Effect of early administration of tranexamic acid on ongoing haemorrhage in dogs with non-surgically treated haemoabdomen

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Wirkung von Tranexamsäure auf anhaltende Blutungen bei Hunden mit nicht operativ behandeltem Hämoabdomen

Tranexamsäure (TXA) ist ein Antifibrinolytikum, das zur Prophylaxe und Behandlung von Blutungen unterschiedlicher Genese eingesetzt wird. Diese retrospektive Studie untersuchte die Wirkung von TXA auf anhaltende Blutungen bei Hunden mit nicht operativ behandeltem Hämoabdomen.

Die Studienpopulation bestand aus 48 Hunden, die im Zeitraum von 2009–2020 an der Kleintierklinik der Vetsuisse-Fakultät Zürich behandelt wurden. 28 von 48 Hunden wurden mit 20 mg/kg TXA IV innerhalb von 3 Stunden nach Diagnose des Hämoabdomens behandelt. Mit und ohne TXA behandelte Hunde wurden über 48 Stunden auf Anzeichen einer anhaltenden Blutung überwacht. Anhaltende Blutungen wurden definiert als eine Zunahme von abdominaler Flüssigkeit, einer Abnahme des abdominalen Hämatokrits von > 5 % oder die Notwendigkeit einer chirurgischen Exploration nach mindestens 12 Stunden medizinischer Behandlung. Transfusionsbedarf, kumulative Menge der Flüssigkeitstherapie, Herzfrequenz, Atemfrequenz, Temperatur, systolischer und mittlerer arterieller Blutdruck, geschätzte Menge der Abdominalflüssigkeit, identifiziert durch FAST-Analyse, venöser Hämatokrit, abdominaler Hämatokrit, Serumalbumin, Serumlaktat und Thrombozytenzahl wurde aus den Krankengeschichten der Hunde 6, 12, 24 und 48 Stunden nach Diagnose des Hämoabdomens entnommen. Die Patientengruppen waren bei der Vorstellung vergleichbar, jedoch zeigten die Hunde der TXA-Gruppe über den untersuchten Zeitraum einen signifikant niedrigeren abdominalen Hämatokrit (37 vs. 45 %, P = 0,034) und eine höhere Flüssigkeitsansammlung (P = 0,019). Keiner der Ergebnisparameter für anhaltende Blutungen unterschied sich signifikant zwischen den Gruppen. Der Transfusionsbedarf war in beiden Gruppen gering und ähnlich.

Summary

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Tranexamic acid (TXA) is an antifibrinolytic drug used for the prophylaxis and treatment of haemorrhage of various origin. This retrospective study investigated the effect of TXA on ongoing bleeding in dogs with non-surgically treated haemoabdomen.

The study population consisted of 48 dogs treated in the period 2009–2020 at the Small Animal Clinic of the Vetsuisse Faculty of Zurich. Twenty-eight of 48 dogs were treated with 20 mg/kg TXA IV within 3h of diagnosis of haemoabdomen. Dogs treated with and without TXA were monitored over 48 hours for signs of ongoing haemorrhage. Ongoing haemorrhage was defined as an increase in abdominal fluid accumulation, a decrease in haematocrit of >5% over time or need for surgical exploration after at least 12 hours of medical treatment. Transfusion requirements, cumulative amount of fluid therapy, heart rate, respiratory rate, temperature, systolic and mean arterial pressure, estimate of abdominal fluid identified by FAST analysis, venous haematocrit, abdominal haematocrit, serum albumin, serum lactate and thrombocyte count were extracted from patient records at 6, 12, 24 and 48 hours after diagnosis of haemoabdomen.

Groups were comparable at presentation, however dogs of the TXA group showed a significantly lower abdominal haematocrit at presentation (37 vs 45%, P=0,034) and a higher fluid accumulation (P=0,019), both persisting over time. None of the outcome parameters for ongoing haemorrhage was significantly different between groups. Transfusion requirement was low and similar in both groups. Of interest, none of the 16 dogs undergoing thromboelastometry showed hyperfibrinolysis at presentation. We conclude that other mechanisms than antifibrinolytic therapy was responsible for cessation of bleeding in the majority of patients.

Keywords: Antifibrinolytic, canine, fibrinolysis, hemoperitoneum, trauma

Interessanterweise zeigte keiner der 16 Hunde, die einer Thromboelastometrie unterzogen wurden, bei der Vorstellung eine Hyperfibrinolyse. Zusammenfassend zeigte die Studie, dass andere Mechanismen als die antifibrinolytische Therapie bei der Mehrheit der Patienten für das Blutstillung verantwortlich waren.

