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Review Article

Antifibrinolytics use during surgery for oncological spine diseases: A systematic review

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ABSTRACT

Background: Data exist of the benefits of antifibrinolytics such as tranexamic acid (TXA) in general spine surgery. However, there are limited data of its use in oncological spine patients.

Methods: A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Cochrane, OVID, and Embase databases were searched. Search terms: "*tranexamic acid*", "*aprotinin*," "*aminocaproic acid*," "*spine surgery*," "*spine tumors*," and "*spine oncology*." Included studies were full text publications written in English with patients treated with either agent or who had surgery for oncological spine disease (OSD).

Results: Seven hundred results were reviewed form the different databases, seven were selected. A total of 408 patients underwent spine surgery for OSD and received antifibrinolytics. There was a male predominance (55.2%) and mean age ranged from 43 to 62 years. The most common tumor operated was metastatic renal cancer, followed by breast and lung. Most studies administered TXA as a bolus followed by an infusion during surgery. Median blood loss was of 667 mL (253.3–1480 mL). Patients with TXA required 1–2 units less of transfusion and had 56–63 mL less of postoperative drainage versus no TXA. The median incidence of deep venous thrombosis (DVT) was 2.95% (0–7.9%) and for pulmonary embolism (PE) was 4.25% (0–14.3%). The use of TXA reduced intraoperative blood loss, transfusions and reduced postoperative surgical drainage output compared to no TXA use in patients with OSD.

Conclusion: In this review, we found that TXA may diminish intraoperative blood loss, the need for transfusion and postoperative drainage from surgical drains when used in OSD without major increase in rates of DVT or PE.

Keywords: Antifibrinolytics, Metastatic spine disease, Spine oncology, Spine surgery, Tranexamic acid

INTRODUCTION

Metastases are indeed the most common type of tumor in the spine.[27] With the expected increase in population age as well as improved in oncological management (systemic chemotherapy, and radiation), patients with spinal metastatic disease are poised to become even more common in years to come.[7,27] Recent studies show that there it is a steady increase of survival of patients treated for metastatic spine disease (MSD) with reports now of up to 60% of survival

improvement with newer surgical and systemic therapies for metastatic kidney cancer, for example.[22] Hence, it is expected that greater survival rates will then translate into encountering more patients as possible candidates for spinal surgery with metastatic spine disease.

Patients with cancer present commonly with nutritional deficiencies and sarcopenia compared to those with spine deformity or degenerative disorders that need spine surgery.[3,23] Thus, cancer patients are usually frail and present a higher risk of perioperative complications, which also render them to be more affected acutely with postoperative blood loss. Further, some tumors have high vascularity and increase risk of bleeding such as metastatic renal carcinoma which makes surgical hemostasis paramount.[20]

Given the exponential growth of spine surgery, in particular larger surgeries, recent studies have shown the benefits of using antifibrinolytic therapy in spine surgery to limit blood loss. A recent meta-analysis by Li *et al*.[12] shows the pooled benefits using these agents for intraoperative blood reduction, postoperative blood loss as well as transfusion rates. Despite increased awareness of these agents, and their use in degenerative spine conditions, little data exist over its benefits and risks for patients undergoing surgery for MSD or primary spine tumors.

In this study, we aim to investigate the use of antifibrinolytic therapy in patients undergoing spine surgery for tumors (metastatic or primary) of the spine with particular interest of blood loss parameters and complications.

MATERIALS AND METHODS

A systematic review of the literature was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[18] to identify studies reporting use antifibrinolytic agents during spine surgery for patients with spine oncological problems [Figure 1]. The search was done, and results retrieved in September 2021. PICO question: *How does patients with metastatic* (*or primary tumor*) *spine disease patients* (*population*) *that receive perioperative antifibrinolytic* (*indicator*) *compared with those who do not* (*comparator*) *differ in perioperative clinical outcome* (*outcome*).

