Retrospective Evaluation of the Safety and Efficacy of Tranexamic Acid (Hexakapron®) for the Treatment of Bleeding Disorders in Dogs

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ABSTRACT

The use of antifibrinolytic drugs in human patients with bleeding disorders is common and effective in reducing redundant the number of blood products per patient. The objective of this study was to evaluate the safety of tranexamic acid (TXA) and its efficacy in decreasing blood component requirements in dogs with bleeding disorders. In a retrospective study, dogs with bleeding disorders treated intravenously (IV) with TXA for a median period of 2 days (range 1-21) at a mean (± standard deviation) dose of 8.6 ± 2.3 mg/kg with or without blood products (n=68) were compared with dogs with bleeding disorders that were not treated with TXA but were treated only with blood products (n=62). No TXA-related adverse effects were noted, with the exception of vomiting, documented in 2 dogs (3%) immediately following administration. When the median number of blood products and their dose per dog were compared between the groups, TXA-treated dogs received significantly less units of blood products and a lower blood component dose ($P < 0.001$). However, when this analysis included only dogs that received blood products in the study group there were no significant differences. It was concluded that intravenous administration of TXA in bleeding dogs at the recommended human dose is safe and that additional studies are warranted to further determine the efficacy of TXA in reducing blood component requirements in bleeding dogs.

Key Words: canine, coagulation, hemorrhage, anti-fibrinolytic, tranexamic acid

INTRODUCTION

Bleeding is commonly encountered in critically ill veterinary and human patients. Blood products are increasingly used in veterinary medicine, however their use is not risk-free, and is often limited by low availability and high cost of blood components. Potential adverse effects of blood component therapy include immune and non-immune transfusion reactions, such as hemolysis, infectious agent transmission, bacterial contamination, microembolism, volume overload, acute lung injury and electrolyte abnormalities (1). To date, several drugs are used to decrease blood loss and requirements of red blood cell transfusion in human medicine, including ε-aminocaproic acid (EACA), tranexamic acid (TXA) and aprotinin. EACA is a synthetic derivative of lysine, with antifibrinolytic effects, primarily through reversible blocking of lysine binding sites on plasminogen, thereby inhibiting fibrinolysis, and, to a lesser extent, through promoting antiplasmin activity. Tranexamic acid has a similar mechanism of action, but is 10-fold more potent. Aprotinin is a natural serine-protease inhibitor, inhibiting plasmin, kallikrerin and trypsin, resulting in attenuation of inflammatory responses, fibrinolysis, and thrombin generation (2-4). In clinical trials of bleeding human patients, all three drugs were shown to effectively reduce blood transfusion requirements compared with placebo (5-7).

Antifibrinolytic therapy in human medicine is indicated in cardiovascular (8) and pediatric surgery (9), heavy menstrual or post-partum bleeding (10), orthopedic surgery, such

as joint replacement (11), trauma (12) and dental procedures (13). A study comparing the effectiveness and adverse outcomes of several antifibrinolytic agents in cardiac surgery (14) has demonstrated that both high- and low-dose aprotinin, EACA and TXA therapy reduced both total perioperative blood loss and blood transfusion requirements, with no differences among these agents in risks of mortality, occurrence of stroke, myocardial infarction, or renal failure, although high-dose aprotinin therapy significantly increased the occurrence of renal dysfunction. Consequently due to lack of evidence supporting a superior efficacy of blood loss reduction compared to EACA and TXA, aprotinin has recently fallen out of favor (15). In addition, the direct pharmacy cost of aprotinin for a 4-hour cardiac procedure in a human patient is above $1,400, compared to less than $4 for EACA or TXA (16).

Antifibrinolytic agents are sporadically used in dogs and cats, largely depending on clinicians' preference and familiarity with this class of drugs. Tranexamic acid (Hexeakapron, Teva Pharmaceuticals, Petach-Tikva, Israel) has been frequently used for several years in our hospital for treatment of clinical bleeding in dogs and cats (e.g., hemoperitoneum, hemothorax, thrombocytopenia and thrombocytopathia, anticoagulant rodenticide intoxication, peri-operative bleeding and feline interstitial cystitis-associated bleeding), when animals failed to respond to conventional therapy, or when the blood component cost prohibited such therapy. The dose administered was extrapolated from the recommended human dose.

