006). Mis-invasive surgeries had less blood loss compared with conventional surgeries (1419(924,1684) mL vs 1638(1142,2169) mL, p=0.099). There were no significant differences in blood loss between other clinical characteristics.

Primary and Secondary Outcome

All Tumor Types (Table 4)

There were no significant differences in the blood loss and amount of blood transfusion between the two groups. The TXA group had significantly less drainage compared with the non-TXA group (1-day post-operation: 210(138,280) mL vs 275(150,390) mL, p=0.007; 3-days post-operation: 455(325,655) mL vs 610(393,813) mL, p=0.007). There were no significant differences in the time of drainage and postoperative hospitalization between the two groups. There was no significant different in the postoperative venous thromboembolism of the lower limb between the two groups.

Non-Hyper Vascular Tumors (Table 5)

The blood loss of the TXA group was significantly less compared with that of the non-TXA group (1216(827, 1709) mL vs 1561(1146, 2019) mL, p = 0.012). The TXA group had significantly less HGB decline at postoperative day one than the non-TXA group (20(10, 31) g/L vs 28(15, 40) g/L, p = 0.008). The non-TXA group had significantly more drainage

Table 3 Clinical Characteristics and Blood Loss of 182 Surgeries

Characteristic	Total Patients (n=182)	*P*
Gender		
Female	1616(1074,2026)	0.650
Male	1584(1134,2137)	
Pathology		
Lung	1438(983,1863)	0.034
Prostate	1527(1109,1981)	
Colon or rectum	1204(385,2096)	
Breast	1711(1156,2339)	
Esophagus	1087(847, None)	
Renal	1954(1603,2719)	
Thyroid	2152(1233,2835)	
Liver	2001(1278,3674)	
Blood supply of primary tumor		
Non-hyper vascular	1469(1036,1962)	0.001
Hyper vascular	2002(1531,2792)	
Systemic therapy (chemotherapy, or targeted therapy, or Immunotherapy)		
Yes	1560(1039,1908)	0.099
No	1643(1151,2218)	
Anticoagulants		
Yes	920(539,2113)	0.205
No	1616(1138,2135)	
Antiplatelet drugs		
Yes	2004(1610,2411)	0.006
No	1517(1033,2086)	
Location of decompression levels		
Cervical	1355(932,2097)	
Thoracic	1527(1074,1924)	0.312
Lumbar	1740(1180,2381)	
Cervical + Thoracic	1506(920,2328)	
Thoracic + Lumbar	1796(995,2175)	
Type of operation		
Conventional	1638(1142,2169)	0.099
Mis-invasive	1419(924,1684)	

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Table 4 Outcome Analysis of 182 Surgeries

Characteristic	TXA Group (n=62)	Non-TXA Group (n=120)	*P*
Blood loss (mL)	1455(920, 2168)	1642(1156, 2131)	0.227
Blood transfusion on operative day (mL)	800(400, 800)	800(0, 800)	0.202
HGB (1-day post-operation, g/L)	104(95,113)	12(91,110)	0.168
HGB declined (1-day post-operation, g/L)	21(11, 36)	28(14, 41)	0.035
Drainage (1-day post-operation, mL)	210(138,280)	275(150,390)	0.007
Drainage (3-days post-operation, mL)	455(325,655)	610(393,813)	0.007
Drainage (Total, mL)	742(498,1134)	900(575,1195)	0.358
Drainage time (days)	7.0(6.0, 10.0)	7.0(5.0, 9.0)	0.092
Postoperative hospitalization (days)	11.0(9.0, 16.0)	12.0(9.0, 16.0)	0.512
Postoperative venous thromboembolism of lower limb			
Yes	2(3.2%)	4(3.3%)	1.000
No	60(96.8%)	116(96.7%)	

Abbreviation: HGB, haemoglobin.

Table 5 Outcome Analysis of Patients with Non-Hyper Vascular Tumors

Characteristic	TXA Group (n=44)	Non-TXA Group (n=98)	*P*
Blood loss (mL)	1216(827, 1709)	1561(1146, 2019)	0.012
Blood transfusion on operative day (mL)	800(400, 800)	800(0, 800)	0.456
HGB (1-day post-operation, g/L)	107(99,115)	102(92,109)	0.026
HGB declined (1-day post-operation, g/L)	20(10, 31)	28(15, 40)	0.008
Drainage (1-day post-operation, mL)	240(150,290)	280(150,395)	0.040
Drainage (3-days post-operation, mL)	450(348,630)	613(398,799)	0.025
Drainage (Total, mL)	655(493,1141)	900(578,1198)	0.263
Drainage time (days)	7.0(5.0, 9.0)	7.0(5.0, 9.0)	0.562
Postoperative hospitalization (days)	11.0(9.0, 13.3)	12.5(9.0, 16.3)	0.023
Postoperative venous thromboembolism of lower limb			
Yes	2(4.5%)	3(3.1%)	1.000
No	42(95.5%)	95(96.9%)	

Abbreviation: HGB, haemoglobin.

compared with the TXA group (1-day post-operation: 240(150,290) mL vs 280(150,395) mL, p=0.040; 3-days post-operation: 450(348,630) mL vs 613(398,799) mL, p=0.025). The TXA group had significantly less postoperative hospitalization compared with the non-TXA group (11.0(9.0, 13.3) days vs 12.5(9.0, 16.3) days, p=0.023).

