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Title:
Trigeminal-mediated headshaking in horses

prevalence, pathology, diagnosis and treatment

Presentation for

PhD by publication

Trigeminal-mediated headshaking in horses: prevalence, pathology, diagnosis and treatment

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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Health Sciences

Words: **48443**

Synopsis:

This work covers research carried out over an 11-year period (2009 – 2020), during which my skills have developed. The research is in trigeminal-mediated headshaking, a neuropathic facial pain condition in horses.

I have an international reputation in this field. I was awarded Fellowship of the Royal College of Veterinary Surgeons for Meritorious Contribution to Clinical Practice, largely due to my work in headshaking.

I am submitting seven publications, five first and two last author, for incorporation into a thesis for a PhD by publication. Five papers have been published in Equine Veterinary Journal, the highest impact factor equine veterinary journal. Three have been given awards, as a result of which they have been circulated widely. One received a further award for being in the top 10% of downloaded papers from that journal in 2019. The last author publications were designed by me and I sourced funding and ethics approval for them. The first authors were postgraduate students conducting their first pieces of original research and therefore required close supervision.

Chapter One reviews current understanding of trigeminal-mediated headshaking in the horse.

Chapter Two: Prevalence. One aspect of the impact of a condition is its prevalence. There was no robust research into the prevalence of trigeminal-mediated headshaking in any country. A questionnaire study of horse owners determined prevalence of headshaking to be 4.6% in the UK.

Ross SE, Murray JK, **Roberts VLH** (2018) 'Prevalence of headshaking within the equine population in the UK' Equine Vet J. Jan;50(1):73-7.

Chapter Three: Pathology. A translational study was performed to determine whether horses with trigeminal-mediated headshaking had focal demyelination of the trigeminal root as do a majority of sufferers of human trigeminal neuralgia, a clinically similar syndrome. No demyelination, and indeed no other gross pathology, was detected. This, alongside other factors, suggests that TMH is a functional rather than structural condition, which could therefore be reversible.

Roberts VLH, Fews D, McNamara J, Love S. (2017) Trigeminal nerve root demyelination not seen in six horses diagnosed with trigeminal-mediated headshaking. Front Vet Sci

section Veterinary Neurology and Neurosurgery. May 15;4:72.doi:10.3389/fvets.2017.00072. eCollection 2017.

Chapter Four: **Diagnosis**. Diagnosis of trigeminal-mediated headshaking is particularly challenging as it is one of exclusion. A useful step can be to demonstrate, using diagnostic local anaesthesia, that headshaking clinical signs are due to facial pain. A significant effect of operator experience on the accuracy, and therefore reliability, of this technique was determined.

Wilmink S, Warren-Smith CM, **Roberts VL.H** (2015) Validation of the accuracy of needle placement as used in diagnostic local analgesia of the maxillary nerve for investigation of trigeminally mediated headshaking in horses. Vet Rec. Feb 7;176(6):148.

Chapter Five: Treatment I. Neurectomy of the infra-orbital nerve has previously been reported as a possible treatment for trigeminal-mediated headshaking but success rates were low, and side-effects could be severe. A modified technique of infraorbital nerve ablation to increase success rates and reduce side-effects was investigated. Whilst this was achieved, only modest success rates were achieved and side effects could still be severe in some cases.

Roberts V.L.H., McKane S.A., Williams A. and Knottenbelt D.C. (2009) Caudal compression of the infraorbital nerve: a novel surgical technique for treatment of idiopathic headshaking and assessment of its efficacy in 24 horses. Equine Vet J. 41(2): 165-7

Roberts V.L.H., Perkins J.D., Skärlina E., Gorvy D.A., Tremaine W.H., Williams A., McKane S.A., White I. And Knottenbelt D.C. (2013) Caudal anaesthesia of the infraorbital nerve for diagnosis of idiopathic headshaking and caudal compression of the infraorbital nerve for its treatment, in 58 horses. Equine Vet J. Jan:45(1):107-10

Chapter Six: Treatment II. Development and validation of a more effective and safer translational treatment based on a minimally-invasive therapy for people suffering neuropathic pain. A pilot study was later expanded to a larger international, multi-centre study.

Roberts V.L.H., Patel N.K., Tremaine W.H. (2016) Neuromodulation using percutaneous electrical nerve stimulation for the management of trigeminal-mediated headshaking: A safe procedure resulting in medium-term remission in five of seven horses. Equine Vet J. 2016 Mar;48(2):201-4.

Roberts VLH, Bailey M, The EquiPENS™ Group, Patel N.K. (2020) Safety and efficacy of EquiPENS™ neuromodulation for the management of trigeminal mediated headshaking in 168 horses. Equine Vet J. Mar;52(2):238-243.

Chapter Seven discusses how my research skills have progressed and consider my published research, its impact, and suggestions for future investigation and improvement.

Dedication and acknowledgements:

I would like to thank my examiners, Professor Monica Aleman and Dr. Sue Dyson and the Chair, Professor Anthony Pickering. I am grateful also to my supervisor Professor Toby Knowles and the invaluable inspiration from Dr. Andy Grist. Dr. Kirstie Pickles has been an excellent technical supervisor, working on a number of drafts in return for definitely not enough chocolate. My line manager, Professor David Barrett has, as I have to come expect from him, been nothing but supportive and helpful.

I would like to thank all my co-authors with particular mention of Professor Derek Knottenbelt and Dr. Shaun McKane, then at the University of Liverpool for starting me on this journey. Mr. Nik Patel at Southmead Hospital continues to support and advise me, largely it seems, in return for being able to present some equine research for light relief at medical conferences! My post-graduate students, Dr. Sanne Wilmink and Dr. Sarah Ross, deserve mention not least for the success they have gone on to attain.

I would also like to thank Coral Winslow-Llewellyn and Sue Daniels at Algotec Research and Development UK and Rachel Foster-Borman from the University of Bristol for their support in the development of EquiPENS™.I also grateful to The Langford Trust for Animal Health and Welfare, The Langford Clinical Services Research Fund, The British Neuropathological Society, The Academy of Medical Sciences and Wellcome Trust Inspire Scheme for funding.

Fortunately, my husband Matthew seems endlessly forgiving and supportive. Perhaps I did not need to test this so soon into married life by immediately falling off my horse and spending our honeymoon in the Limb Reconstruction Unit. After that, doing some extra childcare and enabling me to spend my annual leave writing this thesis pales into insignificance. I would have loved to take this opportunity to thank our two-year-old twins, Joshua and Laura, for their help with this thesis but no, they were no help at all.

Author’s declaration:

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: .....Veronica Roberts.....
DATE:.....27/11/2020.....

List of papers for consideration:

1. Ross SE, Murray JK, **Roberts VLH** (2018) 'Prevalence of headshaking within the equine population in the UK' Equine Vet J. Jan;50(1):73-7.

Awarded most clinically relevant paper in that issue by Equine Veterinary Journal.

2. **Roberts VLH**, Fews D, McNamara J, Love S. (2017) Trigeminal nerve root demyelination not seen in six horses diagnosed with trigeminal-mediated headshaking. Front Vet Sci section Veterinary Neurology and Neurosurgery. May 15;4:72.doi:10.3389/fvets.2017.00072. eCollection 2017.

3. Wilmink S, Warren-Smith CM, **Roberts VL.H** (2015) Validation of the accuracy of needle placement as used in diagnostic local analgesia of the maxillary nerve for investigation of trigeminally mediated headshaking in horses. Vet Rec. Feb 7;176(6):148.

4. **Roberts V.L.H**., McKane S.A., Williams A. and Knottenbelt D.C. (2009) Caudal compression of the infraorbital nerve: a novel surgical technique for treatment of idiopathic headshaking and assessment of its efficacy in 24 horses. Equine Vet J. 41(2): 165-7.

5. **Roberts V.L.H**., Perkins J.D., Skärlina E., Gorvy D.A., Tremaine W.H., Williams A., McKane S.A., White I. And Knottenbelt D.C. (2013) Caudal anaesthesia of the infraorbital nerve for diagnosis of idiopathic headshaking and caudal compression of the infraorbital nerve for its treatment, in 58 horses. Equine Vet J. Jan:45(1):107-10.

6. **Roberts V.L.H.**, Patel N.K., Tremaine W.H. (2016) Neuromodulation using percutaneous electrical nerve stimulation for the management of trigeminal-mediated headshaking: A safe procedure resulting in medium-term remission in five of seven horses. Equine Vet J. 2016 Mar;48(2):201-4.

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Awarded most clinically relevant paper in that issue by Equine Veterinary Journal.

Awarded in the top 10% of downloaded papers from Equine Veterinary Journal 2019.

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Review of trigeminal-mediated headshaking in horses

1.1 Objectives of the thesis

This thesis draws together my original research work in equine trigeminal-mediated headshaking. It encompasses a research journey furthering the understanding of trigeminal-mediated headshaking. The research investigates the prevalence of this condition and then explores the aetiopathogenesis. This is followed by work to improve diagnosis and finally, utilising information gleaned earlier, studies to improve its management. Alongside this journey is my own personal research journey which will be considered in the Discussion.

1.2 Clinical signs of trigeminal-mediated headshaking

Occasional shaking of the head is normal equine behaviour. However, where the headshaking is any or all of: frequent; violent; characterised by flicks and jerks of the head; accompanied by signs of nasal irritation such as snorting, sneezing, rubbing the nose, striking the nose; accompanied by signs of distress or affects riding or handling the horse, then a pathological process must be considered (Pickles, 2014). Conditions which can cause headshaking may include: ear mite infestation, otitis interna, cranial nerve dysfunction, cervical injury, ocular disease, guttural pouch mycosis, dental periapical osteitis (Lane and Mair, 1987), protozoal myeloencephalitis (Moore et al, 1997) and sinusitis (Fiske-Jackson et al, 2012) as well as a behavioural or rider issue (Pickles, 2014). However, where shaking was such that referral veterinary advice was required, there was a 98% chance that no physical cause could be determined, leading to a diagnosis of idiopathic headshaking (Lane and Mair, 1987). As knowledge of this condition has developed, it is likely that most of these horses were suffering what is now termed trigeminal-mediated headshaking (Pickles et al, 2014).

Clinical signs of trigeminal-mediated headshaking are usually of predominantly vertical headshaking, which may be violent (Pickles, 2014). These movements are often accompanied by sharp vertical flicks and signs of nasal irritation (Lane and Mair, 1987). Typically, signs are worst at exercise (Lane and Mair, 1987; Newton et al, 2000; Madigan and Bell, 2001), with only some horses being also affected at rest. Seasonality of clinical signs is reported in approximately 60% of headshaking horses, with the majority of these being documented as Spring/Summer affected (Madigan and Bell, 2001; Mills et al 2002). However, research included in this thesis found that horses were seasonally completely free of signs, as opposed to showing a reduction in signs, in only 25% of cases (Roberts et al,

2020, Paper 7). Even in non-seasonally affected horses, signs may vary with an apparent correlation to weather conditions (Lane and Mair, 1987; Madigan and Bell, 2001; Mills et al 2002).

1.3 Prevalence

Knowledge of the prevalence of headshaking in the worldwide population is fundamental to understanding the scale of the welfare issue caused by trigeminal-mediated headshaking. Whilst there are reports of horses with signs consistent with trigeminal-mediated headshaking from many developed countries, only the UK horse population has been investigated in prevalence studies to date. There may be a complex interaction with environment in this acquired condition of unknown aetiology. For this reason, further information as to whether there is a difference in prevalence between countries, and in particular between developed and developing countries, would be of interest.

The prevalence of headshaking in the UK equine population was first reported by Slater et al in 2013 as part of a general equine health survey. The prevalence of horses reported by their owners to have shaken their heads more than normal on a particular day of the year was reported to be between 1 and 1.5%. A dedicated study into the prevalence of headshaking in the UK equine population was published in 2018 (Ross et al, 2018), which is the subject of Chapter Two. Owners reported that 4.6% of their horses had shaken their heads more than normal in the last year, which increased to 6.2% if any time-point since ownership was considered. However, veterinary advice was sought in only 30% of these horses. This suggests that medically significant headshaking can be expected to affect around 2% of UK horses. Assuming an approximate UK horse population of one million (BETA, 2015), some 20,000 UK horses could be suffering from neuropathic facial pain.

The study by Ross et al. (2018) found the median age of a horse with excessive headshaking to be 12 years but did not identify any association with sex or breed. Other studies have reported that the condition usually first affects adult horses in the prime of their lives, with median ages of onset varying from 6 years (Mills et al, 2002) to 10 years (Mair, 1999). Geldings appear to be over-represented in some studies, comprising 63% (Mills et al, 2002) to 71.5% (Madigan and Bell, 2001) cases but geldings are generally over-represented in a riding horse population (Aune et al, 2020). All breeds appear susceptible (Mills et al, 2002 and Ross et al, 2018). There are no longitudinal studies following disease progression. There is a suggestion that some cases will progress in severity and from seasonal to non-seasonal (Pickles et al, 2014). There is a suggestion that 5% of horses may enter spontaneous long-term remission (Madigan and Bell, 2001).

Whilst trigeminal neuropathy is recognised in small animals (Mayhew et al, 2002), there appears to be limited clinical overlap with equine trigeminal-mediated headshaking. To the author's knowledge there are only isolated anecdotal reports of clinical signs consistent with trigeminal-mediated headshaking, without investigation, in zebra and donkeys (personal observation). In the developed world this may be that other Equidae are not used for riding in any significant number and clinical signs are often only displayed during forced exercise. There may be further potential to explore why horses might be affected but other Equidae are not, or rarely so, as this could potentially give some information as to aetiology. Within the Equidae, discovering differences between horses in developed and developing countries and wild populations may help inform about influence of environment and management.

1.4 Impact

Disease impact encompasses morbidity, mortality and economic burden (WHO, 2018). For trigeminal-mediated headshaking this requires consideration of welfare and economic effects of the condition on the individual horse, the individual owner and the equine industry as a whole. The potential for translational research should also be considered.

Horses suffering trigeminal-mediated headshaking are considered to have a neuropathic facial pain condition, and presence of pain has a negative impact on welfare. The degree of this negative impact can arguably be assumed to correlate with severity of pain. Human patients with neuropathic pain may report signs varying from tingling up to unbearable electric shock like pain, with quality of life significantly reduced (Dobrota et al, 2014). Severity of clinical signs in horses is likely to be our best indicator of their level of pain and severity of headshaking signs commonly varies between, and within, individuals. A variety of grading systems have been used to quantify severity of headshaking signs (Newton et al, 2000; Talbot et al, 2013; Roberts 2014). The system used by Talbot focuses mostly on the effect of signs on the horse's behaviour, that by Roberts on the utility of the horse to the owner and that by Newton is a combination (Table 1). An agreed methodology would be useful for more accurate monitoring of disease progression, treatment efficacy and comparison of published studies (Pickles et al, 2014). It could be inferred that disease of a severity such that horses meet grade 1/5 on Newton's scale, 1/3 on Talbot's scale and 1/3 on Roberts' scale has minimal impact on welfare and utility to the owner and therefore minimal economic impact to the equine industry. Significant welfare and economic impact could be expected at the higher grades, with horses being retired or even euthanased if they cannot perform in their intended discipline. Of note are horses which would be classified as 3/3 on Roberts' scale. These horses suffer even at rest and so can have no respite. For

them, even retirement is not an option, which may leave only euthanasia should treatment options fail.

GRADING SYSTEM	SCALE	CLASSIFICATION
Newton, 2000	1	Intermittent and mild clinical signs. Facial muscle twitching. Rideable.
	2	Moderate clinical signs. Definable conditions under which they occur/develop. Rideable with some difficulty
	3	Rideable but unpleasant ride, difficult to control
	4	Unrideable, uncontrollable
	5	Dangerous with bizarre behaviour patterns
Talbot, 2013	0	No headshaking
	1	Mild signs at exercise
	2	Obvious signs at exercise but no striking at the nose or behavioural changes
	3	Most severe, with severe signs including behavioural changes and refusal to move
Roberts, 2014	0	No signs of headshaking
	1	Mild headshaking, insufficient as to interfere with ridden exercise
	2	Headshaking at exercise of a severity sufficient as to make ridden exercise dangerous or impossible
	3	Headshaking even at rest

Table 1: Grading systems.

At present there are no data considering the proportions of affected horses meeting each grading classification. Such data would allow better assessment of scale of impact, by calculating the proportion of horses with significant welfare compromise, those retired and euthanased and from that, the cost of wastage to the equine industry.

There is potential for translational research, with clinical similarities being present between equine trigeminal-mediated headshaking and human trigeminal neuralgia. This potential may however be limited with the pathology present in most human trigeminal neuralgia patients being absent in equine trigeminal-mediated headshaking.

1.5 Anatomy of the trigeminal complex

The trigeminal complex is made up of both peripheral and central components (De Lahunta and Glass, 2009). Peripheral components are the trigeminal nerve (V cranial nerve), trigeminal ganglion, the 3 main branches (ophthalmic, maxillary, mandibular, Figure 1), and then their branches.

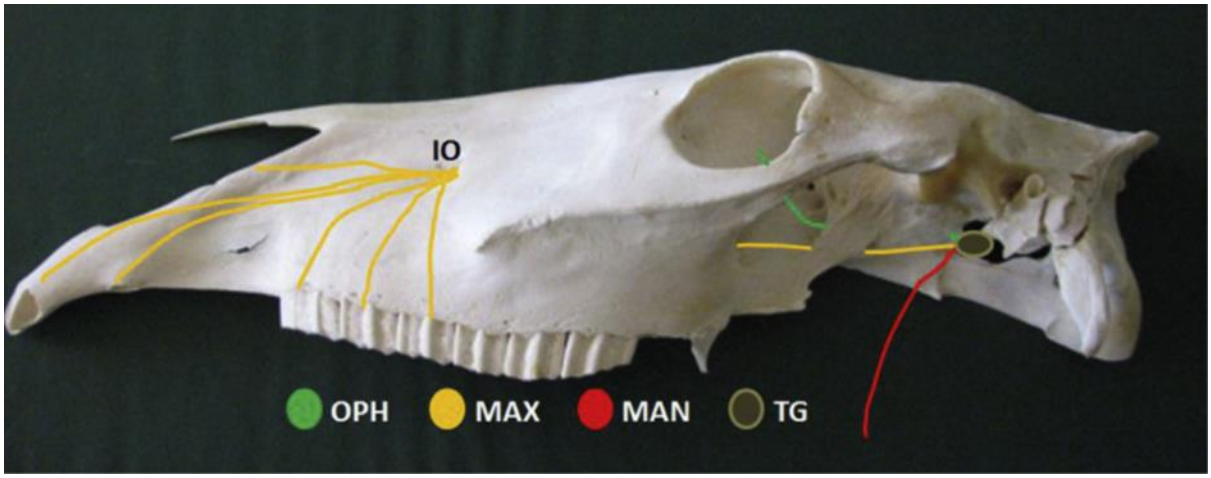

Figure 1: Peripheral components of the trigeminal complex. Ophthalmic nerve (OPH in green), maxillary nerve (MAX and its branch infraorbital nerve [IO], in yellow), mandibular nerve (MAN in red), and trigeminal ganglion (oval brown structure). Not all branches from each nerve are shown. Figure not drawn to scale. Image reproduced with permission from Dr. Monica Aleman (From Pickles K, Madigan J, Aleman M. Idiopathic headshaking: is it still idiopathic? Vet J. 2014 Jul;201(1):21–30; with permission.)

The central components are made up of the spinal tract, likely to the second cervical spinal cord segment, and the nuclei of the trigeminal complex within the brainstem.

The trigeminal nerve is the largest sensory cranial nerve (De Lahunta and Glass, 2009). The trigeminal ganglion has sensory cell bodies for pain and temperature modalities of all the sensory branches with proprioception going to the nuclei of the brainstem (De Lahunta and Glass, 2009). The mandibular branch also has motor function. This motor part of the mandibular nerve runs ventral to the trigeminal ganglion (De Lahunta and Glass, 2009). The ophthalmic nerve is the smallest of the 3 sensory branches and runs lateral to the cavernous sinus. The ophthalmic nerve enters the orbital fissure along with the oculomotor, trochlear, abducens, and sympathetic nerves to the eye. The ophthalmic nerve gives rise to the lacrimal, frontal, nasociliary, and ethmoidal nerves (Budras et al, 2009). The maxillary nerve emerges from the round foramen and continues into the maxillary foramen and infraorbital canal as the infraorbital nerve. The maxillary nerve has several branches which includes the zygomaticofacial, pterygopalatine, major palatine, minor palatine, caudal nasal, and infraorbital nerves (Budras et al, 2009). The caudal nasal nerve has been commonly referred to as the posterior ethmoidal nerve; however, these nerves are distinct structures arising from different branches of the trigeminal nerve. This is further discussed in Chapter Four. The mandibular nerve has many branches, which includes the masseteric, temporal, pterygoid, tensor tympani, tensor veli palatini, mylohyoid, auriculotemporal, buccal, lingual,

and mental nerves (Budras et al, 2009). The maxillary nerve is sensory to the lower eyelid, maxillary teeth, upper lip, maxillary sinus, and nose (Budras et al, 2009). The signs displayed by affected horses seem to be focussed on the muzzle/nose area leading to dysfunction of the maxillary nerve, and within that the infraorbital branch is in particular affected.

1.6. Aetiopathogenesis

The clinical signs of trigeminal-mediated headshaking are consistent with neuropathic pain of the trigeminal nerve. Although this was suspected in even the 19th Century (Williams, 1897, 1899) there have been many other theories, with trigeminal involvement being only recently confirmed (Aleman et al 2013, 2014). Detailed nerve conduction studies of control and headshaking horses identified that the infraorbital branch of the trigeminal nerve of affected horses was sensitised, with a lower threshold for activation than non-affected horses (Aleman et al. 2014). Somatosensory evoked potentials recorded under general anaesthesia determined the threshold for activation for control horses to be greater than 10mA, but less than 5mA for affected horses. It is presumed that trigeminal nerve sensitisation results in neuropathic pain. There were no differences in the neurophysiological characteristics of the action potentials. Additionally, there were no differences between left and right sides, consistent with bilateral involvement of the trigeminal nerve. One seasonally affected horse was tested out of season and demonstrated normal threshold activations, but was not also tested when showing clinical signs, to determine if threshold was then abnormal. Work is required to determine whether in cases where clinical signs resolve, this occurs in parallel with a return to normal nerve threshold function. This could help confirm that altered neurophysiology is potentially reversible.

The reason for the sensitisation of the trigeminal nerve in trigeminal-mediated headshaking remains unknown. Whilst herpes virus is involved in the pathogenesis of some human neuropathic pain syndromes, the virus was shown not to be involved in the pathogenesis of trigeminal-mediated headshaking (Aleman et al, 2012). There seems likely to be a complex association with environment in developing this acquired condition, with anecdotal reports of onset shortly after relocation of the horse and less frequently, signs resolving after relocation. This may be supported by work suggesting a potential role for electrolytes (Sheldon et al 2018, Sheldon et al 2019a, Sheldon et al 2019b) with small studies showing first intravenous administration of magnesium, then oral administration of magnesium and magnesium and boron, to reduce clinical signs in affected horses.

The mechanism by which magnesium supplementation in the form of magnesium alone or magnesium in combination with boron resulted in significant reduction in headshaking behaviour is not completely understood (Sheldon et al, 2019b). Treatment with magnesium in combination with boron induced the greatest reduction in headshaking behaviour. This could be because of boron's ability to increase circulating magnesium concentrations. Magnesium could then provide its physiological channel blocking effects on N-methyl-D-aspartate (NMDA) receptors and reduce ion currents. The NMDA receptors affect trigeminal neurons at the trigeminal *subnucleus caudalis* (the orofacial nocioceptive processing centre) in rats. Boron could also affect neurotransmitters because of its ability to form complexes with sugars. When boric acid forms ester complexes with ribose, a part of adenosine, boric acid will non-competitively inhibit adenosine diphosophate ribosyl cyclase (ADP-ribosyl cyclase). This slows the production of cyclic ADP-ribose (cADPR), in turn slowing mobilization of Ca^{2+}. Furthermore, calcium might be involved in trigeminal neuropathic pain, but the exact mechanism is unknown (Sheldon et al 2019b).

Trigeminal nerve root demyelination is the most frequent cause of human trigeminal neuralgia, a neuropathic facial pain syndrome (Love and Coakham, 2001). However, no histopathological abnormality of the nerve has been discovered in equine trigeminal-mediated headshaking (Roberts et al 2017) which is explored in Chapter Three. Despite the apparent clinical similarities between trigeminal neuralgia and trigeminal-mediated headshaking, differing pathology was expected, as human trigeminal neuralgia sufferers are usually unilaterally affected and have abnormal conduction patterns due to demyelination (Love and Coakham, 2001). It can be considered a potentially positive result, as demyelination would be unlikely to be reversible. The lack of histological abnormality in trigeminal-mediated headshakers may suggest a functional, rather than structural, abnormality of the nerve. This may lead to the potential for developing a treatment which reverses the functional abnormality. The potential for reversal is supported by seasonality in many cases and an approximate 5% spontaneous remission rate (Madigan and Bell, 2001). This is further explored in Chapter Six.