Search strategy and screening

Databases were used included: PubMed, PubMed Central, Cochrane Library, Clinicaltrials.gov, and Embase. The search was catered to gather English language articles published from any beginning date to September 2021. The following antifibrinolytics agents were included: tranexamic acid (TXA), Aminocaproic Acid and Aprotinin. Combinations and variations of key phrases including: "*tranexamic acid*," "*aprotinin*," "*aminocaproic acid*," "*Spine tumors*," "*spine oncology*," "*spine metastasis*," "*spine surgery*," "*spine fusion*," "*Spine fixation*," "*spine decompression*," "*spinal surgery*" with the use of Boolean AND and OR in multiple configurations.

Inclusion and exclusion criteria

Eligible studies used antifibrinolytics during their spinal surgery for spine oncological diseases (metastatic or primary). The inclusion criteria for the reviewed articles included case reports, case series, retrospective, and prospective studies as well. Studies were limited to those written in the English language. Screened studies such as abstracts, posters, indexes, commentaries, author notes, and literature reviews were excluded from the study. Figure 1 shows the selection process for the articles.

Data extraction

All data were taken directly from tables, figures, and texts of included articles. The relevant data was extracted and placed into a custom table which included article's first author and year published, study type, number of patients included, type of antifibrinolytics agent, age and sex details, oncological diagnosis, treatment approach, outcome, and venous thromboembolism events. When data were unclear or unspecified, it was noted in the table as "-".

Characteristics and quality of included studies

To assess the risk of bias of randomized controlled trials, the Jadad Scale[9] was used following the standard score system from 0 to 5 (a higher number on the scale means low risk of bias). The Newcastle-Ottawa Scale[26] was used to assess the quality and the risk of bias of every quasi-experimental study and the retrospective comparative studies included. This scale is based on three dominions: selection of subjects (e.g., patient population and diagnoses), comparability of the groups and outcomes measurement (e.g., follow-up duration and limited loss-to-follow-up rate). The maximum number of stars is nine. Finally, the National Institute of Health Study Quality Assessment Tools[16] were used to evaluate Case Series and Pre-Post Studies with No Control Group: each study is evaluated separately and a quality rating of "Poor, Fair or Good" is given. The results of the bias assessment are found in [Table 1].

Statistical analysis

Although initially planned, a meta-analysis was not performed given the heterogeneity of data including multiple study design, poor quality of reports, missing data, different antifibrinolytics administration protocols, and lack of control group in most studies as well as the inconsistency in reporting clinical outcomes. Therefore, only descriptive statistics were

