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RETROSPECTIVE STUDY

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Retrospective analysis of the use of tranexamic acid in critically ill dogs and cats (2018–2019): 266 dogs and 28 cats

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Abstract

Objective: To describe the signalment, dosing, adverse events, and patient diagnosis for dogs and cats admitted to the critical care unit (CCU) receiving tranexamic acid (TXA).

Design: Case series from 2018 to 2019.

Setting: Private referral and primary care veterinary hospital.

Animals: Two hundred and sixty-six dogs and 28 cats.

Interventions: None.

Measurements and Main Results: Records of dogs and cats admitted to the CCU that received TXA were evaluated. A diagnosis was assigned to each patient based on the International Statistical Classification of Diseases system. "Neoplasia" ([most frequently] hemangiosarcoma) (89/226 [39%]) and "diseases of the blood and blood forming organs" (idiopathic hemoabdomen, pericardial effusion) (78/226 [34%]) were the most common disease processes for which dogs received TXA. In cats, "diseases of the blood and blood forming organs" (idiopathic hemoabdomen) (9/28 [32%]), "neoplasia" (hemangiosarcoma, mast cell tumor, carcinoma) (7/28 [25%]), and "injury, poisoning, or certain other consequences of external causes" (high-rise syndrome) (5/28 [17%]) were most common. One hundred and forty-eight dogs (65%) and 13 cats (46%) underwent an invasive procedure during hospitalization. Thirty percent (70/226) of dogs received a packed RBC (pRBC) transfusion. Administration of TXA before or after pRBC transfusion did not significantly affect median dose of pRBC administered ($P = 0.808$). The median IV dose of TXA was similar for dogs and cats at 10 mg/kg. One cat received a 10 times overdose of TXA and did not suffer any appreciable adverse effects. Adverse events were reported in 1.7% (4/226) of dogs including hypersalivation (3/226) and seizure (1/226) in a dog that received a cumulative dose of 280 mg/kg of TXA. Hypersalivation was the only adverse event reported in 3% (1/28) of cats.

Abbreviations: A10, A20, amplitude at 10 minutes, 20 minutes; APPLE, Acute Patient Physiologic and Laboratory Evaluation; CCU, critical care unit; CFT, clot formation time; CRI, constant rate infusion; CT, clotting time; IQR, interquartile range; LI30, LI45, lysis index; MCF, maximal clot formation; pRBC, packed red blood cell; TXA, tranexamic acid; VCT, viscoelastic coagulation test.

Conclusion: TXA is primarily utilized in critically ill dogs and cats diagnosed with neoplasia, bleeding disorders, and trauma at this institution. Adverse events were infrequent and largely mild.

KEYWORDS
anemia, antifibrinolytics, coagulopathy, fibrinolysis, neoplasia

1 | INTRODUCTION

In critical illness and injury, anemia results from 2 fundamental processes: a shortened RBC circulatory life span and diminished RBC production. Causes of shortened life span include hemolysis, phlebotomy losses, oozing at injury sites, hemorrhage associated with invasive procedures, and gastrointestinal bleeding.[1] Anemia in critical illness has traditionally been treated with RBC transfusions. In people, more than one third of all ICU patients receive transfusions, increasing to 70% when the ICU stay exceeds 1 week.[2–4]

Studies in people have documented an association between increased blood product administration and the risk of mortality in critically ill patients, independent of illness severity, leading to more restrictive transfusion practices in human and veterinary medicine.[5,6] In an attempt to reduce hemorrhage, epsilon aminocaproic acid, a lysine analog that inhibits the conversion of plasminogen to plasmin thereby stabilizing existing clots, has been administered to human and veterinary patients with apparent successes.[7,8] Similar in mechanism of action to epsilon aminocaproic acid, but approximately 10 times as potent, tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis.[9]

Hyperfibrinolysis is the rapid dissolution of hemostatic fibrin resulting in excessive or recurrent bleeding, which can lead to increased hemorrhage and morbidity, and may be fatal.[10] There is strong evidence that dogs are more hyperfibrinolytic compared to people, suggesting that antifibrinolytic agents may be particularly beneficial in this species.[9,11] Current antifibrinolytic therapy in veterinary medicine is largely extrapolated from human medicine.[12] In people, TXA is commonly used in acute trauma and in an attempt to reduce blood loss in perioperative situations.[13,14]

There are limited reports of adverse events associated with the administration of TXA in people; however, there remains controversy regarding potential increased risk of thromboembolic complications, therefore current recommendations include its cautious and selective use.[13] Currently, published reports regarding the use of TXA in veterinary medicine are primarily limited to healthy adult dogs and only 1 study evaluating the use of TXA in dogs with bleeding disorders.[9,15,16] To date, there are no studies assessing the efficacy of TXA in critically ill dogs and cats.

