

Distal Limb Cryotherapy for the Prevention of Acute Laminitis

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Acute laminitis can be a devastating consequence of systemic diseases such as severe colitis, proximal enteritis and metritis. Prophylactic therapies based on enhancing digital perfusion during the developmental phase of laminitis have resulted in only limited efficacy. Recent insights into the pathophysiology of acute laminitis have led to the evaluation of cryotherapy for prevention of the disease. Experimental evidence demonstrates that the equine digit is particularly resilient with respect to the potentially detrimental effects of prolonged, extreme cold. Continuous distal limb cryotherapy during the developmental phase was effective in markedly reducing the severity of laminitis in an experimental model, and limited preliminary data suggests a similar effect in clinical cases of colitis. The mechanisms by which cryotherapy may prevent laminitis are unclear. Potent vasoconstriction of the digital circulation could prevent the delivery of systemic "trigger factors" to the digit. A cold-induced potent hypometabolic state within the lamellar tissue may protect the laminae from damage regardless of the pathophysiological insult. The authors advocate the continuous application of cryotherapy to the distal limbs of clinical cases that are at high risk of developing acute laminitis. There is currently no evidence to support the use of cryotherapy in horses with preexisting acute laminitis.

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Acute laminitis is a common and frustrating sequel to a myriad of systemic diseases in the horse. Frequently, the development of laminitis occurs despite successful treatment and resolution of the primary disease, rendering the horse useless for its intended purpose or necessitating euthanasia. Although the practitioner may be aware that a horse is at high risk of developing acute laminitis, an effective strategy for prevention is lacking.

Division among clinicians and researchers as to the pathogenesis of acute laminitis has resulted in opposing recommendations for prevention and treatment. The traditional pathophysiological theory of lamellar ischemia and necrosis has spawned several preventive and therapeutic strategies aimed at enhancing sublamellar perfu-

sion during the developmental and acute phases of laminitis.¹ These strategies have been associated with only limited efficacy. More recently, the pathophysiological theory based on enzymatic degradation of lamellar attachments² has generated new thought on prevention of the disease.

Eighteenth century references to the usage of cryotherapy for the treatment of laminitis have been cited by Wagner.³ Experimental evidence led Pollitt⁴ to suggest cryotherapy as a potentially effective preventive strategy for acute laminitis. Recently, continuous distal limb cryotherapy has been shown to dramatically limit the severity of acute laminitis in an experimental carbohydrate overload model.⁵ The authors of the current paper have also experienced success using cryotherapy in a limited number of clinical cases of acute colitis.

In this paper we shall review the effects of cryotherapy on the distal limb and the potential mechanisms by which it may prevent lamellar damage. Practical methods of cryotherapy application will be discussed. Appropriate case selection for distal limb cryotherapy, as well as the timing of initiation and duration of application, will be addressed based on current knowledge.

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What Is Cryotherapy?

Cryotherapy can be simply defined as the therapeutic cooling of tissue. However, the term cryotherapy encompasses everything from the application of ice to musculoskeletal injuries for first aid or rehabilitation, to cryosurgical destruction of neoplastic lesions using liquid nitrogen.⁶ Cryotherapy can be intermittent or continuous, and can be applied to the whole body or a specific anatomical region. This article will concentrate on the continuous application of cold (0-5°C) to the equine distal limb for the purpose of preventing acute laminitis.

The Effects of Cryotherapy on Tissue

The physiological mechanisms and subsequent effects of cryotherapy are complex and poorly understood. The literature can be confusing and contradictory, particularly with respect to the vascular effects of cryotherapy. Basically, the application of cold to living tissue results in three major local effects: analgesia, hypometabolism and a vascular response.⁷ Cold has a direct effect on peripheral nerves, reducing the conduction velocity, increasing the threshold for stimulation and increasing the refractory period after stimulation.⁹ Additionally, cold may also act as a counter irritant or may have a suppressive effect on peripheral sensory nerve endings.⁸ The sensitivity of peripheral nerves to cold depends largely on fiber diameter and myelination,⁹ and varies between species.⁸