1.7 Diagnosis

Diagnosis of trigeminal-mediated headshaking is currently made by exclusion, allowing potential misdiagnosis. Some papers' case populations rely mostly on interpretation of clinical signs and even owner-led diagnosis. The use of diagnostic local anaesthesia has a place in proving but not disproving facial pain and does not reveal the cause of facial pain. This is discussed in Chapter Three. Further work demonstrating consistency of lowered

infraorbital nerve threshold potentials could allow for this to be the gold standard for diagnosis but would be limited by a requirement for general anaesthesia. Exploring whether the procedure could be tolerated or modified and remain accurate when used on horses under standing sedation could be a diagnostic breakthrough. It would still be important to show there was no gross pathology such as dental disease leading to sensitisation to complete a diagnosis.

i. Management

With trigeminal-mediated headshaking the aetiopathogenesis is unknown, presenting the greatest challenge to finding effective treatment. It is possible that there is more than one cause with the same clinical manifestation, leading to different response rates to treatment. It is recognised in human medicine that response to treatment for neuropathic pain varies amongst individuals, even with the same diagnosis (NICE guidelines, 2018). Therefore, even if all horses with trigeminal-mediated headshaking have the same underlying condition, response to the same treatment may vary.

To review the literature surrounding management strategies, consideration must be made of the reliability of diagnosis, the mechanism of assessment of response used, and placebo effect. Assessment of response to treatment can be challenging. Horses can vary from day to day and season to season in the severity of their signs and interpretation of these signs is heavily influenced by placebo effect (Pickles et al, 2011 and Talbot et al, 2013). The most objective measure currently available is classification of success as being return to ridden work at the previous level (Roberts et al, 2016, Chapter Six). Should data consistently demonstrate sensitisation of the infra-orbital nerve in horses with trigeminal-mediated headshaking, the next stage for research would be to determine whether in horses judged to have responded to treatment, threshold potentials have returned to normal. This could allow measurement of threshold potentials before and after treatment to give an objective measure of response to treatment. However, the procedure requires general anaesthesia which may limit its practical application (Pickles et al, 2014).

Since there is a considerable placebo effect when interpreting results of treatments for headshaking (Pickles et al, 2011 and Talbot et al, 2013) trials of treatments for headshaking should ideally include placebo or control groups. However, this is not always possible due to welfare considerations in a group of horses suffering a painful condition.

There are many treatments tried by owners of horses with suspected or confirmed trigeminal-mediated headshaking and many of these are not based on published evidence

(Roberts et al, 2020 Paper 7). Assessment of efficacy of unpublished treatments is particularly challenging; it is not known if a veterinary diagnosis was made, or whether the criteria for success are sufficiently robust as to compensate for placebo effect of the owner. Without published data, they are not further considered in this introduction. Published treatments are best considered in two categories: scientifically proven treatments and those with no effective results.

The recent advances suggesting possible reversible sensitisation may give opportunity for advances in therapy, although these remain limited and early in their inception. The rationale behind more established therapies with some evidence of success appears to be to reduce sensory input from the trigeminal nerve, intended or not, even before sensitisation was confirmed.

1. Scientifically proven treatments:

i. Nose-net:

This, shown in Figure 2, is the first treatment to trial as it is cheap, non-invasive, risk-free and is allowed in most competition at most levels. It is reported to give up to 70% relief in 25% cases (Newton et al, 2000; Mills et al, 2002). The mechanism by which a nose-net may work is thought likely to be similar to (but not the same as it does not travel through the spinal cord) gate control theory. The substantia gelatinosa in dorsal horn of spinal cord appears to act as a gate control system. It modulates the synaptic transmission of nerve impulses from peripheral fibres to the nervous system. Small nocioceptive fibres hold the gate in an open position. Stimulation of large mechanoreceptive fibres by touch, pressure or vibration, close the ‘gate’ and inhibit pain transmission to the brain. Small nocioceptive fibres have a higher activation threshold than larger mechanoreceptive fibres. Selective low-level stimulation of mechanoreceptors can therefore prevent or reduce pain transmission and activation of the inhibitory pathway results in release endogenous opioids and other neurocompounds.

There are a wide variety of nose-nets available on the market, although a far more limited range which is competition legal. The author advises owners to trial more than one variety. Some horses appear to show more severe signs when wearing a nose-net (personal observation). The main equestrian sport governing body, the Federation Equestre Internationale will be banning the clipping of the vibrissae of the muzzle from July 2021. Whilst the reasons for this are undoubtedly to improve welfare, as they give much sensory information and are usually clipped off for cosmetic reasons, it may that there is a negative

impact on horses suffering trigeminal-mediated headshaking who can on occasion benefit from the presumed reduction in sensory information given by clipping vibrissiae (personal observation).

Figure 2: Horse wearing nose net. Image reproduced with permission of Dr. Kirstie Pickles.

ii. Pharmaceuticals:

There are drugs available for the treatment of neuropathic pain in people and some of these have been used in horses with trigeminal-mediated headshaking. Even in people with neuropathic pain, these drugs have inconsistent results and may confer side-effects including drowsiness. A challenge to the efficacy of treatment for neuropathic pain is a heterogeneity of the mechanisms of neuropathic pain and therefore heterogeneity of the best way to target its treatment (Fornasari 2017). Carbamazepine, a sodium-channel blocking anticonvulsant, can be effective to treat some cases of trigeminal neuralgia in people and response to treatment can be used to aid diagnosis (Zakrzewska and Linskey,

2014). The mechanism of action is again to reduce central nerve conduction. Not all sufferers respond, some respond only short-term but even a short-term response can aid diagnosis, and some experience side-effects (Zakrzewska and Linskey, 2014). The use of carbamazepine alone, or in combination with cyproheptadine, a centrally acting antihistamine and serotonin antagonist (serotonin plays a role in pain sensation), is published in trigeminal-mediated headshakers (Madigan and Bell 2001, Newton et al, 2000). Results are mixed, and as with people, occasionally a positive response is merely short-term. Some horses may be affected by drowsiness so there may need to be consideration as to whether they are safe to ride/handle.

Of first-line drugs used for neuropathic pain in people, use of gabapentin has been published in the horse (Davis et al, 2007) but not in cases of trigeminal-mediated headshaking, although it is trialled in some cases (personal observations). Gabapentin is an anti-convulsant acting on calcium channels, which are expressed in the spinal cord, and it is this which gives them its analgesic properties; indeed the number of voltage-gated calcium channels can increase in cases of neuropathic pain (Fornasari 2017). Pharmacology and therefore dosing regimen of neuropathic pain pharmaceuticals in the horse is often uncertain, although there is work on gabapentin (Dirikolu et al, 2007). There is evidence for low bioavailability of oral gabapentin (16.2 ± 2.8%, Terry et al, 2010). The highest commonly used dose is 20mg/kg and the low bioavailabilty may suggest this to be insufficient with behavioural effects such as sedation only being seen in a group of horses administered this dose intravenously, not orally (Terry at al, 2010). The author does use treatment trials of the 20mg/kg dose orally and has received reports of horses showing signs of sedation but no clear evidence of alleviation of headshaking signs beyond some reduction in severity which could be attributed to sedation. It is of note that the published case of use of gabapentin in a horse with neuropathic pain used a very low dose (2.3mg/kg per os) (Davis et al, 2007).

It is the author's interpretation of these studies that, as some individuals can respond well, these drugs can be worth trying as long as expectations are managed. It should be noted that use of these medications would not be allowed in competition, and this fact may be sufficient to limit further research in this area. They may also be cost prohibitive for long-term use.

iii. Magnesium and boron:

There are three studies by Sheldon considering the effects of metabolic status on nerve firing and therefore on clinical signs in horses with trigeminal-mediated headshaking

(Sheldon et al, 2018; Sheldon et al, 2019a; Sheldon et al 2019b). Intravenous infusion of hypertonic sodium bicarbonate resulted in short-term alkalaemia, metabolic alkalosis and a reduction but not resolution of clinical signs of headshaking (Sheldon at al, 2018). Whilst this is not a practical treatment, it adds to our understanding which may enable development of practical treatment.

The next studies by Sheldon (Sheldon et al, 2019a; Sheldon et al, 2019b) were based on the understanding that magnesium may have neuroprotective effects on nerve firing that could potentially dampen signs of neuropathic pain. Intravenous infusion of magnesium sulphate solution increased plasma total and ionised magnesium concentrations and significantly decreased clinical signs in horses with trigeminal-mediated headshaking (Sheldon et al, 2019a). Response to intravenous infusion led to trialling oral supplementation, which can be a practical long-term treatment. Oral magnesium supplementation (24.2 mg/kg) of magnesium citrate decreased clinical signs in trigeminal-mediated headshaking, but a better result was obtained when both magnesium citrate (24.2mg/kg) and boron citrate (40mg/kg) were supplemented, with boron increasing uptake of magnesium (Sheldon et al, 2019b). Whilst it should be noted that clinical signs did not resolve in these cases, (median headshakes per minute at trot were reduced from 12 to 4 with an overall 64% reduction across gaits of handshakes per minute) oral supplementation of magnesium and boron should, in the author's opinion, be used as part of a multi-modal approach to managing horses with trigeminal-mediated headshaking.

iv. Homeopathy:

Following homeopathic treatment of varying regimes, as part of a larger study into homeopathy, 93.3 % owners reported they felt their horses were improved (Mathie et al, 2010). The possibility of placebo effect and the use of owners' subjective evaluation should be considered.

v. Sodium cromoglycate eye drops:

Stalin et al (2008) published a short communication where administration of sodium cromoglycate (a mast cell stabiliser) eye drops were effective in three seasonally affected horses, returning them to ridden exercise. This could suggest allergic conjunctivitis as an aetiology in these horses. However, it appears that allergy is not the cause in the majority of headshaking cases and the author has been unable to replicate these results, although trialling treatment is low risk.

vi. Surgery:

Bilateral infraorbital neurectomy (Mair, 1999) was effective in 3/19 horses with serious side effects being common; however, this study was important in that it added to the weight of evidence of involvement of the trigeminal nerve.

Caudal ablation of the infraorbital nerve via coil compression achieved better results (Roberts et al, 2009 and Roberts et al, 2013, Papers 4 and 5) with approximately 50% success rate in 57 horses but 26% relapsed with a median time of nine months (range two months to five years). Most horses (30/48, 63%) developed the side effect of nose rubbing which was short-term in most cases but 4/58 were euthanased due to severity or non-resolution. The author no longer recommends this procedure having developed a safer procedure with better outcomes (Roberts et al, 2020, Paper 7).

vii. EquiPENS™ Neuromodulation:

This technique was translated from percutaneous electrical nerve stimulation neuromodulation, a minimally invasive procedure which can have efficacy for the management of neuropathic pain in people (Bhaskar et al, 2011; Raphael et al, 2011). Potentially, the procedure is effective by normalising neural function, but no basic science has been performed to investigate the mechanism of action. An initial trial, using an electrical protocol based on humans and an initial three procedure course, was published in 2016 (Roberts et al, 2016, Paper 6). This demonstrated that the procedure was possible to perform under standing sedation, had minimal risk of side effects, and returned 5 of 7 horses to ridden work. More data (Roberts et al 2020) on 168 trigeminal-mediated headshakers receiving EquiPENS™ neuromodulation (530 procedures) has followed. The complication rate was 8.8% of procedures and, in all but one case, complications were mild and transient, with no self-trauma. Remission of headshaking following the initial course occurred in 53% (72/136) of horses. Median length of time recorded in remission was 9.5 weeks (range 2 days to 156 weeks ongoing). Where signs recurred, most horses went back into remission following future procedures, usually for longer than from the previous procedure. No predictors for outcome were determined. These data may suggest that EquiPENS™ neuromodulation, whilst clearly carrying limitations, is a good first-line treatment for horses which do not respond to a nose-net. Refinement of this procedure will remain limited, not only until we understand the aetiopathogenesis of trigeminal-mediated headshaking, but also the mechanism of action of neuromodulation, about which little is currently known.

viii. Electroacupuncture:

Electroacupuncture was attempted for the treatment of trigeminal-mediated headshaking, following the initial indication of possible success of EquiPENS™ neuromodulation and resulted in temporary improvement in 6 horses (Devereaux, 2017). Success was considered to be an improvement in signs as judged by the owner, with a median remission time from the third procedure of 18 days (range 6 – 71 days) (Devereaux, 2017). As we do not understand the mechanism of action of neuromodulation or electroacupuncture the only way to make a comparison is to evaluate the use of a uniform electroacupuncture technique to EquiPENS™ over a similar number of appropriately diagnosed horses.

2. Treatments with no effective results:

i. Feed supplement:

Talbot et al, 2013, published a double-blinded, placebo-controlled trial of a commercial herbal feed supplement, marketed for treatment of headshaking. There was no effect of the supplement or the placebo as judged by veterinary surgeons but there was significant placebo effect of both the supplement and the placebo to the owner, who 'felt their horses were improved'. This demonstrates the importance of using as objective a measure of success as possible.

ii. Gonadotrophin releasing hormone vaccine:

The use of this vaccine was investigated as the condition is often seasonal and may be more common in geldings. In a study of 15 horses (Pickles et al, 2011), there was no actual improvement as judged by veterinary surgeons but again one third of owners felt their horses were improved. Vaccination reactions were reported in 4/15 cases, some of which were severe.

iii. Pulsed high dose dexamethasone:

Pulsed high dose dexamethasone was not effective for treatment (Tomlinson et al, 2013). This is consistent with histological findings of no inflammation of the nerve and that trigeminal-mediated headshaking is not a response to allergy.

iv. Various:

Madigan and Bell (2001) performed a survey of owners of headshaking horses. Whilst limited by owner reported diagnosis and outcomes, with success of treatment judged by owner impression of improvement, no treatment stood out as more successful, from:

antihistamines, antimicrobial drugs, corticosteroids, non-steroidal anti-inflammatory drugs, melatonin, chiropractic treatment, acupuncture.

This introduction covers the limited current knowledge of the causes and mechanisms of trigeminal-mediated headshaking, displays the background for the work presented in this thesis and demonstrates its place in the literature. It also displays the need for considerable further research into the condition. Very little is known about neuromodulation, and there is potential to expand this work using horses to improve our knowledge, which could impact on the management of neuropathic pain in people. Determining the aetiology of trigeminal-mediated headshaking may open more doors for translational research.

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Chapter Two: Prevalence.

Prevalence of trigeminal-mediated headshaking within the UK equine population

2.1 Candidate contribution:

Paper One:

The concept of this paper was mine, as I repeatedly found that I needed this information and that it was lacking. I worked with the other two authors to develop the project plan. I obtained ethical permission for the project. I secured an Inspire (Academy of Medical Sciences and the Wellcome Trust) studentship award to support this project, whilst introducing a veterinary undergraduate to basic research concepts. I worked with the first author to obtain the main funding for the project from a fund for postgraduate research within the University of Bristol's veterinary clinics. The second author on this paper was of critical importance for her experience of the questionnaire software and in its analysis. My main role was the close supervision of a postgraduate student in the execution and writing of the second publication of her career.

2.2 Paper One

Prevalence of headshaking within the equine population in the UK

Ross SE, Murray JK, Roberts VLH (2018)

Equine Veterinary Journal 2018 Jan;50(1):73-7. ISSN 0425-1644 DOI: 10.1111/evj.12708

Award: Most clinically relevant paper in that issue by Equine Veterinary Journal.

Prevalence of headshaking within the equine population in the UK

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Summary

Reason for performing study: Headshaking in horses has been reported to be most commonly due to idiopathic neuropathic facial pain (trigeminal-mediated headshaking). The prevalence of headshaking in horses in the UK is unknown.

Objectives: To estimate owner-reported prevalence of headshaking in horses in the UK and to report their case background and disease characteristics, as reported by owners.

Study design: Cross-sectional web-based owner questionnaire.

Methods: The questionnaire was advertised online via social media, horse forums, veterinary websites and equestrian magazines from 17th June 2016, until >1000 responses had been obtained. All UK horse owners were eligible to complete the questionnaire, however only one questionnaire could be completed per owner.

Results: The estimated prevalence of owner-reported headshaking in the sample population of horses (n = 1014), within the last year, was 4.6% (95% confidence interval 3.5–6.1), whereas 6.2% (95% confidence interval 4.9–7.9) of horses were reported by their owners to have shown signs of headshaking at any time-point since ownership. There was no association of sex or breed. Nineteen percent of headshaking horses were reported to show headshaking at rest. Fewer than one-third (30.2%, n = 19) of headshaking horses had been examined by a veterinarian for headshaking. Of horses seen by a veterinarian, the cause for headshaking remained unknown in the majority of cases (57.9% responses) and trigeminal-mediated headshaking was reported as a diagnosis in just one case.

Main limitations: The accuracy in data reporting by horse owners was not verified in this study. There may be a potential for bias towards overreporting due to the nature of survey participation.

Conclusions: Within this sample, owner-reported prevalence of signs of headshaking within the last year, in horses in the UK was 4.6%. Over two-thirds of owners of headshaking horses did not seek veterinary intervention for headshaking. Trigeminal-mediated headshaking was rarely reported by owners as a diagnosis.

Keywords: horse; headshaking; prevalence; questionnaire; laminitis.

Introduction

Headshaking is a condition whereby horses show repeated, uncontrollable, predominantly vertical movements of the head and neck, often accompanied by nasal irritation [1,2]. Headshaking is a significant cause of distress in some horses [1]. Even with extensive investigation, usually no physical cause for headshaking is found [3,4]. In most cases, headshaking is reported to occur due to an idiopathic neuropathic facial pain syndrome (termed trigeminal-mediated headshaking) [1,5,6]. Severely affected horses appear to have compromised welfare and significant self-inflicted trauma has been reported [7]. The determination that many cases occur due to pain is recent [6] and therefore likely to be under-recognised by owners and veterinarians. Many affected horses become dangerous to handle and ride and especially if the condition is not understood, may undergo several futile treatments. Horses that are unsuccessfully treated may eventually be subjected to euthanasia. A diagnosis of trigeminal-mediated headshaking is supported when no defined aetiology can be found on thorough assessment and examination [6]; thus excluding other causes of facial pain which include, but are not limited to, guttural pouch disease, dental pathology and sinus disorders. A recent breakthrough provided evidence that the trigeminal nerve in affected horses is sensitised, firing at too low a threshold [8]. This discovery paved the way for the proposal that the previously favoured term ‘idiopathic headshaking’ be replaced by the term ‘trigeminal-mediated headshaking’ [7,9]. While some progress has been made in recent times towards diagnosing and treating the condition, the prevalence of headshaking within horses in the UK has not been fully elucidated. The prevalence of headshaking within the UK horse population is a fundamental question, which, once answered, would reveal the scale of a potential welfare problem and may endorse further research into the pathogenesis and treatment of the condition. Furthermore, how frequently trigeminal-mediated headshaking is considered the cause for headshaking has not been investigated. The aim of this study was to investigate the owner-reported prevalence of headshaking in the general horse population in the UK. Secondary aims were to report case background and disease characteristics for headshaking in horses, as described by owners.

Materials and methods

An online questionnaire with the ‘neutral’ title Horse Health Questionnaire was compiled using Bristol Online Surveys (BOS)a (Supplementary Item 1). Questionnaires were pretested using a small convenience group of horse owners (n = 6) and then revised

accordingly. An online sample size calculator (Ausvet Epitools [10]) was used to calculate the sample size required to estimate the true prevalence of headshaking signs based on an estimated population size of 1,000,000 (i.e. large population), assumed true prevalence of 4%, assumed sensitivity and specificity of 0.95 respectively, confidence level of 0.95 and desired precision of 0.02. A sample size of 932 was calculated to be required. The questionnaire was advertised online via social media, horse forums, first opinion practices and equestrian magazines on 17th June 2016 and remained open until 10th August 2016, once >1000 responses had been obtained. The questionnaire was accessible via a uniform resource locator (URL). Participants were required to be age ≥18 years, live in the UK, and to own or have owned a horse within the last year. Owners who had sold or had their horse subjected to euthanasia within the last year were eligible to complete the survey. Respondents were restricted to completing a questionnaire for just one horse per owner. Owners of multiple horses were asked to choose the animal whose name came first in the alphabet. The questionnaire took most people <5 min to complete. Questions on headshaking were flanked by questions on laminitis and equine sarcoids. Equine sarcoid data are not presented here. There were 2 purposes to having the distractor questions. One was to disguise the area of interest to minimise response bias. The other, that figures for prevalence of laminitis in horses in the UK have been reported [11]. A comparison of those figures with our own, if similar, would offer reassurance that prevalence figures obtained for owner-reported headshaking are also reliable. The following definition of headshaking was used; 'for the purposes of this survey headshaking is characterised by unexplained and uncontrollable movements of the head and neck that may affect the horse either at rest or during exercise.' The following definition of laminitis was used, 'for the purposes of this survey, laminitis is an episode of lameness which was either; a) diagnosed by a vet as laminitis or b) laminitis was strongly suggested based upon the following; lameness was present in all 4 limbs and the horse or pony stood with an altered stance and/or the horse or pony was reluctant to move and/or there was increased heat in all 4 hooves and/or laminitis was diagnosed by a farrier.' Prevalence values and 95% confidence intervals were calculated using Ausvet Epitools [10]. The Kolmogorov–Smirnov test was used to assess age data for normality. Age was not normally distributed and thus median and interquartile ranges were reported. The Mann–Whitney test was used to compare median age of headshaking and non-headshaking horses. Association of sex (male/female) and breed (7 categories of breed, Table 1) with headshaking (yes/no) was assessed using a chi-squared test and a Fisher's exact test, respectively, to account for cells with fewer than 5

expected data points. Statistical tests were carried out in IBM SPSS Statistics Version 23. Significance was set at $P<0.05$.

Table 1: Age, breed and sex data for non-headshaking and for headshaking horses

Variable	**Category**	**Non-headshaking horses % (n = 949)**	**Headshaking horses % (n = 65)**
Season of purchase	Spring	26.2 (237)[1]	23.1 (15)
	Summer	26.2 (237)[1]	32.3 (21)
	Autumn	25.1 (227)[1]	21.5 (14)
	Winter	16.0 (145)[1]	15.4 (10)
	Don't remember	3.2 (29)[1]	6.2 (4)
	Not applicable (homebred)	3.2 (29)[1]	1.5 (1)
Age this year	1–5 years	8.7 (83)	3.1 (2)
	6–10 years	29.5 (280)	24.6 (16)
	11–15 years	22.7 (215)	26.2 (17)
	16–20 years	18.5 (176)	20.0 (13)
	≥21 years	16.8 (159)	18.5 (12)
	Unknown	3.8 (36)	7.7 (5)
Breed	Arab or Arab X	4.6 (43)[2]	6.2 (4)
	Cob or Cob X	15.4 (145)[2]	20 (13)
	ID, ID X or ISH	13.8 (130)[2]	15.4 (10)
	TB, TB X or TB X WB	18.6 (175)[2]	16.9 (11)
	WB or WB X	12.2 (115)[2]	12.3 (8)
	Native or Unknown pony breed	20.5 (193)[2]	18.5 (12)
	Unknown horse breed or other	15.0 (141)[2]	10.8 (7)
Sex	Female	37.2 (353	44.6 (29)
	Gelding	61.9 (587)	55.4 (36)
	Stallion	0.9 (9)	0 (0)

Data are percentage (number) of responses. X refers to crossbreed. ID, Irish Draught; ISH, Irish Sports Horse; TB, Thoroughbred; WB,

Warmblood.

[1] Indicates % derived from total number of responses with complete data (n = 904).

[2] Indicates % derived from total number of complete data (n = 942).

Results

Prior to closure of the survey, 1016 responses were returned. Two responses were excluded due to failure to comply with the inclusion criteria.

Headshaking prevalence

Of the horses in this sample population (n = 1014), 47 (4.6%, 95% confidence interval [CI] 3.5–6.1) were reported to have shown signs of headshaking in the last year. A further 16 (1.6%, 95% CI 1.0–2.6) were reported to have shown signs of headshaking, but not within the last year. Currently/previously affected horses are hereafter referred to as 'headshakers'. An additional 2 horses were reported by their owners to have died (probably subjected to euthanasia) during the last year as a direct result of headshaking. For horses that were still alive and where no distinction was made regarding time of displaying signs of headshaking, the combined prevalence of headshakers was 6.2% (n = 63; 95% CI 4.9–7.9).

Laminitis prevalence

Of the horses in our sample population (n = 1014), 64 (6.3%, 95% CI 5.0–8.0) were reported to have had laminitis in the last year. A further 83 (8.2%, 95% CI 6.7–10.0) were reported to have had laminitis, but not within the last year. For horses that were still alive and where no distinction was made regarding when the horse suffered from laminitis, the combined prevalence was 14.5% (n = 147; 95% CI 12.5–16.8).

Headshaking background

Questionnaires included data for 65 headshakers.

Age

Age in 2016 was provided for 63 horses (Table 1). Respondents were asked to choose from the nearest whole number age but horses aged ≥21 years were grouped together and therefore exact age for horses aged >20 years could not be ascertained. Fifty headshakers (79.4%, 95% CI 67.8–87.5) were aged ≤20 years; the median age of this subgroup was 12 years (interquartile range 9–15 years). For non-headshakers, 754/949

(79.5%, 95% CI 76.8–81.9) were aged ≤20 years; the median age in this group was 11 years (interquartile range 9–15 years). There was no significant difference between the median age of headshakers and non-headshakers aged <20 years (P = 0.08).

Breed

A wide range of breeds were represented which were combined into 7 subcategories (Table 1). No evidence (P = 0.65) was found for an association between breed category and headshaking.

Sex

In total, 29/65 (44.6%) of headshakers were recorded as female (mare or filly) and 36/65 (55.4%) were recorded as geldings (Table 1). A chi-squared test revealed no statistically significant association between sex and absence/presence of headshaking signs (P = 0.23).

Season of purchase

There was no season of the year for which purchase of headshakers was disproportionate to purchase of non-headshaking horses (Table 1).