The primary objective of this study was to characterize the population of animals being prescribed and administered TXA in 1 large urban private referral and primary care veterinary hospital. The secondary objective of this study was to evaluate the adverse events associated with the administration of TXA in critically ill dogs and cats. Our hypotheses were as follows: (1) TXA is well tolerated in critically ill patients; (2) TXA will reduce packed red blood cell (pRBC) requirements; and (3) those patients that receive TXA sooner in their hospitalization will have improved outcomes.

2 | MATERIAL AND METHODS

2.1 | Criteria for selection of cases

The electronic medical record database of a large, urban emergency and referral center was searched to identify dogs and cats admitted to the critical care unit (CCU) and administered TXA[a] between June 2018 and December 2019. TXA was readily available at the study institution for the first time in June 2018, thus this was the chosen starting date for this study. The following keywords were used in the search criteria to identify cases: "tranexamic" acid and "TXA." To be included, a dog or cat must have been charged for at least 1 unit of CCU hospitalization (12 h) to be considered critically ill, and must have received TXA by any route (IV or PO). Excluded were animals with incomplete medical records, duplicate records present for the same patient, and an inability to verify TXA administration based on review of the inpatient treatment sheet. During this time frame, 317 cases were identified involving 277 dogs and 39 cats. Of these cases, 62 were excluded due to the presence of duplicate records, inability to verify TXA administration, and lack of admission to the CCU. A total of 255 cases, involving 226 dogs and 28 cats, were included in the statistical analysis.

Complete medical records were reviewed for signalment, service the animal presented to (emergency, internal medicine, dentistry, cardiology, oncology, ophthalmology, general medicine, surgery), route of TXA administration (IV or PO), dose of TXA administered (mg/kg), total number of doses of TXA administered, whether TXA was administered as a bolus dose or constant rate infusion (CRI), whether an invasive procedure was performed, if TXA was administered pre-, intra-, or postoperatively, whether a pRBC transfusion was administered, dose of pRBC transfused (ml/kg), adverse effects associated with administration of TXA (during or immediately after administration) as reported by the nursing staff or doctor in charge, and whether viscoelastic coagulation testing (VCT)[b] was performed pre- or post-TXA administration. Data were recorded in a commercially available spreadsheet program.[c] It is important to note that at this institution the dose of TXA administered to animals was at the clinicians' discretion, although

largely influenced by the institutions' recommendation to dose dogs at 10 mg/kg IV every 6 hours. This dosing protocol was based on experimental studies previously performed in dogs given higher doses at 20 mg/kg that may be more effective at inhibiting fibrinolysis; however, the 10 mg/kg dose was chosen to avoid emesis.[15] This dosing protocol was later extrapolated for use in cats.

VCT parameters analyzed included clotting time (CT), clot formation time (CFT), alpha angle, amplitude at 10 (A10) and 20 (A20) minutes, maximal clot formation (MCF), and lysis index at 30 (LI30) and 45 (LI45) minutes. Briefly, CT is the time from the beginning of the test until the time when the amplitude of 1% is achieved; CFT is the time between the 1% and 10% amplitude of the clotting signal; alpha angle is the angle between the time axis and the tangent to the clotting curve through the 1% amplitude point—it describes the kinetics of clotting; MCF measures the firmness of the clot and therefore the clot quality—it is the maximum amplitude that is reached before the clot is dissolved by fibrinolysis and the clot firmness falls again; A10 and A20 represent clot firmness and are the A10 and A20 after CT; and LI30 and LI45 are the amplitude of the clot at 30 and 45 minutes after CT, as a percentage of the MCF, representing clot dissolution via fibrinolysis with a reduced LI30 and LI45 indicative of hyperfibrinolysis.[17]

