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Research Article

Tranexamic Acid in Reducing Intraoperative Bleeding in Dogs Undergoing Thoracolumbar and Lumbar Hemilaminectomy and Intervertebral Disc Fenestration

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ABSTRACT

Hemilaminectomy associated with intervertebral disc fenestration (HF) is the most used spinal decompression surgical technique for the treatment of intervertebral disc extrusion (IVDE). The surgical procedure can be hampered by excessive bleeding from the venous sinuses; however, tranexamic acid intravenously (IV) is a possible adjunct to hemostasis in these patients. This study aimed to verify the effectiveness of tranexamic acid in reducing intraoperative bleeding in dogs with thoracolumbar and lumbar IVDE submitted to HF. Sixteen dogs with IVDE undergoing HF were included. These were distributed into a TXA group (tranexamic acid 20 mg/kg IV bolus, followed by 2 mg/kg/h IV continuous infusion) (n = 8) and a control group, with saline solution (n = 8). Blood loss was measured using the gravimetric method. The difficulty of operative visualization due to bleeding was classified by the surgeon. Median blood loss (%) in patients in the TXA group was lower than those in the control group (2.75 ± 1.23 and 4.99 ± 4.44, respectively) ($P = .028$). Intraoperative visualization difficulty due to bleeding occurred in 10 patients in the control group, and in no patients in the TXA group. A severe arterial thromboembolic complication was recorded, potentially due to tranexamic acid. The use of intraoperative tranexamic acid was effective in reducing bleeding and facilitating operative visualization in dogs with IVDE undergoing hemilaminectomy and intervertebral disc fenestration.

Introduction

Intervertebral disc disease has been the subject of intense research within veterinary neurology since the 19th century, being the most prevalent spinal cord disease in dogs.[1] Numerous articles have already been published regarding the pathogenesis, classification, diagnosis, and treatment of this disease. Hemilaminectomy associated with intervertebral disc fenestration (HF) is the most used surgical technique for the treatment of intervertebral disc extrusion (IVDE).[2]

In this procedure; blood vessels from the skin, subcutaneous tissue, and muscle layers are sectioned or ruptured to access the desired intervertebral space.[3,4] In addition, bone drilling and retrieving disc material from the vertebral canal with possible injury of the vertebral venous sinuses, and tissue dissection for fenestration are also sources of bleeding.[5] Several methods of surgical hemostasis in human and veterinary medicine have already been described.[6–10] All of these aim to minimize blood loss and thus facilitate intraoperative visualization, reduce anesthetic-surgical risk, and facilitate patient recovery.

Tranexamic acid is a synthetic antifibrinolytic drug, analogous to lysine. It works by preventing the binding of plasmin with fibrin, thereby stabilizing the clot and decreasing bleeding.[11] There is substantial evidence for the effectiveness of tranexamic acid in reducing intra and postoperative bleeding in human medicine, including elective procedures.[12–14] Lesser evidence suggests similar effects in veterinary medicine, but are not yet explored in neurosurgery.[15,16] Its use in the intraoperative period of spinal surgery in dogs has the potential to prevent bleeding that would otherwise occur, making it difficult to visualize the operative site, resulting in a greater number of iatrogenic

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injuries and surgical time.

Therefore, this study aims to verify the relationship between the administration of tranexamic acid with intraoperative hemorrhage and visualization, surgical times, and the occurrence of iatrogenic injuries and complications in dogs undergoing HF for treatment of thoracolumbar and lumbar IVDE. We hypothesize that the administration of tranexamic acid is safe and effective in reducing intraoperative hemorrhage and surgical time.

Material and Methods

Animals

This study was prospectively conducted at the Veterinary Neurology and Neurosurgery Service (SNNV) of the Universidade Federal de Santa Maria (UFSM - Brazil) between October 2020 and November 2021. The sample size decision was calculated using Lamorte's power calculator, establishing values of $P < .05$, power of 95%, and anticipated values of blood reduction of 45% in the treated group when compared to the control group.[17] This research was approved by the ethics committee in the use of animals of the institution under the number CEUA 5044020520.