Schlüsselwörter: Antifibrinolytisch, Hund, Fibrinolyse, Hämoperitoneum, Trauma

Introduction

Dogs presenting with haemoabdomen may pose a therapeutic challenge. A recent study indicated that 50% of dogs with haemoabdomen undergoing surgical treatment were hypocoagulable.[14] Little is known about the pathophysiology leading to hypocoagulability in dogs with haemoperitoneum. Fletcher et al. described, that dogs with spontaneous haemoabdomen show signs of hypocoagulopathy, protein C deficiency, and hyperfibrinolysis[6]while the former mentioned study did not identify hyperfibrinolysis.[14]

In people with traumatic haemoabdomen, trauma itself, without massive bleeding, may lead to hypocoagulability and hyperfibrinolysis.[2] Hypocoagulability and hyperfibrinolysis are seen early after trauma and before fluid resuscitation[22], and both are thought to be caused by massive tissue damage in conjunction with hypoperfusion.[1,3] Studies in canine and feline trauma patients have identified hypocoagulability and hyperfibrinolysis as well.[9,10,16,17] Additionally, hyperfibrinolysis has been reported following trauma and the development of acute haemoabdomen in dogs.[11,25]

Hyperfibrinolysis is defined by a disproportionate increase in fibrinolytic activity, which results in poor clot formation, excessive haemorrhage, and increased mortality.[7] Due to an increased plasminogen activator activity, dogs are more susceptible to the imbalance of the fibrinolytic pathway than people.[5]

Hyperfibrinolysis can be treated with an antifibrinolytic agent, such as tranexamic acid (TXA). Tranexamic acid is a lysine analogue and inhibits fibrinolysis by competitively blocking the lysine binding site on plasminogen. This results in the formation of a complex of tranexamic acid and plasminogen, which inhibits the activation to plasmin and the interaction of plasmin with fibrin, preventing fibrin from being degraded.[7] Tranexamic acid is used for the prophylaxis and treatment of haemorrhage in bleeding human patients with both normal and increased fibrinolysis.[15] In people, the drug is used to prevent bleeding in patients undergoing surgery with a high risk of blood loss and to reduce bleeding in patients with existing bleeding. The landmark CRASH-2 study on the use of TXA in trauma haemorrhage was the first study to show a higher survival rate with TXA administration within 3 hours in traumatized people.[21] Other studies in people demonstrated decreased requirement of blood products when TXA was administered.[4,21,22] Likewise, TXA administration to dogs bleeding from various causes was associated with a decreased blood transfusion requirement.[13]

To the best of our knowledge, only one study investigated the relationship between haemoabdomen, efficacy of TXA treatment and transfusion requirement.[14] Hypocoagulopathy, protein C deficiency, and hyperfibrinolysis identified in dogs with spontaneous haemoperitoneum suggest that tranexamic acid is indicated.[6] Hyperfibrinolysis has been identified in dogs and cats with haemoabdomen[25] and tranexamic acid is thought to reduce haemorrhage in dogs with bleeding.[13] In dogs with surgically corrected haemoabdomen, however, the administration of TXA during the stabilisation period prior to surgery did not lead to decreased haemorrhage or transfusion requirements intra- or postoperatively.[14] Surgical ligation of bleeding vessels and therefore no need for an antifibrinolytic drug were considered as explanation for the lack of a positive effect of TXA on ongoing haemorrhage. However, based on the available studies, the timely administration of TXA to dogs with medically treated haemoabdomen is expected to reduce continuous bleeding and possibly transfusion requirements.

The aim of this retrospective study was to evaluate the effect of early administration of TXA on continuous haemorrhage, defined as an increase in abdominal fluid, decrease in abdominal haematocrit or need for surgical intervention >12 hours after medical treatment. A secondary goal was to compare the requirement for blood transfusion and the hospitalization time between dogs treated with and without TXA. These aims were additionally investigated in the subgroup of dogs presenting with traumatic haemoabdomen.

Our null hypothesis was that administration of TXA in dogs with nonsurgically treated haemoabdomen will not

change the incidence of continuous haemorrhage, the need for transfusion requirements or hospitalization times.

