Abstract

Objectives – To determine the frequency of delayed postoperative bleeding in retired racing Greyhounds with appendicular bone tumors undergoing limb amputations. To identify if administration of epsilon-aminocaproic acid (EACA) was effective on the prevention of postoperative bleeding.


Setting – Veterinary university teaching hospital.

Animals – Forty-six retired racing Greyhounds (RRGs) diagnosed with primary appendicular bone tumors that underwent limb amputation were included in the study.

Interventions – None.

Measurements and Main Results – Thirteen of 46 RRGs (28%) included in the study had delayed postoperative bleeding starting 48–72 h after surgery. Bleeding episodes included cutaneous, subcutaneous, and external bleeding that extended from the area of the surgical site that became widespread within hours, and that required administration of blood components. A paired t-test suggests that there was a significant decrease in PCV postoperatively for both dogs that bled and dogs that did not bleed (P < 0.0001). Forty of 46 RRGs (86%) received either fresh frozen plasma (FFP) or EACA or both, for the prevention of postoperative bleeding. A
logistic regression model determined that dogs that did not receive EACA were 5.7 times more likely to bleed than dogs that did receive EACA, when controlling for whether or not they received FFP (95% CI: 1.02–32.15, \( P = 0.047\)).

**Conclusion** – This retrospective study suggests that preemptive postoperative administration of EACA appears to be efficacious in decreasing the frequency of bleeding in RRGs undergoing limb amputation; however, a prospective study is warranted to corroborate its effectiveness.


**Keywords:** coagulation, dog, osteosarcoma, postoperative complications

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>OSA</td>
<td>osteosarcoma</td>
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<tr>
<td>RRGs</td>
<td>retired racing Greyhounds</td>
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<td>FFP</td>
<td>fresh frozen plasma</td>
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<td>EACA</td>
<td>epsilon aminocaproic acid</td>
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<tr>
<td>pRBCs</td>
<td>packed red blood cells</td>
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<tr>
<td>cTnI</td>
<td>Troponin I concentration</td>
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<tr>
<td>OHE</td>
<td>ovariohysterectomy</td>
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<tr>
<td>OSPT</td>
<td>one-stage prothrombin time</td>
</tr>
<tr>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
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<tr>
<td>FIB</td>
<td>fibrinogen concentration</td>
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<tr>
<td>KCL</td>
<td>potassium chloride</td>
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<tr>
<td>TPP</td>
<td>total plasma protein</td>
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<tr>
<td>HELLP</td>
<td>syndrome – Hemolysis, Elevated Liver enzyme Low Platelet count syndrome</td>
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<tr>
<td>CK</td>
<td>creatine kinase</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>NSAIDs</td>
<td>nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>DIC</td>
<td>disseminated intravascular coagulation</td>
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<tr>
<td>TAFI</td>
<td>thrombin activatable fibrinolysis inhibitor</td>
</tr>
<tr>
<td>T-TM</td>
<td>thrombin–thrombomodulin</td>
</tr>
<tr>
<td>PAI-1</td>
<td>plasminogen activator inhibitor-1</td>
</tr>
<tr>
<td>t-PA</td>
<td>tissue plasminogen activator</td>
</tr>
<tr>
<td>CRYO</td>
<td>cryoprecipitate</td>
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<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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</table>

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**Introduction**

Greyhounds and other sighthounds have unique physiological traits that distinguish them from other breeds, including high PCV, hemoglobin concentration, and whole blood viscosity, low white blood cell, neutrophil and platelet counts,\(^1\)–\(^4\) low total serum protein concentration,\(^5\) and acute phase protein concentrations\(^5\),\(^6\) among others.

Canine appendicular osteosarcoma (OSA) is the most prevalent form of cancer reported in RRGs, with a prevalence of 45% for dogs with cancer (42 of 94 RRGs).\(^9\) OSA is also the most common cause of death or euthanasia, accounting for approximately 25% of the deaths in the study period (28 of 113 RRGs).\(^9\) Limb amputation followed by chemotherapy is frequently recommended for the treatment of OSA.\(^10\) The etiology of canine OSA is generally unknown. Bone microtrauma, metallic implants, gonadal status,\(^11\) and genetic abnormalities have all been proposed as possible risk factors.\(^12\) Although we estimate that as many as 4,000 RRG/year will develop OSA,\(^9\) the actual number may be higher, since not all cases are reported nor confirmed.

