A Novel Approach to the Treatment and Prevention of Laminitis: Botulinum Toxin Type A for the Treatment of Laminitis

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ABSTRACT

Laminitis is an inflammation of the lamina of hoofed animals. According to the United States Department of Agriculture (USDA), laminitis impacts approximately 2% of the horse population each year. Because of the severity of the inflammation and chronic pain, it is frequently necessary to euthanize these horses. Surviving horses may be left useless, with resultant economic and social impact on the industry. Current interventions for laminitis are based on supportive care and alteration of biomechanical forces on the digit. The transition from laminitis to laminar failure (founder) is believed to be caused by the “weight of the horse and the forces of locomotion driving the bone down into the hoof capsule.” We hypothesize that an important factor is the torsional forces placed on the distal phalanx (coffin bone) by the deep digital flexor muscle and tendon. The paralyzing effect of botulinum toxin will result in a decrease of these torsional forces and therefore will aid in the prevention or treatment of the sequelae of laminitis. Seven horses with varying degrees of laminitis were evaluated. Each underwent pretreatment and post-treatment radiographs as well as pretreatment and post-treatment Obel grading. Each horse received botulinum toxin type A injected into the belly of the deep digital flexor muscle. In all cases there was radiographic stabilization of pedal displacement from the dorsal hoof wall. Obel scores showed improvement of 1 to 2 grades during the time monitored.

Keywords: Laminitis; Botulinum toxin; Founder; Therapy; NSAIDs; Prevention

INTRODUCTION

Terminology describing laminitis varies within the veterinary literature. In the review by Morrison, laminitis is considered “acute” if the coffin bone has not yet displaced. The “chronic” phase is represented by displacement of the coffin bone in its relation to the hoof wall. “Chronic compensated” differentiates those chronic cases in which the bone is stabilized after initial displacement. “Chronic uncompensated” describes a hoof in which the coffin bone is in the process of changing in the hoof capsule.

The incidence of laminitis in horses was evaluated in the Lameness and Laminitis study published in 2000 by the United States Department of Agriculture (USDA). This study reported that approximately 13% of all equine facilities experience cases of laminitis over a 12-month period, affecting approximately 2% of all horses. Of these, approximately 5% die or are euthanized, and another 20% suffer permanent injury affecting the horse’s use and function. Studies have shown that cases of laminitis treated at referral centers show much higher rates of mortality and morbidity. Despite significant advances in veterinary medicine, laminitis in horses and other hoofed animals remains a major cause of morbidity and mortality. Laminitis is an inflammation of the lamina, the lamellar attachment between the distal phalanx (coffin bone) and epidermis (the inner hoof wall). The sequela of laminitis is characterized by separation of the hoof wall from the distal phalanx because of the deterioration and detachment of the lamina. In most cases, failure of attachment can extend around the perimeter of the hoof, allowing the phalanx to displace distally within the hoof capsule, which is termed a sinker.
Laminitis may occur secondary to various conditions, including overeating, colic, fever, shock, pneumonia, injury, and obesity. Obel stated in his seminal article that rotation of the distal phalanx (coffin bone) may be attributable to a metabolic disturbance (such as carbohydrate load) or to “a discrepancy between the strength of the epidermal laminae and the load they have to support.”

All hoofed animals, and particularly horses, are susceptible to laminitis, and significant economic loss occurs because of severe pain and debilitation. Because of the insidious nature of the disease process, damage to the laminae often occurs before clinical evidence of a problem.

Current medical therapies offer no cure for laminitis. Modalities available to the veterinarian include identification and treatment of the underlying disease, systemic anti-inflammatory medications, various appliances changing the biomechanical forces on the digit, and rest. Additionally, support of the sole, using deep sand flooring, peat moss, and foam sole pads, has met with some success.

A more aggressive treatment of the sequelae of laminitis involves tenotomy of the deep digital flexor tendon. Surgical transection of the deep digital flexor tendon (DDFT) has been used to reduce the shearing forces during the acute phase of laminitis. One study reported a 60% survival rate at 2 years after the procedure. Morrison states that “a discrepancy between the strength of the epidermal laminae and the load they have to support.”

The pathologic processes resulting in laminar inflammation are unknown. Accordingly, there is a need for a protractive treatment that effectively treats or prevents the sequelae of laminitis. We hypothesize that botulinum toxin will effectively treat these sequelae without surgery and the associated risks.

Clostridium botulinum, the bacteria that produces botulinum toxin, was first identified in the late 1800s. Botulinum toxin consists of seven distinct serotypes, A through G. Of these, type A (Botox, Allergan, Irvine, CA; and Dysport, Ipsen, Paris, France) and type B (Myobloc, Solstice Neurosciences, South San Francisco, CA) are commercially available.