Preoperative Management

All patients underwent physical and neurological examinations, followed by complete blood count, serum biochemistry, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Laboratory samples were processed through the UFSM Veterinary Clinical Laboratory. The patients had no underlying systemic disease as demonstrated by clinical and laboratorial exams. Only analgesic and nonsteroidal anti-inflammatory drugs were used prior to the presentation. The dogs underwent myelography (n = 15) (General Electric Radiography System, XR 6000) or magnetic resonance imaging (n = 1) (General Electric, Profile IV, 0.2T) for lesion location, evaluation, and surgical planning.

Anesthetic and Surgical Procedure

All patients were fasted prior to general anesthesia. Diazepam (0.5mg/kg, IV) and propofol (5mg/kg, IV) were used as preanesthetic medication and anesthetic inducer, respectively. After endotracheal intubation, intraoperative anesthesia was maintained using isoflurane in 100% oxygen, to effect. Intraoperative analgesia was maintained with a continuous rate infusion of fentanyl (10 µg/kg/hour, IV, preceded by a bolus of 2 µg/kg, IV). Sodium cephalothin (30 mg/kg IV every 2 hour) was used as a prophylactic antibiotic in all patients.

The patients started the intraoperative period with fluid therapy at a rate of 7ml/kg/hour. Heart rate (HR), respiratory rate (RR), esophageal temperature (ToE), mean arterial pressure (MAP), oxygen saturation, and partial pressure of carbon dioxide (pCO2) were constantly measured and recorded every 5 minutes. The operating room temperature was controlled between 22°C and 24°C. The patients were intraoperatively warmed with a mattress and thermal bags so that their body temperature was maintained between 37°C and 39°C. MAP was measured invasively through catheterization of the left femoral artery, with a 22G 25.4 mm catheter. Surgical exposure of the femoral artery was performed after endotracheal intubation, and the catheter was inserted using a modified Seldinger technique, secured by 2 isolated sutures in the skin. The arterial line was flushed with a dextrose 50% solution to prevent thrombus formation. Dorsolateral approach to the vertebral column was followed by hemilaminectomy[4] and intervertebral disc fenestration.[3] The time of the surgical procedure was measured in minutes, from the first incision to the last skin suture. The size of the incision was determined after extubation, in millimeters. HF were performed by 3 veterinarians with more than 5 years of experience in neurosurgery.

Intraoperative hemostasis was performed using compressive packing with compresses and gauzes (American Medical, Hérika hydrophilic gauze), in addition to bipolar cautery (EMAI Transmai, BP150S, 50W), instillation of refrigerated saline solution, and placement of a gelatin-based hemostatic sponge (Maquira, Hemospon) in the spinal canal.[18,19] The arterial line was removed before recovering the patient from anesthesia. A pressure bandage was placed over the puncture site for 10 minutes, and removed after visual inspection.

Group Distribution and Blood Loss Measurement

The dogs were distributed in 2 groups of equal number; TXA group (tranexamic acid) and control group. The random distribution of the patients was performed using a software available online (random.org). Neurosurgeons, surgical assistants, and anesthetists were blinded to the patient distribution. A separate clinician was in charge of preparing the treatments and placebos, handling them to the anesthesiology team. No attempt was made to balance groups with respect to surgeon or surgical site.

Dogs in the TXA group received a bolus of 20 mg/kg of tranexamic acid (Transamin, Zydus) (Fig 1A) diluted in saline solution (0.9% NaCl), intravenously (IV), 3 minutes before skin incision. Afterward, the dogs were coupled to an IV continuous infusion of tranexamic acid through an infusion pump (SDAMed®, 403 syringe pump), at a dosage of 2 mg/kg/hour, throughout the surgical procedure. The same methodology described for the TXA group was applied to the dogs in the control group, but with the use of saline solution (NaCl 0.9%) instead of tranexamic acid.

Blood loss was estimated according to the gravimetric method. Gauzes, compresses, surgical drapes (plastic and fabric), and surgical gowns used in the procedure were weighed before and immediately after surgery, on a precision scale (Bioscale BL-320AB-BI) (1 g of blood = 1 mL of blood),[20] in addition to the blood aspirated with saline solution (Fig 1). The saline solution used as flush during surgery was discounted after the weighting measurements. In the intraoperative period, gauze and compresses were stored in hermetically sealed containers until they were weighed at the end of the procedure[21] (Fig 1).