Material and methods

The online database of the Small Animal Clinic of the Vetsuisse Faculty was searched for dogs nonsurgically treated for haemoabdomen between 2009 and 2020. Dogs were included when the abdominal effusion haematocrit at presentation was > 15% and/or the veterinary record subsequently confirmed haemoabdomen. Dogs that were surgically treated within 12 hours after diagnosis, dogs that received the first TXA treatment after 3 hours but before 24 hours after diagnosis, dogs that received plasma or any other drug influencing coagulation (for example Vitamin K) within 24 hours of presentation were excluded. Dogs with an effusion haematocrit lower than the venous haematocrit (diluation by any other process such as concurrent uroabdomen) were additionally excluded. Dogs that received plasma after 24 hours were included but data following plasma transfusion was not used for analysis. Dogs that received TXA after 24h were considered not treated with TXA until TXA administration and follow up data after TXA administration was not analysed. The resulting population was divided into the group that received TXA within 3 hours of diagnosis and the group that was not treated with TXA.

In addition to the signalment, the following parameters were recorded at presentation: heart rate, respiratory rate, temperature, systolic and mean arterial pressure, estimate of abdominal fluid identified by FAST analysis, venous haematocrit, abdominal haematocrit, serum albumin, serum lactate and thrombocyte count. The 0 hour value was collected in the first hour after admission to the hospital or when a haemoabdomen was diagnosed in patients already hospitalized. Panting was defined as a respiratory rate of 100 breaths per minute. Shock index (SI) was calculated from heart rate divided by systolic blood pressure. An SI of more than 0,9 was considered to be consistent with haemorrhagic shock.[19] The estimated abdominal fluid (assessed by abdominal focussed assessment with sonography) was classified as none, mild, moderate and severe. Heart rate, blood pressure, SI, venous and effusion haematocrit and amount of abdominal fluid were further determined 6, 12, 24 and 48 hours after presentation. The 6 hour value was defined as evaluated between 4–8 hours, the 12 hour value as 10–14 hours, the 24 hour value as 20–28 hours and the 48 hour value as 34–56 hours after identification of haemoabdomen.

The amount of crystalloid and colloidal fluids administered and the number of whole blood, erythrocyte and plasma transfusions were evaluated over 48 hours. In dogs receiving a blood transfusion, the venous haematocrit following transfusion was no longer included in analysis.

The cause of haemorrhage was extracted from the database and was divided into 4 groups (trauma, neoplasia, postoperative/iatrogenic or miscellaneous) based on history and ultrasonographic findings. The time of the first TXA administration, dosage (mg/kg), and frequency of TXA administration were extracted from treatment sheets.

Continuous haemorrhage was defined as an increase in abdominal fluid between 12–24 hours or between 24–48 hours, a decrease in abdominal haematocrit of more than 5% between 12–48 hours or need for surgery after more than 12 hours of medical therapy due to suspicion of continuous bleeding. At least two parameters listed above had to be evaluated and had to be negative to exclude continuous haemorrhage. Dogs lacking sufficient information to evaluate continuous bleeding were excluded from analysis.

Thromboelastometric assessment (ROTEM Delta, TEM Innovations, Munich) was performed at presentation at the discretion of the clinician in charge.

Statistical analysis

The data obtained was listed in an Excel table and analyzed with a commercially available software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27,0. Armonk, NY: IBM Corp). Dogs were divided into two groups (TXA and nonTXA). Normal distribution of continuous data was tested using a Shapiro Wilk test. As groups were small and most parameters were non-normally distributed, median, minimum and maximum values are reported. For group comparison, chi-square test was used for nominal data and Mann-Whitney U test for the continuous parameters. A P-value > 0,05 was considered significant.

Results

Twenty dogs treated with 20 mg/kg TXA IV within 3 hours and 28 dogs not treated with TXA were included. Weight, age, sex and cause of haemoabdomen were not significantly different between groups (Tables 1 and 2). Dogs treated without TXA were presented between 2009 and 2018, while dogs treated with TXA were presented between 2014 and 2020, when the drug became available. Following 2018, the hospital protocol recommended administration of TXA to patients with haemoabdomen.

Dogs in the TXA group received a median of 2 (range, 1–5) doses of TXA over 1 (range, 1–2) days. Dogs in the TXA group showed a significantly lower abdominal haematocrit (37 vs 45%, P=0,034, Table 1) and a higher fluid score (P=0,019, Table 2) at presentation, while the number of anaemic dogs at presentation was not significantly different (Table 2). Dogs in the TXA group consistently showed a lower abdominal haematocrit over time, again reaching significance at 48 hours after presentation (30 vs 36%, P=0,038) (Table 1). Abdominal fluid score remained significantly higher 6 hours after presentation but was no longer significantly different at later time points.