In a recent study, we demonstrated that 26% of RRGs developed delayed postoperative bleeding after routine gonadectomy (48–72 h).\(^18\) Affected dogs had normal results of preoperative hemostasis assays but significantly lower activities of antiplasmin and antithrombin than dogs that did not bleed, suggesting that the excessive postoperative bleeding in RRGs may be due to abnormalities in clot maintenance or the fibrinolytic system, rather than to primary or secondary hemostatic defects.\(^18\) This prevalence (26%) is considerably higher than previously reported after ovariohysterectomy (OHE) or orchectomy in other dog breeds (0–2%).\(^19\)–\(^21\)

In some RRGs, the delayed postoperative bleeding may progress to a generalized bleeding disorder associated with clinical signs of illness, profuse widespread bruising, mild thrombocytopenia, and hemolysis, and increases in liver and muscle enzyme activities.\(^18\) Thus, owners of RRGs with OSA who elect amputation can potentially face these complications and associated expenses related to blood component therapy and intensive care.\(^22\) Providing a method to prevent or minimize the severity of postoperative bleeding in RRGs will not only have major economic impact but also will markedly decrease the associated complications for owners.

Fibrinolytic inhibitors are a pharmacologic option to manage postoperative bleeding and have proven to be effective in human patients and horses undergoing surgery.\(^28\),\(^29\) Epsilon aminocaproic acid (EACA) is a potent inhibitor of fibrinolysis.\(^30\),\(^31\) EACA prevents activation of plasminogen into plasmin on the surface of the fibrin clot,\(^44\) by preventing the binding of
plasminogen to C-terminal lysine residues on partially degraded fibrin, thus blocking reversibly the plasminogen-binding site (Figure 1), which is essential for efficient plasmin formation. EACA can either block enhanced fibrinolytic activity, or rapidly restore hypofibrinolytic states to normal, thus EACA impedes the dissolution of fibrin clots.

EACA has a wide therapeutic index; no relevant adverse effects were reported in toxicologic studies in dogs, rabbits, and rats, with doses as high as 0.5 g/kg, a 100-fold dosage from that used in this study. Other potential uses of EACA in veterinary medicine include treatment of dogs diagnosed with degenerative myelopathy and as a topical treatment of persistent corneal epithelial defects. To our knowledge, there are no studies on the effects of EACA in spontaneously occurring hemostatic abnormalities in dogs.

The objective of this study was to determine the frequency of delayed postoperative bleeding in RRGs with appendicular bone tumors undergoing limb amputations and to determine if administration of EACA was effective on the prevention of postoperative bleeding. We hypothesized that the administration of a prohemostatic agent, such as EACA would prevent or minimize bleeding after amputation in RRGs.

### Materials and Methods

Medical records from the Hospital for Companion Animals at The Ohio State University Veterinary Medical Center were searched for RRGs that underwent limb amputation for primary appendicular bone tumors from December 2003 to December 2008. Forty-six medical records were reviewed retrospectively and information was collected on the results of physical examinations, anesthesia and analgesia protocols, surgery, postoperative changes in PCV and total plasma protein (TPP), postoperative complications, management of complications (including the use of FFP or EACA), length of hospitalization, and total costs. Due to the fact that we observed postoperative signs compatible with rhabdomyolysis (ie, pigmenturia and high muscle enzyme activities) in some RRGs, postoperative changes in muscle enzyme activities were also evaluated.

Due to the retrospective nature of the present study, the anesthesia, analgesia, and antimicrobial protocols were not fully standardized and had minor variations. The dogs were monitored during surgery with ECG, pulse oximetry, respirometry, capnography, measurement of peripheral arterial blood pressure, and body temperature.

Postoperative bleeding was defined as moderate to severe delayed postoperative cutaneous, subcutaneous, or external bleeding originating in the surgical site that required administration of packed red blood cells (pRBCs), the latter was determined by the attending clinician. Potential variables in the bleeding status included association of bleeding and nonsteroidal anti-inflammatory drugs (NSAIDs), gender and front versus rear. In our clinical experience, rear limb amputations appeared to be associated with more severe bleeding and longer hospital stays than the front limb amputations, thus the location of the tumor was included as a variable.