In 1989 botulinum toxin type A (Botox) was approved for human use by the United States Food and Drug Administration for strabismus (oculomotor dysfunction) and blepharospasm.

All references to botulinum toxin type A in this publication refer to Botox (Allergan).

Botulinum toxin prevents the release of acetylcholine from the nerve terminal by disrupting the release mechanism of the acetylcholine-containing vesicles. This occurs via several mechanisms of action depending on the serotype of botulinum toxin used. Blocking the release of acetylcholine from the nerve terminal temporarily prevents the contraction of the muscle, thereby decreasing the tone of the muscle and the forces exerted at its insertion. Utilization of this procedure decreases the torsional forces on the coffin bone, thereby diminishing the traction on the digital lamina and reducing rotation of the coffin bone within the hoof wall.

When injected into a striated muscle belly the clinical changes are first noted approximately 2 days later, with peak benefit in approximately 2 weeks. The physiologic action dissipates after approximately 3 months, with no permanent changes to the myoneural junction structure.

### Materials and Methods

Horses at varying stages of laminitis were identified, evaluated, and assigned a grade of impairment based on Obel’s stages (Table 1).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>In the standing position the horse lifts the feet incessantly, often at intervals of but a few seconds (“paddling”). At a walking pace it does not show any lameness, but the trotting gait is short and stilty. When the animal is recovering, this stage is characterized by the latter symptom alone.</td>
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<tr>
<td>2</td>
<td>The horse moves quite willingly at a walking pace, but the gait is characteristic for laminitis. A forefoot may be lifted without difficulty.</td>
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<tr>
<td>3</td>
<td>The horse moves most reluctantly. Vigorously resists attempts to lift a forefoot.</td>
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<tr>
<td>4</td>
<td>At this stage, the horse does not move without being forced to.</td>
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Botulinum toxin type A (Botox) was diluted with preservative-free normal saline to 100 units per 2 mL to ensure adequate distribution throughout the flexor digitorum profundus (FDP). The region to be injected was prepared using sterile technique. The injection site is identified by palpation of the medial aspect of the radius approximately 8 cm distal to the point of the olecranon and the belly of the flexor carpi ulnaris. The injection needle was inserted in the groove between the flexor carpi ulnaris and the flexor digitorum superficialis. The needle was advanced to the radius then backed out approximately 1 cm. A total of 4-8 injections of 25 units per site were administered along the axis of the FDP. An Ambu Neuroline Injekt (Ambu Inc, Glen Burnie MD) 24-gauge, 3-inch coated needle electrode was used for electromyography (EMG) guidance. The total amount of botulinum toxin type A injected intramuscularly ranged from 100 units to 200 units per limb, depending on the size of the horse and the involvement of the affected muscles.
The horses were then monitored for a minimum of 12 weeks, except for horse number 2, which was humanely destroyed (see Results).

**RESULTS**

**Horse 1**
An 11-year-old 568-kg Tennessee Walking Horse was examined and evaluated after a sudden onset of severe forelimb lameness. Before the examination, the owner reported that the horse had experienced a rapid weight gain coinciding with the spring annual rye grass growth. Examination revealed a heart rate of 60 beats/minute and temperature of 98.6°F. Additional findings included increased digital pulses of all four feet and a stance characteristic of Obel grade 3 acute laminitis.

Initial therapy included nonsteroidal anti-inflammatory agents, heel elevation, and deep stall bedding with peat moss. The horse became progressively more uncomfortable, outwardly distressed, recumbent, and refused to stand. Plain radiographs at week 1 showed a dorsal hoof wall rotation exceeding 20 degrees. Complete blood count and serum biochemistries were considered within normal range for this age horse. The horse deteriorated, experiencing an acute exacerbation of the chronic laminitis, Obel grade 4 classification (recumbent), with a grave prognosis.

Treatment options were presented to the owner, and informed consent was given for chemical denervation of the deep digital flexor muscle with botulinum toxin. Using EMG guidance, 25 units botulinum toxin was injected into eight sites in the flexor digitorum profundus of each forelimb, for a total of 400 units. The procedure was tolerated well, with no immediate adverse effects noted. The horse was examined daily over the subsequent 12 weeks. At week 2, the horse showed a marked improvement in its ability to stand and ambulate.

Aftercare included the treatment of foot abscesses and pressure sores and correction of the P3 hoof alignment. The owner was instructed to maintain the horse on a complex carbohydrate diet and monitor weight.

At the 2-year follow-up, the horse had returned to functional use to the level of pasture comfort and pleasure riding at all gaits.

**Horse 2**
An 8-year-old stallion Quarter Horse was experiencing an acute exacerbation of recurrent laminitis in two legs (Obel grade 4) of 9 months’ duration. Physical examination findings included a heart rate of 60 beats/minute and temperature of 99.6°F.