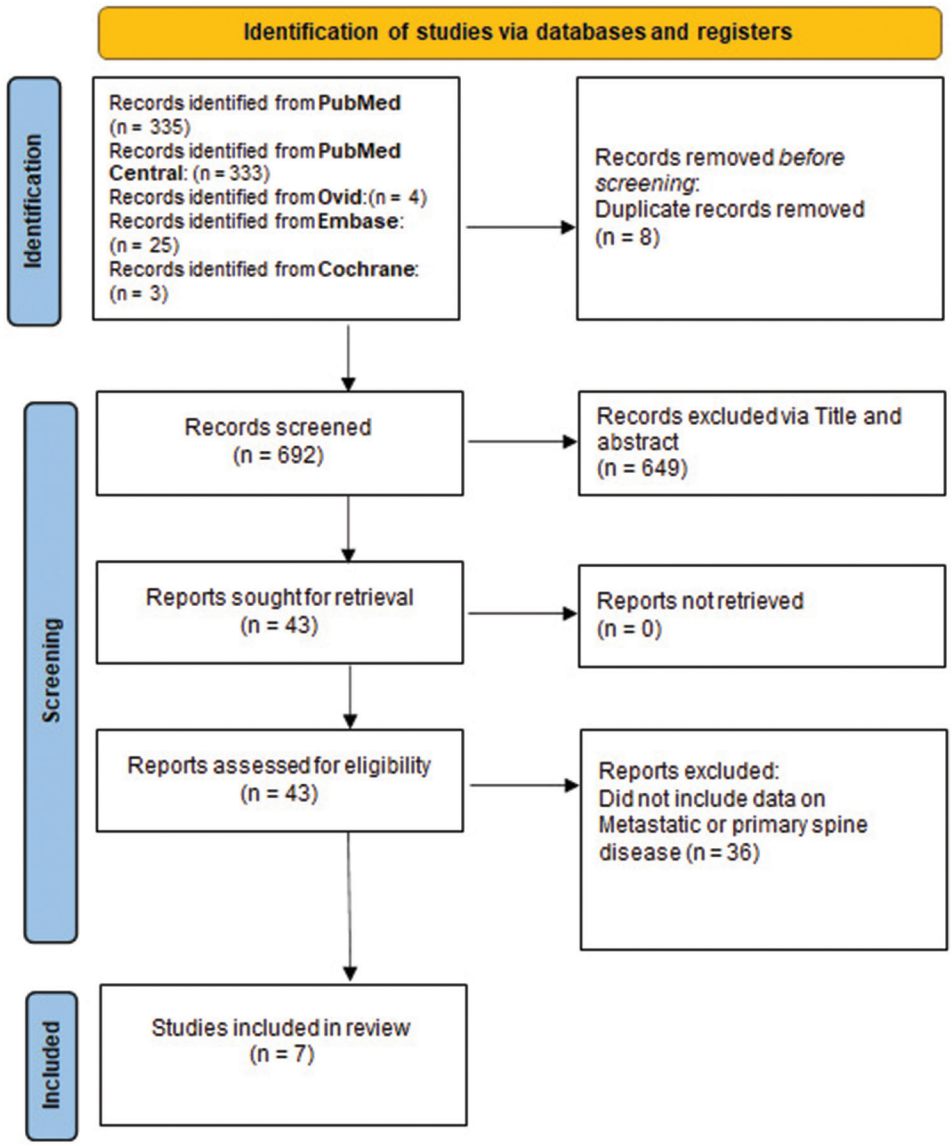

Figure 1: PRISMA flow diagram for database searches and selection process.

Table 1: Bias assessment of the selected articles.

Author	Study Design	Country	Level of Evidence	Jadad Score (for RCT)	New Castle Ottawa Score (observational/ nonrandomized)	NIH Quality Assessment Tool (Good, Fair or Poor)
Elwatidy *et al.* 2008	RCT	Saudi Arabia	I	5		
Yonezawa *et al.* 2020	Retrospective comparative	Japan	III		9	
Zhang *et al.* 2020	Retrospective comparative	China	III		7	
Bednar *et al.* 2006	Case -control	Canada	III		9	
Damade *et al.* 2019	Case series	France	III		8	
Kumar *et al.* 2016	Case series	Singapore	III			Good
Pennington *et al.* 2021	Case-control	USA	III		9	

performed. Data were presented as mean and standard deviation or median and interquartile range, if appropriate. For categorical variables, absolute values and percentages were used.

RESULTS

A total of 700 articles were found in the different databases. After selection by title and abstract, 43 articles were downloaded for full text review. Of these, 36 articles were removed given lack of data for spine oncology patients and seven articles[2,4,5,11,19,28,30] were included for our final analysis [Table 2]. From the selected paper, there were a total of 408 patients treated with antifibrinolytics agents and having tumors involving the spine. There were several types of oncological diagnosis treated, the most common was metastatic renal cancer with 32 patients, followed by metastatic breast cancer with 30. Additional diagnosis included sarcomas, prostate and lung cancer metastases, and myeloma among others [Table 2].

All studies used TXA as the antifibrinolytic of choice.

The studies reported that the use of TXA was done due to the high risk of intraoperative bleeding in these patients. All the studies reported that their patients' cohort who received TXA did not have coagulopathy before surgery measured by preoperatively blood coagulation analysis. Moreover, four studies[2,4,5,30] specifically mentioned in their methods that they excluded patients with coagulopathies and/or receiving anticoagulation.

TXA dosing and timing

Six out of the seven studies reported the dosage used. The TXA dose range was from 1 mg/kg to up to 20 mg/kg with 10 mg/kg being the most common. There were two methods for the timing of TXA administration within the different studies: (a) one dose bolus at the beginning and (b) bolus plus a maintenance infusion during surgery. Five out of the six studies that reported the dose performed a maintenance infusion of TXA throughout the surgery. One study[28] did bolus only administration: one bolus at the beginning and one at the end.