Time of year headshaking first began

Respondents were asked to indicate in which month headshaking first began. The 3 most frequent months with respect to onset of headshaking signs were: May: 21.9% (n = 14); April: 17.2% (n = 11); and March: 14.1% (n = 9; Fig 1). Considering season, 53.1% of horses (n = 34) first showed signs of headshaking in spring (March, April and May) and 17.2% (n = 11) first showed signs in summer (June, July and August).

Time of year affected

Considering horses for which data were available (n = 56), 89.3% (n = 50) were reported to headshake in summer, 76.8% (n = 43). were reported to headshake in spring, 32.1% (n = 18) were reported to headshake in autumn, and 19.6% (n = 11) were reported to headshake in winter (Fig 2). Of 56 headshaking horses, 19.6% (n = 11) were reported to headshake during all 4 seasons and 8.9% (n = 5) were reported to headshake over 3 seasons. A larger proportion of headshaking horses, 42.9% (n = 24), were reported to headshake over just 2 seasons. Of these, the majority, 95.8% (n = 23) were affected during spring and summer. In addition, 39.3% (n = 22) of headshaking horses were reported to headshake during a single season only.

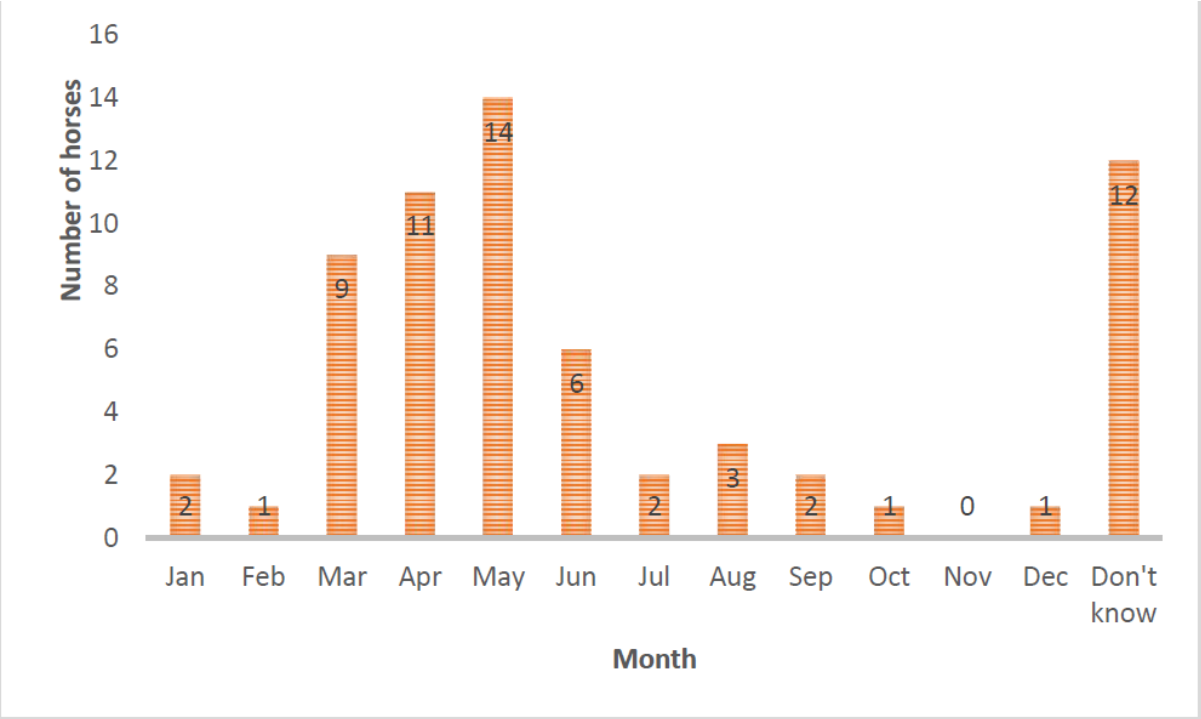

Figure 1: Bar chart displaying the number of headshaking horses reported to first show signs of headshaking for each month of the year.

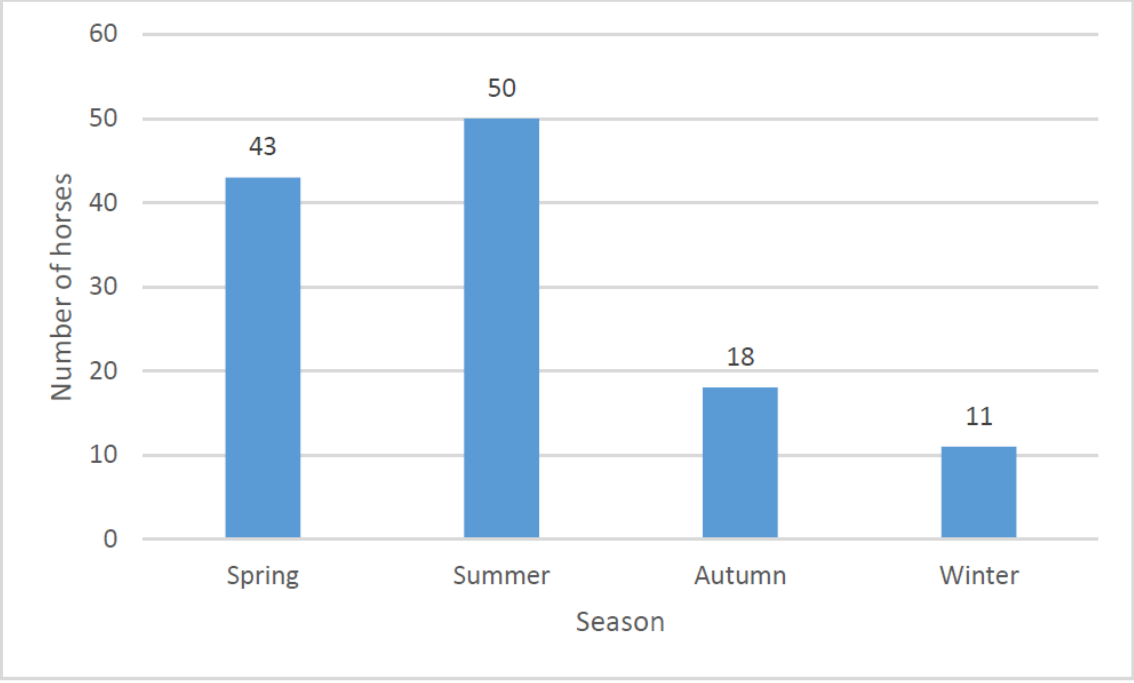

Figure 2: Bar chart displaying the number of horses reported to headshake during each season of the year; spring (March, April and May), summer (June, July, August), autumn

(September, October, November) and winter (December, January, February). Respondents were asked to pick all that applied.

Weather conditions

Respondents were asked to indicate which weather conditions, if any, they associated with headshaking in their horse (Fig 3). Headshaking was reported to be most commonly associated with sunshine in 79.4% (50/63) of horses and heat in 52.4% (33/63) of horses.

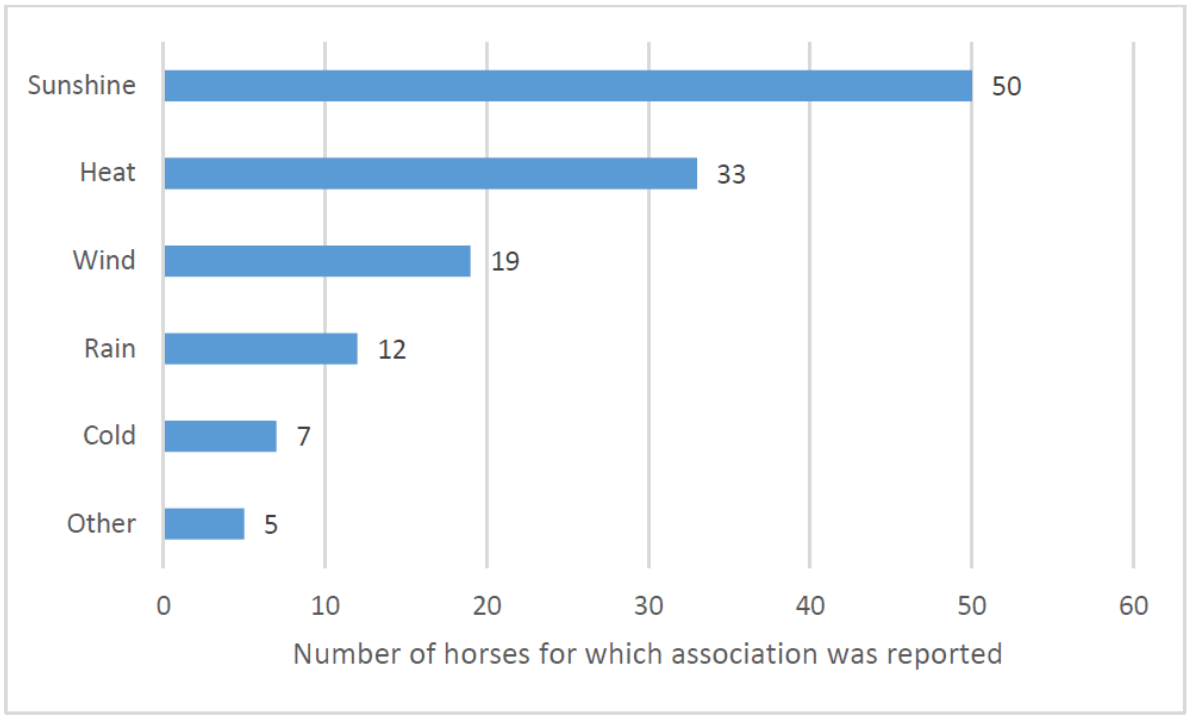

Figure 3: Association between environmental conditions and signs of headshaking. All applicable environmental conditions could be selected.

Clinical signs:

Headshaking was reported to have been gradual in onset in 37.5% of cases (24/64) and sudden in onset in 35.9% of cases (23/64). In addition 26.6% of respondents (17/64) indicated that the horse had been headshaking since the beginning of their ownership. Owners were given a list of clinical signs and were asked to indicate which sign or signs best described their horse whilst headshaking. The most frequently reported clinical sign was vertical head movement reported in 78.5% (51/65) of horses, followed by excessive rubbing of the muzzle in 38.5% (25/65; Fig 4).

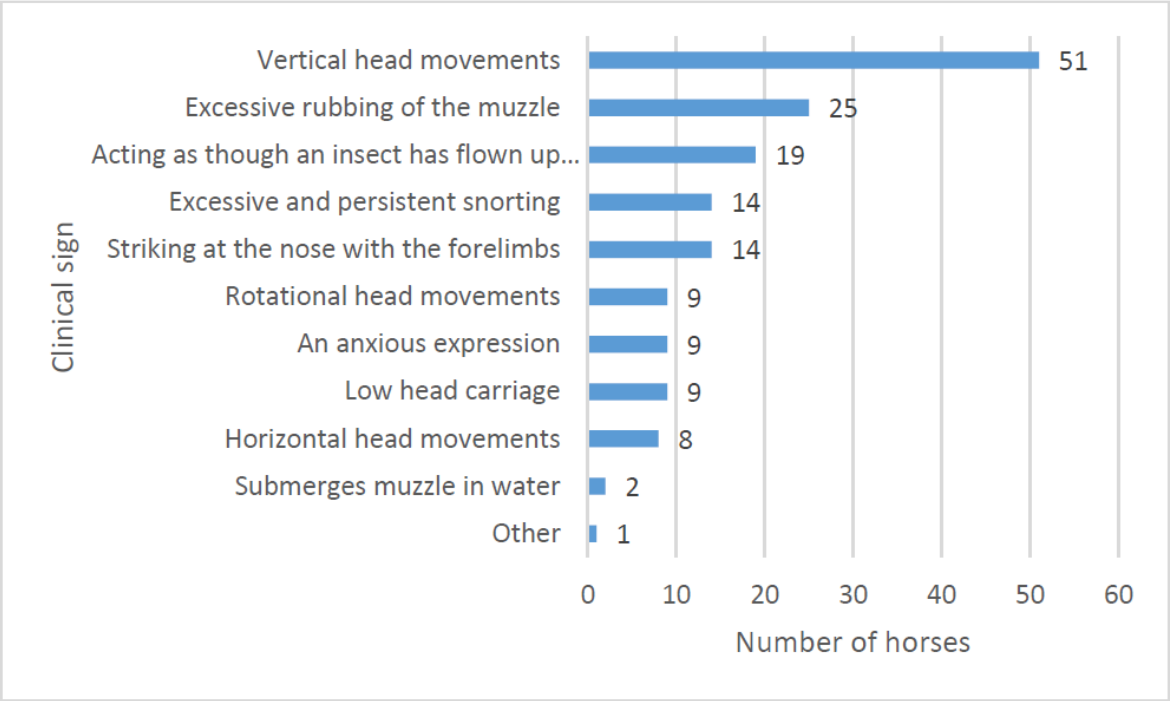

Figure 4: Bar chart displaying observed frequencies of clinical signs reported to be associated with signs of headshaking. Respondents were asked to select all that apply.

Effect of exercise

Of horses that were lunged, 53.2% (25/47) were reported to headshake during lunged exercise. Of horses that were ridden, 95.1% (58/61) were reported to headshake during ridden exercise. Of horses that were turned out, 26.4% (14/53) were reported to headshake at rest. Of horses that were stabled, 12% (6/50) were reported to headshake at rest. 'Don't know' and 'not applicable' options were available.

Severity

Owners were asked to grade the 'usual' severity of headshaking under a range of conditions, based on the following grading criteria:

• Grade 0 – there is no headshaking.

• Grade 1 – there is headshaking, only at exercise but sufficiently mild that

the horse may be ridden.

• Grade 2 – there is headshaking at exercise to a severity as to make

ridden exercise unsafe or impossible.

• Grade 3 – there is headshaking even at rest.

The results are summarised in Table 2. A higher percentage, 31.8% (14/44) of horses were grade 0/3 (asymptomatic) with a nose-net, compared with 11.4% (5/44) of horses recorded as grade 0/3 without a nose-net. There was no apparent association between open spaces vs. hedgerow when considering reported headshaking grade. Respondents were asked to grade their horse considering headshaking at its worst. In total 50.8% (32/63) of horses were considered grade 1/3, 30.2% (19/63) were considered to be grade 2/3 and 19.0% (12/63) of horses were considered to be grade 3/3, at worst (Table 2). The seasons for which the highest percentage of horses were typically assigned grade 0/3 were winter and autumn (Fig 5). The seasons for which the highest percentage of horses were typically assigned grade 1/3 were spring and summer.

Veterinary intervention

Of headshaking horses, 30.2% (19/63) were examined by a veterinary surgeon for headshaking, and 69.8% (44/63) were not. Of the horses examined by a veterinarian, respondents were asked to indicate which diagnostic procedure(s) had been performed, for which 18 responses were obtained. The most commonly performed test was dental examination performed in 83.3% of horses (15/18), followed by aural and ophthalmological examinations performed in 50.0% of horses (9/18) each. Endoscopy was performed less commonly in 38.9% horses (7/18). Radiographs of the head were performed in 22.2% of horses (4/18). The ‘other’ category of response was recorded 8 times and included blood tests, allergy testing and an antihistamine trial. Both computed tomography and diagnostic analgesia were reported infrequently in just one horse each.

Respondents were asked to indicate whether a cause had been diagnosed. Considering only horses that had been seen by a veterinarian, the cause remained unknown in 57.9% (11/19) of cases, allergy was diagnosed in 36.8% (7/19) of cases and trigeminal-mediated headshaking (idiopathic headshaking) was diagnosed in just one case.

Grade of H/S	During the day %	At night %	Indoors %	Outdoors %	Without a nose net %	With a nose net %	In open spaces %	Next to hedgerows %	H/S grade at worst
0	14.8 (9)	88.0(44)	70.6 (36)	13.6 (8)	11.4 (5)	31.8 (14)	16.3 (8)	16.7 (8)	0
1	60.7 (37)	6.0 (3)	17.6 (9)	64.4 (38)	47.7 (21)	52.3 (23)	61.2 (30)	54.2 (26)	50.8 (32)
2	14.8 (9)	2.0 (1)	3.9 (2)	13.6 (8)	34.1 (15)	13.6 (6)	18.4 (9)	25.0 (12)	30.2 (19)
3	9.8 (6)	4.0 (2)	7.8 (4)	8.5 (5)	6.8 (3)	2.3 (1)	4.1 (2)	4.2 (2)	19.0 (12)

Data are percentage (number) of responses. The proportion of horses reaching each grade of headshaking, considering headshaking at its worst severity, is also provided.

Table 2: The usual grade of headshaking (H/S) assigned to affected horses, considering each of the variables listed.

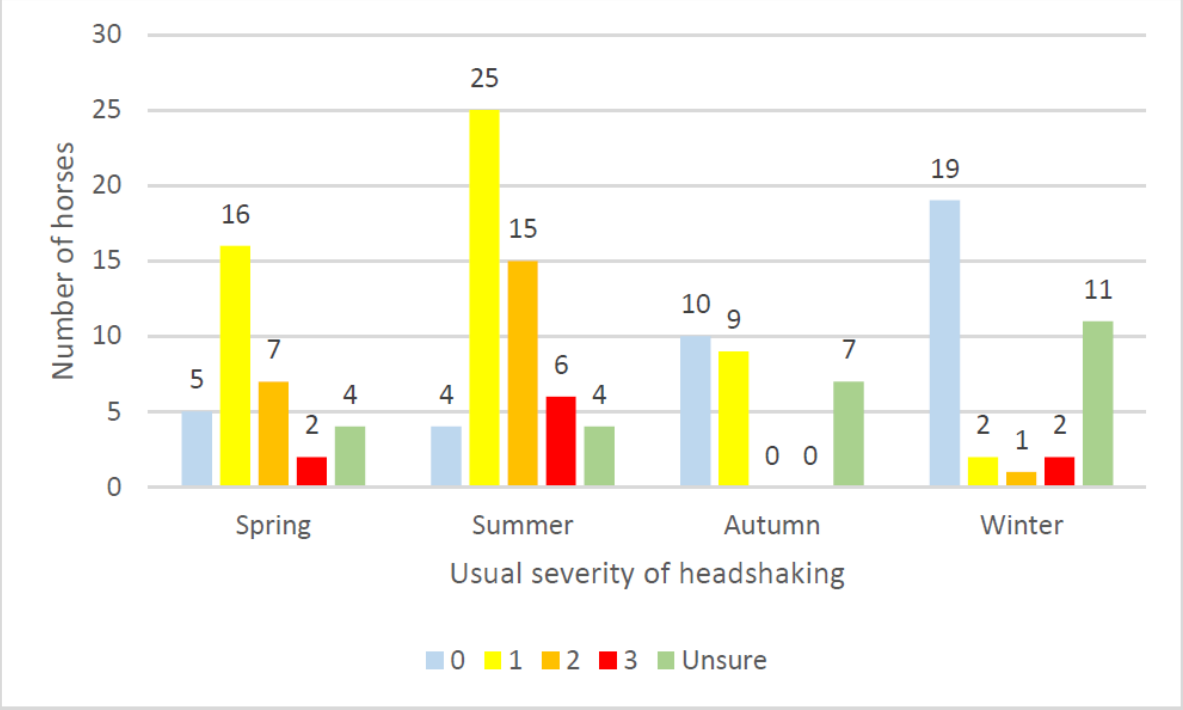

Figure 5: Bar chart displaying the distribution of usual severity of headshaking (based on a 0–3 grading scale) during each season of the year.

Treatments

There were 75.4% (49/65) of respondents that had attempted at least one form of treatment trial. In 12 horses, 3 or more treatments had been trialled. Treatments employed are listed in Table 3. Of all headshakers, 63.1% (n = 41) had been tried with a nose-net. An eye mask was the second most frequently trialled treatment in 35.4% (n = 23) of horses. The treatments were examined individually to determine the effect of each treatment, based on reduction of severity grade (Table 3). Of the horses trialled with a nose-net, no effect of treatment was reported in 73.2% (n = 30); partial improvement was reported in 7.3% (n = 3) and full resolution reported in 19.5% (n = 8) of horses.

Treatment	**Horses in which treatment was tried**	**No effect reported**	**Partial improvement reported[2]**	**Full resolution reported**
Nose-net	63.0 (41)	73.2% (30)	7.3% (3)	19.5% (8)
Eye mask	35.4 (23)	47.8% (11)	13.0% (3)	39.1% (9)
Antihistamines	23.1 (15)	73.3% (11)	13.3% (2)	13.3% (2)
Phenylbutazone	9.2 (6)[1]	80% (4)	20% (1)	0
Steroids	9.2 (6)	66.7% (4)	16.7% (1)	16.7% (1)
EquiPENS	3.1 (2)	0	0	100% (2)
Other	6.1 (4)	-	-	-
Gabapentin	0	-	-	-
Surgery for coil placement	0	-	-	-

Data are percentage (number) of responses. The following criteria were used: No reduction or worsening in grade = no effect. Reduction in grade of 1 or more to a value >0 = partial improvement. Reduction in grade to 0 = full success.[1]Data relating to effect of treatment missing or incomplete for one horse. [2]Partial improvement reported excludes full resolution.

Table 3: Treatments trialled and percentage of horses each treatment was trialled in. Change in severity score was calculated by considering the usual grade (0–3) of headshaking during the day and the usual grade (0–3) of headshaking during treatment.

Discussion

In the population studied, the estimated prevalence of owner-reported headshaking within the last year was 4.6%. The equine population of Great Britain in 2015 was estimated at 944,000 [11]. This represents a significant number of horses that are likely to be afflicted with headshaking. These findings are consistent with results of the 2016 National Equine

Health Survey (NEHS) [12] where headshaking was the fifth most frequently reported internal medicine syndrome, accounting for 1.8% of all reported syndromes.

In the current study, 6.3% of horses developed laminitis in the last year, 8.2% of horses developed laminitis more than one year ago, so the combined prevalence in this sample population was 14.5%. The frequency of equine laminitis has been previously reviewed; however, of the 10 publications deemed by the review authors to be the highest quality publications, only 2 were conducted in a general equine population and neither in the UK [13]. Menzies-Gow et al. [14] investigated the prevalence of laminitis in a UK rescue animal population over a 6-year period and found that each year between 7.9% and 17.1% of the population had at least one episode of laminitis. While the sample populations are non-identical and rescue animals may be at increased risk compared to the general population, our findings are comparable. A more recent study using a population of non-laminitic ponies aged ≥7 years, reported prevalence of pasture associated laminitis to be 4.0, 6.7 and 9.9% after 1, 2 and 3 years cumulatively for that population [15]. Given that the present study did not exclude animals that had previously had laminitis, the results are reassuringly analogous. This provides confidence that the sample and reported prevalence were not leading to over-estimation of the prevalence of laminitis, or headshaking, with this population.

The case background of headshaking horses has been previously reported [3,7]. Our study corroborates the assertion that headshaking is not a condition of the young horse; in this population the median age of headshakers aged ≤20 years was 12 years. No evidence was found for a sex or breed predisposition within the sample studied here. This is in contrast to the findings of Madigan and Bell [3] who reported that geldings and Thoroughbreds were over-represented. Approximately 1 in 5 headshaking horses were reported to headshake all year round, with the remainder affected for a variable proportion of the year. A seasonal component in some headshakers has been previously reported, of these, most started headshaking in the spring [3], in agreement with our findings. Worsening of signs with exposure to sunlight has also been documented [8]; however, the range of environmental conditions associated with headshaking reported here, which include cold and rain as well as heat and sun, highlight the practical difficulties in managing these cases. The results of this study do not support anecdotal speculation that more headshaking horses are sold during autumn or winter.

Our survey suggests that approximately one in 4 headshaking horses show signs when turned out and approximately one in 10 show signs at rest in a stable. It has been reported

that in more advanced cases, of longer duration, signs are more obvious at rest [2]. While it is well documented that exercise precipitates headshaking in many cases [3], horses affected at rest represent a particular welfare issue. Should treatment fail, retirement will not be curative in these cases, leaving euthanasia on welfare grounds as a viable option.

Vertical head movements and rubbing of the muzzle were commonly reported clinical signs in this study. The clinical signs of head shaking can be reasonably interpreted as manifestation of the resulting neuropathic facial pain. The human condition trigeminal neuralgia is an exemplary condition of neuropathic facial pain [16] and one that shares some clinical similarities with trigeminal-mediated headshaking in horses. Pain associated with trigeminal neuralgia is characterised by debilitating electric shock-like pain and can lead to suicide within human individuals [17]. Reasons for the low level of veterinary intervention reported here were beyond the scope of the study and were not investigated. It is possible that horse owners perceive that veterinary investigation is often fruitless. Alternatively, it could be speculated that a lack of veterinary intervention could reflect that many owners simply do not associate signs of headshaking with expression of facial pain.

Consensus in the literature indicates that treatments for headshaking are generally ineffective [1,2,5,8,18]. This study highlights that multiple treatments may be tried for any one horse. Our study reports the perceived effect of treatment from an owner perspective and thus findings must be interpreted with caution as there is evidence for placebo effect [19]. Secondly, due to the known component of seasonality [3,20] and spontaneous remission, any treatment for headshaking cannot be judged to have been effective in the long-term, unless an improvement is sustained for at least 12 months. Furthermore, we are reliant on memory recall and for some categories of treatment the sample size was very small; thus results must be interpreted with caution.