In the right forelimb, a standing deep digital flexor tenotomy was performed, using chemical restraint and regional anesthesia. A 2-cm incision was made over the medial aspect of the limb approximately 6 cm above the proximal sesamoids, and the connective tissue was bluntly dissected. The deep flexor tendon was isolated and severed with a number 10 blade. The skin was then closed using a simple interrupted suture pattern. Redden Ultimate heel wedge shoes (9) were applied to achieve a 20-degree palmar angle. In the left leg, using clean technique and EMG guidance, a total of 400 units botulinum toxin type A was injected into eight separate sites within the flexor digitorum profundus. The Ultimate heel wedge shoe was applied, with a goal of a 20-degree palmar angle.

The horse underwent preprocedure and postprocedure venograms, with no initial difference noted between the legs. The horse tolerated both procedures well and was monitored for 5 weeks. The horse improved from an Obel grade of 4 to an Obel grade of 3, with repeat venograms showing improved venous flow in both digits. On comparing the venograms of the two front limbs at 1 week post procedure, it was our interpretation that there was a more normal venous pattern in the limb having had a transaction of the deep digital flexor tendon than in the opposite supporting limb. At 30 days post-treatment, the venograms of the surgically treated and the botulinum toxin-treated legs were similar.

At the owners’ request, because of persistent severe debilitating pain, the horse was euthanized at week 6 post-treatment.

**Horse 3**
A 21-year-old gelding Quarter Horse suffered a traumatic injury to the right front carpus. Radiographs showed disruption of the normal anatomy of the carpal bones, suggesting tearing of the palmar carpal ligaments. This resulted in severe swelling of the palmar region of the carpus. The working diagnosis was traumatic disruption of the palmar ligaments of the carpal bones, causing an inability to extend the carpus in the non-weight-bearing limb.

In an effort to prevent contralateral laminitis, the horse was treated with 200 units of botulinum toxin type A (Botox) injected into the deep digital flexor muscle of the left forelimb as previously described. A Redden Ultimate shoe was also applied, creating a 20-degree palmar angle.

The horse was monitored over the next 7 months. Examination at week 1 and again at week 4 showed no clinical evidence of laminitis in the left front limb. At 2 months after presentation, the treatment shoe was removed. The horse was “toe touching” in the injured (right) forelimb. At 7 months, the horse showed no evidence of laminitis in the left front foot on clinical or radiographic examination.

**Horse 4**
A 23-year-old, 700-kg Tennessee Walking Horse mare experienced chronic and recurrent laminitis of greater than 20 degrees on radiographic examination in the front feet (Obel grade 4). The mare had a body condition score...
of 8 (significantly overweight), with pressure sores on both hips. Routine laboratory testing was normal.

The horse was shod with a reverse keg shoe. The dorsal-distal hoof wall was trimmed in both front feet to reduce the angle of rotation between the dorsal aspect of the coffin bone and the dorsal hoof wall. Using the previously described method, the horse was injected with 200 units botulinum toxin type A (Botox) in the deep digital flexor muscle of each forelimb.

At 10 days postinjection, the horse’s condition was improved, with an Obel grade 3 score, and at 6 weeks postinjection, the horse was judged to be an Obel grade of 2. Finally, at 5 months postinjection, the horse was an Obel grade 1. No adverse events were reported during the 13-month follow-up, and at 36 months, the horse is pasture sound.

Horse 5
A 19-year-old, 650-kg Tennessee Walking Horse mare was diagnosed with acute laminitis, with a body condition score of 6 and normal physical findings. Results of hematology and serum chemistries were considered to be within normal range.

The horse exhibited an Obel grade 1 at the initial evaluation. Radiographic studies showed no evidence of distal displacement of the coffin bone. Treatment included non-steroidal anti-inflammatory drugs (NSAIDs) and heel elevation with the Redden Modified Ultimate shoe applied with Elastikon (Johnson & Johnson) tape; at 2 weeks the Ultimates were removed, and KB shoes were applied.

One month later, an acute exacerbation of laminitis occurred; treatment with NSAIDs and the Ultimates were resumed. Radiographs of the feet measured a 15-degree rotation of the left foot and a 14-degree rotation of the right foot; the horse was classified as an Obel grade 4.

The owner was offered humane destruction, surgery, or chemical denervation (botulinum toxin type A); they chose treatment with botulinum toxin. The horse was treated with 200 units botulinum toxin type A (Botox), in the deep digital flexors of each forelimb, as previously described, and flunixin meglumine (Banamine, Intervet/Schering-Plough Animal Health; The Netherlands) at 1.1 mg/kg every 12 hours, by mouth, for 5 days, and then 1.1 mg/kg, by mouth, thereafter as needed.

Examination at day 14 showed clinical improvement and was classified as an Obel grade 1. The horse was changed to a reverse keg shoe.

