

ORTHOPEDICS

Yorkshire Terrier's Leg Bones Regrown by UC Davis Surgeons Following a Severe Nonunion Fracture

UC Davis has been utilizing BMP to regrow bones in canine legs and jaws since 2012

It began with a jump off the couch for a 2-year-old Yorkshire terrier named Ethel. Ethel broke both the ulna and radius in her right leg, and two previous surgeries had failed to properly heal them. MaryAnn Lawson, Ethel's owner, consulted with veterinary orthopedic surgeons, all of whom recommended amputating the leg.

When Lawson asked about other options, one surgeon mentioned a new procedure that involves regrowing bone with the use of bone morphogenetic protein (BMP). Lawson was referred to Dr. Amy Kapatkin, DVM, MS, DACVS, with the Orthopedic Surgery Service at the UC Davis Veterinary Medical Teaching Hospital. UC Davis has been utilizing BMP to regrow bones in canine legs and jaws since 2012.



Dr. Amy Kapatkin,
DVM, MS, DACVS

Dr. Kapatkin agreed to perform the surgery, but she told Lawson that there was only a 1% chance to save Ethel's leg. Although BMP grows bone effectively, the bone needs to be stabilized with a bone plate to work and Ethel had almost no bone distal on her radius.

"Because Ethel had not used her leg for so long, her distal bones—carpal and metacarpal bones—had osteopenia," recalls Dr. Kapatkin. "She had almost no distal radius left and we knew it was avascular, so we would have to stabilize her by also doing an arthrodesis across the carpal joint with a bone plate. Her metacarpal bone was smaller than most bone plates made, making this the most difficult part. It was also not that healthy and we were concerned it would not hold screws very well. It is why we gave her a very guarded prognosis. I was concerned that the implants would not hold in her remaining bone."

Bone morphogenetic proteins are endogenous signaling peptides that stimulate mesenchymal stem cells to differentiate into osteocytes, creating new bone formation. Two recombinant human bone morphogenetic proteins (rhBMP-2 and rhBMP-7) are FDA-approved for use in specific human medical conditions in the United States, including maxillofacial, spinal fusions, open tibial fractures, and compassionate use in long-bone unions.

These cases are considered at high risk of failure when using the traditional technique of rigid fixation and autogenous or allogenic bone graft; amputation is often recommended. "The reasons for the nonunions are not necessarily incorrect surgeries," says Dr. Kapatkin.

“Many of the cases I have used it on have had many unsuccessful surgeries and the bone is unhealthy with large gaps.”

The first step in the BMP procedure requires removal of all the failed implants. The bone has to be osteotomized to healthy bleeding bone on either end. The remaining bone ends are rigidly stabilized—usually with a bone plate. “BMP comes as a powder and must be sterilely diluted and allocated,” explains Dr. Kapatkin. “It is then frozen at -80°C until it's used.” The UC Davis team is using the Medtronic compression resistant matrix (CRM) as the graft to hold the BMP. “BMP cannot be injected as a liquid into anything,” notes Dr. Kapatkin. The CRM is sterile soaked with 1 dose of BMP calculated for the correctly sized graft. It is pressed to fit into the gap, followed by routine closure.

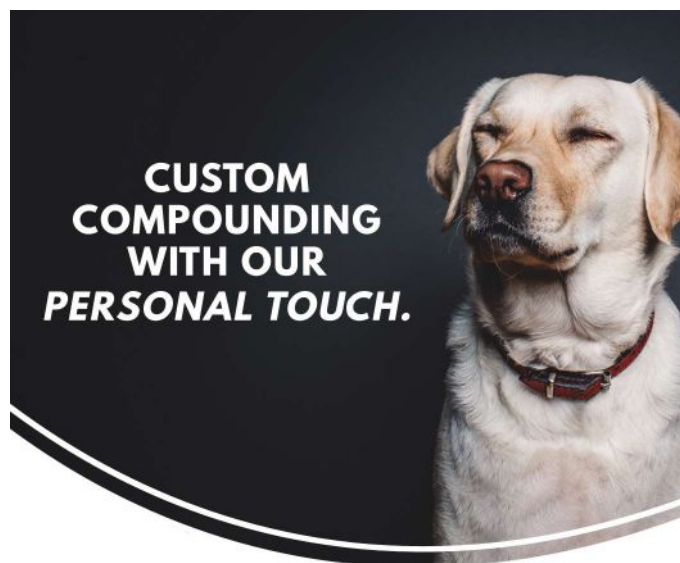
Ethel's case presented challenges, however. “I had to remove all the distal radius and then use the bone plate across the carpal joint and place it on the metacarpal #3 bone,” says Dr. Kapatkin.