This study suggests that trigeminal-mediated headshaking is not a common diagnosis for headshaking in horses attended by a veterinarian, as reported by owners. Diagnosis of trigeminal-mediated headshaking is based on detailed history and observation of phenotypic headshaking, combined with exclusion of other pathology [7]. Roberts [9] states, that the condition is idiopathic should be no excuse for not performing a thorough and systemic diagnostic process to investigate cases. However, this relies on veterinary attention being sought, and also upon owners committing to the financial costs associated with a complete investigation. The knowledge that detectable pathology is unlikely to be found in the vast majority of cases [21] may act to deter owners from consenting to complete investigation, if offered. In this sample population ‘the cause remains unknown’ was indicated much more

frequently; this may reflect lack of awareness of trigeminal-mediated (idiopathic) headshaking as a potential diagnosis or may reflect hampered ability of attending veterinarians to perform complete investigation. A lack of owner familiarity with the terminology is a further possibility and it may be the case that veterinarians do not use the terminology ‘trigeminal mediated’ or ‘idiopathic’ in conversation with clients, to avoid alienating owners with jargon.

The purpose of this survey was to capture data on horses from horse owners in the general population; veterinary intervention was not a criterion for inclusion. The accuracy in data reporting by horse owners was not verified and is a major limitation of this study. The level of knowledge of the respondents completing the questionnaire cannot be vouched for and is a further limitation. In addition, potential exists for bias, particularly towards over-reporting of the condition, despite our efforts to provide both precise definitions and distractor questions. However, referral centres were deliberately not contacted in an effort to avoid potential bias, and over-estimation of prevalence, which may be associated with using a referral population.

In conclusion, the findings of this study estimated the prevalence of owner-reported headshaking in horses within this sample of horses in the UK to be 4.6% for horses affected within the last year, and 6.2% for horses affected at any time point.

Authors’ declaration of interests

No competing interests have been declared.

Ethical animal research

Ethical approval was obtained from the University of Bristol, Ethics of Research Committee, application number 34361. Participants consented to the study.

Source of funding

Funding was provided by the Langford Veterinary Services Clinical Research fund. Jane Murray’s post was funded by Cats Protection. We are grateful to the INSPIRE committee for funding a Vacation Studentship.

Acknowledgements

The authors would like to thank Amy Sawyers, recipient of the INSIPRE Studentship Award, for her help and assistance.

Authorship

All authors contributed equally to study design. Execution was performed by S. E. Ross. Data analysis was 70% S. E. Ross and 30% J. K. Murray. Preparation of the manuscript was 60% S. E. Ross, 20% J. K. Murray and 20% V.L.H. Roberts.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website: Supplementary Item 1: Questionnaire used for the survey.

Chapter Three: Pathology.

Trigeminal-mediated headshaking in horses is not associated with focal nerve root demyelination

3.1 Candidate contribution:

The concept of this study was mine. The project was planned equally by all authors. I obtained ethical permission and ensured all horse owners were giving fully informed consent for donation of their horse's bodies, inclusion in the study and disposal of the body afterwards. I sourced funding from the British Neuropathological Society. I acquired the specimens. I performed dissection together with two of the co-authors. I drafted the manuscript, with all authors involved in the final approval of the version to be published. I presented the work at the 115th Annual Meeting of the British Neuropathological Society (2014).

3.2 Paper Two

Trigeminal nerve root demyelination not seen in six horses diagnosed with trigeminal-mediated headshaking

Roberts VLH, Fews D, McNamara J, Love S. (2017)

Frontiers in Veterinary Science section Veterinary Neurology and Neurosurgery. May 15;4:72.doi:10.3389/fvets.2017.00072. eCollection 2017.

Trigeminal nerve root demyelination not seen in six horses diagnosed with trigeminal-mediated headshaking

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Summary

Trigeminal-mediated headshaking is an idiopathic neuropathic facial pain syndrome in horses. There are clinical similarities to trigeminal neuralgia, a neuropathic facial pain syndrome in man, which is usually caused by demyelination of trigeminal sensory fibers within either the nerve root or, less commonly, the brainstem. Our hypothesis was that the neuropathological substrate of headshaking in horses is similar to that of trigeminal neuralgia in man. Trigeminal nerves, nerve roots, ganglia, infraorbital, and caudal nasal nerves from horse abattoir specimens and from horses euthanized due to trigeminal-mediated headshaking were removed, fixed, and processed for histological assessment by a veterinary pathologist and a neuropathologist with particular experience of trigeminal neuralgia histology. No histological differences were detected between samples from horses with headshaking and those from normal horses. These results suggest that trigeminal-mediated headshaking may have a different pathological substrate from trigeminal neuralgia in man.

Keywords: trigeminal-mediated, headshaking, idiopathic, horse, nerve root, demyelination

Introduction

Headshaking in horses is a syndrome of spontaneous and repetitive movements of the head and neck (1) predominantly in a vertical orientation (2). These movements are often accompanied by signs of nasal irritation (1, 2). The condition is usually worse at exercise (3) but may be seen at rest, in the stable and/or field (2). In the majority (98%) of cases, no physical cause is identified even after extensive clinical investigation (3). It is now widely accepted that most cases of headshaking are due to an idiopathic trigeminal neuropathy (1, 2, 4–9) and the term “trigeminal-mediated headshaking” is the accepted term to describe this condition (10).

The trigeminal nerve in trigeminal-mediated headshakers was shown to be abnormally sensitized, with an abnormally low threshold for activation when somatosensory-evoked potentials were tested (8, 11, 12). In a horse affected seasonally, the activation threshold

was normal when the horse was tested out of season and therefore not showing clinical signs (11). This suggests a reversible disease process, although unfortunately the same horse was not tested when showing clinical signs. There is evidence that trigeminal-mediated headshakers suffer facial pain, as signs can be temporarily abolished by infiltration of local anaesthetic around the caudal portion of the infraorbital nerve bilaterally (9). They do not respond to analgesia with non-steroidal anti-inflammatory drugs (6) but in some cases respond to carbamazepine and/or cyproheptadine (1, 6) or to neuromodulation by percutaneous electrical nerve stimulation (13), which would be consistent with neuropathic pain.

Trigeminal neuralgia is a human neuropathic facial pain syndrome. It is usually caused by demyelination of trigeminal sensory fibers within either the nerve root or, less commonly, the brainstem (14). In most cases, the trigeminal nerve root demyelination involves the proximal, CNS part of the root and results from compression by an overlying artery or vein. Other causes of trigeminal neuralgia in which demyelination is involved or implicated include multiple sclerosis and, probably, compressive space-occupying masses in the posterior fossa (14). Determination of the underlying pathology has facilitated the development of targeted treatment. Initial histopathological examination of the infraorbital nerve of horses' euthanized due to trigeminal-mediated headshaking did not reveal any abnormality but a comprehensive examination of the nerve, including the nerve root, was not reported (11).

In this study, we investigated the possibility that the neuro-pathological substrate of headshaking in horses is similar to that of trigeminal neuralgia in man.

Materials and methods

Histopathological anatomy in normal horses

Cadaver horse heads (four) were collected from an abattoir from horses presented for slaughter. Clinical history was unknown, but all had been assessed as fit for slaughter for human consumption on ante-mortem inspection. Controls were not age-matched to clinical cases. Heads were removed as routine during carcass preparation and immediately put into ice baths for transport. Dissection was performed within 3 h of slaughter.

To access the caudal portion of the infraorbital nerve, the horses' heads were cut using a band saw to access the caudal portion of the infraorbital canal. The first cut was a transverse slice that approximately bisected the angle of the mandible and masseteric fossa of each mandible. The second slice was along the length of the head following the line of the facial crest and allowing removal of the nasal and frontal bones (Figure 1). The dorsal roof of the

infraorbital canal was removed. The caudal third of the infraorbital nerve was transected rostral to the point parallel to tooth 110/210, back to the site of emergence from the brain. The trigeminal nerve on both sides of the head was removed to include the trigeminal nerve root, ganglion, infraorbital, and caudal nasal nerves. Specimens were fixed in 10% neutral buffered formalin, routinely processed to paraffin wax, sectioned at 4 µm, then stained with hematoxylin and eosin, Luxol fast blue/Cresyl violet, solochrome cyanin, or Palmgren silver impregnation.

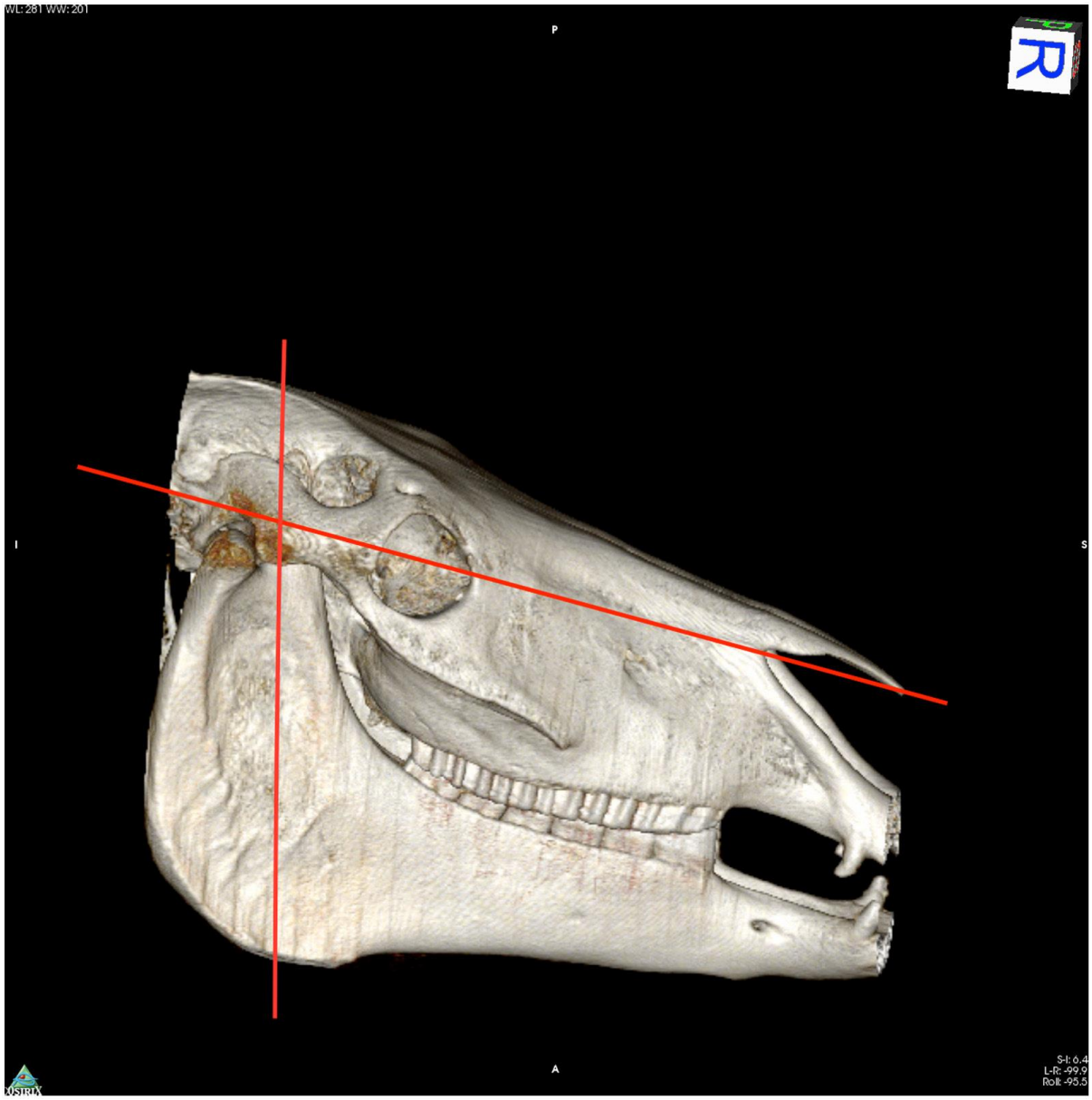

Figure 1: Reconstructed computer tomography image to illustrate cuts made in specimen dissection

Histopathological Anatomy in Trigeminal-Mediated Headshakers

Suitable cases (six) were horses diagnosed with trigeminal-mediated headshaking who had been euthanized following failure to respond to treatment. Owners gave informed consent for the use of their horses' bodies for this study. Dissection was performed either within 1 h after euthanasia or up to 3 h later, when heads were again stored in ice. Dissection and slide preparation were performed by the same technique as for the abattoir specimens. As some cases had undergone "coil compression" of the infraorbital nerve for treatment of headshaking (2 and 9), the section of the infraorbital nerve affected by the surgery (level with the rostral border of tooth 111 and 211) was not used in this study. The histological appearance of samples taken from horses with headshaking was compared to the samples taken from normal horses, by a veterinary pathologist and a neuropathologist with particular experience of trigeminal neuralgia histology. Each sample was sectioned and examined at multiple levels.

Results

There were four assumed normal abattoir specimens and six clinical cases (20 nerves). Of the latter, three had undergone "coil compression" surgery, which had failed to alleviate clinical signs. The portion of the nerve affected by this procedure was not used in this study for any of the specimens (a 2-cm stretch of the infraorbital nerve, level with the rostral border of tooth 111 and 211).

No histopathological abnormalities were detected on microscopic examination of the trigeminal nerve root, trigeminal ganglion, infraorbital nerve (excluding segments directly affected by coil placement), and caudal nasal nerve. In particular, there was no increase in cellularity or reduction of myelin staining to suggest demyelination, such as is often observed, usually in the trigeminal nerve root, in people with trigeminal neuralgia (Figures 2 and 3).

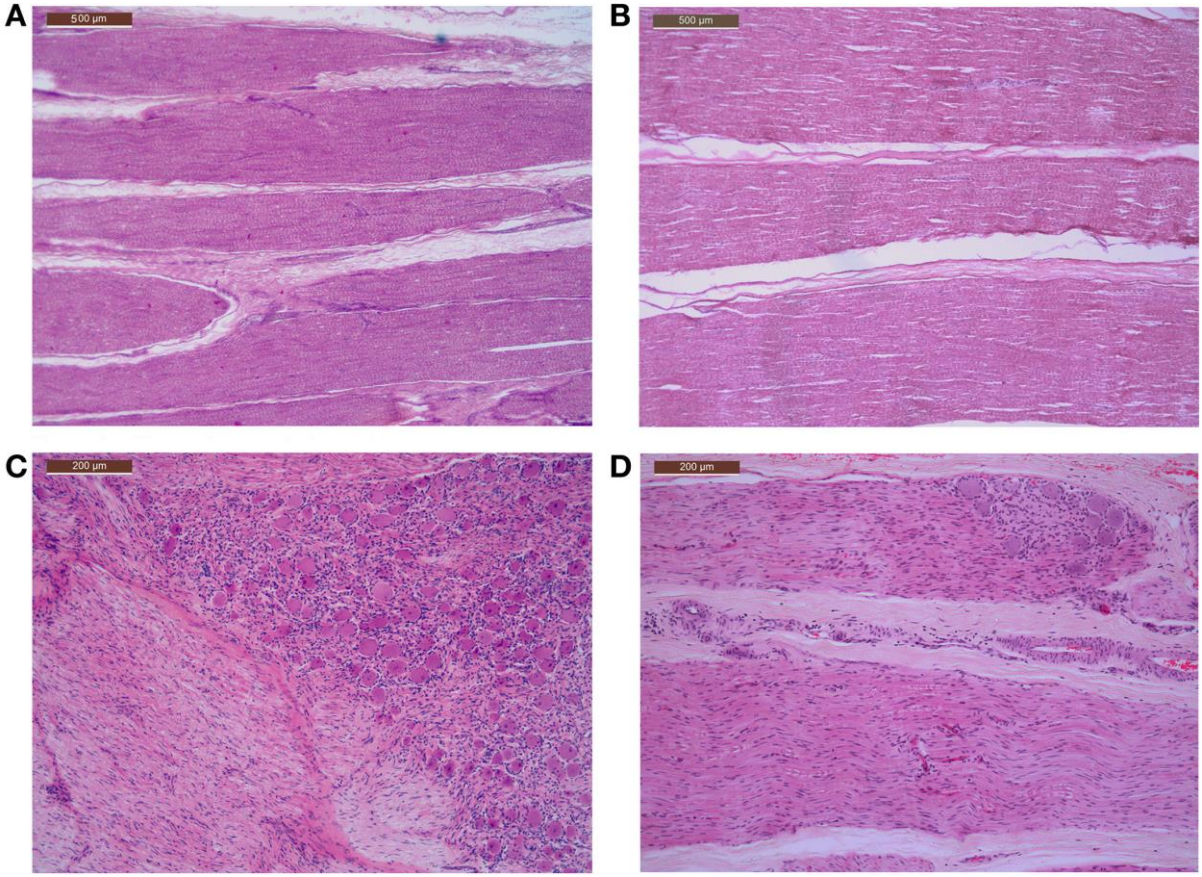

Figure 2: Microscopic features of the trigeminal nerve roots and caudal nasal nerves, including portions of the pterygopalatine ganglion, of control and affected horses, showing normal axons and myelination within the nerves and normal ganglion cells and architecture within the ganglia. (A) Photomicrograph control horse normal trigeminal nerve root H&E stain. (B) Affected horse normal trigeminal nerve root H&E stain. (C) Photomicrograph control horse including a portion of normal caudal nasal nerve and pterygopalatine ganglion H&E stained. (D) Affected horse including a portion of normal caudal nasal nerve and pterygopalatine ganglion H&E stain.

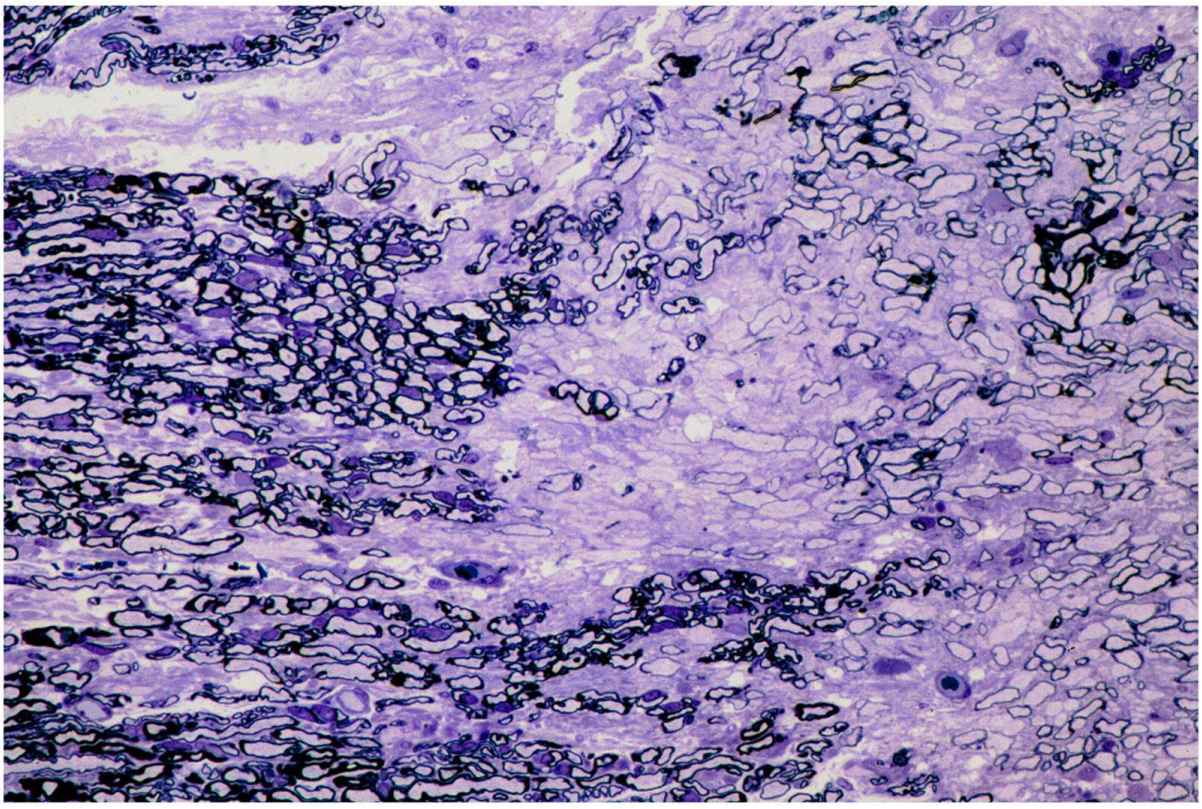

Figure 3: Photomicrograph of semi-thin sections through a region of trigeminal nerve root compression in a human patient reveals a zone of demyelination within the proximal, CNS part of the nerve root, close to the junction with the PNS. Several thinly myelinated fibres are present within the zone of demyelination. Toluidine blue. Reproduced with permission from Ref. (14).

Discussion

These results suggest that, while trigeminal-mediated headshaking in horses has apparent clinical similarity to trigeminal neuralgia in human, it may have a different underlying pathological substrate.

Trigeminal neuralgia in people is a neuropathic facial pain syndrome characterized by a recurrent sudden, severe sharp electric shock-like pain (15). Certainly, trigeminal-mediated headshaking in horses is a facial pain syndrome, with signs of temporary amelioration following infiltration of local anaesthetic around the trigeminal nerve (9). Poor response to non-steroidal anti-inflammatory medication but response in some cases to administration of carbamazepine (6) and use of percutaneous electrical nerve stimulation (13) are consistent with the facial pain being neuropathic in these horses.

Both headshaking and trigeminal neuralgia appear to be acquired, although in people usually in an older equivalent population than in horses (15, 16). There are a number of other clinical differences. In trigeminal neuralgia, there is a slight female predominance (14, 15), whereas trigeminal-mediated headshaking may be more common in neutered males (16) although clearly we cannot make a direct comparison here. Trigeminal neuralgia is typically unilateral (14, 15), whereas in horses the trigeminal nerve is affected bilaterally (11), so indeed the pathology could be central. Symptoms of trigeminal neuralgia are usually triggered by light stimuli, such as touching, chewing, talking, and tooth brushing involving specific mucocutaneous areas of the head, oral cavity, or neck: the “trigger zones” (15). Signs of trigeminal-mediated headshaking may be evident at rest but are often elicited by exercise (16), although in some cases signs manifest only when exercise is performed outdoors and not indoors (personal observation). In some cases, signs may occur only during the spring and summer months and may be worsened in bright sunlight and wind (16). This suggests a complex role of the environment in the development of the condition. People may suffer post-herpetic neuralgia (14), but trigeminal-mediated headshaking has been shown to not be associated with latent herpes virus infection (17).

There are also differences at an electrophysiological level. The electrophysiological features of demyelination, such as temporal dispersion, polyphasia, and conduction block, are not seen in affected horses (18). Trigeminal-mediated headshakers instead, demonstrate sensitization of the trigeminal nerve, as evidenced by a low threshold potential for nerve activation when measured using somatosensory-evoked potentials (8, 11, 12). The sensitization appears to be reversible, as it was not evident in a seasonally affected headshaker when tested out of season and free of clinical signs.

Present findings extend those of Aleman et al (11). There appears to be no structural abnormality in the trigeminal nerve of horses affected by trigeminal-mediated headshaking. A functional, non-structural abnormality may reflect central pathology or membrane instability and raise the possibility that the condition is potentially reversible, as occurs naturally in seasonally affected horses. Limitations of the present study include the small sample size without close age-matching of cases to controls, our assumption that abattoir specimens were not affected by trigeminal-mediated headshaking, and the selection bias for donated affected horses to be non-responders to current available treatments. There was opportunity to blind the pathologists as to origin of specimens and this was not availed of.

Further work should be directed at determining the cause of the functional abnormality and the factors which induce it, as this knowledge would allow the development of targeted treatments.

Ethics statement

This study was performed on cadavers of horses euthanased for veterinary reasons or for human consumption. Owners of clinical cases gave informed consent for the use of their horses' bodies in this study. This study was approved by the University of Bristol Ethics Committee.

Author contributions

VR is responsible for the conception of this research and acquisition of specimens. All authors contributed equally to project design. VR, DF, and JM performed dissection all on cases together. DF and SL examined the histopathology slides separately and together and prepared the photomicrographs. VR drafted the work, with all authors involved in the final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author note

Part of this research was presented at the meeting of the British Neuropathological Society, 2014.

Acknowledgements

The authors would like to thank the British Neuropathological Society for funding, Liphook Equine Hospital and David Rendle for recruiting one of the cases, and University of Bristol pathology technicians and Lucy Meehan for the computed tomography image.

Funding

This work was supported by the British Neuropathological Society (grant number RJ5692).

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Chapter Four: Diagnosis

Accuracy of diagnostic local anaesthesia of the maxillary nerve for investigation of trigeminally-mediated headshaking in horses

4.1 Candidate contribution:

The concept of this study was mine. The project was planned equally by all authors. I obtained ethical permission. I sourced funding from the Langford Trust for Animal Health and Welfare. I acquired the specimens and then performed the procedures and imaging equally with the first author. The second author interpreted and mapped the images with the first author. I supervised analysis of results by the first author. A major role was the close supervision of the first author, postgraduate student in the execution and writing of the first publication of her career.

4.2 Paper Three

Validation of the accuracy of needle placement as used in diagnostic local analgesia of the maxillary nerve for investigation of trigeminally mediated headshaking in horses.

Wilmink S, Warren-Smith CM, Roberts VL.H (2015)

The Veterinary Record Feb 7;176(6):148 10.1136/vr.102518

Validation of the accuracy of needle placement as used in diagnostic local analgesia of the maxillary nerve for investigation of trigeminally mediated headshaking in horses.

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Introduction

Headshaking in horses is commonly a clinical sign of a facial dysaesthesia (abnormal sensation), suspected to be due to a neuropathy of the maxillary branch of the trigeminal nerve (Newton and others 2000, Roberts 2011, Roberts and others 2013, Pickles and others 2014). A diagnosis of facial dysaesthesia can be made by observing a marked decrease in headshaking in response to local anaesthesia of the innervating sensory nerves (Roberts and others 2013, Pickles and others 2014).