Intraoperative blood loss

All studies reported intraoperative blood loss [Table 3]. Median estimated blood loss (EBL) for patients receiving TXA in all the studies was 667 mL with a range of 253.3–1480 mL. The paper by Pennington *et al*.[19] was the one who reported the higher mean EBL in their series with 1480 mL. Of note, in their series, patients receiving TXA had more invasive surgeries. The second study with the highest EBL was the one by Bednar *et al*.[2] with a reported mean blood loss of 1385 mL. Zhang *et al*.[30] compared two groups of patients with spine tumors one receiving TXA and the other did not: the group receiving TXA the mean blood loss was 253.3 mL compared to 362.6 mL for those who did not receive TXA. Damade *et al*.[4] also compared TXA versus no TXA and found that the TXA group their EBL was 444 mL on average compared to 370 mL ($P = 0.85$). Bednar *et al*.[2] found that the group who did not received TXA had an EBL of 1815 mL compared to 1385 mL for the group who received TXA ($P = 0.5$).

Transfusion

Five studies reported the need and amount of blood transfusion [Table 3]. Only two studies reported the criteria for transfusion, and it was a hemoglobin level of <8 g/dL. Of the studies that reported transfusion rates during and after surgery, the highest rate was 59% of the patients in the study by Kumar *et al*.[11] followed by 57% in the study by Bednar *et al*.[2] The lowest amount of mean unit transfused per patients was 1.2 in the study by Damade *et al*.[4] and the highest reported (mean units) was 2.7 units by Pennington *et al*.[19] Elwatidy *et al*.[5] reported 80% less amount of blood transfused in the TXA group compared to the placebo group. In the study by Damade *et al*.,[4] the TXA group received on average 1.2 units of blood compared to 1.8 units on the non-TXA group ($P = 0.04$).

Postoperative blood loss

For this section, we compiled studies that reported postoperative blood loss in surgical drains. Three studies reporting the use of postoperative drains. The study by Zhang *et al*.[30] reported the lowest mean drainage amount in all the selected studies. After surgery for patients who received TXA with 84.3 mL. In addition, Damade *et al*.[4] reported the largest amount of drainage output for patients who received TXA with a mean of 568 mL. Elwatidy *et al*.[5] showed that for operative drains, patients who received TXA averaged 117.4 mL less compared to those who did not receive TXA (TXA patients mean 97.9 mL compared to 215.3 mL in those who did not receive). Similar findings were reported by Zhang *et al*.,[30] patients who received TXA averaged 84.3 mL of postoperative drainage compared to 140.6 mL for the group who did not receive TXA. In the study by Damade *et al*.,[4] they found that patients received TXA had an average of 63 mL less of postoperative blood loss compared to patients who did not receive TXA [Table 3].

Deep venous thrombosis (DVT)

Six out of the seven studies reported the incidence of DVT. Median combined DVT for the studies was 2.95%. In individual studies, fours studies reported 0 DVT events and the highest reported was by Pennington *et al*.[19] with an

Table 2: Characteristics of the seven included studies.