Table 1: Clinical and laboratory parameters of 20 dogs treated with tranexamic acid (TXA) and 28 dogs treated without TXA (nonTXA) at presentation and 6, 12, 24 and 48 hours thereafter

Parameter	nonTXA (n=28)			TXA (n=20)			
	n	Median	Range	n	Median	range	P
Weight (kg)	28	25	2,3–42	20	18,8	2,3–47	0,397
Age (month)	28	56	6–191	20	77	4–145	0,195
Presentation							
Heart rate (per minute)	28	136	72–180	20	155	84–220	0,066
Respiratory rate (per minute)	24	36	24–120	19	30	20–100	0,411
MAP (mmHg)	9	70	32–95	16	73	54–132	0,803
Systolic blood pressure (mmHg)	8	107	52–128	17	117	89–166	0,175
Temperature (°C)	28	38,1	35,4–38,9	20	37,8	35,0–39,4	0,922
Haematocrit (%)	28	41	12–55	20	35	20–55	0,084
Abdominal haematocrit (%)	22	45	12–68	19	37	18–55	0,034
Albumin (g/l)	15	28	7–35	19	25	10–36	0,395
Thrombocyte count (1o9/ml)	13	141	32–334	11	132	31–411	0,776
Glucose (mmol/L)	19	5,8	3,2–16,4	14	6,0	5,1–8,0	0,439
Lactate (mmol/L)	6	2,57	1,1–9,2	17	3,14	1,2–6,8	1,000
Shock index	8	1,21	0,8–2,7	17	1,37	0,7–2,5	0,475
6 hours							
Heart rate (per minute)	27	100	52–180	19	120	67–160	0,202
Systolic blood pressure(mmHg)	17	100	74–182	14	118	74–150	0,215
MAP (mmHg)	15	81	43–100	15	89	47–109	0,325
Shock index	17	0,98	0,4–1,8	14	0,92	0,6–2,2	0,739
Haematocrit (%)	14	34	17–43	15	27	14–43	0,400
Abdominal haematocrit (%)	7	50	30–62	12	36	20–48	0,083
12 hours							
Heart rate (per min)	17	84	56–200	17	100	60–156	0,290
MAP (mmHg)	5	97	77–100	8	70	44–100	0,171
Syst blood pressure (mmHg)	4	108	100–117	7	112	65–134	0,527
Haematocrit (%)	19	34	16–41	14	27	18–41	0,483
Abdominal haematocrit (%)	3	44	41–52	5	34	18–50	0,250
Shock index	4	1,0	0,6–1,9	6	1,20	0,8–2,0	0,476
24 hours							
Heart rate (per min)	20	100	49–156	18	98	79–160	0,534
MAP (mmHg)	5	95	82–110	7	85	70–99	0,149
Systolic blood pressure (mmHg)	4	110	50–140	5	129	106–138	0,413
Haematocrit (%)	15	35	25–47	9	31	17–44	0,084
Abdominal haematocrit (%)	4	43	27–54	4	24	19–37	0,114
Shock index	4	0,74	0,4–3,1	5	0,89	0,7–1,4	1,000
48 hours							
Heart rate (per minute)	15	88	45–164	12	85	60–120	0,943
Haematocrit (%)	8	36	32–46	8	30	17–51	0,038
Outcome							
Hospitalisation time (days)	28	2,5	1–7	20	4	1–6	0,101
Cumulative amount of crystalloid fluids (ml)	21	80	12–279	18	105	16–232	0,967
Cumulative amount of colloidal fluids (ml)	22	0	0–74	19	0	0–75	0,370

Sixteen of 48 dogs underwent thromboelastometric (ROTEM) evaluation at presentation. None of them showed hyperfibrinolysis, defined as maximum lysis above the reference interval.

Overall survival and hospitalization time was not significantly different between groups (P=1,000 and 0,101, respectively). Survival was 93 and 95%, respectively. One dog that did not survive died due to severe head trauma and the other 2 dogs were euthanized due to deterioration of comorbidities and unfavourable prognosis. Four dogs (2 in each group) underwent surgical exploration of the abdomen due to ongoing haemorrhage. Three showed active bleeding during surgery (traumatic splenic laceration, splenic mass, mesenterial artery) and one dog presenting with haemoabdomen after fine needle aspiration had minor bleeding from a hepatic laceration and a large coagulum in the abdomen.