The objectives of this retrospective study were to describe the use of TXA in dogs for control of bleeding, including the doses used and the observed associated adverse effects and to evaluate its efficacy in decreasing blood product requirement in dogs with bleeding disorders.

MATERIALS AND METHODS

Selection of dogs

A computer search was conducted, using the hospital's pharmacy records, for dogs that received TXA intravenously (IV) from January 2006 to December 2010. All dogs included in the study group were diagnosed with clinical bleeding and received TXA as part of their management. Cases with incomplete medical records and those treated with TXA for less than 12 hours or by other routes were excluded. A group of clinically bleeding TXA-negative control dogs that received blood products (e.g., packed red blood cells (pRBC), fresh frozen plasma (FFP), or both), as part of their clinical management was selected based on a computer search in the hospital's database.

Data collection

Data collected from the medical records of all dogs included signalment (age, breed, gender and body weight), bleeding site, final diagnosis, hematological and coagulation test results (i.e., complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT) consecutive packed cell volume (PCV) and total plasma protein (TPP)). Hospitalization time-period, number and type of blood products used, outcome (i.e., discharged, died or euthanized) and treatment cost were also gathered.

Data collected for the study group also included TXA dose, administration route duration and associated adverse effects. The final diagnoses were divided into 7 major categories, including rodenticide anticoagulant intoxication, neoplastic, infectious, immune-mediated, traumatic, surgical and miscellaneous diseases.

Laboratory methods

Complete blood count of blood samples in potassium-EDTA was performed using automated hematology analyzers (Abacus, Diatron, Wien, Austria; Advia 120, Siemens Medical Solutions Diagnostics GmbH, formerly Bayer HealthCare GmbH, Erfurt, Germany). Total plasma protein was measured using a standard clinical refractometer, calibrated weekly with distilled water. Coagulation tests were performed from citrated (3.2%) plasma using automated coagulometric autoanalyzers (ACL 200; ACL-9000, Instrumentation Laboratory, Milano, Italy). In certain cases, during after-hours, PT and aPTT were measured manually (KC-1-micro, Amelung, Lemgo, Germany).

Statistical analysis

The Shapiro-Wilk test was used to assess data distribution. Student's t- and Mann-Whitney U-tests were used to compare quantitative variables between two groups, depending on data distribution. Quantitative variables were compared between more than two groups using ANOVA or the Kruskal-Wallis test, depending on data distribution. The association between two categorical variables was analyzed using χ^2 or

Fisher's exact tests. All tests were two-tailed and a $P ≤ 0.05$ was considered statistically significant.

RESULTS

Dog group characteristics

Seventy-two dogs were treated IV with TXA, however, four were excluded (two due to incomplete medical records, one died within 12 hours post-presentation and one had no evidence of bleeding in the medical record). The control dogs initially included 77 cases; however, 15 were excluded due to absence of clinical bleeding, and when blood components were administered for other reasons. The final study and control groups included 68 and 62 dogs, respectively.