Article	Country	Study	Antifibrinolytic	*n*	Spine oncology diagnosis	Mean Age	BMI	Females	Procedure	Spine
Bednar *et al.* 2006	Canada	CC	TXA	14	2 Breast Ca, 2 Lung Ca, 2 Lymphoma, 2 myeloma, 2 GI tract, 1 Thyroid Ca, 1 osteosarcoma, 2 unknow	59 (29–82)	-	4	"6 patients anterior approaches, 1 had a combined anterior/ posterior procedure in 1 stage, and 7 underwent posterolateral decompression and anterior/ posterior column reconstruction through that approach."	T6 to L4
Elwatidy *et al.* 2008	Saudi Arabia	RCT	TXA	4	Not specified for TXA only	-	-	-	"Laminectomy and excision of spinal tumor"	-
Kumar *et al.* 2016	Singapore	CS	TXA	158	Not specified for TXA only	60±12.5	-	-	-	-
Damade *et al.* 2019	France	CS	TXA	36	14 breast Ca, 7 lung Ca, 4 prostate Ca, 4 other, 3 urinary Ca, 2 myeloma, 1 colorectal, 1 testicle Ca	61.9±14.7	24.3±4.3	18	"Segmental fixation was performed by pedicular screwing. Neurological decompression included laminectomy and arthrectomy or even pediculectomy if necessary."	41 Lesions thoracic, 10 lumbar
Yonezawa *et al.* 2020	Japan	CS	TXA	103	32 Kidney Ca, 12 Sarcomas, 14 Breast Ca, 10 Thyroid Ca, 8 Lung Ca, 3 Colon Ca, 3 Bladder Ca, 17 other organs in, 4 unknown primaries	Three cohorts: <50, 50–65 and >65	Group 1: 23.0±3.0 Group 2: 23.5±3.7 Group 3: 22.6±2.4	44	111 procedures in 103 patients "TES through the posterior approach in 85 patients, a TES through combined anterior and posterior approaches in 19, a hemivertebrectomy via the posterior approach in 2, a hemivertebrectomy through combined ant post in 4, and a corpectomy through the anterior approach in 2."	"Cervicothoracic spine in 4, thoracic and thoracolumbar spine in 80, and the lumbar in 28"
Zhang *et al.* 2020	China	CS	TXA	30	18 Nerve Sheath Tumors, 7 Meningiomas, 5 Ependymomas	43.1±20.6	-	17	Posterior midline approach, Laminoplasty open.	-
Pennington *et al.* 2021	USA	CC	TXA	63	Not specified for TXA only	55.2±15.7	27.5±7.3	31	-	-

Some studies did not reported individual patient data on the patients receiving TXA which is marked with a "-" in the table. CC: Case control, RCT: Randomized control trial, CS: Case series, TXA: Tranexamic acid, Ca: Cancer, TES: Total *en bloc* spondylectomy

Table 3: Main results for Timing of TXA, dosage, blood loss, transfusion, and postoperative drainage in the selected studies.

Article	Timing of TXA	Dosage	Mean EBL (range)	EBL for No TXA	Transfusion	Transfusion in No TXA	PostOperative Drain EBL	PostOperative Drain EBL no TXA
Bednar *et al.* 2006	Bolus at beginning then infusion throughout surgery	Bolus 1 gr, infusion 1 mg/kg/h during surgery	1385 mL (minimal-4000 mL)	1815 mL (400–5000 mL)	57% of the case 4 units each	-	-	-
Elwatidy *et al.* 2008	Bolus at beginning then infusion throughout surgery	Loading dose 2 g in 100 mL and a maintenance dose 1 g in 100 mL infusion at a rate of 100 mg/h	311.25±412.49 mL	584.69±797.30 mL	93.75±267.53 mL	531.25±1275.94 mL	97.94±136.28 mL	15.31±276.04 mL
Kumar *et al.* 2016	-	-	938±805 mL	743±508 mL	59% of the cases. 1.7±2.1 units	-	-	-
Damade *et al.* 2019	Anesthetic Induction then infusion for 8 h.	15 mg/kg	444±356 mL	370±419 mL	1.2±1.4 units	1.8±2.3 units	568±250 mL	631±299 mL
Yonezawa *et al.* 2020	Bolus × 2	1 gr initial, 1 gr at closure.	Group 1: <50 years: 500±291 mL. Group 2: 50–65 years: 583±852 mL. Group 3 >65 years: 751±732 mL	-	-	-	-	-
Zhang *et al.* 2020	Bolus at beginning then infusion throughout surgery	Loading dose of 10 mg/kg, maintenance dose of 1 mg/kg/h"	253.32±54.04 mL	362.57±62.31 mL	-	-	84.34±30.74 mL	140.65±34.35 mL
Pennington *et al.* 2021	Bolus at beginning then infusion throughout surgery	10-mg/kg bolus followed by 1–3 mg/kg/h continuous infusion	1480±1870 mL	920±1000 mL	2.7±4.1 units	-	-	-

Some studies did not reported individual patient data on the patients receiving TXA which is marked with a "-" in the table. The mean value is reported for Postoperative drain EBL. gr: Grams, mg: Milligrams, h: Hours, kg: Kilogram, mL: Milliliter, EBL: Estimates blood loss, TXA: Tranexamic acid

incidence of 7.9% in their series. Yonezawa *et al*.[28] found a higher incidence of DVT in patients younger than 50 (6.5%), compared to those between 50–65 (5.9%).

