Scientific advances in prevention and treatment of laminitis

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INTRODUCTION
A therapeutic regime, using biological or chemotherapeutic agents, able to arrest or block the triggering of laminitis, does not exist. On the other hand, there is a plethora of remedies, used empirically, that symptomatically help the horse after it has acquired laminitis. It is more the extent and severity of the lamellar pathology that influences the outcome for the horse, not the treatment regimen itself. An effective laminitis preventative may emerge when the mechanism behind the disintegration of the anatomy of the hoof wall lamellae is fully understood. Our discovery that a class of enzymes appears to be involved in the lamellar failure of laminitis has led us to commence trials of proteinase inhibitor therapy, specifically targeted at hoof wall matrix metalloproteinases.

Since laminitis usually develops as a sequel to disease processes in body compartments other than the foot, it is of paramount importance that the primary disease is treated urgently and effectively. If the duration and severity of the primary disease can be reduced by intensive therapy, there is a strong chance that the severity of lamellar pathology may also be reduced, thus improving the prognosis for the horse. Nevertheless, severe laminitis is sometimes the outcome despite the best of current therapy.

When the laminitis process is triggered, there is virtually nothing, by way of drug therapy, that will stop its relentless progress. The administration of a nonsteroidal anti-inflammatory drug (NSAID) like phenylbutazone, during the developmental/acute stages, will ameliorate foot pain and create a more comfortable-looking horse, but the disease continues unabated. This creates an ethical dilemma; balancing the need to alleviate pain and suffering against the realisation that most of what is administered is only palliative. When NSAIDs are in use, the patient should be confined to a stall with deep bedding. Exercise in the critical acute phase, while under the influence of painkillers, such as phenylbutazone, is contraindicated.

CRYOTHERAPY
The results of experiments at the AELRU, continuously evaluating foot temperature (and by implication foot circulation), as horses developed laminitis, showed that vasoconstriction during the developmental stage of laminitis may have had a protective effect (Pollitt and Davies 1998). The profound hypometabolic effect of cryotherapy is considered to be the most important mechanism by which cold limits the severity of an injury. Tissue metabolic rate and oxygen consumption are inversely related to temperature. A reduced requirement of cooled tissue for glucose, oxygen and other metabolites enhances the survival of cells during periods of ischaemia. This mechanism is thought to protect tissue and is the basis for the use of cryotherapy in organ transplant surgery. Enzymatic activity is reduced 50% for every 10°C reduction in tissue temperature. The activity of collagenases and pro-inflammatory cytokines is also significantly reduced at lower temperatures. To date clinical recommendations for the duration and temperature of cryotherapy in horses have been extrapolated from human medicine. Our recent studies have challenged these recommendations. The diverse effects of cryotherapy appear to interrupt many of the pathophysiological mechanisms occurring during the developmental and acute phases of the disease.

Enzymatic degradation of lamellar attachments by matrix metalloproteinases (MMPs) forms the basis of our pathophysiological theory for developmental laminitis. It is hypothesized that the inappropriate release of excess, activated lamellar MMPs is mediated by “laminitis trigger factors” delivered to the foot via the digital circulation during developmental laminitis. The delivery of these triggers, which may include cytokines, protein fragments or bacterial products of hindgut origin appear to be limited by cold-induced digital vasoconstriction during the developmental phase of laminitis. This was the basis for evaluating the use of cryotherapy for the prevention of laminitis. The potent local hypometabolic effect of cryotherapy could augment the vasoconstrictive 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 and tumor necrosis factor, during the developmental stage of laminitis. Cryotherapy could also limit secondary inflammatory damage caused by white blood cell infiltration. Similar mechanisms are believed to be the basis for the efficacy of scalp cryotherapy in preventing alopecia in cancer patients undergoing chemotherapy. 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. Alternate pathophysiological the-
ories for laminitis propose that digital hypo-perfusion during the developmental stage leads to lamellar ischemia and necrosis. Profound, cold-induced vasoconstriction would seem contraindicated if digital hypo-perfusion 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 ischaemic damage. Similarly, a profound cold-induced reduction in metabolism could protect the lamellar tissue from a lack of glucose (a proposed initiator of lamellar separation). 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, occurring elsewhere in the body, has abated.