The animal's whole blood was estimated according to its weight (77.5 mL/kg)[22] and blood loss as a percentage of whole blood, according to the formula: percentage (%) of total blood loss = blood measured after surgery (mL) × 100 / 77.5 × patient weight (kg).

After the procedure, the surgeon was asked about: 1) the origin of the bleeding, which could be from: a) skin/subcutaneous, b) musculature, c) vertebral venous plexus, or d) diffuse bleeding; and 2) the difficulty of visualizing the operative site due to bleeding (yes/no).

Postoperative Assessment and Management

After the surgical procedure, the dogs remained hospitalized for 72 hours, receiving analgesia with 0.3 mg/kg methadone (intramuscular route, q4 hour, for 24 hours), associated with 25 mg/kg dipyrone (subcutaneously, q8 hour, for 72 hours), and meloxicam 0.1 mg/kg (subcutaneously, q24 hour, also for 72 hours). Adverse effects such as vomiting, diarrhea, nausea, sedation, suture dehiscence, seroma, drainage of fluid from the surgical wound, and thromboembolic complications were monitored and recorded. New blood samples (2mL) for complete blood count and serum biochemistry were performed 24 hours after surgery.

Statistical Analysis

The data obtained were submitted to the Shapiro-Wilk test to assess normality. Parametric data were described as mean ± standard deviation, while data that was not normally distributed were described as median ± standard deviation. The Mann-Whitney U test was used to compare the nonparametric variables between groups, while the