There were no differences between study and control groups in age (median 7.5 years (range 1-16) *vs.* median 7 years, (range 1-15) respectively, $P=0.09$)), body weight (median 25.0 kg (range 5.5-50.0) *vs.* median 27.0 kg (range 3.4-70.0 kg), respectively, $P=0.53$) and hospitalization time-period (median 3 days (range 0-8) days in both groups, $P=0.26$). Mixed-breed dogs comprised 48% and 53% of the study and control groups, respectively. The study group included 24 males (7 castrated) and 44 females (34 spayed), while controls included 19 males (6 castrated) and 43 females (33 spayed), with no group gender distribution difference ($P=0.57$).
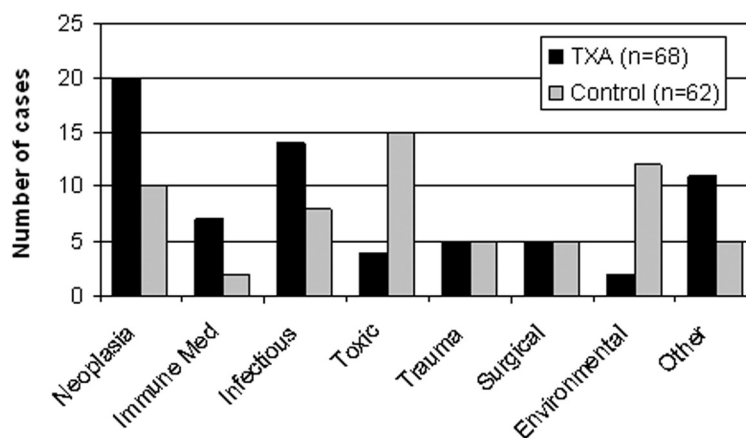
Figure 1: Underlying etiologies in 68 clinically bleeding dogs treated with tranexamic acid (TXA, black bars) and in 62 clinically bleeding negative control dogs that received blood products but no TXA (gray bars).

Causes of bleeding

The indications for TXA treatment (Figure 1) were: bleeding secondary to neoplasia (20 dogs, 29.5%), severe immune-mediated thrombocytopenia, (7 dogs, 10.3%), trauma (5 dogs, 7%), surgery (5 dogs, 7%), anticoagulant intoxication (4 dogs, 6%), *Vipera palaestinae* snakebite (2 dogs, 3%), dental problems, liver failure, lymphoplasmacytic rhinitis and chronic cystitis (1 dog each, 1% each) and infectious diseases (14 dogs, 20%), of which 9 dogs (64%) had monocytic ehrlichiosis leading to epistaxis. Other infectious causes included pyo-

Table 1: Bleeding categories in 62 bleeding dogs treated with Tranexamic acid (TA) and 58 untreated control dogs. In the control group, significantly more dogs presented for rodenticide anticoagulant intoxication, whereas in the study group significantly more dogs presented for blood loss ($P=0.001$ for both)

			Bleeding category				
			PLT[1]	Factor[2]	Blood loss	DIC[3]	Total
TXA[4]	No	Count	3	15	19	21	58
		% within TXA	5.1%	25.4%	32.2%	35.6%	100.0%
		% within bleeding category	15.8%	75.0%	33.9%	84.0%	48.8%
	Yes	Count	16	5	37	4	62
		% within TXA	25.8%	8.1%	59.7%	6.5%	100.0%
		% within bleeding category	84.2%	25.0%	66.1%	16.0%	51.2%
Total		Count	19	20	56	25	120
		% within TXA	15.7%	16.5%	46.3%	20.7%	100.0%
		% within bleeding category	100.0%	100.0%	100.0%	100.0%	100.0%

1) platelet disorders; 2) coagulation factor disorders; 3) disseminated intravascular coagulation; 4) tranexaminc acid.

metra, metriris and septic peritonitis. In 7/68 cases (10%), the final diagnosis was undetermined. Nasal and abdominal bleeding (21 dogs, 34% and 7 dogs, 10%, respectively) were the most common bleeding sites.

The study and control group were divided into 4 categories based on causes for bleeding including platelet deficiency, factor deficiency, blood loss and disseminated intravascular coagulation (DIC) (Table 1). The control group included significantly more dogs that had factor deficiency secondary to rodenticide anti-coagulant intoxication whereas the study groups included more dogs presented for blood loss (*P*=0.001 for both). Sub-group analysis based on bleeding categories was underpowered, and was therefore not performed; however, within the study group, no difference was found in survival among the bleeding categories.

Hematological data

There was no significant difference in mean PCV and TPP at presentation between the treatment and control groups (29.1 ± 11.8 % *vs.* 32.6 ± 15.5 %, *P*=0.08, and 6.59 ± 1.96 g/dL *vs.* 6.16 ± 1.60 g/dL, *P*=0.09, respectively). No differences were found in initial mean platelet counts between the study and control group (159,000 platelets/uL for both, *P*=0.99); however initial mean PT and PTT were significantly longer in the control group, (PT 14.93 ± 24.88 sec vs. 24.05 ± 22.6, *P*=0.05 and PTT 20.91 ± 12.5 sec *vs.* 28.30 ± 16.08, *P*=0.01, respectively), most likely since this group included more dogs that presented for rodenticide-anti-coagulant intoxication.