Additionally, Acute Patient Physiologic and Laboratory Evaluation (APPLE) fast scores were calculated based on available glucose, albumin, lactate, platelet count, and mentation score, obtained within the first 24 hours of admission. Mentation scores were based on intake assessment, whereas the most abnormal value identified over the 24-hour period following admission was utilized for the remaining parameters. A score of 0–14 was then assigned to each parameter and a score was calculated based on the sum of these values.[18]

The 2019 definition, outlined by Cousins et al, of an invasive procedure was utilized for this study. This definition states that an invasive procedure is a "purposeful/deliberate access to the body, gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. Invasive procedures are performed by trained healthcare professionals using instruments, which include but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes."[19]

A diagnosis was assigned to each patient based on the International Classification of Diseases system. Akin to previous veterinary studies, this disease classification system was applied in this study to facilitate comparisons between investigations.[20–22] The International Classification of Diseases title, "injury, poisoning, or certain other consequences of external causes," was simplified to "diseases of external causes" for clarity in reporting results.

2.2 | Statistical methods

Data were analyzed for normality with the Shapiro–Wilk test. For parametric data, the mean ± SD were reported, while for nonparametric data, median and interquartile range (IQR) were reported. However, despite the nonparametric data available for age, the data range is reported to provide a better description of the patient population presented in this case series. A Spearman rank order correlation test was performed to assess for associations between APPLE fast scores, number of TXA doses administered, and dose of pRBC administered to dogs and cats. A Mann–Whitney *U* test was performed to analyze the following comparisons; to compare dose of pRBC administered to dogs and cats when TXA was administered preoperatively compared to postoperatively; to compare dosing parameters of TXA (dose of TXA, number of doses of TXA, and time to TXA administration) in survivors and nonsurvivors; to compare APPLE fast scores between survivors and nonsurvivors; and to compare length of hospitalization between survivors and nonsurvivors. All analyses were performed using 2 online statistical software packages.[d,e]

3 | RESULTS

A total of 226 dogs and 28 cats were included in the statistical analysis. Of the 226 dogs, 109 (48%) were male neutered, 19 (8%) were male intact, 92 (40%) were neutered females, and 6 (2%) were female intact. The median age was 10 years (range: 8 months to 17 years). Sixty-two different dog breeds were represented; however, the most common presentation was a mixed breed dog (53/226 [23.4%]), followed by Golden Retriever (17/226 [7.5%]), Labrador Retriever (17/226 [7.5%]), German Shepherd (11/226 [4.8%]), American Staffordshire Terrier (9/226 [3.9%]), Boxer (7/226 [3%]), Greyhound (6/226 [2.6%]), Boston Terrier (5/226 [2.2%]), and Bernese Mountain Dog (5/226 [2.2%]). The remaining 43% were represented by 54 different dog breeds, with less than 5 representatives, 30 of which occurred once. Dogs were most commonly presented to the emergency service (201/226 [88%]), followed by internal medicine (15/226 [6.6%]), dentistry (2/226 [0.8%]), oncology (2/226 [0.8%]), surgery (2/226 [0.8%]), cardiology (1/226 [0.4%]), general medicine (1/226 [0.4%]), neurology (1/226 [0.4%]), and ophthalmology (1/226 [0.4%]).

TXA was most commonly administered to dogs diagnosed with "neoplasia," "diseases of the blood and blood forming organs," and "diseases of external causes" (Table 1). More than half (62.9%) of the dogs diagnosed with "neoplasia" were either definitively diagnosed with hemangiosarcoma based on histopathology or were presumptively diagnosed based on location and clinical signs such as pericardial effusion with an echocardiographically identified right atrial mass. Of those assigned to the "diseases of the blood and blood forming organs" classification, 39.7% (31/78) were treated for a hemoabdomen of benign or curable etiology and 14.1% (11/78) for pericardial effusion in which no mass was identified or an idiopathic process was prioritized. For the 7.9% (18/226) of dogs that were classified under "diseases of external causes," 66.6% (12/18) suffered from vehicular trauma.