The profound hypometabolic effect of cryotherapy is now considered to be the most important mechanism by which cold limits the severity of an injury.¹⁰ Tissue metabolic rate and oxygen consumption are inversely related to temperature.¹¹ A reduced requirement of cooled tissue for oxygen, glucose and other metabolites enhances the survival of cells during periods of ischemia.¹⁰ This mechanism is thought to protect tissue on the periphery of an injury from secondary hypoxic damage,⁷ and is the basis for the use of cryotherapy in organ transplant surgery.^{12,13} A reduction in metabolic enzymatic activity of approximately 50% has been observed with a reduction in tissue temperature of 10°C.¹⁴ The activity of collagenases¹⁵ and pro-inflammatory cytokines¹⁶ is significantly reduced at lower temperatures.

Cryotherapy causes potent local vasoconstriction.⁸ This is largely mediated by sympathetic nervous control; however, a direct constrictive effect on blood vessel walls may occur, particularly at lower temperatures.¹⁷ Periods of transient vasodilation (the "hunting reaction") reportedly may occur when temperatures are reduced below approximately 18°C.¹⁸ The existence and importance of this phenomenon, however, have been challenged.¹⁹ Such periods of cold-induced vasodilation are thought to be largely due to dilation of blood vessels in muscle tissue.^{18,20} A recent study utilizing direct microcirculatory observation evaluated the effects of cooling on microvascular perfusion.²¹ This study demonstrated marked arteriolar vasoconstriction with local cooling to 8°C for 30 minutes. A significant reduction in blood flow velocity was also noted. It is generally accepted that the application of cryotherapy results in a marked net reduction in local perfusion.¹⁹

Adverse effects of cryotherapy are rare but may include frostbite and nerve palsy.⁷ The temperatures and duration of exposure required to induce frostbite are unclear.²² Nerve palsy is a rare complication of cryotherapy in human patients, and usually involves large superficial nerves.⁷ It is hypothesized that compression (often used in association with cryotherapy in human patients) may contribute to nerve palsy in many cases.²² Prolonged exposure to the combination of cold and moisture has been associated with the development of "immersion foot" and "trench foot" in human patients.²³ These conditions cause local swelling and pain that may progress to blistering of the skin, nerve damage and gangrene.²⁴ Cryotherapy is contraindicated in human patients with peripheral vascular diseases such as Raynaud's phenomenon because of its potent vasoconstricting effect.⁸

Cryotherapy in the Equine Distal Limb

Cryotherapy is commonly used by equine veterinary practitioners, trainers and owners for the treatment of athletic injuries. There are, however, few controlled studies evaluating the effects of cryotherapy in the horse. Worster and coworkers²⁵ evaluated the effect of immersing the equine digit in 4°C iced water for 30 minutes. A significant reduction in soft tissue perfusion was demonstrated scintigraphically in this study. Turner and coworkers²⁶ evaluated the effect of a cold gel wrap (4°C) applied for 30 minutes to the metacarpal region of ten horses. A reduction in surface temperature over the dorsal metacarpal region was sustained in this study for 3 hours. Another study evaluated the effect of ice water immersion and cold pack application to the equine metacarpal region for 30 minutes.²⁷ This study demonstrated a profound and sustained reduction in deep tissue temperature during iced water immersion (maximum reduction 16.3°C), that was far superior to cold pack application. All these studies limited the duration of cryotherapy application to that recommended in human medicine (30-45 minutes).⁷ Similarly, general clinical recommendations for the duration and temperature of cryotherapy in horses are also extrapolated from human medicine.²⁸⁻³⁰ Two recent studies have challenged these recommendations.^{31,32} Petrov and coworkers³¹ used a commercial cooling and compression splint to cool the metacarpal region for 60 minutes. Mean temperature within the superficial digital flexor tendon core was markedly and consistently reduced in the treated limbs, measuring $10.4 \pm 3.7^\circ\text{C}$ at the cessation of cooling. No adverse clinical effects were noted in the 24-hour observation period following cryotherapy in this study. The same study found no reduction in the viability of tendon cells cooled to 10°C for 60 minutes in vitro. Pollitt and van Eps³² evaluated the effect of distal limb cryotherapy continuously applied for 48 hours. An ice and water slurry, applied to a level just above the fetlock, was used to cool one forelimb of each horse. The mean temperature of the cooled forelimbs, measured using probes inserted 7 mm deep in the hoof wall, averaged $5.3 \pm 0.3^\circ\text{C}$ for 46 hours after an initial stabilization period of 2 hours. A marked reduction ($27.1 \pm 0.3^\circ\text{C}$) in treated limb hoof temperature compared with the untreated limbs was noted in this study. No adverse clinical effects were noted in