Pulmonary embolism (PE)

Six out of the seven studies reported the incidence of PE. Four studies reported an incidence of 0% while using TXA. The higher incidence of PE was reported by Pennington *et al*.[19] with 14.3% compared to 6.3% of patients who did not receive TXA. Interestingly, they also found that higher doses of TXA (>20 mg/kg) were associated with a higher incidence of PE. Yonezawa *et al*.[28] found that patients >65 years of age in their cohort were the ones with the higher incidence of PE (10%) compared to those younger than 50 years (6.5%).

DISCUSSION

Given the baseline frailty of cancer patients, adjuvants for intraoperative hemorrhage control while undergoing spine surgery are needed to avoid massive blood loss that may complicate their postoperative course. In addition, cancer patients tend to be anemic at baseline before surgery[2,19] which can further make all the measures to limit blood loss during surgery fundamental.

In this study, we found that patients who received TXA undergoing treatment for tumors in the spine (metastatic and primary) had diminished blood loss, diminished postoperative blood loss (from surgical drains), and less need for transfusions without major increase in venous thromboembolism events. Nonetheless, some individual studies showed no statistically significant difference in blood loss between TXA and non-TXA groups.

Antifibrinolytics agents have shown good results in spine deformity surgery, but they are less studied in spine oncology. Tsantes *et al*.[25] studied the use of TXA in musculoskeletal oncology undergoing orthopedic procedures and found a statistically significant difference in blood loss with less hemorrhage in patients who received TXA. The included studies in this review show benefit of TXA in selected cases. Despite this, some studies showed that patients receiving TXA had a higher mean EBL compared to those who did not receive. Pennington *et al*.[19] showed that the mean EBL for patients who received TXA was 1480 mL compared to 920 mL to those without. Although they do not describe each procedure in detail, they mentioned that patients receiving TXA had more invasive procedures compared to those who did not. Further, in their study, for patients who received TXA the mean duration of surgery was 426 min compared to 304 min for those who did not receive TXA.[19] This is likely a source of selection bias as patients who had bigger and longer surgery were the ones receiving TXA rather that every patient with spine tumors undergoing surgery receiving TXA.

On a broader perspective, the pooled median EBL for the included studies with TXA was 667 mL (range 252–1480 mL) when compared to surgeries such as minimally invasive tumor resection,[29] degenerative spine surgery in elderly patients,[1] our results are higher.[8] It is important to note that the studies included in this review have quite a range of surgical strategies from spondylectomy to laminoplasty. Nonetheless, the median EBL for the spine tumors patients in this review is comparable to publish data 1–2 level of open lumbar spine fusion.[8,14] However, the intra and postoperative impact of the same EBL in these two set of patients with different spine pathologies (frail cancer patients compared to elective patients with degenerative) is probably not comparable.

Although only seven studies were selected these included an overall sample of 408 patients, this is quite comparable with a meta-analysis by Li *et al*.[13] in 2013 that reviewed all randomized controlled trials for TXA in degenerative spine surgery and pooled together 411 patients.

Interestingly, our results showed a wide variety of spinal oncological diseases. Metastatic cancer was the most common diagnosis with renal carcinoma as the number one followed by breast cancer. Additional tumors included sarcomas, thyroid metastases, lung metastases, nerve sheath tumors, myeloma, and meningiomas which show the benefit of TXA in a variety of oncological spine disease treated surgically making our study quite unique in terms of the diversity of diagnosis. To the best of our knowledge, this is the first study to incorporate different oncological diagnosis and the use of TXA during spine surgery.