Where no cause of this facial dysaesthesia can be identified on endoscopy, imaging of the head, ophthalmological and dental examination the dysaesthesia is likely to be neuropathic (Newton and others 2000, Roberts and others 2013).

The maxillary nerve exits the brain via the round foramen, runs cranially and enters the maxillary foramen into the infraorbital canal to become the infraorbital nerve. The infraorbital nerve innervates the upper check teeth and the skin of the muzzle. The caudal nasal nerve (CNN) branches off the maxillary nerve just proximal to the maxillary foramen and enters the caudal nasal foramen before running towards the dorsal meatus of the nasal cavity to innervate the nasal mucosa (Dyce and others 2002). In previous articles, the CNN has been called the ‘posterior ethmoidal nerve’ (Newton and others 2000, Roberts and others 2013), but due to possible confusion with the ethmoidal nerve which branches of the ophthalmic nerve rather than the maxillary nerve, we will refrain from using this term.

Local anaesthesia of the infraorbital nerve as it leaves the infraorbital canal resulted in a decrease in headshaking in 3/19 (16 per cent) horses only (Mair 1999). However, local anaesthesia applied around the maxillary nerve at the location of the maxillary foramen resulted in a marked decrease in headshaking in 11 of 17 (65 per cent) and 23 of 27 (85 per cent) of presumed idiopathic headshakers (Newton and others 2000, Roberts and others 2013). It is suspected there was a false negative result in at least some of the horses, as 3/4 horses which did not respond to diagnostic local analgesia responded well to caudal compression surgery which itself carries a 49 per cent success rate (Roberts and others 2013).

The intended site of deposition of the local analgesic is around the maxillary and CNN (Newton and others 2000, Roberts and others 2013), but accuracy of needle deposition at this location using the approach described by Newton and others (2000) has never been confirmed. Deposition in different locations could explain some of the false negative responses.

The objective of this study was to verify the exact location of injection when performing local anaesthesia of the maxillary and CNN and also to determine whether increased operator experience would result in a more accurate placement of the local analgesic.

Thirty horse cadaver heads with no known clinical abnormalities were obtained from an abattoir. No selection for breed, age or sex had been made. Decapitation had been performed at the atlanto-occipital joint. All procedures were performed within three hours of decapitation.

The heads were randomly assigned to one of three groups, with 10 heads to be injected by an experienced operator (VR) who has used local anaesthesia of the maxillary and CNN routinely on clinical cases (eight years' experience with headshakers consisting 2 per cent of caseload, in total more than 100 cases on which this procedure has been performed). Another 10 heads were injected by a less experienced (learning) operator (SW) who had been trained by the first operator and had performed the procedure in four clinical cases before this study. The last 10 heads were injected by 10 final year veterinary students with no experience in performing the procedure. Prior to performing the procedure, all of the students were given access to the literature available to veterinary practitioners on the technique. This included the guidelines as described by Newton and others (2000), a video on placement of the injection which is included in a commercially available iPhone app (Equine Techniques) (Veterinary Advances, Ireland), anatomy books and an equine skull, but no further explanation was offered and no communication with other performers was allowed. All 12 performers were right hand dominant. The heads were positioned horizontally (ventral part of mandible resting on the table) on the CT machine (Siemens Somatom Emotion, Erlanger, Germany) scanning table. Injection around the maxillary and CNN was then performed bilaterally using the contrast medium amidotrizoate (Urografin 150, Bayer) (Bayer, Newbury, Berkshire, UK) and all performers used the approach as first described by Newton and others (2000) (technique shown in Fig 1). A 19 gauge 90 mm spinal needle was inserted on the ventral border of the zygomatic process of the temporal bone at the narrowest point of the zygomatic arch and directed rostromedially in the direction of the contralateral upper sixth cheek tooth. The needle was inserted to its full length or until

contact with bone was made. Aspiration was attempted before contrast injection and the stylet was replaced before needle withdrawal in an attempt to keep the contrast localised. To ensure good accuracy of measurements, only a 0.1 ml volume of a mixture of contrast medium was injected (Bardell and others 2010).

Figure 1: Location of intended placement location of 19 gauge 19 mm spinal needle demonstrated in a horse skull and a clinical case

Immediately following bilateral injection, CT images were obtained using a 4th generation helical CT scanner (Siemens Somatom Emotion). All heads were scanned from cranial to caudal using a 1.5 mm diameter slice thickness with a pitch of 0.9. Settings were kV of 130, mAs 190 (effective – Siemens CareDose 4D protocol) and a rotation time of one second. Reconstructions were obtained at a thickness of 1.2 mm to ensure that there was sufficient slice detail for multi-planar reconstructions. All images were then reviewed using commercially available DICOM viewing software (Osirix, Pixmeo, Switzerland). Images were initially reviewed in the transverse plane to locate the contrast material. Dorsal images were then reconstructed with the plane aligned with the hard palate using multi-planar reconstruction.

The location of the contrast injected was then noted and the distance from the target site. In some images, due to the three-dimensional nature of the skull, thick slice reconstructions were required to bring the location of the contrast injection into the same plane as the caudal nasal foramen. In order to assess placement zones correctly, the images were then reconfigured as thin slice images and rotated around the axis of the caudal nasal foramen to align the foramen and contrast injection site. All measurements were taken at the closest point of the visible contrast media to the caudal nasal foramen.

The position of the injected contrast medium was divided into four zones depending on its position to determine the accuracy of the injection (Fig 2). Zone 1 represented contrast around the CNN nerve within and including at the entrance of the caudal nasal foramen where the CNN nerve branches off the maxillary nerve. Zones 2 and 3 lie between zone 1 and a line drawn between the hamulus of the pterygoid bone and the caudal lateral tip of the caudal maxillary sinus. This region was then divided into equal portions based on the distance along the maxillary tuber to give zones 2 and 3 (see Fig 2). Zone 4 was all regions outside this area which included the orbit and represents a failure to place the contrast near the maxillary nerve. Designation to the zones were made and recorded by a single independent observer (CWS) blinded to the identity of the performer of the injection.

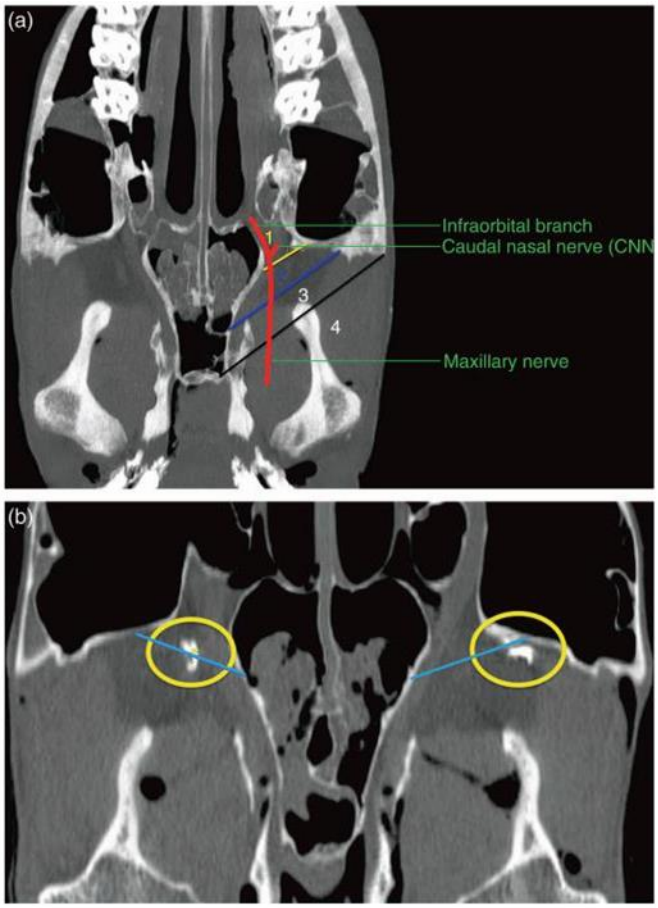

Figure 2: (a) Dorsal view of an equine head at the level of the maxillary foramen, with the location of zones used in this study. The caudal part of the infraorbital nerve and the caudal nasal nerve (CNN) are highlighted in red. Zone 1 represented contrast around the CNN nerve within and including at the entrance of the caudal nasal foramen where the CNN nerve branches off from the maxillary nerve. Zones 2 and 3 lie between zone 1 and a line drawn between the hamulus of the pterygoid bone and the caudal lateral tip of the caudal maxillary sinus. This region was then divided into equal portions based on the distance along the maxillary tuber to give zones 2 and 3 (see Fig 2). Zone 4 was all regions outside this area which included the orbit and represents a failure to place the contrast near the maxillary nerve. (b) Dorsal view of an equine head at the level of the maxillary foramen, with yellow circles highlighting the contrast medium in zone 1 (left) and zone 2 (right).

Data are presented descriptively and a Kruskal-Wallis test was performed to examine the relationship between accuracy and the three groups of performers, followed by a Mann-Whitney U test to examine significance in difference between each pair of groups. When it was then found appropriate to combine groups, a Fisher's exact test was used to examine if

the experienced performer did inject around the maxillary nerve (zones 1, 2 and 3) more often than the other performers did. A Wilcoxon rank-sum test was used to determine the relationship between deposition zone and left or right side of the head. Statistical analysis was performed using SPSS Statistics for Windows V.19 (IBM, New York, United States). Significance was taken as $P<0.05$.

The position of the contrast deposition was recorded for each head and the results for each zone, side of head and group are displayed in Table 1. Contrast is deposited around the maxillary nerve (zones 1, 2 and 3) in 53.3 per cent (32/60) of injections.

	Zone 1	Zone 2	Zone 3	Zone 4	Zone 1+2+3	Total
LEFT						
Non-experienced	0 (0%)	2 (20%)	1 (10%)	7(70%)	3 (30%)	10
Learning	0 (0%)	1 (10%)	2 (20%)	7(70%	3 (30%)	10
Experienced	0 (0%)	6 (60%)	1 (10%)	3 (30%)	7 (70%)	10
Non-experienced + learning	0 (0%)	3 (15%)	3 (15%)	14 (70%)	6 (30%)	20
All performers §	0 (0%)	9 (30%)	4 (13.3%)	17 (56.7%)	13 (43.3%)	30
RIGHT						
Non-experienced	1(10%)	2 (20%)	3 (30%)	4 (40%)	6 (60%)	10
Learning	1(10%)	0 (0%)	3 (30%)	6 (60%)	4 (40%)	10
Experienced	2(20%)	5 (50%)	2 (20%)	1 (10%)	9 (90%)	10
Non-experienced + learning	2(10%)	2 (10%)	6 (30%)	10 (50%)	10 (50%)	20
All performers§§	4(13.3%)	7 (23.3%)	8 (26.7%)	11 (36.7%)	19 (63.3%)	30
BOTH SIDES						
Non-experienced*	1(5%)	4(20%)	4 (20%)	11 (55%)	9 (45%)	20
Learning*	1(5%)	1(5%)	5 (25%	13 (65%)	7 (35%)	20
Experienced	2(10%)	11 (55%)	3 (15%)	4 (20%)	16 (80%)	20
Non-experienced + learning**	2(5%)	5 (12.5%)	9 (25.5%)	24 (60%)	16 (40%)	40
All performers	4(6.7%)	16 (26.7%)	12 (20%)	28 (46.7%)	32 (53.3%)	60

TABLE 1: Number of times contrast was located in each zone at each side of the head for each group of performers. Zone 1 represented contrast around the CNN nerve within and

including at the entrance of the caudal nasal foramen where the CNN nerve branches off from the maxillary nerve. Zones 2 and 3 lie between zone 1 and a line drawn between the hamulus of the pterygoid bone and the caudal lateral tip of the caudal maxillary sinus. This region was then divided into equal portions based on the distance along the maxillary tuber to give zones 2 and 3 (see Fig 2). Zone 4 was all regions outside this area which included the orbit and represents a failure to place the contrast near the maxillary nerve. The *, § symbols indicate which groups were compared with each other, where an equal number of symbols represents no significant difference and a different number of the same symbols represents a significant difference. CNN, caudal nasal nerve.

The Kruskal-Wallis test showed a significant difference in accuracy amongst the three groups ($H(2)=12.148$, $P=0.002$) with a mean rank of 33.50 for non-experienced, 37.60 for learning and 20.40 for the experienced performer. The Mann-Whitney U test showed no significant difference in accuracy between the non-experienced and learning performers ($P=0.478$), but a significant difference between non-experienced and experienced performers ($P=0.018$) and also between the learning and experienced performers ($P=0.001$). Figure 3 shows the distribution over the zones where contrast was deposited by the experienced performer versus the other two groups combined.

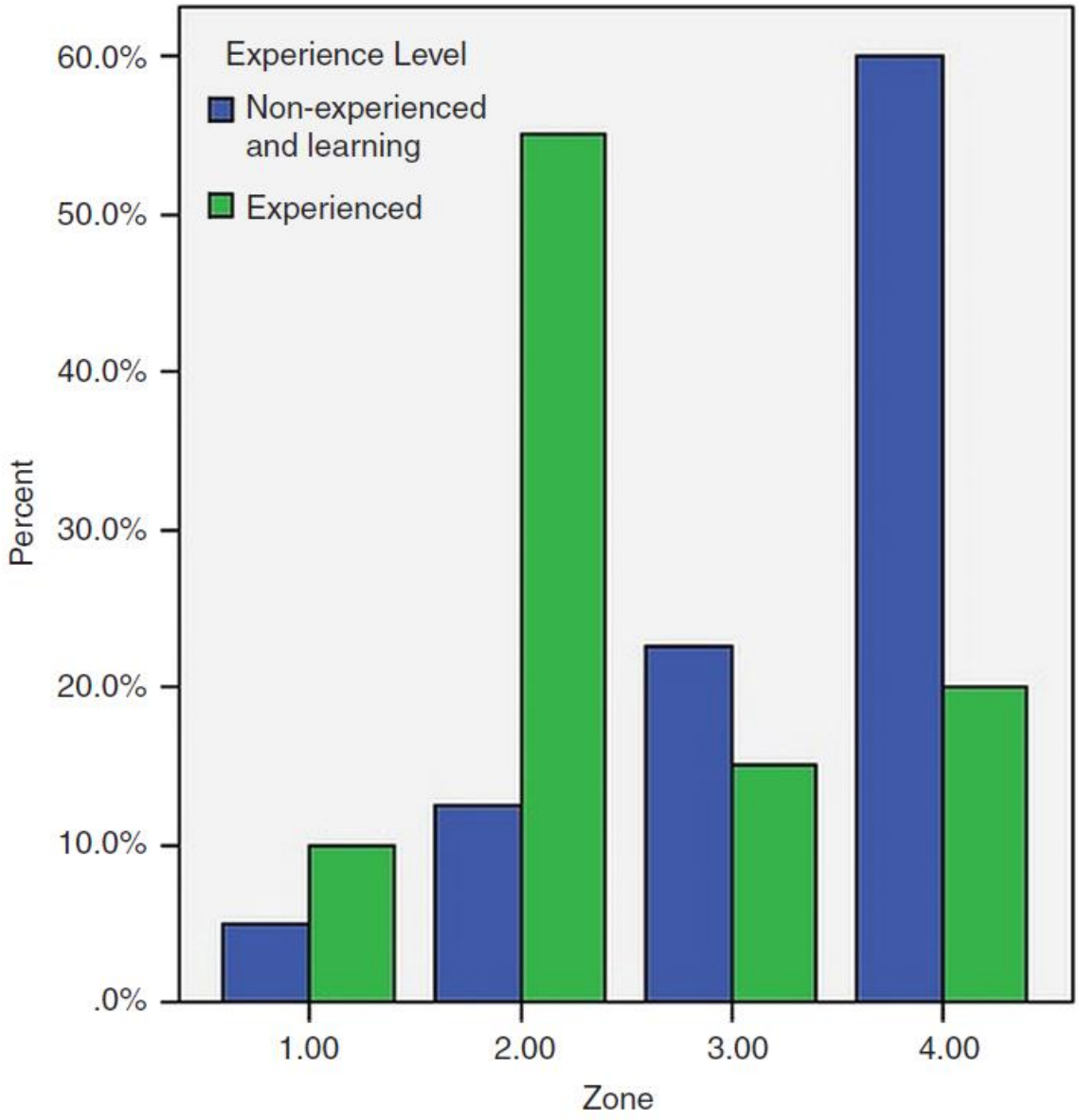

Figure 3: The distribution over the zones where contrast was deposited by the experienced performer versus the other two groups combined.

When the inexperienced group was combined with the less experienced performer into one group, and zones 1, 2 and 3 were combined into a result ‘hit’, a Fisher’s exact test could be used to compare the two groups. This confirmed that the experienced performer placed the injection around the maxillary nerve (zones 1, 2 and 3 combined) significantly (P=0.006) more frequently (80 per cent (16/20 injections)) than the other performers (40 per cent (16/40 injections)).

There was significant difference in accuracy between injections placed on the left or right side of the head, as determined by the Wilcoxon rank-sum test (P=0.046), with greater accuracy on the right as the median of the zones hit on the right-hand side was lower than on the left (zones 3 and 4, respectively). The injection was placed around the maxillary nerve in 43.3 per cent of injections on the left side, and in 63.3 per cent of injections on the right side of the head (Table 1).

This study shows that contrast is deposited around the maxillary nerve (zones 1, 2 and 3) in 53.3 per cent (32/60) of injections, and we found that accuracy is significantly greater when the procedure is performed by a very experienced performer. There was no significant difference in accuracy between those with little or no experience in placing the injection in this study.

The use of one operator per category is not ideal and represents a limitation of the paper. However, given the limited number of experienced operators available, it was not possible to include more operators in the experienced or learning group.

Injection did not always occur around the maxillary nerve as intended. Thus, a negative response to the local anaesthesia of the maxillary nerve in horses could result from failure to deposit local anaesthetic around the nerve. In clinical cases, accurate placement of the local anaesthetic can be confirmed to some extent by assessing sensitivity of the facial skin and nasal passage, which may help to distinguish a true negative from a false negative response.

Injections placed on the right side of the head were significantly more accurate than injections placed on the left side of the head. All performers were right hand dominant. In clinical cases, a false negative response to bilateral local anaesthesia of the maxillary nerve and CNN would be more likely for remaining left-sided facial dysaesthesia. Signs of facial dysaesthesia in headshaking horses are usually bilateral (Aleman and others 2013). Therefore, unilateral application of the local anaesthesia has not been attempted by the authors in clinical cases.

When performing local anaesthesia of the maxillary nerve and CNN in horses, a greater volume of local anaesthetic (5 ml) is used than the volume of contrast medium in this study (Newton and others 2000). Previous to this study, an attempt was made by the authors to analyse the location of deposition of 5 ml contrast medium, but description of anatomical structures involved proved difficult, complicating ensuing statistical analysis had this larger volume been used in the study. The use of a small volume of contrast medium and imaging

modalities rather than dye and dissection techniques enabled us to accurately locate into which zone the injection had been placed. The larger volume used in clinical cases will result in analgesia of a much larger area as the anaesthetic will diffuse along tissues, including more branches of the maxillary nerve than could be visualised in this study. Therefore, in clinical cases, success rate of anaesthetising the maxillary and CNN will be greater than reported in this study. The use of zones rather than absolute distances enabled us to overcome the variation in head size by standardising each head to itself and helped verify the accuracy of placement, although the distance of diffusion could not be accounted for. However, even when using a larger volume, deposition of local anaesthetic in zone 4 is unlikely to result in desensitisation of the maxillary nerve and will not lead to a decrease in headshaking even if this is due to facial dysaesthesia. This occurred in 24/40 (60 per cent) of injections by the non-experienced or less experienced performers and in 4/20 (20 per cent) of the injections performed by the experienced performer, suggesting experience is essential when performing local anaesthesia of the maxillary nerve and CNN.

Possible complications of inaccurate injection of local anaesthesia around the maxillary nerve that have been observed by the authors in clinical cases include temporary loss of sight when the anaesthetic diffuses to or is deposited around the optic nerve, swelling of the retrobulbar fossa when disruption of an artery or vein results in a haematoma, or sudden distress when the needle touches the nerve. These side effects do resolve with time (Tremaine 2007).

We consider it to be good practice to perform diagnostic local anaesthesia around the maxillary nerve and CNN on presumed idiopathic headshakers (Roberts and others 2013). A marked decrease in headshaking in response to application of diagnostic local anaesthesia around the maxillary nerve and CNN without other pathology in the innervated area will support the diagnosis of trigeminal (maxillary) neuropathy to the veterinarian, the owner of the horse and may also be used as proof for insurers. However, the possibility of a false negative outcome must be considered and preferably explained to the client before performing the diagnostic local anaesthesia around the maxillary nerve and CNN.

Acknowledgements

The Langford Trust for Animal Health and Welfare for funding this study and Langford Veterinary Services for funding the first author’s residency training.

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Chapter 5: Treatment I

Modification of the original infraorbital neurectomy technique and consideration of risks

5:1 Candidate contribution

Paper Four was my first original research study. The concept was that of the second and last authors. I was equally involved with them in project planning. I performed the data collection with input from the third author in contacting horse owners. I performed the data analysis under supervision of the second and last authors. I wrote the manuscript with input from the third author and under the supervision of the second and last authors. A clear improvement in my papers can be seen over the years from this start point.

Paper Five built on and expanded the study presented in Paper Four. The concept was mine and I planned the project with the supervision of the last author. I performed the majority of data collection with input from co-authors with data from their own institutions. I performed the data analysis and wrote the manuscript with input and agreement from all authors on the final version submitted for publication.

5.2 Paper Four

Caudal compression of the infraorbital nerve: a novel surgical technique for treatment of idiopathic headshaking and assessment of its efficacy in 24 horses.

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Equine Veterinary Journal 2009. 41(2): 165-170 doi: 10.2746/042516408X342966

Caudal compression of the infraorbital nerve: a novel surgical technique for treatment of idiopathic headshaking and assessment of its efficacy in 24 horses.

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Keywords: horse; headshaking; trigeminal neuropathy; coil compression

Summary

Reasons for designing and reporting technique: Idiopathic headshaking has remarkable similarities to human neuropathic facial pain syndromes associated with post herpetic and trigeminal neuralgia. These derive from abnormal sensory function within the peripheral or central pathways of the trigeminal nerve (TgN). Limiting input from the TgN can be helpful in controlling the perception of pain. Rhizotomy of the infraorbital branch of the TgN as it emerges from the infraorbital canal has been reported but has a poor efficacy. A novel technique involves compression of the nerve at a more caudal location within the infraorbital canal and the technique requires validation.

Hypothesis: Caudal compression of the infraorbital nerve with platinum coils, performed in horses diagnosed with idiopathic headshaking, results in a decrease in clinical signs.

Methods: Caudal compression of the infraorbital nerve, using platinum embolisation coils, was performed under fluoroscopic guidance. Clinical records of 24 idiopathic headshakers that had undergone this procedure were reviewed. Follow-up information was obtained by telephone questionnaire with the owner or referring veterinary surgeon.

Results: All 24 horses had at least one surgical procedure. Median follow-up time was 6 months. There were 2 horses which had surgery 2 weeks before follow-up and these were excluded from the analysis of outcome. Following one surgery, 13/22 horses (59.0%) had a successful outcome. Of the 9 horses that did not improve, surgery was repeated in 6 cases. Two of these horses had a successful outcome. Overall, a successful outcome was obtained in 16/19 horses (84.2%).

Conclusions: This surgical technique is likely to prevent input from the TgN at a more caudal location then the previously described infraorbital neurectomy. The technique requires refinement.

Introduction

The aetiopathogenesis of idiopathic headshaking is probably a trigeminal disorder (Neal and Ramsey 1972; Cook 1980; Wilkins et al. 1993; Newton et al. 2000). There may be abnormal sensory function within the peripheral or central pathways of the trigeminal nerve (TgN) (Weigel and Casey 2004). Whether the disorder has a peripheral or a central origin, either limiting input from the TgN or reducing brain stem response to input can be helpful in controlling the perception of pain associated with summation. This is the rationale behind current therapies for headshaking in horses.

Nose nets have been reported to provide up to 70% relief in 25% of cases (Mills and Taylor 2003). This may result from constant stimulation of the cutaneous components of the maxillary branch of the TgN (Newton et al. 2000). This stimulation is suggested to activate non-nocioceptive signals carried into the spinal cord by large nerve fibres. According to the gate-control theory, the action potentials in the large nerve fibres activate the inhibitory interneuron that would then block the projection neuron and, therefore, block the nocioceptive input.

Reported medical therapies include cyproheptadine and carbemazepine, either alone or in combination. Cyproheptadine, an antihistamine and serotonergic agent, was reported by Madigan and Bell (2001) to result in a moderate to substantial improvement in clinical signs in 43/61 (70.4%) cases. However, Newton et al. (2000) found cyproheptadine alone to be ineffective. The addition of carbemazepine, a sodium-channel blocking anti-convulsant drug, resulted in 80–100% improvement in 80% cases. Carbemazepine alone was effective in 88% cases. However, anecdotally, results are short-lived. Furthermore, long-term drug therapy is expensive and little is known about the pharmacokinetics of these drugs in horses, making it difficult to prescribe a safe and effective dosing regimen. Both drugs cause drowsiness as a side effect, which may mean horses undergoing treatment are unsafe to ride. Furthermore, these therapies are included on the banned substances list for many equestrian competitions.