Table 1 The Potential Mechanisms by Which Continuous Distal Limb Cryotherapy May Prevent Acute Laminitis

Pathophysiological Mechanisms Implicated in the Development of Laminitis	Potential Beneficial Effect of Cryotherapy
Delivery of "laminitis trigger factors" to the digit via the circulation	Profound vasoconstriction limits the delivery of haematogenous "trigger factors" to the digit
Production and activation of excess lamellar matrix metalloproteinases (MMPs)	Profound hypometabolism reduces the production and activation of lamellar MMPs
Enzymatic degradation of lamellar attachments by MMPs	Profound inhibition of enzymatic activity through hypometabolism
Local production and activity of pro-inflammatory cytokines (TNF- α and IL1- β)	Hypometabolic effect reduces the production and activity of cytokines
Inflammatory damage caused by infiltration of polymorphonuclear leukocytes (PMNs)	Vasoconstriction and hypometabolism reduce the delivery and activity of PMNs
Digital hypoperfusion resulting in lamellar ischaemia	Profound hypometabolic effect protects lamellar tissue from ischaemic damage
Reduced cellular glucose availability	Profound hypometabolic effect reduces lamellar requirement for energy substrates

the cooled limbs up to 1 year following cessation of the cryotherapy. Cold-induced pain, observed in human patients when cryotherapy was applied at 5°C for 48 hours,³³ was not noted in this study.

It is clear that the equine distal limb is uniquely resilient to the effects of extreme, continuous cold application. There are no reports of cold-induced edema, swelling or pain in any study on distal limb cryotherapy in the horse, nor are there any reports in the literature of complications directly related to the clinical application of cryotherapy in horses. Additionally, horses show no signs of adverse effects in climates where their distal limbs are continuously immersed in snow (C.C. Pollitt, unpublished data). The phenomenon of reflex intermittent vasodilation (hunting reaction) has not been documented during the local application of cryotherapy to the equine distal limb. The lack of skeletal muscle tissue in the equine distal limb may explain the absence of reflex vasodilation in response to local cryotherapy. Additionally, the absence of subcutaneous fat or muscle tissue enables profound and efficient cooling of deeper structures, including the lamellar tissues.³²

Cryotherapy: Potential Mechanisms for Preventing Lamellar Damage

The pathogenesis of acute laminitis is currently a subject of dispute. The diverse effects of cryotherapy, however, have the potential to interrupt many of the pathophysiological mechanisms that have been hypothesized to occur during the developmental and acute phases of the disease. A summary is presented in Table 1.

Enzymatic degradation of lamellar attachments by matrix metalloproteinases (MMPs) forms the basis of one pathophysiological theory for developmental laminitis. It is hypothesized that the inappropriate release of excess, activated MMPs is mediated by "laminitis trigger factors" delivered to the foot via the digital circulation during developmental laminitis.² The delivery of these trigger factors, which may include cytokines⁴ or bacterial products of hindgut origin,³⁴ could be limited by cold-induced digital vasoconstriction during the developmental phase of laminitis. This was the basis for initial recommendations to

evaluate the use of cryotherapy for the prevention of laminitis.⁴ The potent local hypometabolic effect of cryotherapy, however, may outweigh any effect on the digital vasculature. A cold-induced reduction in the local production and activity of MMPs would limit degradation of the lamellar attachments. A digital hypometabolic state would also limit the local production and activity of pro-inflammatory cytokines, such as interleukin-1 β and tumor necrosis factor- α , during the developmental stage of laminitis. Cryotherapy could also limit secondary inflammatory damage caused by polymorphonuclear leukocyte infiltration.³⁵ Similar mechanisms are believed to be the basis for the efficacy of scalp cryotherapy in preventing alopecia in cancer patients undergoing chemotherapy.³⁶ Vasoconstriction apparently reduces delivery of the chemotherapeutic agent to the scalp, and cellular uptake and metabolism are reduced when residual drug reaches the hair follicles.^{37,38}