At 60 days, she was turned out with her pasture mates with limited access to lush forage. At almost 3 months (80 days) after botulinum toxin treatment, the horse was pasture sound.

Horse 6
A 12-year-old, 477-kg Arabian gelding with a body condition score of 7 was presented to a tertiary equine center and diagnosed with bilateral forelimb laminitis. The horse was initially treated with NSAIDs. Redden Ultimate shoes were placed on both forefeet, and the horse was stall confined. The horse was referred to our center for follow-up care because of a poor response to the prescribed treatment protocol.

On examination, the horse was classified as Obel grade 3 and appeared clinically more painful in the right front limb. Radiographs of the feet, on presentation, indicated an increase in ventral rotation of the coffin bone when compared with the studies performed by the tertiary center. At week 2 postdischarge, the right forelimb showed a rotation of 18 degrees and 12 degrees in the left foot. Routine laboratory testing was normal. The owner was offered continued conservative care, deep digital flexor tenotomy, or injection with botulinum toxin.

At the owner’s request, the horse initially underwent treatment of the right forelimb with 200 units botulinum toxin A in the deep digital flexor muscle as described. Ten days after treatment, the horse showed additional radiographic rotation of the left forelimb and more pain. The horse was treated with 200 units botulinum toxin injected into the deep digital flexor muscle of the left forelimb.

At 33 days after the first injection, the horse was comfortable and classified as a modified Obel grade of 1. At 72 days after treatment, radiographs showed realignment of the coffin bone with the dorsal hoof wall (Fig. 1). At 120 days after treatment, the owner reported no evidence of lameness at the walk.

Horse 7
An 8-year-old Arabian broodmare developed septic metritis immediately after foaling and was treated at a tertiary referral center for chronic laminitis and classified as an Obel grade 3 at discharge.

Our examination supported a diagnosis of chronic founder, with results of the remainder of the physical examination normal. The owner was offered deep digital flexor tenotomy or injection with botulinum toxin.

The owner elected to proceed with botulinum injection of the deep digital flexor muscle. Injections of 200 units botulinum toxin type A were injected into each forelimb as previously described. Two weeks after treatment, the horse showed marked improvement in the right leg more than in the left leg. An additional 100 units of Botox was injected into the left deep digital flexor muscle.

The horse improved clinically and survived but was lost to long-term follow-up.

DISCUSSION
Laminitis is a common, debilitating condition in horses that results in humane destruction and morbidity in the equine population. A United States Department of
Agriculture (USDA) study found the incidence of laminitis to be approximately 2% in the 12-month period studied, with approximately 5% of affected horses not surviving and 20% permanently disabled. We theorize that the mortality and morbidity of laminitis is attributable to the pulling of the deep digital flexor muscle on the coffin bone resulting in rotation of the coffin bone within the hoof wall. We further hypothesize that the pull of the deep digital flexor tendon on the coffin bone impacts the foot in several different ways: (1) the pulling of the DDFT may compromise the normal blood flow to the dorsal lamina, causing decreased laminar perfusion. With a decrease in laminar perfusion, laminar tissue is deprived of much needed glucose and oxygen, weakened, and subject to failure; (2) the strain of the deep digital flexor tendon on the palmar aspect of the digital phalanx creates a destructive force and failure of the basement membrane between the epidermal and dermal lamellar tissue of the hoof wall. Relaxation of the deep digital flexor muscle, using botulinum toxin injections, results in a decrease of the pulling forces, thus preventing the sequela of laminitis.

If the tensile forces acting on the distal phalanx are relieved in the acute stage of the disease, it may prevent the distal phalanx from rotating and entering the chronic phase of laminitis. If the displacement of the distal phalanx can be prevented, an affected horse has a better chance for recovery.

When a horse has entered the chronic phase, the distal phalanx rotates downward and compresses the sole corium, altering the blood flow and normal growth of the hoof capsule. We believe that by causing relaxation of the deep digital flexor tendon, the distal phalanx will realign with relation to the ground surface, and the hoof capsule can begin to repair and grow normally. The goal, therefore, is to reestablish and maintain normal orientation of the distal phalanx relative to the ground surface.

In summary, administering botulinum toxin type A in our hands was safe and effective for the treatment and prevention of laminitis. Botulinum toxin chemically denervates the muscle belly, affecting the pull of the deep digital flexor tendon. The deep digital flexor muscle tendon unit relaxes and decreases the pull on the palmar aspect of the distal phalanx, mimicking a deep digital flexor tenotomy. The temporary nature of the botulinum toxin provides an intervention that is effective yet transient, therefore permitting the horse to return to a more normal routine after recovery from the laminitis. Our study shows promise and with additional controlled studies may be a useful and consistent treatment recommendation for the prevention and treatment of laminitis.

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