Bilateral infraorbital neurectomy was the first reported surgical treatment for idiopathic headshaking (Mair et al. 1992; Mair 1999), with a success rate of 3/19 (15.8%), but 8/19 horses showed an increase in severity of headshaking following that procedure. Post operatively, 16 of 19 horses developed self-trauma to the nostrils or side of the face lasting for 3–8 weeks. Failure of this technique may be expected if the stimulus to headshake originates within the trigeminal nerve branches in a more proximal site closer to the brainstem. Consistent with this, bilateral posterior nasal nerve sclerosis resulted in a 90–

100% resolution of clinical signs in 5/5 horses (Newton et al. 2000). However, the benefit lasted only 6 weeks to 10 months.

Caudal compression of the infraorbital nerve was designed to permanently limit input from the TgN at a proximal location. Compression using platinum coils was chosen since neurectomy is not feasible due to anatomical location and is undesirable owing to the risk of neuroma formation. It was hypothesised that coil placement results in pressure degeneration of the nerve. Due to variation in anatomy of the TgN between individuals (Newton 2001), the technique may also cause compression in a location that reduces function of the posterior nasal branch in some cases.

In this paper, the surgical technique and results in 24 cases of idiopathic headshaking are described.

Materials and methods

The clinical records of 24 horses that had undergone caudal compression of the infraorbital nerve using platinum coils at The Philip Leverhulme Equine Hospital between June 2004 and October 2007 were reviewed. The surgical procedure was performed only in those cases where investigations found the horses to be idiopathic headshakers. Furthermore, these horses had all been non- or poorly responsive to more conservative therapy, such as use of a nose net.

Case selection and details

On admission, owners were interviewed and the information recorded included general details about the horse (age, sex, breed, use) and more specific information about the headshaking. The type of headshaking (horizontal, vertical or both) and whether it was accompanied by striking at the nose with the forelimbs or rubbing the nostrils were noted. On occasion, nose rubbing resulted in the development of facial sores, so the presence or absence of skin damage was recorded. Owners were asked in which situations their horse would headshake: at rest, in the stable, at pasture, ridden and when lunged. Owners also indicated in which of these situations they deemed the headshaking to be most severe. Trigger factors were further investigated, with the owners reporting whether the horse showed signs in sunny weather, windy conditions, rain or any combination of these. Where horses had a longer than a 12-month history of headshaking attempts were made to assess whether the complaint had a seasonal pattern.

Investigations were carried out to rule out causes of headshaking other than an idiopathic condition. This involved a full clinical examination, dental examination and ophthalmic

examination. Lateral-lateral radiographs[1] were taken of the skull at exposures suitable for viewing the roots of the cheek teeth and sinuses. Endoscopy[2] was performed of the upper respiratory tract and guttural pouches of all cases. Moderate pharyngeal lymphoid hyperplasia (PLH) was detected at endoscopy of Case 22. This horse was discharged on a course of inhaled corticosteroid and then presented for re-examination 6 weeks later. Endoscopy showed the PLH had resolved but there had been no change in headshaking suggesting that the inflammation was likely to be an incidental finding. No significant abnormalities were detected in the other cases. There appeared to be a wide variation between individuals in the configuration of the infraorbital canal, which ranged from straight to curved.

All horses were observed to headshake during hospitalisation, either at rest, on the lunge, ridden and/or during treadmill exercise. The horses that underwent treadmill exercise evaluation were trained to trot on an indoor treadmill[3]. Pollen was released into the airstream created by the fan positioned approximately 1.5 m in front of the horse's nose. Once horses were seen to headshake consistently, diagnostic local analgesia of the posterior nasal nerve (Newton 2000) was performed in those judged to be suitable candidates for the procedure on the grounds of temperament. These horses were then reassessed under the same conditions.

A total of 31 surgical procedures were performed on 24 horses diagnosed as idiopathic headshakers, therefore fulfilling the criteria for caudal compression of the infraorbital nerve using platinum coils. There were 6 horses (Cases 1, 4, 7, 14, 19 and 17) that received a second surgery after showing poor response to a first surgical attempt. Radiography showed that the coils had migrated in all of these cases and were therefore unlikely to be applying suitable pressure to the nerve within the infraorbital canal. A third surgery was required in Case 7. Case 12 had shown preoperative nose rubbing only on the left side. It responded to a unilateral posterior nasal nerve block on the left side so coils were implanted only into the left infraorbital canal.

Surgical technique

Following induction of general anaesthesia, the horse was placed in lateral recumbency, and a 5 x 5 cm area centred over the infraorbital foramen surgically prepared. A 2 cm skin incision was made over the infraorbital foramen, parallel to the facial crest. Blunt dissection was used to separate the subcutaneous tissue and the levator nasolabialis muscle was either displaced dorsally or split longitudinally over the foramen. Where the muscle was

grossly hypertrophied (as is common in headshaking horses) it had to be split to allow access to the infraorbital foramen.

Firstly, one platinum embolisation coil introducer[4] (Fig 1) was prepared by removing the platinum coil and inserting a stylet to a point level with the tip of the introducer, to provide the necessary rigidity for initial advancement. The introducer with stylet was advanced along the infraorbital canal parallel with its natural path, under fluoroscopic guidance. Once the introducer was located securely in the canal, the stylet tip was advanced beyond the distal end of the introducer. This created a semiflexible guide to assist the passage of the more rigid introducer as it followed the curvature of the infraorbital canal. Static and continuous fluoroscopy[5] were used to image the position of the introducer to ensure that it did not break out of the fragile infraorbital canal. The introducer was gently advanced along the canal until the point was just rostral to the most caudal maxillary cheek tooth, i.e. at the maxillary foramen (Fig 2).

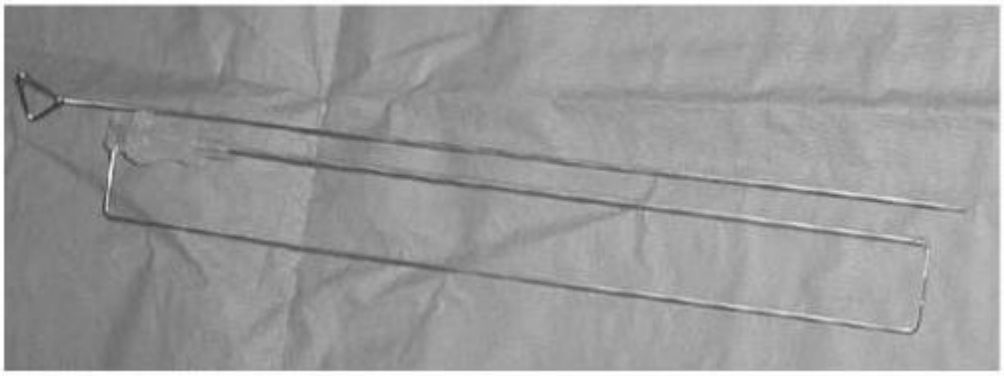

Figure 1: Introducer (containing platinum coil) and stylet.

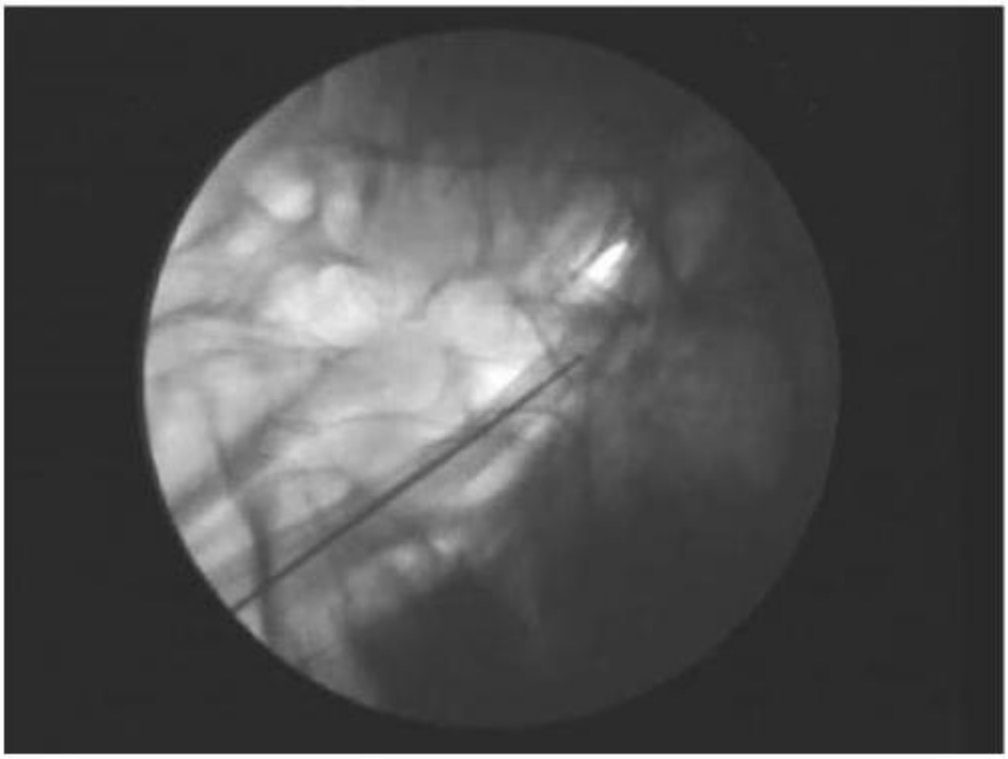

Figure 2: Fluoroscopic image of placement of first introducer.

Once the first introducer was in position, the procedure was repeated with 2 or 3 additional introducers placed to completely fill the canal (Fig 3). At this stage, the stylet was removed from the first of the pre-placed introducers and another introducer, this time containing a platinum coil, was inserted into the hub of the first pre-placed introducer. The stylet was then used to advance the coil into the canal of the first preplaced introducer. The second introducer was detached and the stylet used to advance the coil out into the infraorbital canal, where the material's memory causes it to form tight coils (Fig 4). Continuous fluoroscopy was used to observe accurate deployment of the coil. This was repeated for the other 2 or 3 preplaced introducers. The objective was to fill the width of the canal with tightly packed platinum coils to maximise pressure necrosis of the nerve. The introducers were removed and the skin incision closed using absorbable suture material in a sub-cuticular pattern. Where the muscle had been split, this was not sutured. The horse was then turned over and the procedure repeated on the contralateral side.

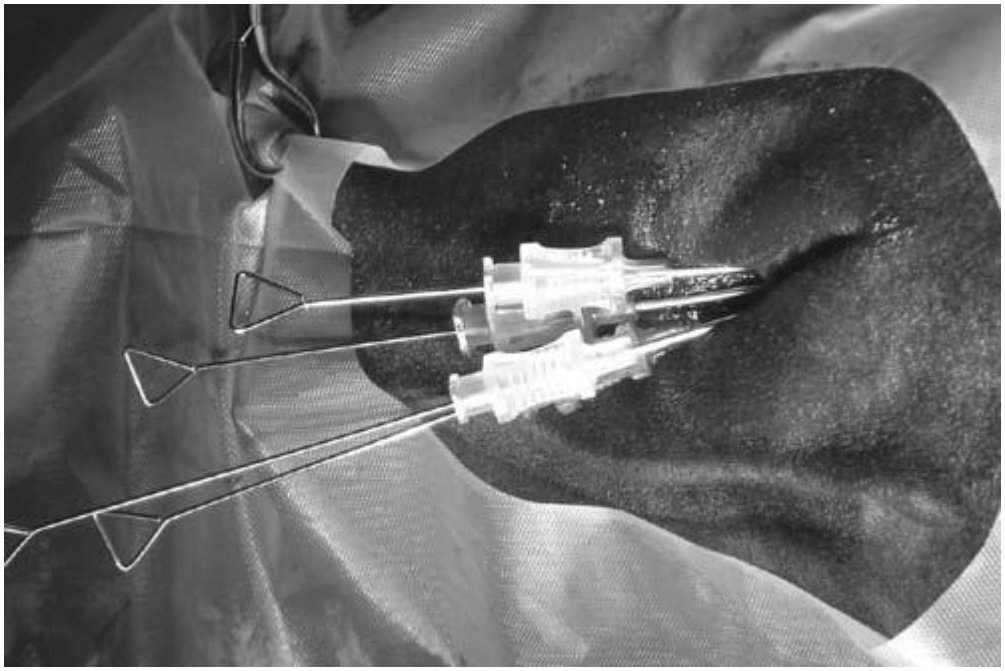

Figure 3: Four introducers in place, with stylets.

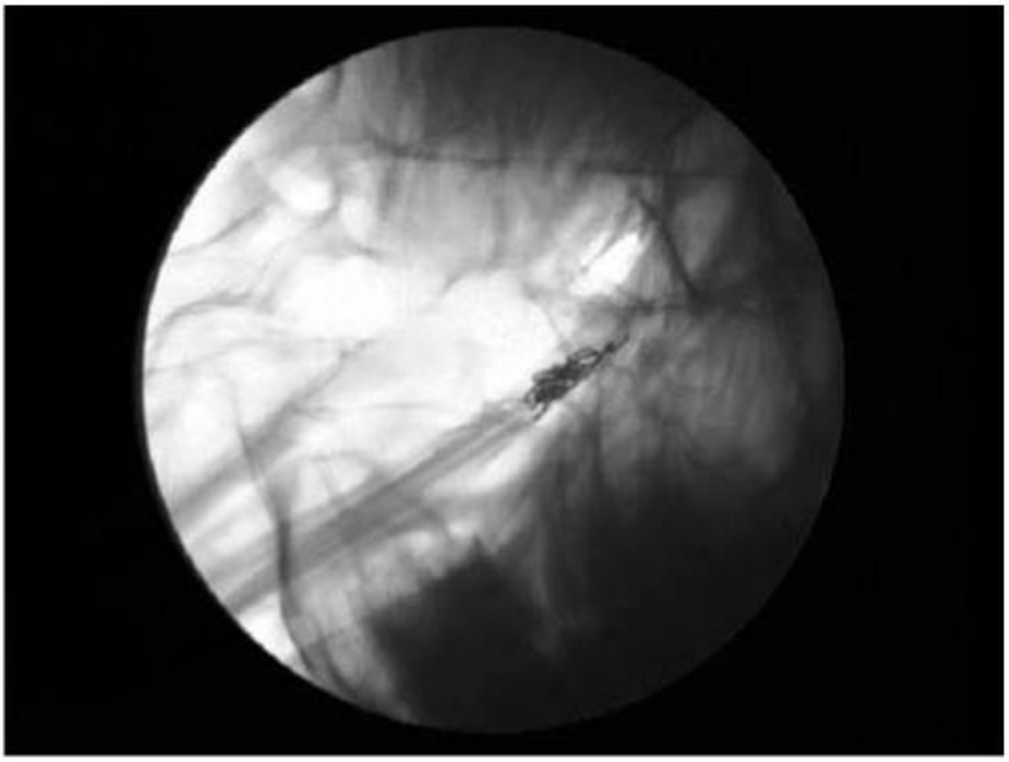

Figure 4: Intraoperative fluoroscopic image of 4 coils placed into the infraorbital canal.

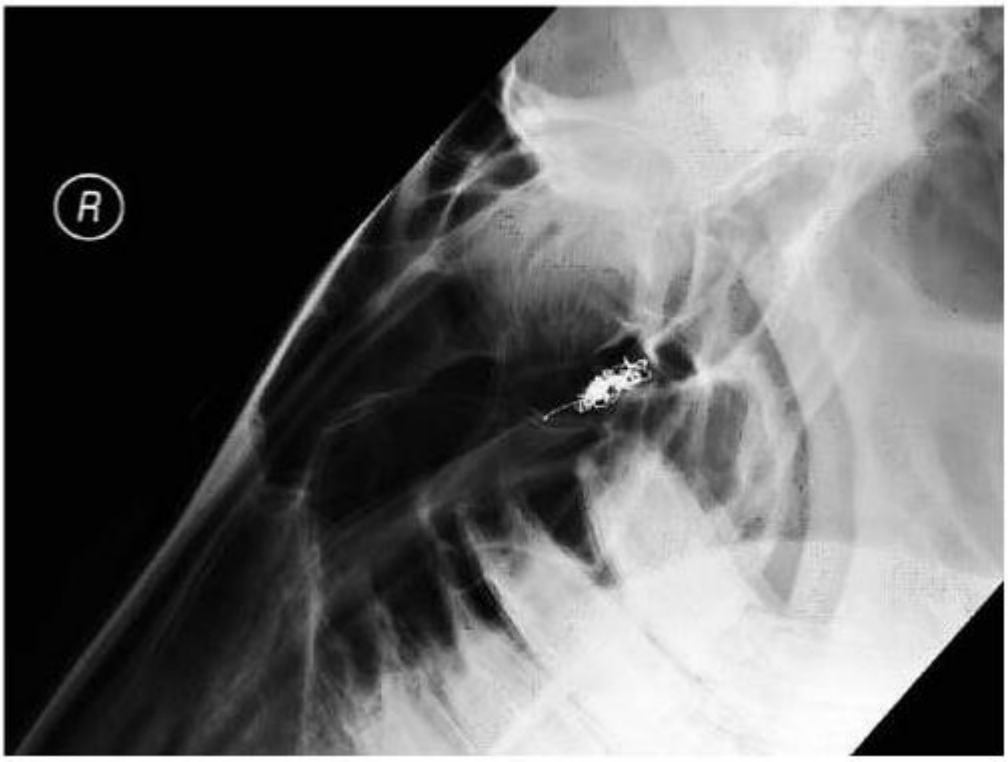

Figure 5: Post-operative radiograph showing positioning of coils.

Peri- and post-operative care

Antimicrobial therapy was provided with penicillin (Depocillin[6], 12 mg/kg bwt, i.m.) administered as a single dose preoperatively only, unless any perioperative complication, such as an introducer puncturing through the infraorbital canal wall into the sinus, suggested a longer course was advisable. Flunixin meglumine (Meflosyl[7], 1.1 mg/kg bwt, i.v.) and morphine (Morphine B.P.[8], 0.3 mg/kg bwt, i.v.) were administered to provide perioperative analgesia. Post-operative analgesia was maintained with phenylbutazone (Equipalazone[9], 2.2 mg/kg bwt, per os) as required. Horses were discharged from the hospital between 2 and 5 days after surgery.

Intra-operative complications

During surgery, care had to be taken not to force the introducer needle through the wall of the canal into the sinuses, which would result in epistaxis. When this occurred the needle was re-directed.

Some individuals had more pronounced curvature of the infraorbital canals than others. This was identified by preoperative lateral skull radiography or by intraoperative fluoroscopy. In

these individuals it proved necessary to bend the introducer to accommodate the curvature prior to insertion.

Post-operative complications

Transient nose-rubbing, usually resulting in self-trauma and often accompanied by headshaking at rest, was a frequent post-operative complication. Where horses developed this problem after hospital discharge, they were managed by their attending veterinary surgeon. If the post-operative complication began before discharge, then a single dose of dexamethsone (0.1 mg/kg bwt, i.v., Duphacort)[7] was administered and acepromazine (0.15 mg/kg bwt daily, per os, Sedalin)[10] prescribed as required. In these cases, number of days from surgery to onset of the complication was recorded.

Follow-up information was obtained for all 31 procedures in the 24 horses by telephone interview with the owner. Owners were asked whether the horses had shown self-trauma from nose-rubbing after surgery and, if so, when this had occurred and when it resolved.

The outcome of surgery was classified as successful if signs were alleviated sufficiently to allow the horse to be ridden when exposed to the stimulus that historically had caused it to headshake most severely. Hence some horses with a successful outcome may still have exhibited a mild degree of headshaking on occasion. There were 2 horses that were most affected when at rest. Case 14 was most severely affected in the stable and therefore success for this horse was judged on whether signs had alleviated when stabled. Case 8 was an unbroken yearling whose signs were triggered by rain and success was therefore judged on the owner's report of the horse's behaviour when turned out during rainfall. Horses not yet back in work after surgery were excluded from analysis of outcome.

All information was recorded in an Excel spreadsheet and descriptive statistics were generated.

Results

Descriptive information on the 24 horses is included in Table 1. There were 17 geldings and 7 mares. A wide range of breeds was represented. The most common use was general riding (12/24) with 5 dressage horses, 2 showjumpers, 2 used predominantly for ridden showing, one eventer and one child's mounted games pony. Cases 6, 10 and 24 had previously been racehorses. Median age at presentation was 8.5 years (mean 8.7 years, range 1–14 years). Weight at first surgery was recorded for 23/24 horses. Median weight was 551 kg (mean 533 kg, range 354–660 kg).

Identity	Age (years)	Breed	Sex (mare/ gelding)	Use	Weight (kg)
1	6	Irish Sports Horse	G	Dressage	660
2	4	Rhinelander	G	Dressage	516
3	8	Hanoverian	G	Dressage	615
4	10	TB x ID	G	Showjumping	618
5	14	Welsh X Haflinger	G	Mounted games	400
6	11	TB	G	General	570
7	10	Welsh Section D	G	General	540
8	1	TB x	M	Unbroken	350
9	10	Cob	G	General	450
10	13	TB	G	General	550
11	8	Belgian WB	G	Showjumping	575
12	12	TB x ID	G	General	561
13	8	TB x	G	General	465
14	7	Irish Sports Horse	G	Showing	620
15	7	WB x TB	G	Showing	628
16	6	Welsh Section D	G	General	410
17	12	Irish Sports Horse	M	General	645
18	14	Connemara	M	General	521
19	8	Cob x	M	General	587
20	9	Dutch WB	M	Dressage	553
21	10	Pony	G	General	345
22	10	Oldenburg	G	Dressage	550
23	6	Welsh Section D	M	General	490
24	4	TB	M	Eventing	590

TB = Thoroughbred; ID = Irish Draught; WB = Warmblood.

Table 1: Age, breed, sex, use and weight of 24 cases of horses subjected to surgery.

Specific information regarding the headshaking characteristics in each horse is shown in Table 2. There were 20/24 cases for which the owners knew whether or not the condition had a seasonal pattern. Of these, 11/20 (55%) were classified as seasonal headshakers and 9/20 (45%) displayed headshaking behaviour all year round. Signs in seasonal headshakers were generally alleviated in the winter months. Considering possible trigger factors, 10/20 (50%) horses showed increased severity of headshaking in sunny weather, 8/22 (36.4%) in the rain and 9/22 (40.9%) in windy conditions. Most horses (22/23, 95.7%) were judged by

their owners to show most severe headshaking signs when ridden. Not all owners had attempted lungeing their horses but of the 21 that had, 18 (85.7%) horses also showed headshaking on the lunge. Of the horses that displayed headshaking at rest there were 13/22 (59.1%) that showed signs in the field and 11/22 (50%) that showed signs when stabled.

		Occurs when in:				Occurs most in:			Type:		Nose	Strike	Facial
Case	Seasonal	Stable	Field	Lunge	Ridden	Sun	Rain	Wind	Horizontal	Vertical	rubbing	nose	sores
1	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No
2	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
3	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
4	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
5	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No
6	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
7	Yes	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No
8	No	Yes	Yes	UB	UB	No	Yes	Yes	No	Yes	Yes	Yes	No
9	Unknown	NR	NR	NR	Yes	NR	NR	NR	NR	NR	Yes	NR	NR
10	Yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
11	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
12	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
13	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No
14	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No	Yes
15	Unknown	No	No	No	Yes	NR	Yes	No	No	Yes	No	No	No
16	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
17	Yes	Yes	No	Yes	Yes	NR	Yes	No	Yes	No	No	Yes	No
18	No	Yes	No	No	Yes	No	No	No	No	Yes	No	No	No
19	Yes	NR	NR	NR	Yes	NR	NR	NR	No	Yes	NR	NR	NR
20	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No
21	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No
22	Unknown	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
23	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
24	Unknown	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No

NR = not recorded; UB = unbroken.

Table 2: Details (season, location, activity, meteorology, behaviour and presence of sores) headshaking occurrence and behaviour as reported by owner in 24 horses subjected to surgery for headshaking.

Considering the type of headshaking, a majority (21/23, 91.3%) showed vertical headshaking. There were 5/23 (21.7%) that showed horizontal headshaking with 3 horses (Cases 16, 23 and 24) showing both patterns. Striking at the nose was a feature in 14/21 (57.1%) cases. Nose rubbing occurred in 16/23 (69.6%) resulting in facial sores in 6 of those cases.

Details and results of surgery are recorded in Table 3. All 24 horses underwent at least one procedure. There were between 2 and 5 coils placed into each infraorbital canal. Surgery was performed bilaterally in 23 horses and unilaterally in Case 12.

Case	No. coils left side	No. coils right side	Time to follow-up (months)	Post op nose rubbing	Success	2nd surgery performed	Time to follow-up (months)	Success
1	NR	NR	5	No	No	Yes	0.5	R
2	4	4	5	No	No	No	N/A	N/A
3	3	3	11	No	No	No	N/A	N/A
4	3	3	11	No	No	Yes	0.5	R
5	4	4	14	No	Yes	N/A	N/A	N/A
6	3	3	14	No	Yes	N/A	N/A	N/A
7	NR	NR	6	Yes	No	Yes	12	No
8	3	4	16	No	Yes	N/A	N/A	N/A
9	NR	NR	24	No	Yes	N/A	N/A	N/A
10	2	2	26	No	Yes	N/A	N/A	N/A
11	5	5	29	Yes	Yes	N/A	N/A	N/A
12	4	0	26	No	Yes	N/A	N/A	N/A
13	3	3	6	Yes	Yes	N/A	N/A	N/A
14	NR	NR	2.5	Yes	No	Yes	6	Yes
15	4	4	3	Yes	Yes	N/A	N/A	N/A
16	4	4	4	No	Yes	N/A	N/A	N/A
17	NR	NR	6	Yes	No	Yes	2	U
18	4	4	6	Yes	Yes	N/A	N/A	N/A
19	4	4	8	Yes	No	Yes	6	Yes
20	NR	NR	5	Yes	No	No	N/A	N/A
21	5	5	1	No	Yes	N/A	N/A	N/A
22	4	4	2.5	Yes	Yes	N/A	N/A	N/A
23	4	4	0.5	No	R	N/A	N/A	N/A
24	4	4	0.5	Yes	R	N/A	N/A	N/A

NR = not recorded; R = still convalescing from surgery (less than one month post operatively); U = unable to assess as has not returned to work after surgery for other reasons; N/A = not applicable.

