Kevin T. T. Corley, BVM&S PhD DACVIM DECEIM DACVECC MRCVS

Veterinary Advances Ltd Ireland

kcorley@equineadvances.com

CRITICAL CARE AT THE EDGE - HOW I QUACK AND WHAT IS THE EVIDENCE FOR MY QUACKERY?

According to Wikipedia, "Quackery" is the promotion of unproven or fraudulent medical practices. In equine critical care, unfortunately we have to use 'unproven' therapies all the time, as the level of evidence we have supporting any treatment is minimal to non-existent. Indeed, if we were to use only 'proven' treatments in our critically-ill patients with a multi-center randomized clinical trial is the level of proof required, we could treat them only for orthopedic pain, gastric ulcers and intestinal parasites and give lidocaine for ileus and sedate horses with colic. If we were to require properly powered randomized clinical trials, then we could no longer use lidocaine or sedate horses with colic. So we are left with unproven treatments. We base these treatments on our understanding of physiology, pathophysiology and pharmacology, but also largely on previous experience. This dependence on previous experience is essential, but also introduces a dangerous "last three case" bias – if the last three cases went well, the treatment works….! And so we all enter the world of "Quackery". In this lecture, I will give insights into a couple of the less mainstream treatments I use, where I got them from, and what evidence there is to back up their use.

Cold foals

In 2002, there were two papers published in the New England Journal of Medicine showing much better neurological outcomes when adult human patients were cooled after CPR [1, 2]. This led to exploration whether therapeutic hypothermia might be beneficial in other circumstances, including perinatal asphyxia syndrome [3]. There is now a good body of evidence showing that therapeutic hypothermia is beneficial in human infants with perinatal asphyxia [4]. In addition to improving overall outcome and neurological function, therapeutic hypothermia has been shown to reduce myocardial damage and reduce acute kidney injury in human neonates with perinatal asphyxia. Based on this growing and large body of evidence in human infants, we and others [5, 6] have been exploring therapeutic hypothermia in foals.

The first step we made was not actively heating foals that present with perinatal asphyxia. This is obviously technically easy to achieve (although it does sometimes require restraint of the well-meaning nurses with their duvets and hot water bottles for the poor cold foals). We have then tried to achieve some degree of whole body or localized cooling. Whole body cooling to the 32-34°C that was described in the original papers is very hard to achieve in a busy veterinary hospital with limited budgets. In these studies, they gave the cooled patients neuromuscular blockers to stop shivering and mechanically ventilated them. There are also a number of complications of hypothermia including thrombocytopenia, sinus bradycardia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperglycemia [4], and changes in drug pharmacokinetics.

We have tried a degree of active cooling with ice and have been somewhat successful in lowering the core body temperature (as measured by esophageal thermometer). However, it is hard to get the temperature as low as 34°C. Our current policy is to not actively rewarm any foals with a suspected diagnosis of perinatal asphyxia syndrome. We try to actively cool the most severely affected foals with ice, hot water bottles filled with cold water and intravenous fluids from the fridge. A new paper offers low cost two methods of cooling (gel packs or phase changing materials) that were successful in human infants [7], which I will try next foal season. The only foals that we actively warm are premature foals and foals undergoing or recovering from anesthesia.

Low molecular weight heparin

This is probably the least "quack" of treatments I am going to discuss. Heparin is a mix of different size molecules. In horses, the larger size fragments are responsible for erythrocyte agglutination. Removing the high molecular weight component results in increased anti-Xa activity, reduced anti-thrombin activity and no erythrocyte agglutination [8]. There are several different low-molecular weight heparins available. For two of these, there is pharmacological data in horses [8-10] and foals [11].
There is also some efficacy data in horses. A trial in horses with colic showed a lower incidence of thrombophlebitis with dalteparin than with unfractionated heparin [12].

A study showed that enoxaparin may be effective at preventing laminitis after colic surgery. In this study the mean laminitis grade was lower in 304 treated subjects than in 56 historical controls [13]. There is also evidence from human sepsis and sheep models of endotoxemia that (unfractionated) heparin administration is associated with improved survival. Lastly, there is an in vitro study suggesting that low molecular weight heparin blocks Equid herpes virus type-1 (EHV-1) induced platelet activation [14].

I use enoxaparin in foals with sepsis and severe perinatal asphyxia syndrome. I also use it in horses that have undergone colic surgery for strangulated intestine. I used to administer dalteparin during the surgery for these horses. However, I can't currently get dalteparin in Ireland and we suspect that administering enoxaparin during surgery increases the incidence of bleeding from the surgical incision.

Glutamine

There is one quack I used to do, which is perhaps not the best idea. Glutamine has been shown to be orally absorbed in horses [15], safe in horses and to facilitate mucosal restitution in oxidant damaged equine right dorsal colon [16]. In 2010, the human literature was strongly supportive of its use [17]. There is also a large amount of evidence in laboratory animals showing benefit. I gave this drug, especially to foals with perinatal asphyxia syndrome and to horses with severe colic – to aid intestinal healing.
There were many small studies in human medicine suggesting that Glutamine decreases mortality in critically-ill patients, results in fewer infection complications and a shorter hospital stay. However, a large randomized clinical trial in 1223 critically-ill patients showed increased mortality in patients treated with glutamine [18].
If I thought that a large multi centre trials in humans were a lower level of evidence than a small study in normal horses, or a small laboratory study in induced disease - I would continue to use Glutamine.

The editorial accompanying the Glutamine trial said "Probably the most important contribution of the present trial is that it provides firm support for the need for large adequately powered, randomised controlled trials in critical care medicine to investigate whether what we intuitively consider to be the best treatment for our patients also is effective and without harm".

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