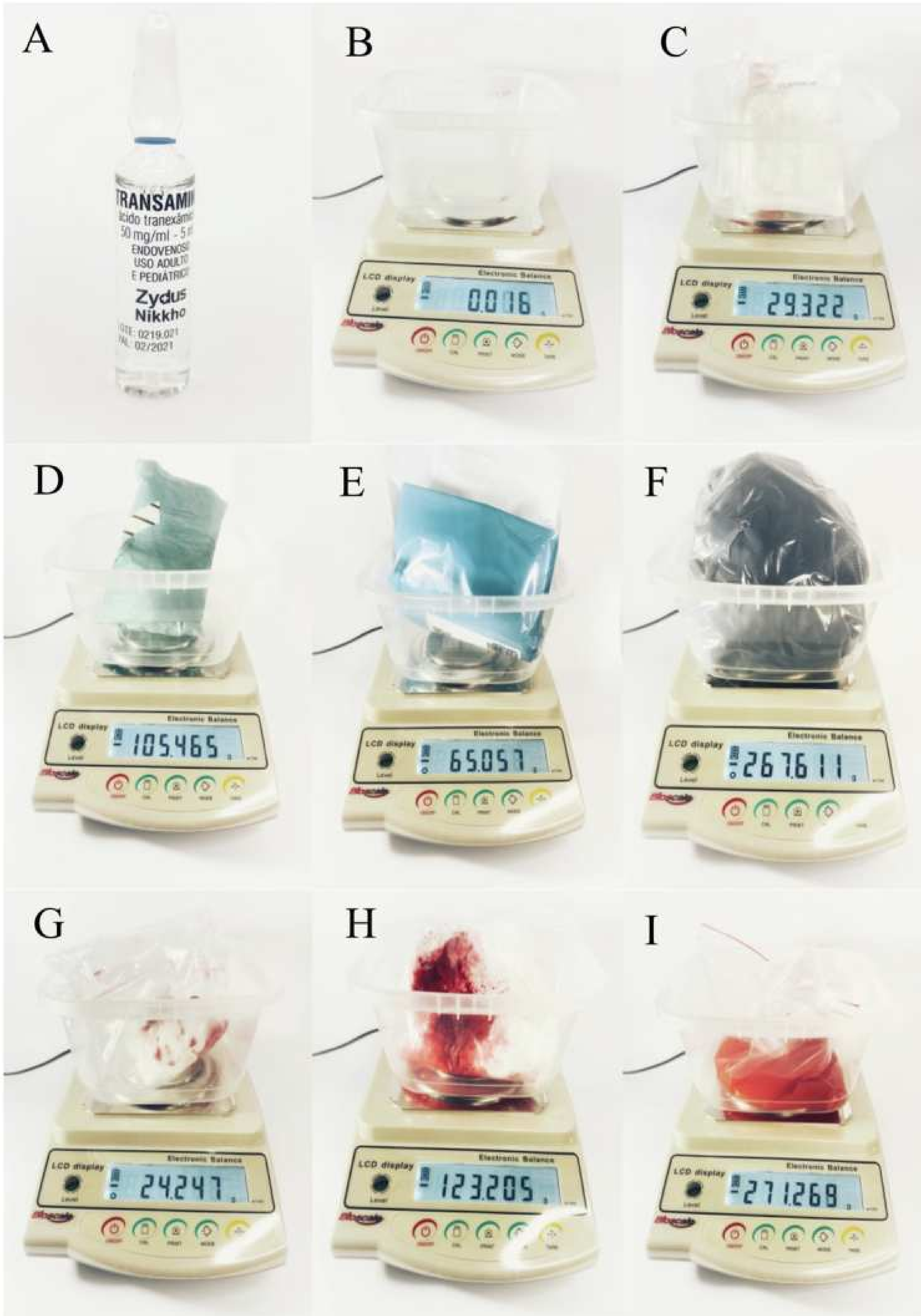

Fig 1. Tranexamic acid and gravimetric weighing method to measure intraoperative blood loss. (A), Tranexamic acid in the formulation for intravenous use (Transamin®, Zydus). (B), Precision weighing scale (Bioscale, BL-320AB-BI). (C), Weighing of gauze in its original packaging, before the surgical procedure. (D), Weighing of sterile compresses, before the surgical procedure. (E), Weighing of sterile plastic drapes, before the surgical procedure. (F), Weighing of surgical gown, after the surgical procedure. (G), Weighing of gauzes soaked in blood, after the surgical procedure. (H), Weighing of compresses soaked in blood, after the surgical procedure. (I), Weighing of fluid aspirated during surgery.

Student's t test was used to compare the parametric variables. To assess T°E, HR, and MAP between groups throughout the procedure, the Friedman test was used. Spearman's test was used to correlate data between blood loss and procedure time, incision size, PT, aPTT, and platelets. The statistical programs used were Jamovi version 1.6.23 and GraphPad Prism (version 5.01). Statistical significance was set at $P < .05$.

Results

Sixteen dogs with a median weight of 7.7 ± 5.31 kg and a median age of 5 ± 3.65 years were included. Of these, 9 were females (6 spayed, 3 intact) and 7 were males (5 neutered, 2 intact). None of the females included were in estrus. The breeds involved were mixed breed (n = 6), Dachshund (n = 4), Lhasa apso (n = 2), German Spitz (n = 2), French Bulldog (n = 1), and Shih-tzu (n = 1). The most prevalent intervertebral space was T12-T13 (n = 7), followed by T11-T12 (n = 3), L1-L2 and L4-L5 (n = 2 each), L2-L3 and T13-L1 (n = 1 each) (Table 1).

Table 1
Distribution of Affected Intervertebral Discs According to Group (TXA and Control)

Affected Intervertebral Disc	TXA Group	Control Group
T11-T12 (n = 3)	n = 2	n = 1
T12-T13 (n = 7)	n = 3	n = 4
T13-L1 (n = 1)	n = 1	—
L1-L2 (n = 2)	N = 1	n = 1
L2-L3 (n = 1)	—	n = 1
L4-L5 (n = 2)	n = 1	n = 1

The 16 dogs were divided into a TXA group (n = 8) and a control group (n = 8). The animals in the TXA group had a lower blood loss (%) than those in the control group (2.75 ± 1.23 and 4.99 ± 4.44, respectively) (P = .028) (Fig 2). There was no difference between groups regarding age, weight, sex, procedure time, and incision size (P = .490, .636, 1.0, .663, .916, respectively) (Fig 2) (Table 2). The platelet count, hematocrit, and hemoglobin values before and after surgery (24 hours), in addition to PT and aPTT, showed no difference between groups and between serial assessments (P = .443-.953) (Table 2). No patient presented platelet count or PT and aPTT values outside the reference values.[23,24]

The intraoperative values of MAP, T°E, and HR showed no difference between groups (P = .758, .196, .769, respectively). Animals in the control group presented greater difficulty for the surgeon to visualize the operative site (n = 5/8) than those in the TXA group (n = 0/8) (P = .001) (Fig 2) (Table 2). In the TXA group, 3 patients had a greater origin of