Table 3: Details (number of coils) period of follow-up, post-operative rubbing, second surgery success in 24 horses subject to surgery for headshaking and results of surgery.

Median time to follow-up after the first surgery was 6 months (mean 9.5 months ranging from 2 weeks to 29 months). Cases 23 and 24 had surgery only 2 weeks before follow-up information was sought. These had not yet been brought back into work and so were excluded from the analysis of outcome. Considering the remaining 22 horses, after one surgery 13/22 (59.0%) had a successful outcome; 9 did not respond to a first surgery, of which 6 (Cases 1, 4, 7, 14, 17 and 19) were returned for re-evaluation. All of these showed evidence of coil migration on skull radiography and a second procedure was therefore performed. Of these 6, 2 were still in the post-operative recovery period at the time of follow-up and one had been unable to be ridden since surgery due to laminitis. These 3 were excluded from analysis of outcome. Considering the remaining 3, 2 had a successful outcome and one did not. This individual (Case 7) returned for a third procedure, which had a successful outcome.

Overall, therefore, a successful outcome was obtained in 16/19 (84.2%) cases. Of these, 13 were in ridden work throughout the year and one was as yet unbroken. There were 2 horses (Cases 7 and 11) that could not be ridden through 2 summer months due to headshaking, where previously they had each been un-rideable for 9 months of the year.

Nose-rubbing, resulting in self-trauma to the skin of the face and muzzle and often accompanied by headshaking at rest, was a frequent post-operative complication. Following the first surgery, 11/24 (45.8%) horses displayed nose-rubbing. Median time from surgery to onset of this complication was 4 days (mean 3.6 days, range 1–5 days). Duration of this complication was, for most horses, less than one month but Cases 17 and 11 were affected for 4 and 5 months each. Therefore, median time of duration of nose-rubbing was 14 days (mean 35.7 days, range 3–150 days).

Discussion

Caudal compression of the infraorbital nerve is an effective surgical treatment for idiopathic headshaking, where the aetiology is suspected to be a trigeminal nerve (TgN) disorder and no other possible causes are detected on investigation. It is suggested that the technique is likely to limit the sensory input from the TgN distal to the position of the coils, without actually obliterating it.

Where the stimulus for an individual to headshake originates from a position distal to the coils, this should be effective in alleviating clinical signs associated with summation within the nerve. We suspect that prevention of transmission occurs because placement of the coils within the infraorbital canal results in pressure degeneration of the nerve. This is the case in rabbits subjected to balloon compression of the TgN (Brown et al. 1996). It is not possible however, to confirm our hypothesis without performing a necropsy examination some weeks post-surgery. We have not yet had the opportunity to do this. Without necropsy examination, it is also not known whether the presence of the coils has an effect on circulation in the blood vessels in the infraorbital canal. Due to variation in anatomy between individuals (Newton 2001), the interruption in nerve transmission may occur distal or proximal to the origin of the posterior nasal nerve branch. Without experimental neurophysiological studies and necropsy examination of both individuals in which surgery has been successful and those in which it has failed, it is not yet possible to determine the importance of preventing transmission from this nerve in alleviating headshaking. However, it is clear that, as most headshakers appear to have maxillary related signs, this approach would seem rational.

It is unclear when to expect pressure degeneration of the nerve to be complete and, therefore, at what time after surgery to test the results. Therefore, owners were advised to test the results by exposing the horse to the stimulus to which it normally headshakes at one month after surgery, or 2 weeks after nose-rubbing ceases should the horse develop that post-operative complication. If at that stage the surgery is unsuccessful repeating the test at

monthly intervals was recommended. Horses that continue to headshake beyond 3 months after the time of surgery or cessation of nose-rubbing were found not to show any further improvement.

The surgical technique continues to be refined and further validation is required in the future. Furthermore, repeat follow-up of the 24 horses is required in order to determine the longevity of success. Mair (1999) reported only 3 cases that had long-term success following infraorbital neurectomy, but a further 3 cases had short-term resolution of signs. Of these, clinical signs recurred 6–20 months after surgery. In the present study, because the surgical technique has only recently been developed, median follow-up time was 6 months, range 0.5–29 months. Therefore, recurrence of clinical signs in some of the horses classed as successes in this study is still possible. Recurrence of signs may be due to nerve regrowth or it may be that some individuals had not been exposed to their trigger factors in the time between surgery and follow-up.

This study defines success as being a substantial improvement, the criteria also chosen for previous studies (Mair 1999; Newton 2000; Madigan and Bell 2001). However, the ideal situation would be complete resolution and this should be considered in future studies. It is suggested that further refinement of surgical techniques is likely to be required to result in complete resolution of signs for a majority of horses.

Reasons for a lack of response to surgery are likely to include misdiagnosis, failure to target the nerve in a sufficiently proximal location or migration of the coils allowing a greater than desired conduction of impulses along the nerve to persist following surgery. Coil migration was detected in all horses in which a first surgery had failed, and some of these horses went on to have a successful outcome from a repeat of the procedure. However, horses in which surgery was successful have not been routinely radiographed post operatively. Therefore, it is possible that there is coil migration in these cases also and that it does not affect success. For this reason, routine post-operative radiographs are recommended to assess coil positioning in all future cases. However, radiography provides a 2-dimensional image only, with which it is impossible to determine that the entire lumen of the infraorbital canal is filled. For this reason, computed tomography of the head is probably the best assessment of coil positioning. This would aid in determining its relationship with outcome from surgery.

A possible cause of failure is that the stimulus to headshake might originate in the TgN in a more proximal location than the surgical site or within the ophthalmic or mandibular branches of the nerve. A majority of techniques in man target the nerve as it enters the brainstem (Weigel and Casey 2004). It is probable that a method of accessing the nerve at

or near its ganglion in the horse must be developed. We have not been able to access the nerve in such a proximal location due to the anatomy of the equine skull. However, a new technique of intracranial endoscopy to access the trigeminal nerve ganglion is being pioneered in man (Mourgela et al. 2007) and may allow access to the root entry zone and ganglion of the horse in the future.

The most frequent post-operative complication was self-trauma to the nose. This is the same situation as for infraorbital neurectomy (Mair et al. 1992; Mair 1999). Prevalence of this complication in the present study was 45.8% cases, lasting 3–150 days. This is similar to the situation in Mair's study (1999) where prevalence of this complication was at 84.2%, with signs lasting 21–56 days. It is likely that while the nerve is degenerating in response to pressure from the coils, an irritant stimulus is produced. Human patients that have had destructive surgery of the TgN for trigeminal neuralgia commonly report a burning, aching pain post operatively (Zakrzewska 2006) and this may be the stimulus for self-trauma in horses. Newton (2000) reported 5 cases of sclerosis of the posterior nasal nerve. This was effective in significantly reducing headshaking but only for 6 weeks to 9 months. However, none of these horses exhibited self-trauma. It may therefore be possible to avoid the side effect by performing sclerosis concurrently with coil compression. If the nerve was sclerosed at a site posterior to the position of the coils, then any irritant sensation during development of pressure necrosis may not be transmitted.

Veterinary clinical studies are often limited by small sample size, as in this study. Even within the small number of cases there are many confounding variables. Furthermore, retrospective studies are limited by reliance on the scope of clinical records. Telephone follow-up from owners and referring veterinary surgeons, who are not blinded to the severity of the horse's previous clinical signs, may result in an element of bias. Future studies should aim to follow a larger number of cases over a longer period. Ideally, determination of success should be based on a quantitative assessment of performance, such as winnings, although this is difficult to achieve in a pleasure horse population. A larger sample size of cases that had all undergone the same surgical technique would allow statistical analysis between outcome of surgery and findings from anamnesis and clinical investigations at presentation.

Despite the limitations of these data, this study suggests that a substantial improvement in clinical signs of headshaking can be expected following this procedure. Further refinement of the technique is required in order to achieve total resolution in more individuals, to reduce the number of cases requiring revision of the surgery, and to reduce the prevalence and severity of self-trauma post operatively.

Acknowledgements

The authors are grateful to The Horse Trust for funding the first and third authors' residencies. We are grateful to Bianca Schwarz and Sophie Mosseri for their help with data collection and to colleagues at The Philip Leverhulme Equine Hospital for their support and help. Our largest debt of gratitude is to the owners and referring veterinary surgeons of the horses in this study for their willingness to try a new technique, for their understanding that the outcome was unknown, and for keeping us fully informed of their horse's progress.

Manufacturers' addresses

1. Siemens Ltd, Milton Keynes, Buckinghamshire, UK.
2. Olympus Ltd, Southend-on-Sea, Essex, UK.
3. SATO Equine Treadmills, Uppsala, Sweden.
4. Boston Scientific Ltd, Hemel Hempstead, Hertfordshire, UK.
5. CMT Medical Technologies Ltd., Yoqneam Ilit, Israel.
6. Intervet U.K. Ltd, Walton, Milton Keynes, UK.
7. Fort Dodge Animal Health Ltd., Southampton, UK.
8. UCB Pharma Ltd, Slough, Berkshire, UK.
9. Arnolds Veterinary Products Ltd, Harlescott, Shropshire, UK.
10. Vetoquinol U.K. Ltd, Buckingham, UK.

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5.3 Paper Five

Caudal anaesthesia of the infraorbital nerve for diagnosis of idiopathic headshaking and caudal compression of the infraorbital nerve for its treatment, in 58 horses.

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Equine Veterinary Journal 2013 ISSN 0425-1644 DOI: 10.1111/j.2042-3306.2012.00553.x

Caudal anaesthesia of the infraorbital nerve for diagnosis of idiopathic headshaking and caudal compression of the infraorbital nerve for its treatment, in 58 horses.

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Summary

Reasons for performing study: Idiopathic headshaking is often a facial pain syndrome, but a diagnostic protocol has not been described. In a previous study, caudal compression of the infraorbital nerve for treatment offered a fair success rate, but low case numbers and short follow-up time were limitations.

Objectives: To describe a diagnostic protocol for headshaking, examining the role of bilateral local analgesia of the posterior ethmoidal nerve (PET block). To report longer-term follow-up after surgery of the original cases and further cases and to determine whether changes to the technique influence success rates and complications.

Methods: Records of horses that had undergone PET block and caudal compression surgery at 3 hospitals were reviewed. Modifications to the surgical technique included placing additional coils into the infraorbital canal and/or performing concurrent laser cautery of the nerve. Follow-up information was obtained by telephone contact with owners.

Results: The PET block was performed in 27 horses, with a positive result in 23 of 27 (85%). Surgery was performed in 58 horses. A successful outcome was initially achieved in 35 of 57 (63%) horses, but recurrence occurred between 9 and 30 months later in 9 (26%). Surgery was repeated in 10 of 31 (32%) horses. Final success rate, considering only

response to the last performed surgery, was 28 of 57 (49%) horses with median follow-up time of 18 months (range 2–66 months). Nose-rubbing was reported post operatively in 30 of 48 (63%) horses. This resolved in all but 4 horses, which were subjected to euthanasia. Response to PET block or change in surgical technique did not appear to influence outcome or complications.

Conclusions and potential relevance: The diagnostic protocol described is recommended for the investigation of headshakers. Caudal compression offers the best prognosis fora successful outcome compared with other treatments, for horses in which the only alternative is euthanasia. Surgical treatment of the disorder requires refinement, and the pathogenesis of the disorder requires investigation.

Keywords: horse; headshaking; trigeminal neuropathy; facial pain; nerve compression

Introduction

There is mounting evidence that in many horses, idiopathic headshaking is a facial pain syndrome, probably due to a trigeminal neuropathy [1–8]. Although the pathophysiology of the disease remains unknown, some progress has been made towards both diagnosing and treating the condition [1,3,4].

A diagnosis of idiopathic headshaking is supported when no defined aetiology can be found on clinical examination. Typically, examination includes clinical assessment and observation of behaviour, oral examination, ophthalmic examination, skull radiography and endoscopy of the upper respiratory tract, including guttural pouches. Examination may also include more advanced imaging modalities, such as computed tomography (CT) of the head or scintigraphy. A diagnosis of idiopathic headshaking may still be reached when a possible cause is detected, but when this is treated successfully there is no resolution of headshaking. In a study of 100 headshaking horses, Lane and Mair [9] found a putative primary cause in only 4 individuals. Following treatment of these abnormalities, headshaking signs were resolved in only 2 cases. In another report of 5 horses, fungal sinusitis was suspected to be the underlying cause for headshaking, but the mechanism was still considered to be via a trigeminal neuropathy [8]. Although it appears likely that the majority of idiopathic headshakers do suffer from a facial pain syndrome, any diagnosis reached by exclusion may be considered inconclusive. Indeed, the absence of a conclusive diagnostic test has been a major obstacle to the acceptance by clinicians, horse-owners and insurance companies that headshaking is often a facial pain syndrome.

Diagnostic local analgesia is a well-established and accepted method to localise the source of pain in equine orthopaedic examinations and can be used to aid in diagnosis of trigeminal neuropathic pain. Bilateral local analgesia of the rostral portion of the infraorbital nerve (at the infraorbital foramen), albeit simple to perform, did not appear useful for diagnosis [4]. Bilateral posterior ethmoidal nerve analgesia (PET block) proved more useful for diagnosis, with 13 of 17 (76%) horses showing a positive response [4]. In the present study, we reviewed results from PET block in further individuals and consider whether response to PET block can be used as a prognostic indicator for likely response to surgery (caudal compression of the infraorbital nerve).

The technique of caudal compression of the infraorbital nerve using intravascular coils for the treatment of idiopathic headshaking was first described in 2009 [1]. With a median time to follow-up of 6 months, 13 of 22 (59.0%) horses were considered by their owners to be significantly improved following a single surgery. Low patient numbers and short median follow-up time were major limitations of that first study. The present updated study reports longer-term follow-up of the original horses and 36 further cases.

Materials and methods

The clinical records of horses that had undergone caudal compression of the infraorbital nerve at 3 referral hospitals (The Philip Leverhulme Equine Hospital, University of Liverpool; The Royal Veterinary College; and Specialistdjursjukhuset Häst Strömsholm) between June 2004 and January 2011 were reviewed.

Historical data recorded included the situation in which the horse showed signs consistent with the syndrome (in the stable, at pasture, on the lunge and ridden). Where horses had a history of headshaking of more than 12 months' duration, seasonality of signs was defined as either seasonal or nonseasonal.

Comprehensive investigations to determine the cause of headshaking were carried out at the referral hospitals or by referring veterinary surgeons. This included a general clinical examination, dental examination and ophthalmic examination. The skull was imaged either through CT or radiography at exposures suitable for viewing the roots of the cheek teeth and sinuses. Endoscopy of the upper respiratory tract and guttural pouches was performed routinely.

The majority of horses were observed to headshake during hospitalisation. A small number had only been observed to headshake by the referring veterinary surgeon, and the owners had recorded video footage. Once horses were seen to headshake consistently, bilateral

PET block was performed on all horses, unless precluded on the grounds of temperament. These horses were then reassessed in the same conditions.

A bilateral PET block was performed following the technique described by Newton et a!. [4] (Figs 1, 2), but with the addition of mild sedative premedication with xylazine (Virbaxyl 10%)[a] (0.2–0.5 mg/kg bwt i.v.) to facilitate the procedure. Bilateral 3 - 4 cm areas ventral to the zygomatic arch were clipped and aseptically prepared. Mepivacaine (Intra-epicaine 2.0%)[b] (0.5 ml) was injected subcutaneously either below the transverse facial artery or between this artery and the zygomatic arch, depending on individual anatomical variation in the location of the facial artery. A 70 mm x 0.9 mm spinal needle was inserted in a rostroventral direction towards the upper sixth cheek tooth. The stylette was then removed and 5 ml mepivacaine injected and the needle withdrawn. Effects on headshaking were assessed once signs of sedation had resolved at 30 min, and then at 1 and 1.5 h.

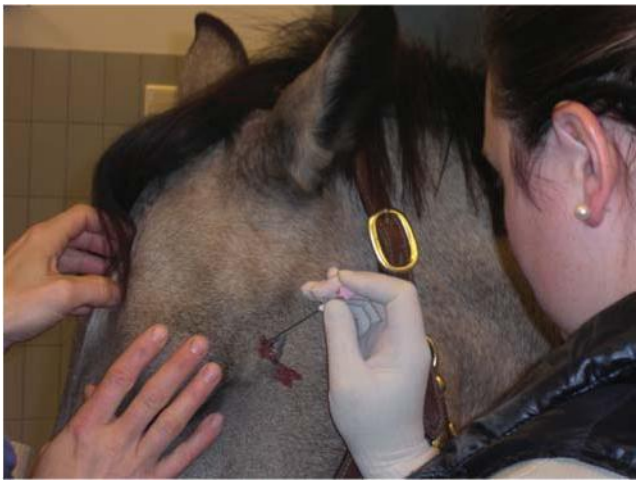

Figure 1: Technique for caudal anaesthesia of the infraorbital nerve.

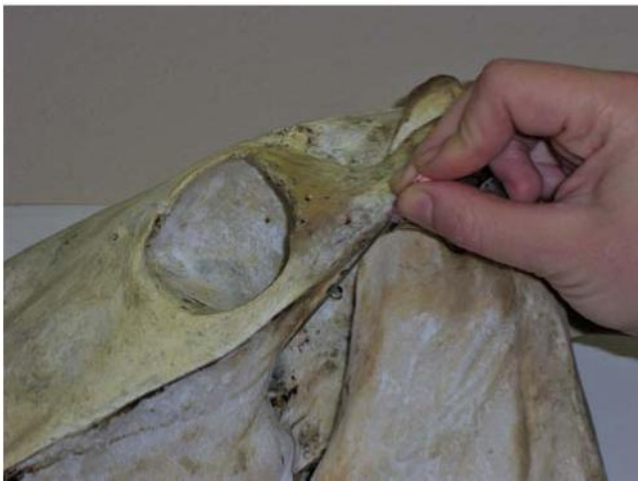

Figure 2: Landmarks for caudal anaesthesia of the infraorbital nerve.

Surgery was performed in these horses, which were all diagnosed with a trigeminal nerve facial pain syndrome by a positive response to bilateral PET block without other mitigating pathological findings, or with idiopathic headshaking diagnosed by exclusion. Cases had previously undergone conservative treatments, such as use of a nose net, which were unsuccessful, and euthanasia was the only other option under consideration by the owners for these horses.

The surgical technique as described by Roberts et al [1] was used, which involved the placement, under fluoroscopic guidance, of platinum embolisation coils[c] (40 mm x 6 mm platinum embolisation coil) within the caudal portion of the infraorbital canal via the maxillary foramen in order to compress the nerve. In an attempt to improve outcome, a few modifications were applied to this technique in later cases. These involved increasing the number of coils deposited within the canal and the use of laser cauterisation of the nerve. For the latter modification, following insertion of the coils a diode laser fibre was introduced into the canal via an empty stylette, until the tip of the laser could be imaged just beyond the end of the stylette. The laser was activated for 2 periods of 0.1 s, at 25 W. Peri- and post-operative management was as described by Roberts et al [1].

Details of any post-operative complications were recorded. Follow-up information was obtained by telephone interview with the owner. As previously [1], the outcome of surgery was classified as successful if the horse was considered by the owner to be significantly improved. Most horses could not safely be ridden prior to surgery, and for these, outcome was classed as successful if they were back in ridden work.

Results

Fifty-eight horses met the selection criteria (34 at the University of Liverpool, 7 at The Royal Veterinary College and 17 at Specialistdjursjukhuset Häst Strömsholm). There were 16 mares (28%) and 42 geldings (72%), with the most frequently represented breeds being Warmbloods (19 of 58; 33%) and Thoroughbred or Thoroughbred crosses (13 of 53; 22%). The most common use was general riding (21 of 58; 36%) followed by dressage (13 of 58; 22%). Median age at first presentation was 9 years; range 1–17 years.

All horses were reported to have shown headshaking when at exercise, with 33 of 48 (69%) also showing signs at rest. Headshaking was known to be seasonal (spring and/or summer) in 16 of 48 (33%) horses. The PET block was performed in 27 cases, with a positive result in 23 of 27 (85%). In the 4 horses in which there was a negative response to PET block,

findings from the other investigations were consistent with idiopathic headshaking, as for those where PET block could not be performed.

In the majority of horses (38 of 51; 75%) for which it was recorded, up to and including 4 coils were placed into each infraorbital canal at the first surgery. There were 13 of 51(25%) horses in which between 5 and 8 coils were placed. Laser was used as an adjunct in 27 of 58(47%) of first surgeries.

Following first surgery, 30 of 48 (63%) horses were reported by their owners to have shown nose-rubbing, which resulted in significant self-trauma, and 4 owners reported increased severity of headshaking signs following surgery. This complication was observed to start between 2 and 5 days after surgery. Administration of acepromazine (0.15 mg/kg bwt per os every 12–24 h) and/or gabapentin (2.5 mg/kg bwt per os every 12 h) was reported by some owners to reduce signs. In most cases, owners reported the complication to have resolved gradually by 4 weeks following surgery. There were, however, 4 horses that required euthanasia, between 2 and 5 months after surgery, owing to non-resolution and/or severity of this complication.

A successful outcome from the first surgery was achieved in 35 of 57 (63%) horses, with one being excluded from analysis owing to being rested from work for other problems. However, signs of headshaking then recurred in 9 of these 35 (26%). The median length of time until relapse of the condition was 9 months (range 2–60 months). Of the horses that relapsed, 4 were known to have seasonal headshaking. Median time to relapse for these horses was 10.5 months (range 9–30 months).

Surgery was repeated in 10 of 31 (32%) horses where the first surgical procedure had failed or the condition had recurred. There was a successful outcome in 5 of 8(63%) of these, with 2 being excluded because of being out of work due to other problems or being lost to follow-up. Of these 5, however, recurrence occurred in 3 individuals, of which 2 were known to have seasonal headshaking. Median time to relapse was 12 months (range 10–24 months). Surgery was performed for a third time in one seasonally affected individual, with signs recurring again at 12 months following the procedure.

Final success rate, considering only response to the last performed surgery, was 28 of 57 (49%) horses. Median follow-up time from the last performed surgery was 18 months (range 2–66 months). The PET block had been performed in 27 cases, with a positive result in 23. These cases were fairly evenly split between surgical success (11 of 23, 3 of 4 respectively) and surgical failure (12 of 23, 1 of 4 respectively).

Final success and failure were approximately evenly divided between horses that had up to and including 4 coils placed in each side at the first surgery (20 of 38, 53% success; 18 of 38, 47% failure) and those which had between 4 and 8 coils per side placed at the first surgery (7 of 13, 54% success; 6 of 13, 46% failure). Final success and failure also appeared evenly divided between horses that had only coils placed and those where laser was used as an adjunct. Of 25 horses where it was known that only coils were placed, 15 of 25 (60%) were successful, whereas when laser was used as an adjunct 15 of 31 (48%) cases were successful. Nose-rubbing postoperatively was recorded to have occurred in 14 of 25 (56%) horses where only coils had been placed, and in 14 of 21 (67%) horses where laser was used.

Discussion

The rationale behind current therapies for headshaking is to limit input from the trigeminal nerve (TgN) or to reduce brainstem response to TgN input. Reported medical therapies include administration of cyproheptadine and/or carbemazepine, but results have been variable and short lived [4,5]. Nose nets have been reported to provide up to 70% relief, but only in 25% of cases [6]. Response to medical/conservative therapy is poor in most horses. This was the case for all the horses in this study, leaving no options other than trying surgery or electing for euthanasia.

The first reported surgery for idiopathic headshaking was bilateral infraorbital neurectomy, performed rostral to the infraorbital foramina [3,10], with a success rate of3 of 19(15.8%). Failure of this technique may be expected if the stimulus to headshake originates within the trigeminal nerve branches in a more proximal site. Bilateral caudal nasal nerve sclerosis resulted in a 90–100% resolution of clinical signs in 5 of 5 horses [4], supporting a stimulus originating further distally, although the benefit was short lived. Caudal compression of the infraorbital nerve is currently the only surgical treatment for idiopathic headshaking that appears to result in a fair long-term success rate.

Interpretation of the success rate is reliant upon the correct diagnosis. Horses were diagnosed either with idiopathic headshaking by exclusion, or with facial pain syndrome through use of a PET block. The PET block was used alongside a diagnosis by exclusion so that a positive response to local analgesia could be attributed to a trigeminal neuropathy rather than facial pain from other pathology. However, a diagnosis by exclusion may be considered unsatisfactory. Furthermore, the reliability and exact site of action of the PET block have not yet been established; it is likely that it is, in fact, the infraorbital nerve as it enters the maxillary foramen and its caudal nasal branch that are affected by the deposition

of local anaesthetic in this position. Some individuals with a negative response to PET block had a successful outcome from surgery. A successful outcome from surgery can be considered to confirm the diagnosis, so it is clear that the PET block is useful for diagnosis, but not conclusive. This is the case for all diagnostic local analgesia, where a false negative may be obtained in a number of situations, including misplacing the anaesthetic and in chronic or severe pain [11]. Accordingly, a positive response to PET block could not be used as a prognostic indicator for response to surgery. However, in the majority of cases, PET block was positive. It is, therefore, considered by the authors to be good practice to use the PET block in the investigation of headshakers, where headshaking signs are consistent and the horse is amenable to the procedure, as the most objective available measure of facial pain.