### Statistical analysis

Descriptive statistics were performed for all the variables measured. The D’Agostino and Pearson omnibus
test was used to evaluate for data normality. Variables that were normally distributed were compared using an independent samples t-test, and those that were not normally distributed were compared using nonparametric analysis (Mann-Whitney test); results are reported as mean ± SD when normally distributed or median (interquartile range) when data were not normally distributed.

Parameters from before and after surgery were compared using a paired t-test or a Wilcoxon rank sum test as appropriate for the distribution of the data, a nonparametric test (Mann-Whitney test) was used to compare length of hospitalization and the medical expenses between dogs with front and rear limb amputations, and between Group 1 and Group 2. A commercially available statistical software was used for statistical analysis. For all analyses, values of P < 0.05 were considered significant. A Holm’s procedure was used to adjust for the type 1 error as a result of performing multiple comparisons.

Logistic regression was used to evaluate potential predictors of whether or not bleeding occurred. The primary variable of interest was whether or not a dog received EACA so this variable was forced in the model. Other potential variables in the bleeding status included association of bleeding and NSAIDs, gender, and front versus rear. Variables with values of P ≤ 0.25 in the initial bivariate analyses were included in the multivariate logistic regression analysis. Variables were removed from the full multivariate model on the basis of results of the Wald test. Standard statistical software was used.

### Results

#### Clinical features

Forty-six RRGs underwent amputation due to primary bone tumors. The RRGs included in this study were divided into two groups; Group 1 included the dogs that developed delayed postoperative bleeding within 48–72 h, Group 2 included the dogs that did not bleed postoperatively. Thirteen dogs (28%) were included in Group 1; there were eight neutered males and five spayed females, and their ages ranged from 4 to 13 years (median, 8 years). The median weight was 31.3 kg (range 21.3–43 kg). Eleven dogs had a histopathologic diagnosis of appendicular OSA (84.6%), one had hemangiosarcoma (HSA) (7.6%), and one had a histiocytic sarcoma (7.6%). Thirty-three dogs (71%) were included in Group 2, there were 21 neutered males and 12 spayed females, and their ages ranged from 5 to 11 years (median, 8 years). The median weight was 32.4 kg (range 23.5–43.3 kg). Thirty-two dogs had a histopathologic diagnosis of appendicular OSA (96.6%), one had hemangiosarcoma (HSA) (3.4%).

### Preoperative clinicopathologic evaluation

Forty-one RRGs had blood sampled preoperatively for a CBC and serum biochemical profile; the remaining five dogs had a CBC and serum chemistry profile done by the referring veterinarian; 39 of 46 dogs had complete hemostasis panels (ie, one-stage prothrombin time [OSPT], activated partial thromboplastin time [APTT], and fibrinogen concentration [FIB]) only one of the seven dogs that did not have hemostasis panels developed postoperative bleeding, the remaining six dogs were included in Group 2. All the dogs had PCV, TPP, and systolic blood pressure measured prior to and after surgery. The results of the PCV, TPP, CBC, serum biochemical profile, hemostasis panels, and systolic blood pressure were within reference intervals for the breed in all dogs.

The results of the CBC and serum biochemical profile done by the referring veterinarians were within reference intervals for the respective laboratories, but the data were not available for statistical evaluation. No dogs had comorbidities at the time of surgery.

### Anesthesia, fluid therapy, antibiotic, and analgesic protocols

Most dogs were premedicated with acepromazine (0.025–0.05 mg/kg IM) and morphine (0.2 mg/kg IM). Anesthesia was induced with propofol (4–6 mg/kg IV); lidocaine (50 μg/kg/min IV), and isoflurane in oxygen was used for maintenance (1–3% induction, 0.5–2.0% maintenance). All of the dogs received intraoperative fluid therapy consisting of a balanced electrolyte solution at 5 mL/kg/h IV.

The postoperative analgesia/sedation protocols included continuous rate infusion of fentanyl (1–8 μg/kg/h IV), lidocaine (25–50 μg/kg/min IV), ketamine (10–15 μg/kg/min IV), morphine (0.01–0.03 mg/kg/h IV), and hydromorphone (0.008–0.03 mg/kg/h), singly or in combination. Pain control protocols also included tramadol (1–4 mg/kg), deracoxib (3–4 mg/kg), and carprofen (1–2 mg/kg). Cefazolin sodium (22 mg/kg IV) was used as prophylactic antimicrobial therapy in 27 dogs, at the discretion of the surgeon. Eight RRGs (61%) included in Group 1 and 21 RRGs (63%) included in Group 2 had received NSAIDs orally (eg, deracoxib, carprofen, meloxicam) prior to surgery. NSAIDs administration did not have a significant effect on bleeding (P > 0.05).