One hundred and forty-eight dogs (65%) underwent an invasive procedure during hospitalization. The most common procedure performed in dogs was splenectomy (28/148 [18.9%]), followed by pericardiocentesis (24/148 [16%]), combined splenectomy and partial hepatectomy (21/148 [14%]), and partial hepatectomy (7/148 [4.7%]). The remaining 46.4% were represented by 46 different procedures ranging from

TABLE 1 Canine ICD classification summary with examples of underlying diagnosis ($n = 226$)

ICD classification	n/N	%	Diagnosis	n/N
2: Neoplasia	89/226	39.3%	Hemangiosarcoma	56/89
3: Disease of the blood and blood forming organs	78/226	34.5%	Hemoabdomen	31/78
			Pericardial effusion	11/78
4: Endocrine, nutritional and metabolic disorders	3/226	1.3%	Chronic hepatitis	1/3
			Diabetic ketoacidosis	1/3
			Hepatic encephalopathy	1/3
6: Disease of the nervous system	2/226	0.8%	Intervertebral disc disease	1/2
			Left forebrain lesion	1/2
9: Diseases of the circulatory system	1/226	0.4%	Pulmonary hypertension	1/1
10: Diseases of the respiratory system	9/226	3.9%	Epistaxis	5/9
			Rhinitis	3/9
			Upper airway obstruction	1/9
11: Disease of the digestive system	2/226	0.8%	Inflammatory bowel disease	2/9
12: Diseases of the skin and subcutaneous tissue	1/226	0.4%	Incision dehiscence	1/9
14: Diseases of the genitourinary system	9/226	3.9%	Vaginal hemorrhage	2/9
			Ovariohysterectomy complication	2/9
			Urosepsis	1/9
			Ureterolith	1/9
			Closed pyometra	1/9
			Neuter complication	1/9
			Interductal papilloma	1/9
19: Trauma	18/226	7.9%	Hit by car	12/18
			Traumatic hemoabdomen	2/18
			Attacked by dog	2/28
			Snake envenomation	1/18
			Radius ulna fracture	1/18

Abbreviations: ICD, International Classification of Diseases; TXA, tranexamic acid.

aspiration of an intraabdominal or intrathoracic structure, endoscopy, fracture repair, hemilaminectomy, enucleation, and abdominal, thoracic, or oral surgery. Sixty-two percent (92/148) of dogs received TXA preoperatively, 6.7% (10/148) received TXA intraoperatively, and 37.8% (46/148) received TXA postoperatively. Of the Greyhounds (6/226 [2.6%]), all received TXA pre- or intraoperatively.

Thirty percent (70/226) of dogs received a pRBC transfusion (median dose 10.8 ml/kg [IQR 5.5]). Median dose transfused to the 26 and 44 dogs that received TXA pre- and post-pRBC transfusion were 10.75 ml/kg (IQR 5.69) and 11.1 ml/kg (IQR 5.41), respectively. Median dose of pRBC administered was not significantly different between TXA administration before or after transfusion ($P = 0.808$).

APPLE fast scores were calculable for 50% (114/226) of dogs, mean score was 23.6 ± 7.3. There were 45 dogs that had both a calculated APPLE fast score and received a dose of pRBC. No statistically significant difference was found between mean APPLE fast score in dogs that received a pRBC transfusion and those that did not ($P = 0.12$). There was no statistically significant correlation between APPLE fast score and dose of pRBC administered or APPLE fast score and doses of TXA administered ($r_s = 0.058$; $P = 0.35$ and $r_s = -0.01$; $P = 0.45$, respectively).

VCT was performed in 11% (25/226) of dogs (Table 2). Of these 25 dogs, all but 9 were hyperfibrinolytic with 7 of 9 (77.7%) receiving TXA prior to VCT evaluation. Three dogs had a VCT pre- and post-TXA administration (Table 3), one of which received a pRBC transfusion between pre- and post-VCT analysis. All 3 dogs displayed improvement in CT, CFT, alpha angle, A10, A20, LI30, and LI45, representing improved clot strength and CT and reduced fibrinolysis.

The median IV dose of TXA administered was 10 mg/kg (IQR 0). TXA was exclusively given IV in this population of animals and primarily as a bolus dose every 6 hours; however, 2 dogs received TXA as a CRI for approximately 3 hours in 1 dog and 27 hours in the other. Both of these dogs received a 1-time 10 mg/kg IV bolus of TXA followed by a TXA CRI of 10 mg/kg/h IV, diluted in 0.9% sodium chloride.[f] Dogs that received the boluses of TXA received a median of 4 doses (IQR 4), approximately every 6 hours. Median duration of hospitalization was 48 hours (IQR 51). Presumed adverse events associated with TXA administration were reported in 1.7% (4/226) of dogs including

TABLE 2 Canine VCT results for pre-TXA ($n = 16$) and post-TXA ($n = 12$) administration for independent populations