The alternate pathophysiological theory for laminitis proposes that digital hypoperfusion during the developmental stage leads to lamellar ischemia and necrosis.³⁹ Profound, cold-induced vasoconstriction would seem contraindicated if digital hypoperfusion was the primary mechanism behind the development of laminitis. However, despite a reduction in digital perfusion, the hypometabolic effect of cryotherapy could protect the lamellar tissue from ischemic damage. Similarly, a profound cold-induced reduction in metabolism could protect the lamellar tissue from a lack of glucose (proposed as an initiator of lamellar separation in one study).⁴⁰

Until the true pathophysiology of laminitis is discovered, the apparent resilience of the equine distal limb to prolonged, extreme cold may hold the key to successfully preventing the disease. Continuous distal limb cryotherapy during the developmental stage of laminitis has the potential to preserve the lamellar tissue until the systemic insult has abated.

The Efficacy of Continuous Distal Limb Cryotherapy for the Prevention of Acute Laminitis

Experimental Data

Currently available are the results of only one controlled study on the efficacy of cryotherapy for the prevention of

laminitis.⁵ Laminitis was induced in six horses using a carbohydrate overload model. Each horse had one forelimb immersed in ice and water (mean temperature $0.5 \pm 1.7^\circ\text{C}$) for the entire 48 hour experimental period, achieving a mean internal hoof temperature of $3.5 \pm 0.9^\circ\text{C}$. All horses developed mild to severe clinical and histological laminitis in one or more of the untreated limbs. The cooled limbs did not develop clinical laminitis and had significantly reduced lamellar histological damage. In 2 of the 6 horses lamellar histology in the cooled limbs was normal, and in the remaining 4 horses the histopathology was less than that required for categorization as "mild." The study also showed significantly reduced up-regulation of lamellar matrix metalloproteinase-2 (MMP-2) mRNA in the cooled limbs when compared with the untreated limbs; however the levels were significantly higher than that detected in normal lamellar tissue. Although cryotherapy markedly reduced the severity of laminitis in this study it did not completely prevent minor histological changes in 4 of the 6 horses. Additionally, it is unclear whether laminitis could have developed following cessation of cryotherapy at 48 hours, as the horses were euthanized at that time. Cryotherapy was instigated immediately following administration of the carbohydrate induction bolus in this study. In a clinical case of grain overload or acute colitis such prompt initiation of cryotherapy may not be possible. It is unclear from this study whether such a potent prophylactic effect would occur if cryotherapy was initiated later in the course of the disease. Despite its limitations, this study demonstrates the potential of cryotherapy for the prevention of laminitis, and justifies further experimental and clinical evaluation of the technique.

Clinical Data

Anecdotal evidence of the successful use of cryotherapy to prevent acute laminitis has surfaced following the initial evidence-based recommendations for its use.⁴ The authors of the current paper have trialled continuous distal limb cryotherapy for the prevention of laminitis in 7 cases of acute colitis (5 Thoroughbred geldings, 1 Thoroughbred colt and 1 Arab mare). All cases presented with pyrexia ($>39.5^\circ\text{C}$), profuse watery diarrhea and signs of endotoxaemia and circulatory shock (injected mucous membranes with poor capillary refill time, tachycardia, tachypnoea and depression). Only one horse had signs of laminitis before the initiation of cryotherapy. This horse had increased intensity of digital pulses in all four limbs, though lameness was not obvious. All cases were placed into a plastic tub with a rubber floor. Shoes, if present, were not removed. Water, then cubed ice, was added to the tub to submerge the fore and hind limbs. The level of ice and water was maintained at the upper third of the cannon bones (approximately 10 cm below the "point" of the accessory carpal bone). Approximately 100 kg of cubed ice was required to cool the water initially. Subsequently, 50 kg of ice was added at 4- to 8-hour intervals to maintain the temperature within the bath at less than 5°C . All horses were treated (while in the cold bath) with intravenous polyionic fluids and plasma, antibiotics, nonsteroidal antiinflammatory drugs and activated charcoal and paraffin oil by nasogastric tube. Lucerne hay and water were provided ad libitum. The cases were monitored constantly and remained in the cold