Only two studies reported preoperative embolization; Yonezawa *et al*. who presented the largest series of renal carcinoma metastasis performed embolization in all their patients[28] and Bednar *et al*. in one patient with thyroid cancer.[2] Given the lack of data, we elected to not include in the analysis but mentioned it here for clarity.

There was variety in the dosing and method of administering TXA in the different studies; the majority of the studies performed an initial bolus of TXA and continued an infusion throughout the surgery. As with the published literature for spine deformity, there is no clear agreement on the optimal dosing. A recent review and meta-analysis favored a lower dose of TXA (200–500 mg) compared to higher dose (1–3 g).[6] On the other hand, a recent article evaluating different regimes found that the lower doses (<20 mg/kg) had a statistically lower effectiveness for hemorrhage control compared to higher doses.[21] Given that TXA is used off label for spine surgery in general, additional studies should aim to find the optimal dosage as well as method (bolus vs. bolus and infusion) to achieve the best intraoperative hemostasis.

Our results showed that despite the administration of TXA, spine tumor patients do not appear to be at an unusual

increased risk of venous thromboembolism events, one of the major concerns of using these hemostatic agents. Several of the included studies reported 0% incidence of DVT/PE.[2,4,5,30] The study with the higher incidence was by Pennington *et al*.[19] with an incidence of 14.3% of PE. Interestingly, in a subgroup analysis they found that patients receiving a higher dose of TXA (>20 mg/kg) were at even higher risk that those receiving less than that. In general, cancer patients have 4–7 folds increase of VTE compared to the general population with 20–30% of DVTs diagnosed as part of an initial cancer diagnosis.[24] In a large database sample, Khorana *et al*.[10] found that in cancer patients the overall VTE rate was 5.7%. Further, they found that patients undergoing chemotherapy had higher incidence at 4.9% and certain cancers such as lung with 5.1% of VTE and as high as 8.1% for pancreatic cancer. Hence, compared to the results for DVT/PE in this series of patients undergoing spine surgery for spine tumors with the use of TXA the rates of DVT/PE are, if not lower than published data, comparable with the expected general incidence of patients with a cancer diagnosis.

There is a lack of randomized trials in spine oncology and use of antifibrinolytics agents. Despite our extensive database search only one RCT was found, and this study included a mix of degenerative and oncological patients, the rest of the studies were retrospective case series from individual hospitals. Ideally, a multi-center prospective randomized trial may help validate our findings. In particular, if there are any differences in terms of the spinal oncological diagnosis and the effectiveness of the antifibrinolytics agent. Our results suggest that there is probably no difference.

With the advancement of separation surgery[15] to treat some of these tumors and incorporation of minimally invasive techniques to address spine metastases,[17] TXA could also serve as an adjuvant to prevent large amount of hemorrhage in these frail patients who are commonly anemic even before surgery from their baseline cancer status.

Limitations

The study has several limitations. The majority of included studies are retrospective case series which renders our results of a low evidence given the available studies. The highest level of evidence in this series is a Level I for Elwaitidy *et al*.[5] study that is a Randomized trial that included mixed patients (degenerative patients were the majority with a handful of patients with oncological spine diseases). The rest of the studies have evidence of Level III. We only selected articles written in the English language which may have limited additional reach of the selection process. Importantly from a surgical perspective there were different surgical techniques (i.e., corpectomies and laminectomies) included which add heterogeneity to the results so they should be interpret with caution. Finally, TXA use in spine surgery remains off label which also may pose an inherent bias against publication. We suspect as TXA use among spine surgeons continues to increase given positive results in the scoliosis/degenerative literature further expansion into other subset of spine patients (i.e., oncology) will continue to occur.

CONCLUSION

The use of antifibrinolytics agents in surgery for spine tumors is not well studied. In this systematic review, we found that the use of TXA during surgery for spine tumors may diminish intraoperative blood loss, the need for transfusion and postoperative drainage from surgical drains without major increase in rates of DVT or PE. Additional randomized controlled multi-center studies are needed to further support these findings.

Author's Declaration

Portions of this work were presented as an Oral presentation at the 2022 AANS/CNS Spine summit in Las Vegas, NV.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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