Variable (units)	Pre-TXA median (IQR)	Post-TXA median (IQR)	Reference interval
CT (s)	399.5 (136)	349.5 (284.5)	241–470
CFT (s)	205.5 (212.5)	202.5 (264.5)	104–266
Alpha angle (degrees)	48 (29.5)	51.5 (21)	43–64
A10 (mm)	20.5 (14.5)	22 (18)	16–30
A20 (mm)	22 (16)	28.5 (19.5)	22–38
MCF (mm)	24 (15)	33 (15.5)	29–44
LI30 (%)	84 (42)	100 (0)	99–100
LI45 (%)	75 (37.5)	100 (4.5)	98–100

Abbreviations: IQR, Interquartile range; TXA, tranexamic acid; VCT, viscoelastic coagulation test.

TABLE 3 Pre- and post-TXA administration VCT results for 3 dogs

Variable (units)	Pre-TXA median (IQR)	Post-TXA median (IQR)	Reference interval
CT (s)	504 (77)	303 (118.5)	241–470
CFT (s)	452 (342.5)	220 (178)	104–266
Alpha angle (degrees)	34 (14)	54 (10)	43–64
A10 (mm)	12 (7)	18 (7.5)	16–30
A20 (mm)	15 (5)	24 (9.5)	22–38
MCF (mm)	24 (15)	33 (15.5)	29–44
LI30 (%)	50 (7.5)	100 (3.5)	99–100
LI45 (%)	43 (10)	100 (16.5)	98–100

Abbreviations: IQR, Interquartile range; TXA, tranexamic acid; VCT, viscoelastic coagulation test.

hypersalivation (3/226) and seizure (1/226). Of note, the singular dog that suffered a grand mal seizure was the same dog that received a TXA CRI for approximately 27 hours, at which point the CRI was discontinued due to the seizure activity. This patient had no prior history of seizures, traumatic brain injury, or neoplasia. The dog was hospitalized for treatment of melena secondary to suspected gastrointestinal ulceration due to a nonsteroidal anti-inflammatory overdose. This patient did not have any further seizures prior to discharge after the TXA CRI was discontinued.

One hundred and fifty-seven dogs (157/226 [69.4%]) survived to discharge. Of those that did not survive, 10 (14% [10/69]) died while hospitalized and 59 (85% [59/69]) were humanely euthanized. There was no significant difference between median APPLE fast score for survivors versus nonsurvivors ($P = 0.454$). Comparison of TXA dosing between survivors and nonsurvivors (Table 4) revealed that survivors received significantly more doses of TXA ($P < 0.001$) and were hospitalized for a significantly longer period of time ($P < 0.001$). No difference, however, was noted between median time to TXA administration between survivors and nonsurvivors.

Of the 28 cats, 11 (39%) were male neutered, 13 (46%) were neutered female, and 4 (14%) were female intact. Median age was 12 years (range: 3 months to 18 years). Five different cat breeds were represented, with the Domestic Shorthair being the most common (23/28 [82%]), followed by Maine Coon (2/28 [7%]), Domestic Long Hair (1/28 [3.5%]), Ragdoll (1/28 [3.5%]), and Peterbald (1/28 [3.5%]). Cats most commonly presented to the emergency service (26/28 [92.8%]), followed by internal medicine (1/28 [3.5%]) and general medicine (1/28 [3.5%]).

TXA was most commonly administered to cats diagnosed with "diseases of the blood and blood forming organs," "neoplasia," and "diseases of external causes" (Table 5). Of note, 33.3% (3/9) of cats classified as "diseases of the blood and blood forming organs" were represented by patients undergoing treatment for hemoabdomen secondary to a suspected primary coagulopathy. Only 2 of the 3 cats had further coagulation testing performed, ranging from partial to full coagulation factor assays and von Willebrand factor antigen testing. Neither of these patients were confirmed to have a primary coagulopathy. The third cat survived to discharge, although was lost to follow-up. The remaining cat (1/4) suffering from a hemoabdomen had noted liver nodules; however, these were never definitively diagnosed as benign or malignant.

Thirteen cats (46%) underwent an invasive procedure during hospitalization. No one procedure was most commonly performed in this population of cats, with 13 different procedures being represented once. Procedures performed included aspiration of an intraabdominal or intrathoracic structure, abdominal surgery, and oral biopsy. Approximately 53.8% (7/13) of cats received TXA preoperatively and 46% (6/13) received TXA postoperatively.