bath for a minimum of 72 hours (Fig. 1C). All horses tolerated the cold bath well, without attempting to escape. The decision to remove the horses from the cold bath after the 72-hour period was based on resolution of clinical signs. Each horse was removed when the rectal temperature stabilized below 38.5°C , the manure was formed, and the mucous membranes returned to normal color. Five of the horses were removed at, or shortly after, 72 hours. The remaining 2 horses were removed from the bath at approximately 96 hours. None of the horses were lame on removal from the cold bath; however, all had increased intensity of digital pulses in all four limbs for the ensuing 24 hours. Variable distal limb edema was also present. The horse that had signs of ensuing laminitis before commencement of cryotherapy became mildly lame (Obel grade 2)⁴¹ between 12 and 24 hours after removal from the cold bath. The lameness improved over the subsequent 10 days of hospitalization and radiographs of this horse revealed no displacement of the distal phalanx within the hoof capsule. The remaining 6 horses were sound throughout the hospitalization period, and no lameness was detected on subsequent re-examinations 4 to 6 weeks later. All horses have returned to athletic activity, reportedly at previous levels. At the time of publication, three of the Thoroughbred horses have won metropolitan races since discharge.

After examination of hospital records, the authors estimate the incidence of acute laminitis in previous similar cases of acute colitis (that were not treated with cryotherapy) to be 40 to 50%. One of the treated cases mentioned did develop mild laminitis. This horse had signs of laminitis before commencement of cryotherapy. It is unclear whether cryotherapy may have reduced the severity, had no effect, or had a deleterious effect on the development of laminitis in this case. Although these are very limited numbers, the authors believe the prophylactic use of continuous distal limb cryotherapy in similar cases at risk of developing laminitis is worthy of further clinical evaluation.

Current Recommendations

Case Selection

Any horse that is at immediate risk of developing acute laminitis is an appropriate candidate for continuous distal limb cryotherapy. Deciding which cases are at immediate risk of developing acute laminitis is largely a matter of clinical experience. Primary diseases known to predispose horses to acute laminitis include colitis, proximal enteritis, metritis, pleuropneumonia, myositis, peritonitis, equine monocytic ehrlichiosis and complicated colic.^{39,42-46} Horses with known exposure to Black walnut wood shavings, horses known to have ingested excess carbohydrate, and horses with known access to hay/pasture containing the toxic plant *Hoary alyssum* (*Berteroa incana*)⁴⁷ should be considered to be at high risk of developing acute laminitis. These horses are also appropriate candidates for prophylactic distal limb cryotherapy.

Timing and Duration

The target period for distal limb cryotherapy is the developmental phase of laminitis. This has been defined as the period between the initial causative insult and the first appearance of