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

We have completed two controlled studies on the efficacy of cryotherapy for the prevention of laminitis. In the first study (van Eps and Pollitt 2004) laminitis was induced in six horses using the oligofructose overload model. Each horse had one forelimb immersed in ice and water (mean temperature 0.5-1.7°C) for a 48 hour experimental period, achieving a mean internal hoof temperature of 3.5-0.9°C. All horses developed 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. The study also showed significantly reduced up-regulation of lamellar MMP mRNA in the cooled limbs when compared with the untreated limbs. Although cryotherapy markedly reduced the severity of laminitis it did not completely prevent minor histological changes in 4 of the 6 horses. In a second study cryotherapy was applied to all 4 limbs of 6 horses for 72 h. Laminitis was induced as before and the observation period was extended until 7 days post oligofructose dosing. The horses showed either no or very mild clinical signs of laminitis and histology of lamellar tissues taken 7 days post induction showed no laminitis. Control horses were lame at 7 days and had moderate to severe laminitis histopathology (van Eps and Pollitt 2004). Cryotherapy was instigated immediately following administration of the carbohydrate induction bolus in these studies. In a clinical case of grain overload or acute colitis such prompt initiation of cryotherapy may not be possible. It is unclear whether such a potent prophylactic effect would occur if cryotherapy was initiated later in the course of the disease when lameness was already present. Thus the potential of cryotherapy to prevent laminitis has been demonstrated and further clinical evaluation of the technique is justified.

**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. The authors 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 fever (>39.5°C), profuse watery diarrhoea and signs of endotoxaemia and circulatory shock (injected mucous membranes with poor capillary refill time, rapid heart rate 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 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, NSAIDs 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. 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, faeces was formed, and the mucous membranes returned to normal colour. 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 oedema was also present. One horse that had signs of incipient laminitis before commencement of cryotherapy was mildly lame between 12 and 24 hours after removal from the cold bath. The lameness disappeared over the subsequent 10 days of hospitalization and radiographs of this horse revealed no displacement of the distal phalanx within the hoof capsule. It is un-
clear whether cryotherapy reduced the severity, stabilized the pathology or had no effect on the development of laminitis in this case. 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 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%. 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.

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 be applied to the entire distal limb below the carpus. We suggest cooling the limb up to the proximal metacarpus/tarsus, as this appears to result in more effective cooling of the lamellar region. This takes advantage of the unique distal limb anatomy of the horse; the major arteries are subcutaneous in the fetlock region and the blood they are delivering to the foot can be cooled on its way down. Cooling just the feet is not enough. Laminitis breaks through and is not prevented when only the feet are cooled. Ice and water immersion is effective, practical and inexpensive. Commercial cryotherapy cuff devices and gel packs can be modified to include the hoof and effectively cool the feet. 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 refrigerated pump, re-circulating water at around 2°C, can reduce or replace the requirement for ice. Continuous distal limb cryotherapy is now a proven preventive for acute laminitis. The apparent resilience of the equine distal limb to prolonged, extreme cold can be harnessed and holds the key to successfully preventing the disease.

MANAGEMENT PRACTICES TO AVOID PASTURE ASSOCIATED LAMINITIS
Our research provides strong circumstantial evidence that fructan in the hindgut of horses triggers laminitis. Horses can ingest fructan rich pasture rapidly in amounts exceeding (Longland and Byrd 2006) that used to induce experimental laminitis (van Eps and Pollitt 2006). Owners of horses predisposed to laminitis should develop strategies to reduce risk. Most horse owners in temperate regions are committed to pasture feeding regimens throughout the year so a combination of both pasture and horse management practices need to be considered. The aim is to reduce the concentrations of water soluble carbohydrate (WSC) in pasture and to prevent its consumption by the grazing horse.