There was also no significant difference in mean PCV prior to and after TXA administration in the treatment group (0.271 ± 0.102 L/L *vs.* 0.247 ± 70 L/L respectively; *P*=0.4) as well as in TPP (62 ± 19 g/L *vs.* 58 ± 16 g/L, respectively; *P*=0.07). Mean PT and aPTT tended to decrease post TXA administration (13.1 ± 16.2 sec *vs.* 9.8 ± 4.2 sec, respectively; *P*=0.06 and 21.3 ± 12.5 sec *vs.* 18.4 ± 8.0 sec, respectively; *P*=0.058).

TXA dose and adverse effects

 TXA was administered at a mean dose of 8.6 ± 2.2 mg/kg (range 5.9 to 16.5 mg/kg) q6-8h for a median duration of 2 days (range 1-21 days). Vomiting was the only observed TXA-associated adverse side-effect noted in the study, and occurred in two dogs (3%), which received relatively high TXA doses (11.0 and 16.5 mg/kg), and occurred immediately after TXA administration.

Blood product requirement

In the TXA group, 38/68 dogs (56%) received blood products, of which, 26 (68%) received only pRBC, two (5%) re-
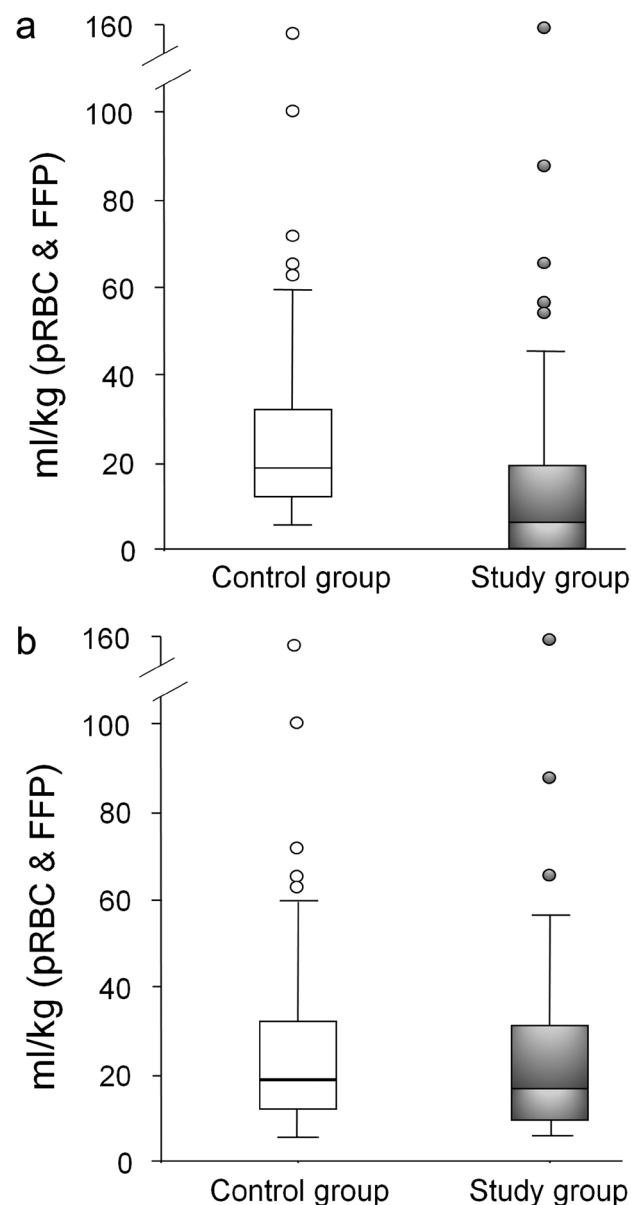
Figure 2a: Dose (mL/kg) of blood component therapy in 68 clinically bleeding treated with tranexamic acid (TXA) with or without blood transfusions, compared to 62 TXA-untreated control dogs yielded significant (*P* <0.001) difference between the groups.