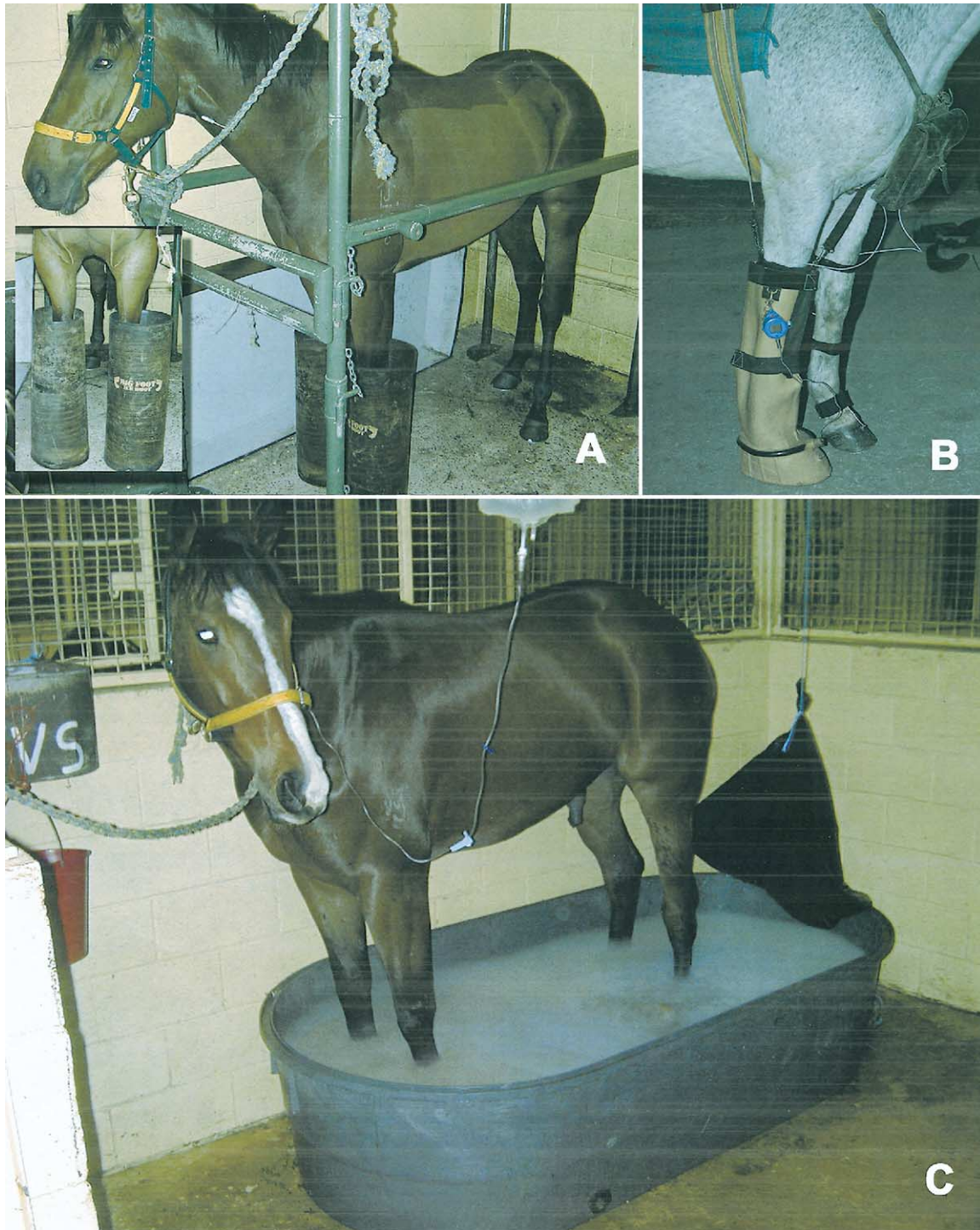


Figure 1 Methods of distal limb cryotherapy application. Freestanding (A) and fixed (B) boots for ice and water immersion. These devices are extremely difficult to apply to the hind limbs. A tub, filled with ice and water to a level just distal to the carpus, is the most practical means of cryotherapy application to all four limbs in the authors' experience (C). This clinical case of acute colitis remained in the cold bath constantly for 72 hours and did not develop acute laminitis.

acute lameness identifiable as laminitis.⁴⁸ The duration of the developmental phase is highly variable. In experimentally induced cases of carbohydrate overload, the developmental phase appears to last between 20 and 72 hours, with an average duration of approximately 40 hours. A similar duration appears to exist in clinical cases of acute bacterial colitis. The developmental phase appears to be much shorter (≤ 24 hours) in cases of *Hoary alyssum* poisoning⁴⁹ and equine

monocytic ehrlichiosis.⁴³ A longer and more variable duration may exist in association with other diseases such as pleuropneumonia. It is currently impossible to accurately predict the development of laminitis in individual cases, and therefore it is impossible to determine that a horse is within the developmental phase of laminitis. Initiation of cryotherapy must therefore be based on a high probability that a horse is within the developmental phase of laminitis; ie, the horse has

no clinical signs of laminitis but is considered at high risk of imminent development of the disease. There is currently no evidence to support the initiation of cryotherapy in horses with preexisting clinical signs of laminitis (horses that have progressed to the acute phase of laminitis).