### Surgery

Eight of 13 RRGs in Group 1 (61.5%) underwent coxofemoral disarticulation and five dogs (38.4%) underwent scapulohumeral amputation. Fifteen of 33 in Group 2 (45.4%) underwent coxofemoral disarticulation or midfemoral amputation (for tibial tumors), and
18 (54.5%) underwent scapulohumeral amputation. Eight dogs (61.5%) in Group 1 and 15 (45.4%) in Group 2 underwent right limb amputation, while five dogs in Group 1 (38.4%) and 18 dogs (54.5%) in Group 2 had left limb amputation. Front versus rear leg and right versus left leg amputation did not have a significant effect on bleeding ($P > 0.05$).

**Postoperative complications**

None of the dogs experienced intraoperative or immediate postoperative bleeding over a 5-year period; however, four of the first six RRGs (66.6%) that underwent limb amputation during the study period developed severe bleeding complications and required transfusion of blood components. These were the index patients where the problem was first identified; none of them had received prophylactic prohemostatics.

After identifying this bleeding complication, FFP was preemptively administered immediately after inducing anesthesia (10–15 mL/kg, IV, starting dose) in the following 15 RRGs that underwent amputation. Five of these 15 dogs (33%) developed postoperative bleeding, requiring additional administration of blood components.

In an attempt to prevent postoperative bleeding and decrease transfusion requirements and related costs, EACA was administered in 25 RRGs that underwent limb amputation during the last 3 years of this study. Four RRGs received both FFP and EACA, none of them developed the postoperative bleeding. The first dose of EACA ($500–1,000$ mg, IV total dose or $15–40$ mg/kg) was administered immediately after surgery (1 mL diluted in 15 mL of 0.9% NaCl over 30 min), followed by administration of EACA tablets ($500–1,000$ mg of EACA PO, total dose, q8 h, for 5 days). FFP was administered at the clinician’s discretion, if bleeding developed. Four of the 25 RRGs (16%) that received EACA developed bleeding complications; two of them had received both EACA and FFP preemptively. Only one of the four dogs required a pRBC transfusion.

The observed signs of bleeding consisted of cutaneous bruising that extended from the area of the surgical site, and became widespread within hours. There was no bleeding from mucosal surfaces or in areas distant from the surgical site (Figure 2). In total 13 of 46 RRGs (28%) had delayed postoperative bleeding starting 36–48 h after surgery, four of the 13 dogs in Group 1 (30%) developed postsurgical local infection and sepsis. Three of them (75%) had undergone hindlimb amputation, and one (25%) had forelimb amputation. In the study reported here none of the RRGs that received EACA had any adverse effect.

Nine of the 13 dogs in Group 1 had biochemistry profiles postoperatively; all of them had marked postoperative increases in creatinine kinase (CK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) activities. A paired $t$-test demonstrated that the CK activity in Group 1 significantly increased after amputation from $320$ (147–2,208) U/L to $12,600$ (4,587–33,720) U/L, reference interval 76–254 U/L ($P = 0.0425$), ALT from $46.0$ (33.0–57.0) to 220.0 (123.0–277.0) U/L, reference interval 28–82 U/L ($P = 0.012$), and AST from 42.0 (32.0–118.0) to 1,253 (601.0–2,168) U/L reference interval 24–57 U/L ($P = 0.012$) (Table 2).

A multiple logistic regression model was used to predict factors associated with bleeding. After evaluating EACA administration, FFP administration, NSAID administration, gender, front versus rear leg amputation, and right versus left leg amputation, only EACA administration had a significant effect on bleeding. Dogs that did not receive EACA were 5.7 times more likely to bleed than dogs that received EACA, when controlling for whether or not they received FFP (95% CI: 1.02–32.15, $P = 0.047$). Interestingly, dogs that did not receive FFP were not significantly more likely to bleed than those that received FFP (95% CI: 0.51–15.7, $P = 0.230$).