Figure 2b: Dose (mL/kg) of blood component therapy in 38 clinically bleeding dogs treated with tranexamic acid (TXA), and blood transfusions, compared to 62 TXA–untreated control dogs yielded insignificant difference. pRBC, packed red blood cells; FFP, fresh frozen plasma.

ceived only FFP and 10 (26%) received both products. All 62 controls received blood products, of which, 11 (17%) received only pRBC, 23 (36%) received only FFP, and 28 (44%) received both products. The median number of blood products transfused per dog was one unit (range 0-7) in the TXA group, compared to two units (range 1-7) in the control group. When the TXA group was compared to the controls, there was a significant ($P<0.001$) difference in the total number of blood products units (pRBC's and FFP combined) transfused between groups (mean 1.1 ± 1.4 unit/dog *vs.* 2.2 ± 1.3 unit/dog) and in the dose of transfused blood components (15.1 ± 25.6 mL/kg *vs.* 29.6 ± 28.7 mL/kg, respectively; Figure 2a). However, when a similar comparison was performed, between the TXA-treated dogs that received blood products and the controls, there were no differences in the mean number of transfused blood products units (pRBC and FFP combined) (2.0 ± 1.2 unit/dog *vs.* 2.2 ± 1.3 unit/dog, respectively, $P=0.95$) or the transfused blood products dose (27.2 ± 29.2 mL/kg *vs.* 29.6 ± 28.7 mL/kg, $P=0.34$, Figure 2b). The median number of pRBC units per dog was one in both groups (ranges 1-3 and 1-5 in the TXA and control groups, respectively). There was no difference in the total number of pRBC units transfused per dog (1.4 ± 0.7 *vs.* 1.6 ± 0.9 units, $P=0.16$), total pRBC volume per dog (280 ± 141 mL *vs.* 323 ± 188 mL, $P=0.13$) and dose (17 ± 12 *vs.* 17 ± 15 mL/kg, $P=0.48$) between groups.

There was no difference in the mean treatment cost between groups (1155 ± 814 USD *vs.* 1389 ± 796 USD, $P=0.26$). The mortality rate was significantly lower in the TXA group compared to the control group (14/68, 21% *vs.* 25/62, 40%, respectively; $P=0.016$). Non-survivors included eight (12%) euthanized cases and six (9%) of death in the study group, compared to 15 (24%) euthanized and 10 (16%) death cases among the controls. The mortality rate of TXA-treated dogs that had received blood products (n=38) was lower, albeit insignificantly, compared to that of the controls (26% *vs.* 39%, respectively; $P=0.18$).

DISCUSSION

To the best of our knowledge, this is the first report documenting the clinical use of TXA in bleeding dogs. Because TXA therapy is of low cost, has been proven effective in reducing transfusion requirements and is widely used in human patients, evaluation of both its safety and efficacy in dogs is warranted.

The present results suggest that TXA, administered at 7-10 mg/kg IV q6-8 hours to dogs, is safe, with only occasional transient, self-limiting vomiting as a side-effect. Moreover, this vomiting occurred only at high TXA doses. In humans, TXA is well tolerated, with nausea and diarrhea noted in approximately 12% of the cases following oral administration, as the most frequent adverse effects. (3,17) Other adverse effects are rare; however one report has documented seizures and hyperammonemia in a human patient following IV TXA administration. (18) The true prevalence of TXA-related adverse effects in dogs may have been underestimated in the present study, because some clinical signs might have been mistakenly attributed to the primary disease rather than to TXA administration.

The present results have shown that when the entire TXA-treated group was compared with the controls, there was a significant reduction in use of the number of all blood component as well as pRBC units per dog, suggesting that TXA therapy may decrease the requirement for blood products in clinically bleeding dogs. However, this finding should be interpreted with caution for several reasons. First, the retrospective nature of this study renders it impossible to determine whether pure financial or pure medical considerations dictated the decision to avoid blood transfusion therapy in some TXA-treated dogs. Possibly, in certain dogs, blood product therapy was clinically indicated, and was limited by financial constraints, and TXA therapy was selected as a "poor man's" choice. Second, the mortality rate was significantly higher in the control group compared to the TXA group, probably reflecting higher severity of the diseases in this group, and somewhat limiting the conclusion that can be made from such comparison. Finally, when the comparison included only dogs that have received blood products of both groups no group difference was observed.