Table 2
Comparison Between the TXA Group and the Control Group Regarding the Profile of the Animals and Data Collected in the Perioperative Period

Variable	TXA Group	Control Group	*P* Value
Age (years)	5 ± 3.24	5.5 ± 4.10	.490
Weight (kg)	7.7 ± 4.61	8.3 ± 6.16	.636
Female (n)	5	4	1
Male (n)	3	4	1
Blood loss (%)	2.75 ± 1.23*	4.99 ± 4.44*	.028
Procedure time (min)	103.5 ± 16.36	107 ± 21.44	.663
Incision size (mm)	106.5 ± 13.13	107.5 ± 22.51	.916
Intraoperative difficulty (%)	0*	62.5*	.011
Preoperative hematocrit (%)	53.2 ± 8.82	51.25 ± 6.69	.902
Postoperative hematocrit (%)	38.5 ± 9.27	41.5± 10.57	.885
Preoperative hemoglobin (g/dL)	18.2 ± 2.89	18.2 ± 2.99	.608
Postoperative hemoglobin (g/dL)	14 ± 3.31	16.5 ± 3.36	.801
Platelets (10^3, µl)	327 ± 40.41	287 ± 36.23	.068
PT (sec)	8.26 ± 1.66	6.94 ± 1.75	.902
aPTT (sec)	13.25 ± 1.52	12 ± 2.3	.398

TXA = tranexamic acid; PT = Prothrombin time; aPTT = Activated partial thromboplastin time.
* Represents difference between groups in the same variable.