TABLE 4 Canine survival data in relation to TXA administration, length of hospitalization, and APPLE fast score ($n = 226$)

Variable (units)	Survivor median (IQR)	Nonsurvivor median (IQR)	*P*-value
n/N	69.4% (157/226)	30.5% (69/226)	
Dose of TXA (mg/kg)	10 (0)	10 (0)	0.959
Number of doses of TXA	4 (3)	2 (3)	<0.001
Time to TXA administration (min)	170 (445)	120 (300)	0.12
Length of hospitalization (h)	48 (48)	20 (51)	<0.001
APPLE fast score	24 (10)	25 (8)	0.454

Abbreviations: IQR, Interquartile range; TXA, tranexamic acid; VCT, viscoelastic coagulation test.

TABLE 5 Feline ICD classification summary with examples of underlying diagnosis ($n = 28$)

ICD classification	*n/N*	%	Diagnosis	*n/N*
2: Neoplasia	7/28	25.0%	Hemangiosarcoma	2/7
			Mast cell tumor	2/7
			Carcinoma	2/7
			Sarcoma	1/7
3: Disease of the blood and blood forming organs	9/28	32.1%	Hemoabdomen	4/9
			Hemothorax	1/9
			Eosinophilic ulcer of the palatine artery	1/9
			Spontaneous oral hemorrhage	1/9
			Spontaneous subcutaneous hemorrhage	1/9
11: Disease of the digestive system	4/28	14.2%	Gastrointestinal hemorrhage	2/4
			Hematemesis	1/4
			Intestinal perforation	1/4
12: Diseases of the skin and subcutaneous tissue	1/28	3.5%	Incisional revision	1/1
14: Diseases of the genitourinary system	1/28	3.5%	Polypoid cystitis	1/1
15: Disease of pregnancy and parturition	1/28	3.5%	Hemorrhage post parturition	1/1
19: Trauma	5/28	17.8%	High-rise syndrome	3/5
			Dog bite-associated polytrauma	2/5

Abbreviations: ICD, International Classification of Diseases; TXA, tranexamic acid.

Eighteen (18/28 [64%]) cats received a pRBC transfusion (median dose 11.3 ml/kg [IQR 5.1]). APPLE fast scores were calculable for 57% (16/28) of cats. The mean score was 26.6 ± 10.07. Given the small sample size, no comparisons between TXA dosing, APPLE fast scores, and pRBC transfusions could be made for cats.

VCT was performed in 17.8% (5/28) of cats. Only 1 (1/5 [20%]) cat had a VCT performed prior to TXA administration. No cat had both a pre- and post-TXA VCT performed and 4 (4/5 [80%]) cats had a post-TXA VCT performed (Table 6).

The median IV dose of TXA administered to cats was 10 mg/kg (IQR 0.35). TXA was exclusively given IV as a bolus dose every 6 hours. Median number of doses of TXA was 4 (IQR 3.5). Median duration of hospitalization was 60 hours (IQR 62.4). One cat received an unintentional 10 times overdose of TXA and did not suffer any appreciable adverse effects. Hypersalivation was the only presumed adverse event reported in 1 (1/28 [3%]) cat.

Twenty-one cats (21/28 [75%]) survived to discharge and of those that did not survive, all 7 were humanely euthanized. There was no significant difference between median APPLE fast score for survivors versus nonsurvivors ($P = 0.5$). Comparison of TXA dosing between survivors and nonsurvivors (Table 7) revealed that survivors received significantly more doses of TXA ($P = 0.04$); however, survivors were not hospitalized for a significantly longer period of time ($P = 0.055$). No difference was noted between median time to TXA administration between survivors and nonsurvivors.

4 | DISCUSSION

This report provides an overview of the use of TXA in critically ill dogs and cats at a large, urban emergency and referral center. The population analyzed was subjectively critically ill, evident by admittance to

TABLE 6 Feline VCT results post-TXA administration ($n = 4$)

Variable (units)	Post-TXA median (IQR)	Reference interval
CT (s)	638 (291)	233–406
CFT (s)	214.5 (112)	63–290
Alpha angle (degrees)	45 (7.5)	35–71
A10 (mm)	22 (12)	15–32
A20 (mm)	26 (14.5)	20–40
MCF (mm)	26 (15.5)	23–44
LI30 (%)	95.5 (13)	99–100
LI45 (%)	81 (36.5)	98–100

Abbreviations: IQR, Interquartile range; TXA, tranexamic acid; VCT, viscoelastic coagulation test.

