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# Follow-up on Post-Operative Bleeding in Greyhounds and What It May Mean for Deerhounds

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Reprinted from the September/October 2014 *Claymore*

In [2011 I wrote about research underway at Ohio State University \(OSU\)](#) to investigate the cause of excessive post-operative bleeding that occurred in many Greyhounds one or two days after surgery. Evidence suggested that affected dogs formed normal blood clots, but that the clots dissolved too quickly. Acting on a hunch from Dr. Couto, veterinarians at OSU began using a human drug called epsilon aminocaproic acid (Amicar®) to reduce the risk of bleeding or treat the problem if it occurred.

When I interviewed Dr. Couto in 2011, one of his post-doctoral students (Liliana Marín) and her research team were in the midst of two studies to evaluate the drug's safety and effectiveness: a retrospective study in Greyhounds that had a limb amputated for osteosarcoma, and a prospective clinical trial in Greyhounds that would be spayed or neutered. Although both studies were in their early stages, the results had been so encouraging that OSU had

already begun to use Amicar® routinely for every Greyhound undergoing surgery.

In my article, I noted that when the results of the OSU studies were published, we would have a better idea of the safety and effectiveness of Amicar® in dogs. But I also recommended that Deerhound owners not wait for this information but instead begin using Amicar® to prevent or treat delayed post-operative bleeding.

The OSU studies are now complete, and the results have been published. This month I will share the results and update my recommendations about using Amicar® in Deerhounds.

### **Retrospective Study in Greyhounds**

In this study published in 2012, the authors evaluated records for 46 retired racing Greyhounds that underwent amputation between 2003 and 2008 for treatment of osteosarcoma. They assessed the incidence of delayed post-operative bleeding, the site of bleeding, and whether transfusion of blood components was required. Tumor location was included as a variable because prior experience at OSU suggested that rear limb amputations were associated with more severe bleeding.

Blood clotting function was tested in most of the dogs (39 of 46) before surgery, and all results were normal. Other blood tests (complete blood cell counts and serum chemistry profiles) were done in all dogs before surgery, and results were normal. Most dogs (40 of 46) were given either Amicar®, fresh frozen plasma (FFP), or both to prevent post-operative bleeding. Altogether, 25

dogs were given Amicar® as an initial intravenous dose (500-1000 mg total, which was 15-40 mg/kg) immediately after surgery, followed by 500 to 1000 mg orally every eight hours for five days. The other 21 were not.

Delayed post-operative bleeding was less frequent in dogs that got Amicar® (4 of 25 dogs) than in dogs that did not (9 of 21). In fact, a dog was about 6 times less likely to experience delayed post-operative bleeding if given Amicar®. This was true whether or not a dog was given FFP.

### **Prospective Clinical Trial in Greyhounds**

In this study published in 2013, the authors conducted a double-blind, placebo-controlled clinical trial in 100 retired racing Greyhounds that were randomized to receive either Amicar® (500 mg orally every eight hours starting the night of surgery) or placebo for three days after a routine spay or castration surgery. Each group had 32 bitches and 18 males. Blood clotting function was evaluated before surgery and again 24, 48, and 72 hours after surgery. Post-operative bleeding was scored daily on a scale from 0 to 4, and photos of the surgical area were taken daily. Dogs were classified as bleeders if they had a score of  $\geq 2$ .

Delayed post-operative bleeding was less frequent in the group given Amicar®; specifically, it occurred in 30% (15 of 50) of the dogs in the placebo group but only 10% (5 of 50) of the dogs in the Amicar® group. Bleeding was limited to cutaneous bruising at the surgical site. Blood clotting function tests showed that blood clotted faster from dogs receiving Amicar® than dogs given placebo, and

also that the clot was more stable.

There were no adverse side effects in any of the dogs that got Amicar®. The authors did point out that their blood clotting test results showed that Amicar® might have enhanced the “hypercoagulable state” that occurs in all dogs after surgery. They suggested that further studies were warranted to investigate this possibility. A “hypercoagulable state” means that the blood is primed to clot and so will clot more quickly. Enhancement of the “hypercoagulable state” could theoretically increase the chance that a clot might form at the wrong place or time.