In the subgroup of dogs with traumatic haemoabdomen (n=33), increase in abdominal fluid score was significantly higher in dogs treated with TXA (P=0,047) while the need for surgery (P=0,097) and continuous bleeding (P=0,438) was not significantly different (Table 3). Clinical signs and laboratory parameters at presentation were not significantly different between traumatized dogs treated with and without TXA (data not shown).

Table 2: Frequencies of various parameters including abdominal fluid scores of 20 dogs treated with tranexamic acid (TXA) and 28 dogs treated without TXA (nonTXA) at presentation and 6, 12, 24 and 48 hours thereafter

Parameter	Definition	nonTXA n/N (%)	TXA n/N (%)	P-value
Sex	Male	2	1	0,806
	Male castrated	8	8	
	Female	10	5	
	Female spayed	8	6	
Anaemia at presentation	Haematocrit < 40%	12/28 (43%)	14/20 (70%)	0,083
Hyperlactatemia	Lactate > 2,0 mmol/L	3/6 (50%)	12/17 (71%)	0,621
Shock at presentation	Shock index > 1,0	5/8 (63%)	15/17 (88%)	0,283
Cause of haemoabdomen	Miscellaneous	3/28 (11%)	2/20 (10%)	0,085
	Trauma	22/28 (78%)	11/20 (55%)	
	Postoperative	1/28 (4%)	6/20 (30%)	
	Neoplasia	2/28 (7%)	1/20 (5%)	
Fluid scores over time				
Abdominal fluid at diagnosis	Slight	15/27 (56%)	5/20 (25%)	0,019
	Moderate	11/27 (41%)	9/20 (45%)	
	Severe	1/27 (4%)	6/20 (30%)	
Abdominal fluid 6 hours after diagnosis	Slight	3/5 (60%)	0	0,012
	Moderate	0	7/10 (70%)	
	Severe	2/5 (40%)	3/10 (30%)	
Abdominal fluid 12 hours after diagnosis	None	1/6 (17%)	1/14 (7%)	0,139
	Slight	4/6 (67%)	7/14 (50%)	
	Moderate	0	6/14 (43%)	
	Severe	1/6 (17%)	0	
Abdominal fluid 24 hours after diagnosis	None	2/8 (25%)	1/14 (7%)	0,401
	Slight	5/8 (63%)	8/14 (57%)	
	Moderate	0	3/14 (21%)	
	Severe	1/8 (13%)	2/14 (14%)	
Abdominal fluid 48 hours after diagnosis	None	¼ (25%)	1/11 (9%)	0,526
	Slight	¾ (75%)	8/11 (73%)	
	Moderate	0	2/11 (18%)	
	Severe	0	0	
Outcome				
Increase in abdominal fluid		1/24 (4%)	5/19 (26%)	0,072
Decrease of abdominal haematocrit > 5%		4/6 (67%)	3/7 (43%)	0,592
Need for surgery		2/28 (7%)	2/20 (10%)	1,000
Ongoing haemorrhage		6/28 (21%)	5/20 (25%)	1,000
Erythrocyte transfusion		4/28 (14%)	1/20 (5%)	0,385
Survival to discharge		26/28 (93%)	19/20 (95%)	1,000

Discussion

The administration of TXA within 3 hours after diagnosis of haemoabdomen in dogs with a nonsurgically treated haemoabdomen did not lead to a significant reduction of continuing haemorrhage, transfusion requirement or hospitalization time in dogs treated with and without TXA. Dogs presenting with a traumatic haemoabdomen showed similar results, however, traumatized dogs treated with TXA had a significant increase in abdominal fluid over 48 hours.

The hypothesis that dogs treated with TXA would show less continuing bleeding is drawn from both human and veterinary studies that showed a reduction in bleeding tendency in patients treated with TXA.[8,13,20–22] In our patient population, approximately one quarter of dogs showed signs of ongoing haemorrhage and the incidence was not significantly different between groups. Ongoing haemorrhage was defined based on an increase in abdominal fluid accumulation and/or decrease in abdominal haematocrit over time and/or the need for surgical exploration despite at least 12 hours of medical treatment. At least two of the three parameters had to be negative to qualify as cessation of bleeding.