TABLE 7 Feline survival data in relation to TXA administration, length of hospitalization, and APPLE fast score ($n = 28$)

Variable (units)	Survivor median (IQR)	Nonsurvivor median (IQR)	*P*-value
n/*N*	75% (21/28)	25% (7/28)	
Dose of TXA (mg/kg)	10 (0.29)	10 (0.15)	0.32
Number of doses of TXA	5 (3)	3 (2)	0.04
Time to TXA administration (min)	300 (450)	360 (900)	0.21
Length of hospitalization (h)	72 (51)	36 (31.5)	0.055
APPLE fast score	22 (15)	32 (4)	0.5

Abbreviations: APPLE, Acute Patient Physiologic and Laboratory Evaluation; IQR, interquartile range; TXA, tranexamic acid.

the CCU, and objectively, based on mean APPLE fast scores approaching 25, indicative of an increased risk of mortality.[19] Of note, there is a wide diversity of services that admitted these patients to the CCU and elected TXA as a therapeutic agent. This may be associated with recent literature advocating the use of TXA in veterinary patients or institutional convention based on a previous institutional study evaluating anti-fibrinolytic therapy.[8,9,12,23]

There is increasing research into the utility of TXA across a wide array of pathologic hemorrhagic conditions. Other than its use in acute trauma and reduction of perioperative blood loss, TXA is often used in people for hemoptysis secondary to primary pulmonary disease, epistaxis, coagulopathy, and thrombocytopenia secondary to hematologic malignancy, hemophilia, Von Willebrand disease, and other disorders of coagulation.[13,14] At the time of this study, there were 416 trials listed on clincaltrials.gov related to TXA. Some of the novel areas of investigation include topical application of TXA in pediatric spine deformities, burn surgeries, upper gastrointestinal hemorrhage, chronic subdural hematomas, acute cerebral hemorrhage, and coronary surgery.[24] TXA was prescribed for a wide array of diseases in this study with "neoplasia," "diseases of the blood and blood forming organs," "diseases of external causes" and "diseases of the digestive system" predominating. It is surprising that "diseases of external causes" was not the primary indication for TXA administration in this population given the available literature regarding its efficacy in human trauma victims and the level II veterinary trauma center status that this institution maintains.[25] These data elucidate a need for randomized controlled clinical trials evaluating the efficacy of TXA in veterinary species and in their absence, the need for expert-generated consensus guidelines for the use of fibrinolytics in critically ill veterinary species.

Previous studies analyzing the use of TXA in human trauma victims identified a significant association between early administration of TXA and improved patient outcomes.[25,26] Although there was no significant difference in median time of TXA administration between survivors and nonsurvivors in the present study, survivors received significantly more doses of TXA. In the canine population, this is likely related to survivors having been hospitalized for a significantly longer period of time and not succumbing to their disease process or owners electing humane euthanization. Perhaps a similar argument can be made for the feline population; however, a significant difference in hospitalization times for survivors versus nonsurvivors was not identified. Without a control group of similarly ill animals, it cannot be determined whether TXA influenced outcome in any meaningful way. Future prospective randomized clinical trials are necessary to determine if there is a similar causal relationship, as found in humans, between TXA administration and survival in veterinary patients.

Perioperative hemostasis is an integral component of reducing transfusion requirements and improving patient outcomes. Previous studies in humans have analyzed the universal perioperative use of TXA, finding significant reductions in postoperative bleeding and transfusion requirements.[27,28] A large meta-analysis and meta-regression of the effect of TXA on surgical blood loss in humans was performed in 2013, finding that blood loss was reduced by approximately 30% in

surgical patients receiving TXA as compared to placebo.[29] In the current investigation, approximately 65% of dogs and 46% of cats underwent an invasive procedure, with only 62% and 53%, respectively, receiving TXA preoperatively. Given that blood transfusions represent inherent risks to our veterinary patients, with controversy surrounding transfusion practices in those that are critically ill, a prospective investigation of perioperative use of TXA and its effects on hematocrit and transfusion requirements is needed in veterinary species.[6]