Table 6 Outcome Analysis of Patients with Hyper Vascular Tumors

Characteristic	TXA Group (n=18)	Non-TXA Group (n=22)	*P*
Blood loss (mL)	2184(1657, 2719)	1919(1218, 2847)	0.532
Blood transfusion on operative day (mL)	1000(400, 1600)	800(700, 1300)	0.503
HGB (1-day post-operation, g/L)	101(88,106)	100(87,111)	0.663
HGB declined (1-day post-operation, g/L)	29(13, 39)	26.5(14, 48)	0.935
Drainage (1-day post-operation, mL)	180(50,270)	225(150,364)	0.138
Drainage (3-days post-operation, mL)	483(285,668)	603(355,820)	0.118
Drainage (Total, mL)	838(501,1135)	845(494,1171)	0.924
Drainage time (days)	8.0(7.0, 10.0)	7.0(5.8, 8.0)	0.014
Postoperative hospitalization (days)	16.0(13.0, 22.5)	12.0(9.0, 16.0)	0.048
Postoperative venous thromboembolism of lower limb			
Yes	0(0.0%)	1(4.5%)	1.000
No	18(100.0%)	21(95.5%)	
Pre-operative embolization			
Yes	2	7	0.149
No	16	15	

Abbreviation: HGB, haemoglobin.

Hyper Vascular Tumors (Table 6)

The TXA group had significantly more drainage time (8.0 (7.0, 10.0) day vs 7.0 (5.8, 8.0) day, p = 0.014) and postoperative hospitalization (6.0 (13.0, 22.5) day vs 12.0 (9.0, 16.0) day, p = 0.048) than the non-TXA group. There were no significant differences in blood loss, amount of blood transfusion and drainage, and postoperative venous thromboembolism between the two groups.

Discussion

The Effectiveness of Tranexamic Acid

The results of this study differ from previous research findings abroad.[13–16] This is mainly due to differences in the selection of research subjects and the measurement of blood loss.

Blood loss during spine surgery can be divided into dominant and recessive. The dominant blood loss mainly comes from expanded epidural venous plexus and cancellous bone surface, while recessive blood loss is mainly related to interstitial oozing and hemolysis. Unlike patients with degenerative spinal diseases, intraoperative blood loss in patients with spinal metastases mainly comes from tumor wounds, especially hyper vascular tumors, such as renal cancer and thyroid cancer. The hemorrhage of the non-hyper vascular tumors is similar to that of cancellous bone. The primary tumor was an essential factor affecting perioperative blood loss in patients with spinal metastases.[17] Our previous study shows that a hyper vascular tumor (kidney, thyroid, and liver) is an independent risk factor for blood loss in posterior surgery.[4] The present study also shows that patients with hyper vascular tumors had significantly more blood loss compared to patients with non-hyper vascular tumors. The effect of TXA may be varied in patients with different primary tumors. Tumors in this study are stratified into two groups: hyper vascular tumors and non-hyper vascular tumors. Based on the results of this study, we recommend routine preoperative intravenous TXA in patients with spinal metastases from non-hyper vascular tumors to reduce blood loss in posterior decompression surgery. For patients with spinal metastases

from hyper vascular tumors, embolization should be first considered to reduce intraoperative blood loss rather than simply using a hemostatic drug.[19]

The Safety of Tranexamic Acid

Hypercoagulability in patients with malignant tumors is a risk factor for lower extremity venous thrombosis. The occurrence of lower extremity venous thrombosis in patients after the application of tranexamic acid was also explored in this study. Studies on the safety of TXA have mainly come from the field of joint replacement. For patients receiving total hip/knee arthroplasty, TXA is not associated with increased complications, even for patients with high-risk status at baseline.[24,25] A large retrospective study shows that the application of TXA is not associated with increased venous thromboembolism in patients undergoing surgery for spine tumors. However, stratified analysis shows that patients with high TXA (≥20mg/kg) have increased odds of deep vein thrombosis and pulmonary embolism.[15] The present study shows that 1g TXA prophylactic intravenous does not increase the occurrence of venous thrombosis of the lower limb during postoperative hospitalization. The data on tranexamic acid in patients with spinal metastases are few and retrospective, which needs further confirmation by the randomized controlled study.

Limitations of the research.

There are limitations to the present study. First, it is limited by its retrospective and non-randomized nature. However, the two groups have no significant difference in baseline data. Selection bias may still affect the results. Second, due to missing data on postoperative Hct at 72 hours postoperatively, the postoperative Hct in the Gross formula was selected on the first morning after the operation. Patients' hemodynamics may not be stable at this time, and fluid shifts are not generally complete. Third, this study is a respective cohort study. It is uncertain whether the intraoperative application of TXA was due to more bleeding. So, patients with intraoperative application of TXA are ruled out. Fourth, the transfusion indication may need to be more stringently enforced due to this study's retrospective nature. Fifth, patients do not routinely perform a B-ultrasound examination of lower limbs during hospitalization. B ultrasound is only carried out after relevant symptoms, which may underestimate the occurrence of lower limb vein thromboembolism. Last, limited by the nature of retrospective studies, the information on patients receiving systematic therapy needs to be more comprehensive. It is impossible to stratify different systemic therapies, which could bias the results.

Conclusions

Preoperative intravenous TXA demonstrated a trend toward decreased perioperative blood loss in posterior decompression surgery of spinal metastases with non-hyper vascular tumors. The effect of TXA on metastatic spinal tumor should be validated by randomized controlled trials in the future.

Data Sharing Statement

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval and Consent to Participate

This study was retrospective. There was no follow-up requirement in this study. Collecting blood samples and other samples of the patients was unnecessary, and no additional examination was required. The research ethics boards of Peking University First Hospital approved the study protocol (2022 scientific research 417-001) and waived the need for informed consent. Researchers would strictly keep patients' personal information confidential. Identifiable information would not be disclosed to persons other than research members unless permission was obtained from the patient. All research members were required to keep the identity of patients confidential. No patients' personal information would be disclosed when the research results were published. This study was conducted following the ethical standards in the 1964 Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest. Each author certifies that no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.

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