Dogs treated with TXA were treated with 20 mg/kg IV at least once and within three hours of diagnosis. The CRASH-2 study showed the best benefit of tranexamic acid when administered within three hours of trauma or start of haemorrhage.[22] It is important to note here, however, that in veterinary medicine, it is difficult to estimate from the history when bleeding started. Furthermore, TXA administration interval and duration was not standardized in our study population.

The maximum TXA concentration in plasma is dose-dependent and the therapeutic dose in people is 10 mg/kg.[15] Dogs are more hyperfibrinolytic than people, thus higher doses of TXA than in people are required to fully inhibit fibrinolysis.[5] A dose of 20 mg/kg IV resulted in a plasma TXA concentration of > 150 µg/mL in dogs shortly after administration.[18] The dose of 20 mg/kg kept plasma levels high enough for inhibition of hyperfibrinolysis for at least 6 hours.[18] Another study showed that administration of 10, 20, or 30 mg/kg TXA IV to dogs had an antifibrinolytic effect within 20 minutes and lasted for up to 24 hours.[12] A single intravenous treatment with 20 mg/kg TXA to dogs is therefore expected to lead to a sufficiently high plasma concentration of TXA shortly after administration and for at least

Table 3: Outcome parameters for 33 dogs with traumatic haemoabdomen

Parameter		nonTXA (n=22) n/N (%)	TXA (n=11) n/N (%)	P-value
Abdominal fluid score				
Fluid T6	None	0	0	0,050
	Slight	3 (75%)	0	
	Moderate	0	3 (75%)	
	Severe	1 (25%)	1 (25%)	
Fluid T12	None	1 (25%)	0	0,055
	Slight	3 (75%)	2 (29%)	
	Moderate	0	5 (71%)	
	Severe	0	0	
Fluid T24	None	1 (17%)	1 (14%)	0,556
	Slight	4 (67%)	3 (43%)	
	Moderate	0	2 (28%)	
	Severe	1 (17%)	1 (14%)	
Fluid T48	None	1 (33%)	1 (17%)	0,509
	Slight	2 (66%)	3 (50%)	
	Moderate	0	0	
	Severe	0	2 (34%)	
Outcome				
Increase in abdominal fluid		1/19 (5%)	4/11 (36%)	0,047
Decrease abdominal haematocrit > 5%		4/6 (67%)	2/4 (50%)	1,000
Need for surgery		1/22 (5%)	2/11 (18%)	0,097
Ongoing haemorrhage		5/22 (23%)	4/11 (36%)	0,438
Erythrocyte transfusion		2/22 (10%)	1/11 (9%)	1,000
Survival to discharge		20/22 (90%)	10/11 (91%)	1,000

12 or even 24 hours. Our dogs were monitored for continuous bleeding over 48 hours, however, all dogs that were considered to be haemorrhaging were identified within 12–24 hours, indicating that the interval of TXA was probably not the cause for the lack of an effect seen. However, while the above studies support a single TXA treatment, the cumulative amount of TXA to completely stop fibrinolysis in clinical patients is unknown. In one case report, a significant improvement of lysis indexes was observed with a 20 mg/kg dose[16] while studies in haemorrhaging dogs due to *A. vasorum* infection[24,26] recommend higher dosages for complete inhibition of hyperfibrinolysis.

Several additional reasons can be discussed as a possible explanation for the lack of a significant effect of TXA treatment on bleeding tendency in dogs with haemoabdomen. The most reasonable explanation is the absence of hyperfibrinolysis. Tranexamic acid is an antifibrinolytic agent, which inhibits hyperfibrinolysis by blocking the lysine binding site on the plasminogen molecule and preventing activation to plasmin.[15] None of the 16 dogs undergoing thromboelastometric analysis showed hyperfibrinolysis, which may be due to lack or hyperfibrinolysis or due to the need for a t-PA supplemented viscoelastic test[6]. Another recent study of dogs presenting with spontaneous, surgically treated haemoabdomen, identified no dogs with thromboelastometric signs of hyperfibrinolysis.[14] However, there are several studies reporting hyperfibrinolysis in dogs with haemoabdomen, indicating that haemoabdomen indeed is associated with hyperfibrinolysis, at least in some patients.[6,25,27] Hyperfibrinolysis is expected in patients with severe haemoabdomen and haemorrhagic shock, as hypotension caused by blood loss increases fibrinolysis[6] and the patients in our study population may not have been haemorrhaging enough to present with hyperfibrinolysis.