Finally, the authors recommended that, while Amicar® was given at 500 mg/dog in their study, a dose of 15 mg/kg might be more appropriate in order not to under-dose larger individuals. They based this recommendation on the fact that a dog’s chance of bleeding in their study increased by 19% for every 1kg increase in body weight.

### **Putting It All Together for Greyhounds**

The OSU studies suggest very strongly that delayed post-operative bleeding occurs in Greyhounds because they are prone to dissolve blood clots too quickly after surgery. Why would so many Greyhounds have a tendency to dissolve clots quickly when this could lead to excessive blood loss after an accidental wound or routine surgery? The answer appears to be that humans unintentionally selected for this trait when they created a superior canine athlete.

Greyhounds differ from other breeds in ways besides the visible ones. Many of the differences are in the cardiovascular system—not just the heart and blood vessels, but also the blood itself. Greyhound blood has more red blood cells per unit volume, which allows the blood to carry more oxygen but also makes the blood thicker than the blood of other breeds. Greyhounds have larger hearts and thicker arteries than other breeds—large enough not only to cope with thicker blood, but also to pump that blood faster and at higher pressure than in other breeds. All of this is necessary to send enough oxygen to a Greyhound's massive muscles to produce the explosive acceleration for which the breed was selected over thousands of years.

But there is a price to pay for this sort of high performance circulatory system: blood racing faster and at higher pressures through the vessels produces more damage to the vessel walls.

Blood vessels are lined by a thin layer of cells called endothelial cells. Like roof shingles in a high wind, these cells regularly shear off, exposing the tissue beneath. The exposed tissue triggers a tiny blood clot to form. This micro-clot covers the gap and gives the adjacent endothelial cells time to repair the damage, both by spreading themselves more thinly and by dividing to make new endothelial cells.

Each time a micro-clot forms, there is a risk that the blood clotting process will get out of control and make a clot so big that it blocks the blood vessel, or even trigger blood clots to form throughout the blood stream. That's where something called the fibrinolysis

system comes into play, to make sure the micro-clot forms only where it's needed and that it stays intact only as long as necessary.

Because Greyhound blood is thicker and moving faster, Greyhounds experience more endothelial cell damage and form more micro-clots than other breeds. This, in turn, can put their fibrinolysis system into high gear. And this shifts the balance more toward clot dissolution than clot formation.

### **What Does This Mean for Deerhounds?**

Like Greyhounds, Deerhounds have thick blood moving at high speed and under high pressure, and consequently have more frequent blood vessel damage and micro-clot formation. As a consequence many Deerhounds almost certainly have fibrinolysis systems that are hyperactive, putting them at risk for delayed post-operative bleeding.

In a paper published in 2008, the OSU authors also speculated that the situation in Greyhounds probably existed in other sighthounds. They put it like this:

“The [state of enhanced fibrinolysis] in retired racing Greyhounds could be an adaptational mechanism to racing or an evolutionary trait designed to prevent clotting of blood with high viscosity... that circulates through large muscle masses, as has been reported in human athletes... [and] in transgenic mice [with high-viscosity blood]. ...It is very tempting to think that a similar phenomenon may occur in [all] sight hounds and that they have evolved to be “hypocoagulable” in order to prevent intravascular thrombosis

during strenuous exercise.”

Speculation is fine, but what about facts? As it happens, delayed post-operative bleeding does occur in Deerhounds, as many of you readers already know. Every few months I hear of another Deerhound that has unexpected bleeding after surgery. The stories are much the same. Dogs typically emerge from surgery in good shape and go home with their owners, only to begin bleeding 24 to 36 hours later. The bleeding doesn't originate from a single blood vessel; instead, blood seems to seep from every vessel that was cut during surgery. Indeed, the only vessels that don't bleed are those that were specifically tied off or cauterized during surgery.

Some Deerhounds that have delayed post-operative bleeding survive, but only with heroic and expensive supportive care. Many don't. Some dogs are simply found dead the morning after surgery.

The discovery of an inherited Factor VII gene mutation in Deerhounds led some people to speculate that this might explain the delayed post-operative bleeding, since Factor VII is one of many proteins that help create a blood clot. Unfortunately, the Factor VII mutation does not explain the delayed post-operative bleeding problem in Deerhounds. Delayed post-operative bleeding has occurred in dogs with two normal Factor VII genes.