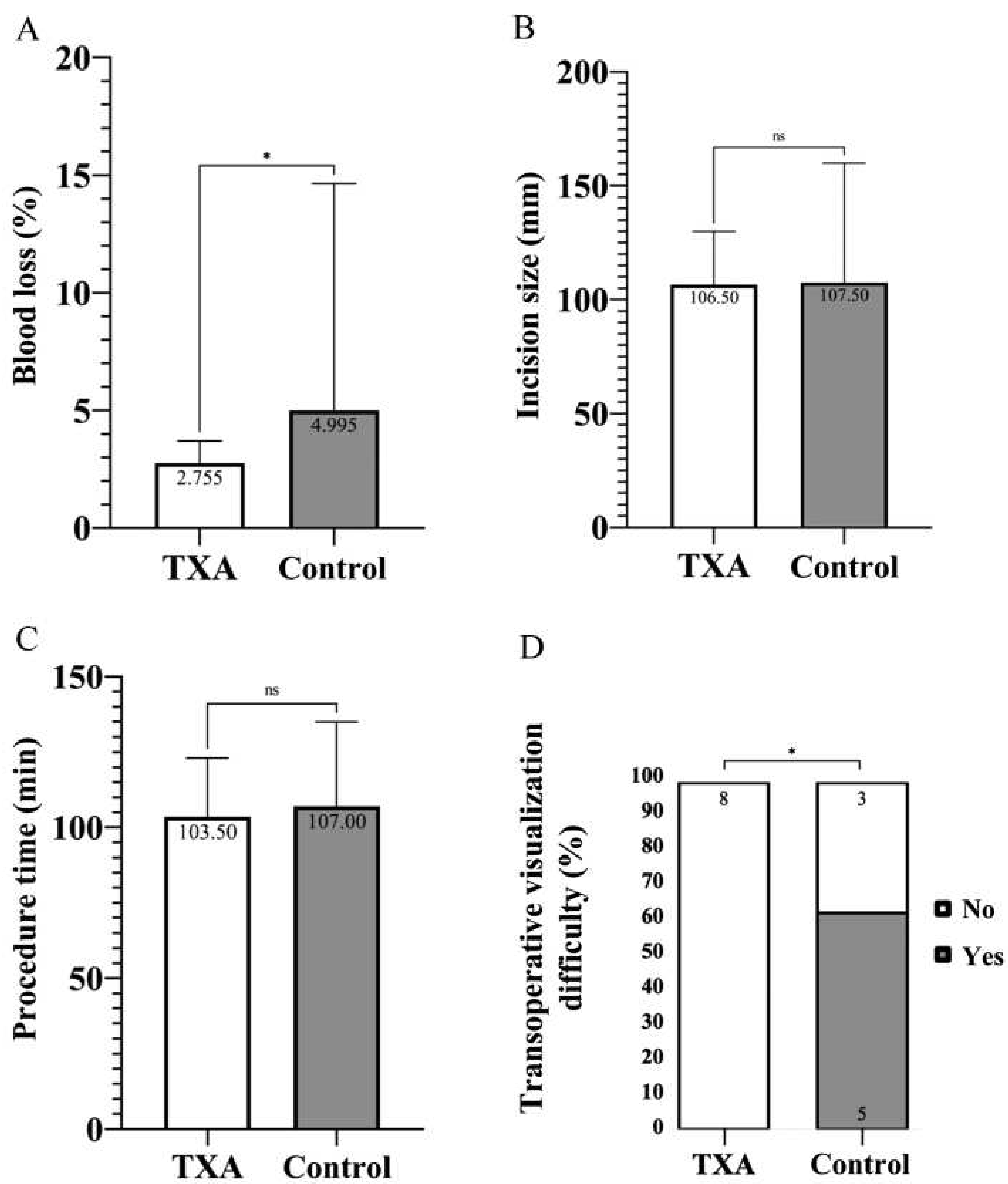

Fig 2. Comparison graph between TXA and Control Groups concerning blood loss (A), incision size (B), procedure time (C), and intraoperative visualization difficulty due to bleeding (D). *Represents difference between groups (<0.05). ns=no difference between groups.

bleeding from the vertebral venous plexus, 3 from the skin/subcutaneous, and 2 from the musculature. In the control group, 4 had diffuse bleeding, 2 from the vertebral venous plexus, and 2 from the musculature. There was no difference between bleeding sites and groups or between bleeding site and intraoperative visualization difficulty ($P = .06$ and .438, respectively).

One dog in the control group had diarrhea (1 episode) in the immediate postoperative period. One patient in the TXA group developed an arterial thromboembolic event. After 24 hours of the procedure, this dog presented pain on manipulation of the left pelvic limb, below the distal portion of the tibia. Vascular Doppler was used and there was no pulse below this region, irrigated by the caudal and cranial branches of the saphenous vein and the distal portion of the cranial tibial artery. After 72 hours of clinical treatment with heparin 200 IU/kg (subcutaneously, 8/8 hours) and acetylsalicylic acid 0.5 mg/kg (orally, 24/24 hours), the absence of arterial pulse persisted, and the animal was referred for partial limb amputation and prosthesis placement.

Discussion

Tranexamic acid is widely used in human medicine to reduce intra and postoperative bleeding, but little is explored in veterinary medicine. Our study indicated a reduction in intraoperative bleeding of 44.88% in the TXA group when compared to the control group ($P = .028$). This reduction was also evidenced when the difficulty of visualizing the surgical site by the surgeon was evaluated, being pointed out in 62.5% of the dogs in the control group and in none of those that received tranexamic acid ($P = .001$).

It is believed that even minor bleeding can make it difficult to perform surgical procedures on the spine, due to limited access space to the nervous tissue, which often does not support conventional hemostasis methods such as electrocautery, clamping, or compressive packing with gauze.[7]

Both the blood loss values found in the TXA and control groups did not offer any risk in the trans and postoperative periods. Studies on blood volume indicate that only losses greater than about 9% and 18% begin to change anesthetic parameters, such as stroke volume and cardiac output, and that losses greater than 36-41% of total blood volume would lead to serious implications, such as falls of MAP and death.[25,26] Other studies have reported hemorrhage in patients undergoing spinal procedures, based solely on the surgeon's opinion.[27] In our study, the gravimetric (objective) method, associated with the surgeon's opinion (subjective) was used,[21,27,28] making it possible to associate numerical values (%) to the difficulty of surgical visualization due to intraoperative bleeding.