Other mechanisms than inhibition of fibrinolysis may have led to cessation of bleeding. The cause of haemoabdomen may be of importance as traumatic haemoabdomen and coagulopathies have different pathomechanisms leading to haemorrhage. Coagulopathies as a cause of haemoabdomen were excluded in our patient population as these patients received additional procoagulant drugs such as vitamin K or plasma transfusion. The majority of dogs in this study presented with a traumatic haemoabdomen. Statistical analysis of this subgroup revealed the same outcome findings as in the overall population, however, trauma patients treated with TXA had a significant increase in abdominal fluid over 48 hours. The reason for the increase in abdominal fluid over time despite TXA treatment is speculated to be due to ongoing bleeding due to other causes than hyperfibrinolysis. We exclude bias in the decision to treat dogs with TXA based on more severe bleeding, as presenting parameters were not significantly different in traumatized dogs with and without TXA treatment.

Traumatic haemoabdomen in dogs is generally treated nonsurgically, as mild to moderate haemorrhage is expected to stop without surgical intervention.[23] This approach is supported by our findings, as TXA treated dogs did not require more surgical interventions despite the increase in abdominal fluid over time. The mechanism(s) resulting in cessation of bleeding remain unknown, mesenteric vasoconstriction due to hypovolemia and a trend towards hypercoagulability within 6–12 hours after trauma[10] may be mechanisms to consider.

Administration of transfusions was identical in both study groups indicating that TXA has no effect on the transfusion requirement. Of note, the transfusion rate was very small, in both patient groups and most dogs were only moderately anaemic. In people, the use of antifibrinolytics reduced the number of blood products per patient.[4,8] Kelmer et al. reports a reduced need for blood products in dogs with haemorrhage of various origin treated with tranexamic acid.[13] Our results do not support this finding. However, administration of blood products was not standardized and was based on the decisions of the clinician in charge and the availability of blood products.

The administration of TXA further had no effect on hospitalization time or survival in our study population and 95% of dogs were discharged. The landmark CRASH-2 study on the use of TXA in trauma haemorrhage was the first study to show a higher survival rate when TXA was administered within 3 hours of trauma in people.[20] One can argue that our patient population, compared to studies in people, did not show severe abdominal haemorrhage as dogs presented with mild to moderate abdominal effusion. As dogs in the TXA group presented with a higher abdominal fluid score and lower haematocrit, we cannot completely exclude that some dogs in the TXA group received TXA because the clinician in charge expected more severe bleeding compared to dogs in the non-TXA group that did not receive TXA due to insignificant amounts of fluid present in the abdomen. In this case, TXA could have had decreased continuous bleeding as the transfusion requirement was not higher in these dogs. However, cardiopulmonary parameters at presentation were not different between groups, indicating that dogs were not more critically ill or experienced a more severe haemorrhage. Additionally, the fluid score remained higher in the TXA group over time, indicating that the trend in fluid resorption/production was the same in both groups.

Limitations

As with all retrospective studies, not all parameters that were of interest could be evaluated. Specifically, only one third of dogs underwent ROTEM evaluation, therefore the exact incidence of hyperfibrinolysis is unknown. Evaluation of bleeding parameters and TXA treatment was not standardized and while populations were comparable at presentation, some bias in treatment (decision for transfusion or surgery) cannot be excluded. Additionally, the estimation of abdominal fluid by ultrasound is highly subjective and was assessed by different clinicians. The small number of dogs and the different causes of haemorrhage represent the clinical picture, but larger studies are warranted to support our findings.

Conclusion

In this study population of dogs presenting with mild to moderate haemoabdomen, TXA did not decrease transfusion requirements, hospitalization time or survival. Parameters used to identify continuous abdominal haemorrhage were not significantly different between dogs treated with and without TXA.

Effet de l'administration précoce d'acide tranexamique sur l'hémorragie en cours chez les chiens souffrant d'un hémoabdomen non traité chirurgicalement

L'acide tranexamique (TXA) est un médicament anti fibrinolytique utilisé pour la prophylaxie et le traitement des hémorragies d'origines diverses. Cette étude rétrospective a examiné l'effet du TXA sur les saignements en cours chez les chiens présentant un hémoabdomen traité sans chirurgie.