The biggest mystery surrounding delayed post-operative bleeding is also the biggest clue to what may be happening; specifically, the time when bleeding begins. It is as if the Deerhound forms normal blood clots after surgery, but those clots “come unglued” the next

day. In other words, the problem is not in the dog's ability to form a blood clot, but instead in the dog's ability to maintain the blood clot for a normal length of time. Another clue that points in the same direction is that some Deerhounds with delayed post-operative bleeding had pre-surgical workups that included tests to evaluate blood clotting function, and the test results were normal. This also suggests that the problem is not in the dog's ability to form a blood clot.

Where does this leave us? We know that some Deerhounds experience delayed post-operative bleeding that seems similar to what happens in Greyhounds. The time at which bleeding occurs (24–36 hours after surgery) and the nature of the bleeding (seeping from multiple blood vessels) is similar in both breeds and is consistent with blood clots that don't last like they should. We can speculate that Greyhounds have this tendency because it is part of the package that our ancestors inadvertently selected for in developing a large, athletic, racing and hunting hound. If so, then it is possible that our ancestors accidentally did the same thing in developing Deerhounds.

### **Recommendations for Deerhounds**

Three years ago I recommended that Deerhound owners adopt the same approach for their dogs that OSU takes for Greyhounds. I still feel the same.

Every Deerhound that undergoes surgery should be given Amicar® for the next 3 to 5 days to reduce the risk of delayed post-operative bleeding. Amicar® is available in 500-mg scored tablets. Doses



should be given three times a day, approximately 8 hours apart.

The dose level should be as follows:

### **Amicar® Dose for Deerhounds**

Dog weight	Dose every 8 hours
55 to 79 lbs	500 mg (1 tablet)
80 to 104 lbs	750 mg (1½ tablet)
≥105 lbs	1000 mg (2 tablets)

I do not make this recommendation lightly, but because I think that the potential benefits of using Amicar® far outweigh any potential risks. On the benefit side, it is clear that the drug is effective in Greyhounds, giving hope that it might also be effective in Deerhounds.

On the risk side, every drug may cause side effects in a given dog, and Amicar® has not been studied in Deerhounds. However, Amicar® has been studied in Greyhounds in a controlled clinical trial and produced no side effects, which is more than can be said for many of the drugs we use routinely in Deerhounds. More importantly, the veterinary staff at OSU concluded that the benefits of Amicar® in preventing life-threatening delayed post-operative bleeding far outweigh any risk of potential side effects.

Amicar® was approved for human use in 1964, at a time when relatively little animal testing was done with human drugs. It is

available as an injectable liquid and as pills. The product label contains two references to potential side effects in dogs, but only when the drug is given intravenously:

- “Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose.” The maximum human dose is about 32 mg/lb, which is about 70 mg/kg. Therefore, the dose range reported to cause fatty degeneration of the heart in dogs is about 55 to 230 mg/kg. This is approximately 3 to 13 times the dose recommended to prevent delayed post-operative bleeding (15 mg/kg).
- “An intravenous... dose of 2,300 mg/kg was lethal in the dog.” This is about 130 times the dose recommended to prevent delayed post-operative bleeding.

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Thanks to the folks at OSU and their studies in Greyhounds, we at least have a theory for why delayed post-operative bleeding occurs in Deerhounds. Better yet, there is an available drug (Amicar®, also known as epsilon aminocaproic acid) that may prevent post-operative bleeding and save Deerhound lives. For my part, I will not put another of my Deerhounds through surgery without giving aminocaproic acid for 5 days afterwards to reduce the risk of delayed post-operative bleeding. I urge you to consider doing the same.

EDITOR'S NOTES: Aminocaproic acid is not kept in stock by many veterinarians, including many emergency or specialty hospitals, and it is not always easy to find. You need to ask, at least a couple of weeks before any elective surgery, whether your vet carries it or can order it. You can also get it from compounding pharmacies.

Aminocaproic acid is not available in Canada; a suitable substitute is tranexamic acid.