The safety and efficacy of TXA have primarily been evaluated in healthy adult dogs.[15,30–33] To date, there is only 1 previous study analyzing safety in adult dogs with bleeding disorders, recognizing vomiting as the only adverse effect in 2% of dogs.[16] This is the first study to evaluate safety in a critically ill population of dogs and cats. Presumed adverse events were rare and for the most part mild. It is unsurprising that TXA caused hypersalivation in this population of dogs as it has been investigated as an emetic agent at doses of 11–50 mg/kg.[16,30–33] Of note, TXA caused hypersalivation in a cat administered a dose of TXA well within accepted limits, while no adverse event was associated with a 10 times overdose (100 mg/kg) in another cat suggesting either pharmacologic variability of TXA in cats or that hypersalivation is an idiosyncratic reaction in this species. These patients were routinely administered antiemetic agents, including maropitant[g]; therefore, it is unclear if more patients would have suffered from vomiting or other signs of nausea as maropitant has been demonstrated to be efficacious as a prophylactic antiemetic agent when TXA is administered at doses of up to 50 mg/kg.[33] Not appreciated in this study, although noted in a previous 2002 study of 30 cats, acute lung injury with alveolar wall destruction and collagen accumulation in lung tissue was observed at high doses of TXA at 100–200 mg/kg. Acute lung injury was suspected to be secondary to inhibition of the fibrinolytic system rather than a direct effect of TXA.[34]

The most concerning presumed adverse event was a generalized seizure in a dog that was administered TXA as a CRI as a therapy for treating a bleeding gastrointestinal ulcer. This dog had received a TXA CRI at 10 mg/kg/h for 27 hours, after an initial loading dose of 10 mg/kg, for a total cumulative dose of 280 mg/kg, far in excess of the more commonly used 40 mg/kg daily dose resulting from a patient administered 10 mg/kg IV every 6 hours. While an idiosyncratic reaction cannot be ruled out, it seems possible this adverse event was dose dependent. A previous 1982 experimental study of 12 cats, in which TXA was topically applied to the cortex, and 5 cats, that were administered intravenous TXA at 500–600 mg/kg, revealed that TXA was capable of inducing feline generalized epilepsy. This study suggested that at normal clinical doses, the amount of TXA crossing the blood–brain barrier is too low to induce epileptic activity; however, the possibility of an epileptic seizure during treatment of TXA should not be excluded in patients with a previous history of epilepsy or if there is a reasonable suspicion that the blood–brain barrier is not intact.[35] With this said, however, the recent 2019 CRASH-3 trial found that TXA is safe in people with traumatic brain injury and treatment within 3 hours of injury reduced head injury-related death.[26]

Several limitations of this study make assessment of the safety, efficacy, and indications for the prescription of TXA difficult. The retrospective nature introduces the risk that adverse events could have been missed due to lack of index of suspicion for adverse events by the attending nurses and clinicians and failure to note in the medical record more subtle adverse effects. Some patients may have been inappropriately excluded if they were administered TXA but it was not recorded due to error. The comparatively small sample size of the feline population reduces confidence in any statement of safety and tolerance of the drug. Furthermore, the study design is not appropriate for evaluation of treatment efficacy or safety regarding the use of TXA in dogs or cats.

In conclusion, TXA at this institution is primarily utilized in critically ill dogs and cats diagnosed with neoplasia, bleeding disorders, and trauma. No patient suffered irreversible adverse effects and most adverse events were mild; however, clinicians should be aware of the possible side effects noted in this study.

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ENDNOTES

[a] Tranexamic acid, Alvogen Pharmaceuticals, Pine Brook, NJ.
[b] VCM Vet, Entegrion Animal Health and Sciences, Durham, NC.
[c] Excel, Microsoft Office 2003, Redmond, WA.
[d] Lowry R. VassarStats: Website for Statistical Computation. http://vassarstats.net/ Accessed April 2020-August 2020.
[e] Statistics Kingdom, Melbourne, Australia. http://www.statskingdom.com. Accessed April 2020-August 2020.
[f] 0.9% Sodium Chloride Injection USP, Baxter Healthcare Corporation, Deerfield, IL.
[g] Maropitant, Zoetis incorporated, Kalamazoo, MI.

CONFLICT OF INTEREST

Dr. Sinnott-Stutzman is an editor of the Journal but did not participate in the peer review process other than as an author. The authors declare no other conflict of interest.

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