La population étudiée était composée de 48 chiens traités entre 2009 et 2020 à la clinique pour petits animaux de la faculté Vetsuisse de Zurich. Vingt-huit des 48 chiens ont été traités avec 20 mg/kg de TXA IV dans les 3 heures suivant le diagnostic de l'hémoabdomen. Les chiens traités avec et sans TXA ont été surveillés pendant 48 heures pour détecter les signes d'hémorragie en cours. L'hémorragie en cours a été définie comme une augmentation de l'accumulation de liquide abdominal, une diminution de l'hématocrite de >5% dans le temps ou la nécessité d'une exploration chirurgicale après au moins 12 heures de traitement médical. Les besoins transfusionnels, la quantité cumulative de traitement liquidien, la fréquence cardiaque, la fréquence respiratoire, la température, la pression artérielle systolique et moyenne, l'estimation du liquide abdominal identifié par l'analyse FAST, l'hématocrite veineux, l'hématocrite abdominal, l'albumine sérique, le lactate sérique et la numération des thrombocytes ont été extraits des dossiers des patients à 6, 12, 24 et 48 heures après le diagnostic d'hémoabdomen.
Les groupes étaient comparables à la présentation, mais les chiens du groupe TXA présentaient un hématocrite abdominal significativement plus faible à la présentation (37 vs 45 %, P=0,034) et une accumulation de liquide plus importante (P=0,019), ces deux phénomènes persistant dans le temps. Aucun des paramètres de résultat pour l'hémorragie en cours n'était significativement différent entre les groupes. Les besoins en transfusion étaient faibles et similaires dans les deux groupes. Il est intéressant de noter qu'aucun des 16 chiens soumis à la thromboélastométrie ne montrait d'hyperfibrinolyse à la présentation. Nous concluons que d'autres mécanismes que le traitement anti fibrinolytique étaient responsables de l'arrêt des saignements chez la majorité des patients.

Mots clés: Anti fibrinolytique, canin, fibrinolyse, hémopéritoine, traumatisme

Effetto della somministrazione precoce di acido tranexamico sull'emorragia in corso in cani con emoaddome non trattato chirurgicamente

L'acido tranexamico (TXA) è un farmaco antifibrinolitico utilizzato per la profilassi e il trattamento di emorragie di varia origine. Questo studio retrospettivo ha analizzato l'effetto del TXA sulle emorragie in corso nei cani affetti da emoaddome non trattato chirurgicamente.

La popolazione dello studio era costituita da 48 cani trattati nel periodo tra il 2009 e il 2020 presso la Clinica dei piccoli animali della Facoltà Vetsuisse di Zurigo. Ventotto dei 48 cani sono stati trattati con 20 mg/kg di TXA IV entro 3 ore dalla diagnosi di emoaddome. I cani trattati con TXA, o senza, sono stati monitorati per 48 ore alla ricerca di segni di emorragia in corso. L'emorragia in corso è stata definita come un aumento dell'accumulo di liquidi addominali, una diminuzione dell'ematocrito del >5% nel tempo o la necessità di esplorazione chirurgica dopo almeno 12 ore dal trattamento medico. Le necessità di trasfusione, la quantità accumulata di terapia con fluidi, la frequenza cardiaca, la frequenza respiratoria, la temperatura, la pressione arteriosa sistolica e media, la stima del fluido addominale identificato dall'analisi FAST, l'ematocrito venoso, l'ematocrito addominale, l'albumina sierica, il lattato sierico e il numero di trombociti sono stati estratti dalle cartelle cliniche dei pazienti a 6, 12, 24 e 48 ore dalla diagnosi di emoaddome.

I gruppi erano comparabili alla presentazione, tuttavia i cani del gruppo TXA mostravano un ematocrito addominale significativamente più basso alla presentazione (37 risp. 45%, P=0,034) e un maggiore accumulo di liquidi (P=0,019), entrambi persistenti nel tempo. Nessuno dei parametri del risultato per l'emorragia in corso era significativamente diverso tra i gruppi. Il fabbisogno trasfusionale era basso e simile in entrambi i gruppi. È interessante notare che nessuno dei 16 cani sottoposti a tromboelastometria mostrava iperfibrinolisi alla presentazione. Concludiamo che altri meccanismi, diversi dalla terapia antifibrinolitica, erano responsabili della cessazione dell'emorragia nella maggior parte dei pazienti.

Parole chiave: Antifibrinolitico, cane, fibrinolisi, emoperitoneo, trauma

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[28] Table 1: Clinical and laboratory parameters of 20 dogs treated with tranexamic acid (TXA) and 28 dogs treated without TXA (nonTXA) at presentation and 6, 12, 24 and 48 hours thereafter

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