Ideally cryotherapy should be applied for the entire duration of the developmental phase of laminitis. The maximum duration of the developmental phase in experimentally induced cases of carbohydrate overload appears to be 72 hours; ie, horses that do not have acute laminitis by 72 hours after administration of carbohydrate do not develop the disease. This can be used as a guide for the duration of cryotherapy application in clinical cases of carbohydrate overload. As stated previously, the duration of the developmental phase can be variable in association with other primary diseases. Resolution of the primary disease may be used as an indicator for timing the cessation of cryotherapy in individual cases. Although no direct link between endotoxin and laminitis has been established, clinical signs of endotoxaemia usually accompany clinical and experimentally-induced cases of acute laminitis.⁵⁰ Abatement of clinical and laboratory signs of endotoxaemia can be used as a marker for cessation of distal limb cryotherapy in many cases. We suggest the continuation of cryotherapy for approximately 12 hours after the signs of endotoxaemia have ameliorated. The authors have maintained continuous distal-limb cryotherapy for a maximum of 96 hours without apparent complications; however we currently have no experience with durations longer than this. We do not suggest the intermittent use of cryotherapy to prevent laminitis. Vasodilation is thought to be a feature of intermittent cryotherapy,¹⁹ and could potentially be detrimental.

The authors have noted profound reflex vasodilation in experimental and clinical cases after cessation of cryotherapy. This is manifest as an increase in the amplitude of digital pulses and warming of the feet. The phenomenon lasts between 12 and 24 hours after removal of cryotherapy and could be confused with the onset of acute laminitis. Horses should be closely monitored during this period for the development of lameness typical of acute laminitis. Acute laminitis should be appropriately treated using conventional therapy.

Application Methods

Any means by which the distal limbs can be continually exposed to temperatures of 0 to 5°C is acceptable. The cooling method should include the hoof and its solar surface. We suggest cooling the limb up to the proximal metacarpal/metatarsal region, as this appears to result in more effective cooling of the lamellar region.⁵ Ice and water immersion is effective, practical and inexpensive. Commercial cryotherapy cuff devices could be modified to include the hoof, though this is practically difficult. These devices are usually designed for compression as well as cooling. The effects of prolonged compression on the equine distal limb are currently unknown. The authors have had experience with a range of boots and tubs for ice and water immersion (Fig. 1A-C). We have found that the use of a tub, 200 cm long, 80 cm wide and 50 cm high, most practical for prolonged, continuous application of cryotherapy to all four limbs. A water-tight door at one end for ease of access, and a rubber floor are

suggested. Temporary or permanent stocks, together with cross-tying the head may assist in keeping the horse stationary. A refrigerated pump, recirculating water at around 2°C, can reduce or replace the requirement for ice. Overall, vigilance should be exercised to maintain immersion temperatures below 5°C to maximize the protective effect.

Conclusion

Continuous distal limb cryotherapy shows considerable promise as a technique for preventing acute laminitis. There is, however, an obvious requirement for further research in this area as current experimental and clinical data are very limited. A trial evaluating the efficacy of cryotherapy applied to all four limbs during the developmental phase of experimentally induced laminitis is underway in the primary author's laboratory. Horses in this experiment will be evaluated at extended periods after cessation of cryotherapy to establish that the onset of laminitis is not simply delayed. The authors will continue to evaluate cryotherapy in clinical cases at risk of developing laminitis, and welcome correspondence from others engaged in similar pursuits.

Currently the most challenging aspect of cryotherapy in the clinical situation is the identification of cases that will develop laminitis, and subsequently deciding when to initiate and cease cryotherapy in these cases. A biological marker to identify horses at imminent risk of developing laminitis is needed. Such a marker would define the clinically silent developmental phase of laminitis in individual cases, and greatly improve the potential for prevention of the acute disease. Undoubtedly genetic markers exist for the early identification of horses developing laminitis. Up-regulation of MMP-2 mRNA early in the acute phase of laminitis has been demonstrated in lamellar tissue.⁵¹ If this process begins during the developmental phase of laminitis, particularly within the blood, skin, ergot or chestnut tissue, a diagnostic potential exists.

The eventual discovery of the exact pathophysiology of laminitis will surely lead to effective and direct methods of prevention and therapy. In the meantime, the apparent resilience of the equine distal limb to prolonged, extreme cold may hold the key to successfully preventing the disease.

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