PASTURE FACTORS
Some pasture species are notorious fructan accumulators (they are selected and bred for this) and if possible should not be fed to horses. The WSC content of grass can reach 56% of its total dry matter (DM) of which fructan can be 44%. Grass that is actively growing tends to store less WSC. Maintaining soil moisture and fertility and keeping grass short by mowing or grazing encourages leaf growth and WSC consumption (Watts and Chatterton 2004). WSC accumulation in grass is driven by photosynthesis and takes time to occur. It peaks in the afternoon and early evening and high WSC intake can be avoided by allowing grazing only in the early morning. Likewise, pasture shaded by treelines and windbreaks accumulates less WSC and susceptible horses can be strip grazed behind electric fences in these areas. Some horse managers will poison selected paddocks to eliminate pasture altogether and at time of high risk keep their horses on these “dry lots”. Times of risk are conditions of high light intensity and low ground temperatures such as in spring and autumn. Particular care is indicated at these times. Under these conditions photosynthesis and WSC production is relentless but growth and metabolism is slow; hence WSC accumulation. Using a cash flow analogy; the bank balance is greatly in credit - cash income exceeds expenditure. Drought or periods of low soil moisture may also drive WSC accumulation and even dry looking pasture can have a high WSC concentration. Drought breaking rain can also be a trap. WSC accumulated in subsoil roots during dry times is rapidly mobilized to new shoots and many a pony has foundered on insignificant looking pasture after rain. Another trap is slashed or heavily grazed pasture or stubble after harvesting. Most of the WSC of grass is stored, not in the green leaves, but in the lower, pale green stems that are the plants WSC reservoir. Grass that has gone to seed in summer is usually low in overall WSC content in its leafy tissues but could still pose a risk from the starch in the seeds. A yield of starch from the seed of perennial ryegrass has been estimated at 360kg/ha per growing season (Longland and Byrd 2006). Horses will selectively strip seed from standing pasture and could conceivably consume sufficient starch to trigger laminitis from hindgut fermentation.
HORSE FACTORS
Grazing muzzles have been successfully used to limit grass and thus WSC intake by horses at pasture (Figure 3). The hole in the muzzle limits intake and confines consumption to leafy tops that are lower in WSC content. When horses and ponies have no access to pasture and are yarded or confined to dry lots what are they to be fed? The usual solution is grass or forage hay. However the haymaking process may not always reduce WSC and sometimes the most innocent looking hay may have dangerous WSC levels. If possible hay made from mature, summer pasture that has gone to seed. Hay could still be dangerous if harvested during periods of plant stress such as autumn and spring. Analysis of the WSC content of such hay is warranted but not always practical. Fortunately soaking hay in fresh water leaches out WSC (but not starch) and reduces the WSC content significantly. Sixty minutes of soaking and draining removed an average of 31% of the soluble sugars from 15 hay samples (Watts and Chatterton 2004). Pony breeds in particular are prone to obesity and insulin resistance and obese individuals are at high risk of developing laminitis. The diet of obese individuals can be modified so that energy intake is derived from fat and fibre rather than from high glycaemic sources. Owners should monitor the body weight and learn to condition score their horses aiming for more optimum weights. Insulin resistance can be reversed by weight reduction and regular aerobic exercise. “Founder guard” (Virbac Australia, Milperra, NSW 2214, http://www.virbac.com.au/) is an antibiotic formulation that can be fed to horses and ponies at pasture and when present in the hindgut limits the proliferation of Streptococcus bovis. When “predosed” it may control hindgut carbohydrate fermentation to levels that prevent serious laminitis.

ENDOTOXAEMIA THERAPY
Horses diagnosed with toxaemia during enteritis, colitis, strangulating colic, pleuropneumonia, septic metritis (retained placenta) and grain overload are at high risk of developing laminitis and ideally, cryotherapy, antibiotic formulation that can be fed to horses and ponies at pasture and when present in the hindgut limits the proliferation of Streptococcus bovis. When ‘predosed’ it may control hindgut carbohydrate fermentation to levels that prevent serious laminitis.

V ASODILATOR THERAPY
The use of vasodilatory therapy and hot water footbaths during the developmental stage of laminitis appears to be contraindicated. Drugs with vasodilator action such as isoxsuprine hydrochloride, ace promazine and glyceryl trinitrate (applied as a patch to the pastern) may be beneficial after lamellar damage has occurred, when healing is required, but should be administered with caution during the developmental phase. Exercise of an intensity which raises core temperature and local anesthetic blockade of the palmar or planter nerves both result in hoof wall heating (and by implication vasodilation) and are contraindicated during the developmental stage. In addition, horses given local anaesthetic to block foot pain, and then encouraged
to walk, will almost certainly sustain greater lamellar damage than a rested, confined horse. Forced exercise to any horse with acute laminitis is strongly contraindicated.

**FREE RADICAL SCAVENGERS**

Dimethylsulfoxide (DMSO) may be given intravenously for its free radical scavenging and anti-inflammatory effects. DMSO (90% solution) mixed with polyionic solutions and 5% dextrose is best administered slowly at about 8 litres per hour. The concentration of DMSO must remain below 20% to avoid the risk of intravascular haemolysis. However, despite the potential of DMSO, its promise as an effective laminitis therapy has not been fulfilled. There is no evidence that ischaemia, reperfusion injury and the generation of free radicals are involved in the pathogenesis of most cases of laminitis.

**A RECOMMENDED TREATMENT STRATEGY**

The list of pharmaceuticals that have been administered to horses with laminitis is long and, apart from the NSAIDs, none have achieved particular prominence. The author’s recommended treatment strategy is to aggressively treat the primary disease entity, systematically addressing the problems the horse may have as proactively as possible. Fluid and electrolytes, antibiotics and NSAIDs are administered as required. Horses with septic metritis/retained placenta also require uterine lavage.

The administration of 4 litres of mineral oil four times /day may be beneficial in the case of laminitis developing from grain overload. It has a laxative effect and its presence in the large intestine is said to block the absorption of toxins. Similarly, activated charcoal is an effective adsorbent of a range of toxins and may be useful in cases of grain overload if administered promptly. In Australia, doses of 1.5 g/kg/day have been used to treat plant toxicoses in large animals. The higher dose is indicated if a large quantity of grain has been consumed. However activated charcoal has not been tested against alimentary laminitis, so its true effectiveness is unknown. The application of cold therapy to the front feet, strict confinement to a stall with a deep bedding of sand or shavings and mechanical support for the distal phalanx are also recommended.

**REFERENCES**