The tranexamic acid dose used in this study (20mg/kg IV bolus followed by 2mg/kg/hour IV continuous infusion) is within the range used in spinal cord surgery in humans and experimentally in dogs.[16,29,30] The dosage and route of administration used were effective in reducing intraoperative bleeding in hemilaminectomy and disc fenestration. On the other hand, a group of researchers did not find a decrease in blood loss when using tranexamic acid in the intraoperative period of orthopedic surgeries in dogs at a dose of 10 mg/kg IV (bolus) and 1mg/kg/h IV (continuous infusion).[31] The difference between the result of our work and theirs may fall on the dosage of the drug or the surgical approach to the stifle compared to the approach to the vertebral column and spinal cord. The tibial plateau leveling osteotomy technique does not require extensive muscle dissection, and sinus bleeding is not a concern. Therefore, further studies are needed to determine the ideal dose, route, or method for the administration of tranexamic acid in dogs (single/multiple boluses and/or continuous infusion), and to which techniques it would be valuable. Even though the dose and route of administration may influence the efficacy of tranexamic acid, the hyperfibrinolytic characteristic in certain dogs is another factor, suggesting that higher doses than those used in humans are needed to efficiently prevent fibrinolysis and consequent reduction of blood loss.[15]

One animal in the TXA group suffered with an arterial thromboembolic event that culminated in the partial amputation of its pelvic limb, which is a devastating complication. Arterial thromboembolisms occur when there is an ischemic injury due to an intravascular aggregate of fibrin and platelets, which is transferred from its place of origin to other sites in the body.[32] Some human studies have already correlated the use of tranexamic acid with the occurrence of aortic or venous thromboembolism.[33,34] However, more abundant evidence indicates that there are no greater thromboembolic morbidities with the use of tranexamic acid compared to those who did not receive the medication.[29,30,35–38] In the veterinary literature, tranexamic acid has already been used to prevent the dissolution of thrombi or emboli in dogs as experimental models for the study of chronic pulmonary thromboembolism.[39] Despite this, there are no reports of arterial or venous thromboembolic complications from the use of tranexamic acid in this species, only conjectures.[40] The most reported complications in dogs are vomiting, nausea, and epileptic seizures.[16,41]

We speculate that the arterial thromboembolic event of the dog in this study was caused or facilitated by the tranexamic acid administration. In a human medicine report, a patient who received intraoperative tranexamic acid developed distal ulnar arterial thrombosis.[42] Similar to the dog in this study, the thrombus developed in the same location as the arterial access used for anesthetic monitoring, which could infer a relationship between the in situ complication and the arterial access. Studies with a greater number of animals using tranexamic acid as an intraoperative antifibrinolytic drug are suggested to verify the prevalence of this complication, which would be determinant on its clinical use.

Limitations of this study include the sample size, which was calculated to compare blood loss reduction between groups. A larger multicentric study would be needed to assess the prevalence of complications associated with tranexamic acid treatment as well as to determine whether reduced blood loss identified is associated with decreased surgical times and/or incision length. The absence of more advanced tests to check for coagulopathies is another limitation. In addition to platelet, PT, and aPTT tests, thromboelastography, and thromboelastometry viscoelastic tests could endorse the coagulation profile of the dogs included here. However, these tests are not available at our institution. We chose not to use the mucosal bleeding time test due to its limitations, such as being influenced by hematocrit, blood viscosity, mucosal thickness and temperature, age, sex, and inter and intraoperator variability.[43]

This clinical study is relevant because: 1) lends evidence for intraoperative blood loss reduction and improved surgical visualization with the administration of tranexamic acid in dogs undergoing HF, despite similar surgical times between groups; 2) determines blood loss estimates for HF surgery in dogs, and 3) demonstrates the feasibility of the gravimetric method in measuring blood loss in dogs undergoing HF.

Conclusion

This study demonstrates that tranexamic acid was effective in reducing transoperative bleeding and in improving surgical site visualization in dogs undergoing hemilaminectomy and intervertebral disc fenestration in the thoracolumbar and lumbar regions. However, its administration did not influence surgical times and an arterial thromboembolic event was reported in 1 dog.

Declaration of Competing Interest

None.

Author Contributions

Dênis Antonio Ferrarin: Conceptualization, investigation, execution, data curation, writing - original draft; Marcelo Luís Schwab:

Conceptualization, visualization, resources, data acquisition; Mathias Reginatto Wrzesinski: Resources, data acquisition; Júlia da Silva Rauber: Resources, data acquisition; Julya Nathalya Felix Chaves: Resources; Angel Ripplinger: Resources, data acquisition; Alexandre Mazzanti: Supervision, execution, writing - review & editing.

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