**Pre- and postoperative PCV, TPP, and platelet count**

Forty-five dogs (98%) had postoperative PCV and TPP recorded 48–72 h after surgery. The PCV decreased significantly after surgery in both groups. In Group 1, the PCV decreased from $0.55$ (0.50–0.60) to $0.33$ (0.24–0.40) L/L; reference interval, 0.50–0.68 L/L, (55.0 [50.0–60.5] to 33.0 [24.5–40.0]%; reference interval 50–68%) ($P < 0.0014$; Table 1); in Group 2 the PCV also decreased from $0.52$ (0.51–0.57) to 0.36 (0.34–0.43) L/L, reference interval 0.50–0.68 L/L, 52.0 [51.0–57.7] to 36.5 [34.2–43.2%], reference interval 50–68% ($P < 0.0013$; Table 1). The postoperative PCV was not significantly different between the two groups ($P = 0.27$). There were no significant
Table 1: Results of preoperative and postoperative packed cell volume (PCV), total plasma protein (TPP), and systolic blood pressure (BP) in Group 1 (RRGs that bled) and Group 2 (RRGs that did not bleed)

<table>
<thead>
<tr>
<th>Analyte (Greyhounds reference interval)</th>
<th>Group 1 Pre-Sx median (range) (n)</th>
<th>Group 1 Post-Sx median (range) (n)</th>
<th>P value</th>
<th>Group 2 Pre-Sx median (range) (n)</th>
<th>Group 2 Post-Sx median (range) (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (0.50–0.68 L/L) [50–68%]</td>
<td>0.55 (0.50–0.60) (13)</td>
<td>0.33 (0.24–0.40) (13)</td>
<td>0.0014</td>
<td>0.52 (0.51–0.57) (32)</td>
<td>0.36 (0.34–0.43) (32)</td>
<td>0.0013</td>
</tr>
<tr>
<td>TPP (48–63 g/L) [4.8–6.3 g/dL]</td>
<td>66.0 (61–69) (13)</td>
<td>44.0 (39–52) (13)</td>
<td>0.0012</td>
<td>65.0 (60.0–69.0) (32)</td>
<td>42.5 (40.0–48.0) (32)</td>
<td>0.0011</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>115 (100–145) (12)</td>
<td>160 (127–177) (12)</td>
<td>0.0720</td>
<td>120 (110–140) (29)</td>
<td>146 (125–167) (29)</td>
<td>0.0344</td>
</tr>
</tbody>
</table>

Platelet Count (145–309 × 10⁹/L) 217.0 (193.5–260.5) (9) 80.1 (58.5–91.8) (9) 0.0015 229.0 (202.5–263.0) (5) 198 (117.5–245.0) (5) 0.0224

Notes: Data are presented as median (interquartile range 25th–75th percentile). Sx, surgery.
Reference interval in parentheses next to analyte.

There were significant differences between the postoperative PCV of dogs that underwent rear versus front limb amputations ($P = 0.12$).

There was also a significant decrease in TPP after amputation in both groups; in Group 1 the TPP decreased from 66.0 (61–69) to 44.0 (39–52) g/L, reference interval 48–63 g/L (6.6 [6.1–6.9] to 4.4 [3.9–5.2] g/dL, reference interval 4.8–6.3 g/dL) ($P < 0.0012$) and in Group 2 the TPP also decreased from 65.0 (60.0–69.0) to 42.5 (40.0–48.0) g/L, reference interval 48–63 g/L, (6.5 [6.0–6.9] to 4.2 [4.0–4.8] g/dL) ($P < 0.0011$), but there was no difference in TPP postoperatively between groups ($P = 0.51$).

Nine RRGs in Group 1 and five in Group 2 had a complete CBC postoperatively, the platelet count in the nine dogs in Group 1 significantly decreased from 217.0 (193.5–260.5) to 80.1 (58.5–91.8) × 10⁹/L, reference interval 145–309 × 10⁹/L ($P < 0.0015$). There was no difference detected between the platelet count before and after surgery in the five dogs in Group 2 (229.0 (202.5–263.0) to 198 (117.5–245.0) × 10⁹/L). There was a significant difference between platelet counts postoperatively between groups ($P = 0.0224$; Table 2).