The study group included dogs treated with TXA due to a various bleeding causes and mechanisms. However, TXA exerts its beneficial effect through decreasing fibrinolysis and increasing clot strength (3,16,19). Possibly, the apparent lack of efficacy observed herein was partly due to the high variability of the bleeding etiologies in the TXA group. In 16 of 64 TXA-treated dogs (25%), bleeding probably resulted from primary hemostasis failure due to thrombocytopenia (e.g., monocytic ehrlichiosis and immune mediated thrombocytopenia) leading to almost exclusively small blood vessel

bleeding, where the primary platelet plug has a major role in hemostasis, while the secondary fibrin clot plays minor role. It would seem likely that in such conditions, the beneficial TXA effect is expected to be less significant. In contrast, in cases were bleeding occurred secondary to trauma, surgical procedures or a ruptured spleen, the clot-stabilizing effect of TXA may play a more significant role. These hypotheses should be weighed cautiously, because evidence show that TXA increases platelet function in horses (20), and is used as an adjunctive treatment of human von Willebrand disease and factor XI deficiency (21,22).

Selection of a more homogenous study group, in terms of the bleeding tendency mechanism, might have resulted in a more pronounced beneficial effect of TXA. In a recent study, post-operative EACA administration decreased both bleeding occurrence and severity in retired racing greyhounds undergoing ovariohysterectomy or orchiectomy (23). In this breed, altered fibrinolysis is hypothesized to cause bleeding tendencies, and the beneficial EACA effect was hypothesized to improve this derangement. High variability in bleeding severity among TXA-treated dogs might have also contributed to this group's heterogeneity. In this retrospective, uncontrolled study, there was no way to quantify bleeding severity, rendering a comparison of bleeding severity between groups, as well as TXA effect prior to and after its administration or blood components treatment, impossible.

Although theoretically there is a concern that anti-fibrinolytic drugs may increase the risk of thromboembolic complications, such as deep vein thrombosis and acute myocardial infarction, no such risks were observed in clinical trials of TXA in humans (3,14). A large meta-analysis in humans undergoing orthopedic surgery receiving antifibrinolytic agents has demonstrated significant decrease in blood loss, with no increase in the risk for venous thromboembolism, although their efficacy remains somehow questionable (11) in other meta-analyses, due to insufficient controlled studies (10). In the present study, thrombosis was not observed clinically in any of TXA-treated dog; however, as markers of thromboembolism (e.g., D-dimer and fibrin degradation products levels and antithrombin activity) were rarely measured, its occurrence cannot be completely excluded.

In conclusion, this study is the first to document TXA use in a relatively large group of clinically bleeding dogs. TXA administered IV at 7-10 mg/kg q6-8 hours is safe in dogs, however its efficacy in reducing the number and dose of blood components remains to be further investigated.