In most cases, BMP patients are discharged a few days following surgery, but in Ethel's case the veterinary team decided she should remain at UC Davis veterinary hospital for observation during recovery. “Nonunion after long-bone fracture repair in dogs represents a potentially devastating complication,” says Dr. Kapatkin. One postsurgery complication that arose for Ethel was that the bone plate used to stabilize the fracture—which typically remains in the patient permanently—started protruding from her leg due to the limited soft tissue and thin skin in her tiny distal limb. When it was decided that the plate was no longer needed, Dr. Kapatkin removed it to allow Ethel's tissue to heal completely around the bone.

At Ethel's 3-month recheck appointment, she was able to run on her new leg. “Without Dr. Kapatkin and her amazing team at UC Davis, Ethel's story would be very different,” says Lawson. “She's our little miracle.”

“We're optimistic that our use [of BMP] in orthopedics will have long-term positive results,” says Dr. Kapatkin.

BMP is not commercially available in the USA; UC Davis is using it for research and has access.¹ ■



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ONCOLOGY

The V Foundation Announces Grants to Treat Cancer in Dogs and People

The V Foundation for Cancer Research announced an innovative grant-making program to accelerate research



¹ *Vet Comp Orthop Traumatol.* 2017 Mar 20;30(2):153-159. doi: 10.3415/VCOT-16-05-0082. Epub 2017 Jan 17.

in the field of comparative oncology. Canine comparative oncology enables researchers from human and veterinary medicine to explore new cancer therapies for humans and dogs. Five veterinary schools are receiving research grants to work with cancer centers that treat people.

Researchers will explore treatments that will have better success and less toxicity for dogs and people, according to a news release from The V Foundation. The foundation was founded by Jim Valvano, the late North Carolina State basketball coach, who died in 1993 after being diagnosed with adenocarcinoma.

Canine tumors often share multiple characteristics with human cancers, including responses to specific therapies. Some of the most prevalent cancers diagnosed in humans and dogs include sarcomas, melanoma, lymphomas, breast and bladder cancer. Cancer is the leading cause of death in dogs, with 1 in 4 developing the disease in his or her lifetime; while for humans, it's 1 in 3.

“Because certain cancers are very common in dogs, and because a dog’s life is much shorter than a human’s, we have an incredible opportunity to find new treatments while helping both humans and animals,” says William Eward, M.D., a surgical oncologist at Duke Cancer Institute. “For rare cancers, like sarcoma, dogs provide us with remarkable insight. For every human child with osteosarcoma, there are at least 50 dogs with osteosarcoma. These dogs share our environment and have nearly identical immune systems. In studying dogs with sarcoma, we not only learn more about this type of cancer, we also gain a chance to help ‘man’s best friend.’”

The V Foundation, based in Cary, N.C., has awarded more than \$700,000 in the past three years for canine comparative oncology research. More than \$200 million in cancer research grants have been awarded since 1993, when Valvano, then an ESPN commentator, founded the organization.

The schools involved include University of Pennsylvania School of Veterinary Medicine, teamed with Abramson Cancer Center at UPENN; North Carolina State College of Veterinary Medicine, with Duke Cancer Institute; University of Wisconsin Madison School of Veterinary Medicine, with Flint Animal Cancer Center; and University of Minnesota College of Veterinary Medicine. **TVP**

Heartgard® (ivermectin/pyrantel) Plus

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.

For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.

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