Postoperative mortality, length of hospitalization, and total cost of hospitalization

None of the dogs died perioperatively. The length of hospitalization in Group 1 (median 7, range 3–14 days) was significantly longer than in the Group 2 (median 5, range 3–13 days) ($P = 0.009$). The hospital bill in Group 1 (median $4,775 USD; range $1,215–6,187 USD) was significantly higher than in Group 2 (median $2,687 USD; range $1,767–4,786 USD) ($P = 0.0002$).

Discussion

Over a 5-year period (2003–2008), 28% of the RRGs that underwent amputation due to primary bone tumors developed a delayed postoperative bleeding complication. Ninety-three percent of the Greyhounds included in this study had a histopathologic diagnosis of OSA, consistent with findings in previous studies.¹³

All the RRGs in Group 1 dogs had a normal platelet count before surgery. The significant decrease in their platelet count was concomitant with the decrease in PCV, which suggests that this degree of thrombocytopenia may be due to blood loss. In addition, a platelet count of 80,000 × 10⁹/L is unlikely to result in spontaneous bleeding. The diagnosis of disseminated intravascular coagulation (DIC) in veterinary medicine is traditionally based on three or more abnormal hemostatic parameters, including OSPT, APTT, FIB, D-dimer concentration, platelet count, and erythrocyte morphology.¹⁸ Both the postoperative OSPT and APTT values from dogs in Group 1 were within the reference interval; therefore,

Table 2: Results of preoperative and postoperative of creatine kinase (CK) activity, and bilirubin and creatinine concentrations in dogs in Group 1

<table>
<thead>
<tr>
<th>Analyte (Greyhounds reference interval)</th>
<th>Group 1 Pre-Sx median (range) (n)</th>
<th>Group 1 Post-Sx median (range) (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (76–254 IU/L)</td>
<td>320 (147–2,208) (9)</td>
<td>12,600 (4,587–33,720) (9)</td>
<td>0.0425</td>
</tr>
<tr>
<td>ALT (28–82 IU/L)</td>
<td>46.0 (33.0–57.0) (9)</td>
<td>220.0 (123.0–277.0) (9)</td>
<td>0.012</td>
</tr>
<tr>
<td>AST (24–57 IU/L)</td>
<td>42.0 (32.0–118.0) (9)</td>
<td>1,253 (601.0–2,168) (9)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Notes: Data are presented as median (interquartile range 25th–75th percentile). Sx, surgery.
Reference interval in parentheses next to analyte.
DIC was an unlikely cause of bleeding in this patient population.

Although the analgesia protocol was not standardized and had minor variations, it is unlikely that the drugs administered perioperatively contributed to the bleeding outcomes. In this study, 52% of the RRGs had received NSAIDs prior to the surgery, but there was no association between the bleeding and administration of NSAIDs. Thus drug-associated platelet dysfunction is not likely the mechanism responsible of the postoperative complication in the RRGs. Moreover, platelet dysfunction typically results in intraoperative bleeding rather than delayed postoperative bleeding.

Independently of the use of FFP, administration of EACA was the only parameter that had a significant effect on the frequency of bleeding in the RRGs in this study, in people EACA has been used to manage postoperative bleeding since the 1960s after prostatectomy, after abnormal hemorrhage in women with intrauterine devices, and to treat hematuria and excessive bleeding after dental extractions in hemophiliacs. Since then, EACA has been studied broadly for its efficacy in reducing perioperative blood loss in various types of surgery, including cardiovascular, spinal, acute trauma, and orthopedic surgery. The in vitro and in vivo actions of EACA in dogs were extensively studied in the 1950s and 1960s, but to our knowledge there are not any reports of the use of EACA in dogs since then. Interestingly, in dogs EACA neutralizes bleeding states created experimentally by infusion of plasmin or a plasminogen activator. The dose of EACA used in this study was extrapolated from the dose used in people. None of the RRGs that received EACA had any adverse effect.

The delayed local postoperative bleeding in most of the RRGs in Group 1, progressed to a generalized bleeding disorder associated with profuse widespread bruising, mild thrombocytopenia, anemia, and increases in liver and muscle enzyme activities. The mechanism responsible for these changes may be similar to that observed in women with preeclampsia and HELPP syndrome, where massive endothelial dysfunction leads to similar clinicopathologic changes. The use of specific plasma markers such as big endothelin 1, von Willebrand factor, vascular endothelial growth factor (VEGF), and hyaluronic acid will be needed to confirm the presence of endothelial dysfunction in the RRGs. The rhabdomyolysis could also have been the results of muscle hypoxia due to hypoperfusion or thrombembolism.