REFERENCES

1. Jutkowitz, L. A.: Blood transfusion in the perioperative period. Clin. Tech. Small Anim. Pract. 19:75-82, 2004.
2. Slaughter, T. F. and Greenberg, C. S.: Antifibrinolytic drugs and perioperative hemostasis. Am. J. Hematol. 56:32-36, 1997.
3. Dunn, C. J. and Goa, K. L.: Tranexamic acid: a review of its use in surgery and other indications. Drugs. 57:1005-1032, 1999.
4. Peters, D. C. and Noble, S.: Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. Drugs. 57:233-260, 1999.
5. Henry, D.A., Carless, P.A., Moxey, A.J., O'Connell, D., Stokes, B.J., Fergusson, D.A. and Ker, K.: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 16. CD001886, doi: 10.1002/14651858. CD001886.pub4.2011.
6. Fergusson, D., Glass, K. C., Hutton, B. and Shapiro, S.: Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clin Trials. 2:218-229; discussion 229-232, 2005.
7. Laupacis, A. and Fergusson, D.: Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. Anesth. Analg. 85:1258-1267, 1997.
8. Henry, D. A., Carless, P. A., Fergusson, D. and Laupacis, A.: The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. Cmaj. 180:183-193, 2009.
9. Schouten, E.S., van de Pol, A.C., Schouten, A.N., Turner, N.M., Jansen, N.J. and Bollen, C.W.: The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr. Crit. Care Med. 10:182-190, 2009.
10. Ferrer. P., Roberts. I., Sydenham. E., Blackhall, K. and Shakur, H.: Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. BMC Pregnancy Childbirth. 9:29, 2009.
11. Kagoma, Y. K., Crowther, M. A., Douketis, J., Bhandari, M., Eikelboom, J. and Lim, W.: Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb. Res. 123:687-696, 2009.
12. Shakur, H., Roberts, I., Bautista, R., Caballero, J., Coats, T., Dewan, Y., El-Sayed, H., Gogichaishvili, T., Gupta, S., Herrera, J., Hunt, B., Iribhogbe, P., Izurieta, M., Khamis, H., Komolafe, E., Marrero, M.A., Mejía-Mantilla, J., Miranda, J., Morales, C., Olaomi, O., Olldashi, F., Perel, P., Peto, R., Ramana, P.V., Ravi, R.R. and Yutthakasemsunt, S.: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 376:23-32, 2010.
13. Garfunkel, A.A., Galili, D. Findler, M., Lubliner, J. and Eldor, A.: Bleeding tendency: a practical approach in dentistry. Compend. Contin. Educ. Dent. 20:836-838, 840-832, 844 passim, 1999.

14. Brown, J. R., Birkmeyer, N.J. and O'Connor, G.T.: Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation. 115:2801-2813, 2007.

15. Mangano. D. T., Tudor. I. C. and Dietzel, C.: The risk associated with aprotinin in cardiac surgery. N. Engl. J. Med. 354:353-365, 2006.

16. Umscheid, C. A., Kohl, B. A. and Williams, K.: Antifibrinolytic use in adult cardiac surgery. Curr. Opin. Hematol. 14:455-467, 2007.

17. Wellington, K. and Wagstaff, A. J.: Tranexamic acid: a review of its use in the management of menorrhagia. Drugs. 63:1417-1433, 2003.

18. Wang, C. S., Yang, C. J., Chen, S. C., Chen, H. C. and Huang, M. S.: Generalized convulsion resulted in hyperammonemia during treatment with tranexamic acid for hemoptysis. Ir. J. Med. Sci. 180:761-763.

19. Serna, D. L., Thourani, V. H. and Puskas, J. D.: Antifibrinolytic agents in cardiac surgery: current controversies. Semin. Thorac. Cardiovasc. Surg. 17:52-58, 2005.

20. Ross, J., Dallap, B. L., Dolente, B. A. and Sweeney, R.W.: Pharmacokinetics and pharmacodynamics of epsilon-aminocaproic acid in horses. Am. J. Vet. Res. 68:1016-1021, 2007.

21. Livnat T., Tamarin I., Mor Y., Winckler, H., Horowitz, Z., Korianski, Y., Bar-Zakay, B., Seligsohn, U. and Salomon, O.: Recombinant activated factor VII and tranexamic acid are haemostatically effective during major surgery in factor XI-deficient patients with inhibitor antibodies. Thromb. Haemost. 102:487-492, 2009.

22. Mannucci, P. M.: Treatment of von Willebrand's Disease. N. Engl. J. Med. 351:683-694, 2004.

23. Marín, L.M., Iazbik, M.C., Zaldivar-Lopez, S., Guillaumin, J., McLoughlin, M.A. and Couto, C.G.: Epsilon aminocaproic acid for the prevention of delayed postoperative bleeding in retired racing greyhounds undergoing gonadectomy. Vet Surg. 2012 Jul;41:594-603. doi: 10.1111/j.1532-950X.2012.00965.x. Epub 2012 Jun 19.