The standard of care for small animal patients with spontaneous bleeding is the administration of plasma components, such as FFP, cryoprecipitate, or cryopoor plasma. FFP is the most commonly used plasma component, since it contains all clotting factors and inhibitors such as antithrombin (AT) and protein C, which are used in patients with inherited deficiencies of these inhibitors. The cost of a transfusion of FFP for a Greyhound (average weight 32 kg) using 10–15 mL/kg or 320–480 mL (approximately 3–5 units) ranges from $330 to $550 USD, whereas a 5-day course of EACA costs approximately $45 USD, thus enhancing the appeal of this perioperative hemostatic agent in RRGs for the prevention of postamputation bleeding. The mean length of hospitalization and total hospital bill were significantly higher in Group 1 than in Group 2. Roughly, the length of hospitalization was 50% longer and the bill almost twice as high for the dogs in Group 1.

Platelet number and function abnormalities, intrinsic, extrinsic, and common pathway abnormalities, von Willebrand’s disease and von Willebrand’s syndrome, fibrin stabilization defects and fibrinogen activity have been ruled out as likely causes of the bleeding in RRGs. In addition to the absence of abnormalities in the hemostasis profile, RRGs with delayed postoperative bleeding have lower antiplasmin activity than the nonbleeders. Thus, we propose that the mechanism of the bleeding is likely a “clot maintenance disorder” (eg, enhanced fibrinolysis) or it is associated with endothelial dysfunction.

Limitations of this study include its retrospective nonrandomized design, the lack of controlled variables, the limited sample size, and the fact that we did not account for variations on costs over time. Although we found a potential protective effect of EACA in Greyhounds with bleeding tendencies, our confidence intervals were wide, thus a prospective randomized study is needed to determine if RRGs that undergo other surgical procedures will benefit from administration of EACA.

In conclusion, this retrospective study suggests that preemptive postoperative administration of EACA appears to be efficacious in decreasing the frequency of bleeding in RRGs undergoing limb amputation. However, a prospective study is warranted to corroborate its effectiveness.

**Acknowledgments**

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**Footnotes**

a Gary Guccione, National Greyhound Association, personal communication.
b Cell-Dyn 3500 R, Abbott Laboratories, Abbott Park, IL.
c LaserCyte, IDEXX Laboratories, Westbrook, MD.
d Roche Laboratories, Indianapolis, IN.
e ACL® 7000, Beckman Coulter, Inc, IL, USA.
f Prism version 4.0, GraphPad Software Inc, San Diego, CA.
g Stata, version 10.0, StataCorp, College Station, TX.
h Aceproject, Butler Animal Health Supply, Dublin, OH.
References

minimising perioperative allogeneic blood transfusion. Cochrane
47. Cliffton EE. I. Evidence that a hypercoagulable state precedes mas-
sive oozing during and after major surgery. 2. Effect of epsilon-
aminocaproic acid (EACA) in control of surgical oozing. Bibl
48. Jordan D, Delphin E, Rose E. Prophylactic epsilon-aminocaproic
acid (EACA) administration minimizes blood replacement
829.
49. Pokorny F. Toxicological experiments with cyclohexamine oxine, e
CAProlactein and e aminocaproic acid. Mutual biological compari-
50. Lang K, Bitz H. Metabolism of e aminocaproic acid. Biochem Z
51. Polizopoulou ZS, Koutinas AF, Patsikas MN, Soubasis N. Evalua-
tion of a proposed therapeutic protocol in 12 dogs with tentative
52. Regnier A, Cazalot G, Cantaloube B. Topical treatment of non-
healing corneal epithelial ulcers in dogs with aminocaproic acid.
53. Rosenberger JA, Pablo NV, Crawford PC. Prevalence of and intrinsic
risk factors for appendicular osteosarcoma in dogs: 179 cases (1996–
55. Hoffman M, Monroe DM. Coagulation 2006: a modern view of
56. Kraft P, Schwarz T, Meijers JCM, et al. Thrombin-activatable fibri-
nolysis inhibitor (TAFI) deficient mice are susceptible to intracere-