The mechanism of action of caudal compression of the infraorbital nerve is unknown. Likewise, detailed understanding of the role of the caudal nasal nerve, a branch of the maxillary nerve from the trigeminal nerve, in the condition remains unclear. This nerve is responsible for most of the sensory innervation of the caudal nasal cavity and the paranasal sinuses, and its involvement in headshaking would seem to fit the observations, especially in horses that appear to have an inhaled trigger factor. Anatomical variation suggests that in some 30% of horses the site of coil deployment, as in the current technique, would be rostral to the origin of the caudal nasal nerve from the maxillary nerve (personal communication, J. D. Perkins), and this could be a potential cause for failure. Logically, we would suspect that the degree of compression inflicted on the nerve would be greater if more coils were used, and greater nerve damage might result if laser cautery was used, and we would therefore speculate that these modifications might increase successful outcomes. Percutaneous balloon compression of the trigeminal nerve at the level of the trigeminal ganglion against bone is a similar procedure used for the treatment of trigeminal neuralgia in man, and in these cases success is correlated to the severity of nerve damage [12]. However, this has not been replicated in our procedure. Where horses either did not respond to the first procedure or relapsed, some benefited from a repeat procedure. In the majority of these cases, this ultimately resulted in 8 platinum coils being present within each infraorbital canal. However, despite this repeat procedure sometimes producing a positive result, there was no greater success rate obtained at the first procedure if a greater number of coils were implanted initially. This would suggest that the mechanism of action of the surgery may simply be the nerve damage arising from performing the procedure, rather than the number of coils that were used. Histopathology or electron microscopy of the infraorbital nerve following coil placement, both in horses which had a successful and in those with an

unsuccessful outcome, is required to improve understanding of the mechanism of action of this procedure.

Post-operative nose-rubbing with possible self-trauma and increased severity of headshaking was reported in 63% of horses, a slightly lower incidence than reported following bilateral infraorbital neurectomy (84%) [3,10]. There appeared to be no proportional risk from the number of coils placed or the use of laser on this side effect, but case numbers are insufficient for statistical analysis. Following surgical techniques for treatment of trigeminal neuralgia, some human patients report a burning ‘pins and needles’ (neuropraxia) sensation in the face, and it is possible that these horses are experiencing a similar sensation. Although in most cases these unpleasant side effects were short lived, 4 horses had to be subjected to euthanasia owing to their severity and/or nonresolution. It is for this reason that the authors advocate that caudal compression of the infraorbital nerve should only be used as a treatment for headshaking in cases after conservative treatments have failed and where the only alternative is euthanasia.

Caudal compression of the infraorbital nerve resulted in an initial success rate of 63%. As in the previous study [1], the assessment of success is based on a subjective owner opinion, which required the horse to be significantly improved and not necessarily completely free of clinical signs. About one-quarter of cases showing an initial improvement may be expected to relapse based on our results. It is relevant to consider the effect of seasonal headshaking on these figures, which may influence apparent amelioration of the signs if coincidental with surgery. Distinguishing between a case where surgery did not alter signs, which then returned seasonally, and one where there was initial improvement followed by relapse after some months could prove challenging. Although this may have been the case in some individuals, the long follow-up period, including those where the time taken to relapse was up to 30 months following the procedure, suggests that misinterpretation of the outcome due to seasonal effects was not likely in most cases. The cause for relapse of clinical signs is unknown, but our outcomes are remarkably similar to those reported after percutaneous balloon compression for trigeminal neuralgia in humans, where 15–22% relapsed at 3 years [13,14].

In conclusion, caudal compression of the infraorbital nerve currently appears to be the best available treatment for idiopathic headshaking due to trigeminal neuropathy in horses for which the only alternative is euthanasia. The surgical treatment of the disease clearly requires refinement and improvement. However, even in human trigeminal neuralgia there is no universally effective, minimally invasive surgical treatment that immediately and

completely relieves signs with consistent long-term results and without side effects [15]. It is imperative that we continue to investigate the aetiopathogenesis of this pain syndrome in order to develop improved medical and surgical therapies. Headshaking remains a significant cause of distress for some horses, which justifies the application of this treatment in selected cases even though the failure rate is finite.

Authors' declaration of interests

No conflicts of interest have been declared.

Source of funding

No external funding was received for this study.

Acknowledgements

The authors would like to thank Nina Stein for data collection in Sweden.

Manufacturers' addresses

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[b]Dechra Veterinary Products Ltd, Shrewsbury, Shropshire, UK.

[c]Boston Scientific Ltd, Hemel Hempstead, Hertfordshire, UK.

[d]Sedalin 35 mg/ml oral gel; Vetoquinol UK Ltd, Great Slade, Buckingham, UK.

[e]Gabapentin capsules 400 mg; Actavis, Barnstaple, Devon, UK.

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Chapter 6: Treatment

Development of percutaneous electrical nerve stimulation as a neuromodulatory treatment in horses

6.1 Candidate contribution for Papers Six and Seven

The concept of Paper Six was shared equally between the first and second authors. All authors contributed equally to study design. I obtained ethical permission and funding from the Langford Trust for Animal Health and Welfare. Execution of the study was mostly by myself with contribution by the last author, as was data analysis. Preparation of the manuscript was largely by myself, with all authors inputting into and approving the final version.

For Paper Seven, the concept was mine. I made the most contribution to study design, with input from the second and last authors. I sourced ethical permission. I secured an Inspire (Academy of Medical Sciences and the Wellcome Trust) studentship award to support this project, whilst introducing a veterinary undergraduate to basic research concepts. Study execution was by myself and all members of the EquiPENS™ Group in their respective institutions. Data analysis was by the second author with my contribution. I prepared the manuscript with input from some members of the EquiPENS™ Group and the final version was approved by all authors.

6.2 Paper Six

Neuromodulation using percutaneous electrical nerve stimulation for the management of trigeminal-mediated headshaking: A safe procedure resulting in medium-term remission in five of seven horses.

Roberts V.L.H., Patel N.K., Tremaine W.H.

Equine Veterinary Journal 2016 ISSN 0425-1644 DOI: 10.1111/evj.12394

Award: most clinically relevant paper in that issue by Equine Veterinary Journal.

Neuromodulation using percutaneous electrical nerve stimulation for the management of trigeminal-mediated headshaking: A safe procedure resulting in medium-term remission in five of seven horses.

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Summary

Reasons for performing study: There are no consistently safe and effective methods for the treatment of trigeminal-mediated headshaking in horses. In affected horses, the trigeminal nerve is sensitised, appearing to result in neuropathic pain. Percutaneous electrical nerve stimulation (PENS) therapy is a minimally invasive neuromodulatory treatment used in people to manage neuropathic pain.

Objectives: To determine whether PENS therapy is safe, tolerated and effective for the management of trigeminal-mediated headshaking in horses. Study design: Descriptive case series.

Methods: Seven horses diagnosed with trigeminal-mediated headshaking and currently showing clinical signs were studied. All procedures were carried out in sedated horses with a needle-prick sized area of skin desensitised with local anaesthetic to facilitate probe insertion. A disposable PENS probe was advanced subcutaneously adjacent to the nerve, rostral to the infraorbital foramen under ultrasonographic guidance. The nerve was stimulated for 25 min following a protocol of alternating frequencies and a perception threshold based on human clinical data. The probe was removed and the procedure repeated on the contralateral side. The protocol used comprised a series of 3 or 4 treatments, with treatments being repeated when signs of headshaking recurred.

Results: All horses tolerated the procedure well. Three horses developed a haematoma at the site on one occasion and 2 had increased clinical signs for up to 3 days following first treatment. Six horses demonstrated a positive response to their first treatment, returning to ridden work at the same level as prior to onset of headshaking, with 5 continuing to respond. Median remission time for first treatment was 3.8 days (range 0–8 days, n = 7), second treatment 2.5 weeks (0–8 weeks, n = 7), third treatment 15.5 weeks (0–24 weeks, n = 5) and fourth treatment 20 weeks (12–28 weeks ongoing, n = 2).

Conclusions: Percutaneous electrical nerve stimulation therapy is a safe, well tolerated, minimally invasive, repeatable management option for trigeminal-mediated headshaking, with encouraging efficacy for amelioration of clinical signs in the short- to medium term.

Keywords: horse; headshaking; trigeminal-mediated; neuromodulation; percutaneous electrical nerve stimulation PENS

Introduction

At present, there are no consistently safe and effective methods for the treatment of trigeminal-mediated headshaking in horses. Treatments include the use of a nose-net which improves clinical signs by 70% or greater in one-third of horses [1], medication including carbamazepine and cyproheptadine [2–4] that has inconsistent results and is associated with high cost, possible side effects of drowsiness and governing sport federation prohibition, and surgical treatment by compression of the infraorbital nerve using platinum coils which has been reported to have an approximate 50% success rate [5]. Side effects sufficiently severe as to result in euthanasia occurred in 4 of 58 horses and thus this procedure is recommended only in cases where euthanasia is the only alternative [5].

Advance in treatment for trigeminal-mediated headshaking is undoubtedly hampered by our incomplete understanding of the aetiopathogenesis of headshaking. However, somatosensory-evoked potentials have demonstrated the trigeminal nerve of affected horses has a reduced threshold for activation [6]. This sensitisation appears to result in neuropathic pain.

Percutaneous electrical nerve stimulation (PENS) therapy[a] is a repeatable, minimally invasive neuromodulatory therapy which may be used under National Institute for Health and Care Excellence (NICE) guidelines [7] for the management of neuropathic pain in people. A disposable probe is placed subcutaneously perineurally and a previously derived protocol of electrostimulation is applied with the aim to decrease the sensitivity of the target nerve [8]. Side effects reported include temporary bruising at the site of probe insertion and a few individuals reported a slight increase in pain in the short term, although may still go on to experience relief from pain [7]. The NICE guidelines advise that the procedure is repeated when symptoms resume. Anecdotally, the desensitisation following the initial procedure may last from a few hours to several days and, after the second treatment, remission may last a few days up to 2 weeks and remission following the third treatment may last about 3 months. The duration of remission following the third treatment is usually the maximum attained and is likely to remain consistent following further treatments. The use of PENS therapy in

human trigeminal neuropathic facial pain has been predominantly for patients suffering neuropathic pain secondary to radical surgery and/or radiotherapy for cancers of the head and neck. In a small study of 8 such patients with refractory neuropathic trigeminal pain [9], 7/8 patients reported significant pain relief immediately after treatment. The minimum duration of pain relief was 14 days and the maximum was ongoing at 175 days at the time of follow-up. Treatments were repeated when pain returned, with the procedure being well tolerated. In another randomised, double-blind, sham-controlled crossover study of 31 patients with surface hyperalgesia, median numerical rating scale for neuropathic pain changed from 7.5/10 before treatment to 0.5/10 with a follow-up time of one week [10].

Our hypothesis was that minimally invasive neuromodulation using PENS therapy of the maxillary branch of the trigeminal nerve may be a safe, well tolerated, repeatable therapy to manage neuropathic pain in trigeminal-mediated headshakers in the short- to medium term.

Materials and methods

Horses

Eligible cases were trigeminal-mediated headshakers referred to the University of Bristol's Langford Veterinary Services Equine Centre between August 2013 and August 2014. Horses included were displaying clinical signs at the time of first treatment and did not, or were not known to, show complete seasonal remission. In all cases, the diagnosis of trigeminal-mediated headshaking was made following a standard diagnostic protocol that included history, observation, clinical examination, diagnostic local anaesthesia around the caudal portion of the infraorbital branch of the maxillary nerve in the pterygopalatine fossa, computed tomography of the head, oral examination, ophthalmic examination and endoscopy of the upper respiratory tract including guttural pouches. The severity of headshaking was graded following a 0–3 point scale, with 0 being asymptomatic, 1 described as headshaking only at exercise and sufficiently mild that the horse may be ridden, 2 being headshaking at exercise to a severity as to make ridden exercise unsafe or impossible and 3 being headshaking at rest as well as at exercise [11]. They could have previously received, but responded insufficiently to, other treatments for headshaking but horses which had undergone coil compression surgery would be unsuitable candidates for neurostimulation due to the presence of implants. Where horses had received other treatment, a minimum one-month washout period was applied before starting treatment.

Procedure

Following placement of an i.v. jugular catheter, horses were restrained in stocks. Sedation was with i.v. detomidine hydrochloride (Domidine)[b] at a loading dose of 10 mg/kg bwt and was maintained by i.v. infusion at 0.025 mg/kg bwt/h. Two 5 x 5 cm squares were clipped over the infraorbital foraminae and a 10 x 10 cm square over the shoulder area for the grounding pad[a]. On each side, 2 cm caudo-dorsal to each infraorbital foramen, 0.25 ml of 2% mepivacaine hydrochloride (Intra-epicaine)[b] was injected subcutaneously using a 0.64 x 25 mm needle in order to facilitate probe placement. The small volume was used to reduce the risk of anaesthetising the infraorbital nerve. The skin in this anaesthetised region was perforated with a 1.6 x 38.1 mm hypodermic needle. A disposable 50 x 0.75 mm electrically conductive PENS therapy probe[a] was inserted percutaneously through the incision in a diagonal rostro-ventral direction (Figure 1). Ultrasonographic[c] guidance was used to direct the probe approximately 1 mm superficial to the infraorbital nerve. The NeuroStimulator PENS therapy device[a] was connected to the grounding pad and probe. After a standard test stimulation (to check equipment function and tolerance of the horse), the nerve was stimulated at 2 and 100 Hz alternating every 3s for a period of 25 min at voltages ranging from 0.2 to 2.7 volts (V). The device is voltage-controlled with the current delivered varying in line with potentially varying impedances encountered (such as distance of placement from the nerve fibres) and being set by the patient's response of twitching of the facial muscles within their tolerance level for the procedure. A video is available as supplementary online to this paper. Treatment prescribes that the current perception level be maintained throughout the procedure by increasing or decreasing the voltage. The stimulation was started at 0.2 V and gradually increased in 0.1 V increments (at both frequencies) to a voltage sufficient to stimulate this twitching of the facial muscles but within the tolerance level of the individual horse. As time elapsed during each procedure, the maximum voltage tolerated could usually be increased to maintain the same effect. The procedure was then repeated on the contralateral side. Horses were able to be discharged from the hospital on recovery from sedation and owners were advised to return them to normal management and ridden work from the following day and to report back on their progress. Procedures were repeated as soon as possible following the return of signs of neuropathic pain.

Figure 1: Horse with PENS probe in situ during electrostimulation.

Results

Seven horses were recruited to the trial. Details are in Table One.

HORSE	**AGE** (at first presentation, years)	**BREED**	**SEX** (Mare/ Gelding/Stallion)	**INTENDED USE**	**GRADE OF HEADSHAKING /3 AT ENROLLMENT**	**SEASONALITY OF SIGNS**
1	7	Thoroughbred	G	Point-to-point racing	3	Improves to grade 2/3 in Winter
2	14	Irish Sports Horse	G	Riding club activities	3	Improves a little in Summer but remains grade 3/3
3	4	Thoroughbred	M	Riding club activities	2	Not known
4	11	Cob	G	Riding club activities	3	None
5	6	Polish Warmblood	G	Riding club acitivities	3	Not known
6	11	Irish Draught cross	G	Riding club activities	2	None
7	5	Pony	M	Eventing	2	Not known

Table 1: details of horses used in the study.

All horses were displaying clinical signs at the time of enrolment on the trial. Severity of headshaking was graded at least as 2/3. One horse (Horse 1) was reported to have a history of showing milder clinical signs through the winter months and one (Horse 2) milder signs through the summer months although, even during periods of improvement, they remained significantly affected with their signs then graded 2/3 and 3/3, respectively. For 3 horses, seasonal variation in signs was unknown, having presented with clinical signs of fewer than 6 months' duration. Most horses had previously received and responded insufficiently to one or more recognised treatments for headshaking but none had undergone coil compression and no other treatments had been used for at least one month prior to neurostimulation.

A total of 24 bilateral procedures were carried out on the 7 horses over the study period (August 2013 to August 2014). Further details of the individual procedures are recorded in Table 2. The stimulation resulted in facial muscle twitching throughout the procedure on all treatments bar one (Horse 2, second treatment). In that horse the procedure did not result in remission of clinical signs, although the 3 other procedures which did cause twitching in the same horse were associated with remission.

HORSE	Duration of remission (0/3 or 1/3) from 1st treatment	Duration of remission (0/3 or 1/3) from 2nd treatment	Duration of remission (0/3 or 1/3) from 3rd treatment	Duration of remission (0/3 or 1/3) from 4th treatment	Adverse effects / comments
1	3 days	6 weeks. Returned to training 48h after treatment.	Still in remission at 4 months when pasture rested due to other problems	N/A	Haematoma at first treatment. Slight increase in clinical signs for 2 days following this treatment
2	4 days	None	2 months	Ongoing at 7 months	No twitching induced by 2nd treatment
3	8 days	4.5 weeks	3.5 months with a gradual return of clinical signs	In remission at 12 weeks when rested due to orthopaedic injury	Slight increase in clinical signs for 3 days after 1st treatment. Haematoma at 2nd treatment.
4	12 days	Still in remission at 8 weeks when rested due to fracture	N/A	N/A	Returned for treatment 30/05/14 and 05/06/14. Remission ongoing at 5 weeks
5	3 days	2.5 weeks	Ongoing at 6 months	N/A	
6	0/3 for 3 days	None	None	N/A	Haematoma at 1st treatment
7	None	None	None	N/A	

Table 2: Details of procedures and responses.

All horses tolerated the procedure well. Three horses developed a haematoma at the site on one occasion and 2 showed a slight increase in clinical signs for up to 3 days following first treatment.

Owners reported on their horse's progress with data provided being whether or not the horse was back in ridden work at the level prior to onset of headshaking, the presence and severity of any signs when ridden and at rest and, where applicable, a competition record. The criterion for success was a return to ridden work at the level prior to the onset of headshaking. Details are recorded in Table 2. Videos are available as online supplementary information to this paper, of Horse 6 before and 3 days after his first treatment and Horse 5 before starting treatment, 10 days and 15 weeks after the third treatment.

Six horses showed remission of clinical signs after the first treatment, returning to ridden work at their previous level, with 5 continuing to respond to further treatments. Median remission time for first treatment was 3.8 days (range 0–8 days, n = 7), second treatment 2.5 weeks (0–8 weeks, n = 7), third treatment 15.5 weeks (0–24 weeks, n = 5) and fourth treatment 20 weeks (12–28 weeks n = 2) with one of these horses still being in remission at the time of follow-up.

Horse 1 returned to race training but following a severe respiratory tract infection 4 months after his third treatment he was pasture-rested until the next point-to-point season so has yet to be returned to work and be fully assessed, as the criterion for success for this study was return to ridden work. For the purpose of this study, his remission time has been recorded as 4 months. However, it was reported that while the presence of clinical signs at exercise could no longer be tested, this horse remained free of clinical signs when in the field at follow-up 7 months following his third treatment; a time of year when he displayed clinical signs pre-treatment during turnout.

Horse 3 sustained an orthopaedic injury 12 weeks following the fourth treatment, at which time she was still in remission. Again, as the criterion for success was return to ridden work, for the purposes of this study remission time was recorded as 12 weeks. During periods of remission, the owner reported this horse to be grade 0/3 or grade 1/3 for the majority of the time but she had occasional days at 3/3 and benefited from the use of a nose-net.

Horse 4 showed total remission following 2 treatments and was still free of clinical signs of headshaking 8 weeks after the second treatment at which point he was box-rested due to an orthopaedic injury. It was deemed not possible to assess him comparatively thereafter. Four months after the injury, he returned to turnout and work at which time signs of headshaking returned. This horse re-started the treatment course with the first and second treatments being administered 6 days apart. While we can report his response to be ongoing remission at 5 weeks, we have excluded results from this second treatment course in our descriptive statistics. Horse 6 showed a period of total remission following the first treatment but then failed to respond to the second or third treatments. Horse 7 did not respond to any of the 3 treatments.

Discussion

There is a strong clinical need for a safe, effective and sustainable treatment for trigeminal-mediated headshaking. These results suggest that PENS is safe and effective and can achieve medium-term control of clinical signs in some cases, even if a permanent cure remains elusive.

With current therapies for headshaking, medium- to long-term prognosis for horses to continue as athletes is guarded [12]. The results from this pilot study are very encouraging especially if they are reproduced when used in a greater number of cases. Successful control of trigeminal neuropathic pain in people is likely to vary depending on the cause of that pain [7]. It is important therefore to have accurately diagnosed trigeminal-mediated

headshaking before prescribing PENS therapy and to select patients carefully for recruitment to PENS. The best diagnostic investigation for case selection would include a diagnosis of sensitisation using somatosensory-evoked potentials as this therapy is applicable mainly to sensitised peripheral nerves, although the practical feasibility of this is limited as it requires general anaesthesia [12]. A key feature of diagnosis in the cases in this study was response to diagnostic local anaesthesia around the region of the caudal portion of the infraorbital nerve. Treatment is directed rostrally to this, which may confound efficacy, although where twitching is induced one may assume the nerve stimulation impulse has travelled the length of the nerve.

As is the case with human patients, we have been unable to achieve a 100% success rate. Further knowledge about the aetiopathogenesis of trigeminal-mediated headshaking and the mechanism of action of neurostimulation would help us to better understand what makes a treatment successful and why one has failed, which is perhaps of particular interest in those cases where response has been inconsistent. There are many limitations to merely transferring a treatment and protocol used in people directly to horses and further knowledge of both trigeminal-mediated headshaking, how that compares with human neuropathic facial pain syndromes and the mechanism of action of PENS neurostimulation could allow for a more targeted approach. There is an important role in further work to not only expand numbers but to refine the treatment protocol specifically for treatment of headshaking syndrome in horses; alternation and strength of voltage and frequency, duration of stimulation and interval between treatments.

National Institute for Health and Care guidelines [7] state that better results can be expected as the operator's experience in probe placement increases. Subjectively, we found the number of attempts required to place the probe in the correct position as judged by ultrasonography, markedly decreased through the study. It appears important for the stimulation to result in twitching, which is interpreted as evidence of appropriate nerve stimulation by our experiences gained during the study. Hence it is probable that the therapy will be more successful when performed by an experienced operator.

In addition to its efficacy, there are other factors upon which the success of this treatment is measured. Our criterion for a successful outcome is to enable the horse to return to ridden exercise at the same level at which it was ridden prior to the onset of headshaking [5]. Remission of signs to allow ridden work requires remission to grade 0/3 or grade 1/3. However, some disciplines such as dressage would require remission to grade 0. None of

the horses in this study were used for affiliated level dressage and this would be a greater test of success.

There must also be a practical duration of treatment benefit for a management intervention to be useful. We consider owner compliance to be unlikely if the duration of remission of clinical signs after the primary course of 3 treatments is less than 2 months. In human medicine, where there is good response to PENS, patients may be considered for permanently implanted devices [7]. While this may be technically feasible in horses, it is unlikely to be a practical option financially or in horses competing under the rules of sport governing bodies (e.g. Fédération Equestre Internationalé) so permanent implants are unlikely to have a future in competition horses, although leisure horses may have this possibility.

The owners' interpretation of successful treatment of headshaking syndrome is affected by the placebo effect [13]. We have reduced this risk in this study by applying an objective criterion of success, that being a return to ridden work in cases which were unsafe or impossible to ride previously [11], rather than a subjective assessment of an improvement of signs [13]. On 3 occasions in our study, owners judged PENS therapy to have been ineffective but had with previous or later treatments been able to return the horses to ridden work again. The ability of these owners to differentiate between successful and unsuccessful procedures acts as a type of internal control for the placebo effect. As used by Raphael et al. [10], a double-blinded sham-controlled crossover study of the efficacy of PENS neurostimulation would have much improved the merit of this study but was not practical at this early stage.

A better attempt to quantify partial success of modification of signs might be useful in the future, to critically evaluate this and other therapies. The incomplete follow-up in some cases due to unrelated conditions and the inclusion of 3 cases where a history of seasonality was unknown may compromise our data. There is a risk that in the 3 horses with unknown seasonality there is an effect of season in the length of time of their remission; however, not in the fact each treatment resulted in initial remission as all horses were symptomatic at the time of the treatment. We will continue to collect data on all the horses in this study.

The safety of the procedure is important, particularly in light of the morbidity of alternative treatments. For example, coil compression treatment, while effective in approximately 50% of cases, carries a serious risk of potentially fatal side effects [5]. None of the horses in this study experienced significant adverse effects, a finding we expected and is consistent with the PENS data in man [7]. The protocol for success indicates that the procedure must be

repeated, initially frequently and therefore it is important that it is well tolerated by a conscious horse. The procedure was tolerated well under standing sedation by all the horses in the study and anecdotally human patients report the procedure to give a pleasant sensation. However, we advise careful probe placement under ultrasonographic guidance as penetration of the nerve by a probe could result in an extreme reaction.

Although it is clear that further work is required, including expanding the number of cases and refining treatment protocols, it is our opinion that, at present, PENS therapy should be considered as a first-line treatment for trigeminal-mediated headshakers which have failed to respond to conservative treatment such as nose-nets, at equine treatment centres with appropriate facilities and expertise.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

Informed consent was obtained from horse-owners and, where appropriate, from the insurers of individual animals. The study received University of Bristol ethics approval, registered with Veterinary Investigation Number 13/022.

Source of funding

We are grateful to The Langford Trust for Animal Health and Welfare for funding this study.

Authorship

The 3 authors contributed equally to study design. Execution was 75% V.L.H. Roberts and 25% W.H. Tremaine. Data analysis was 75% V.L.H. Roberts and 25% W.H. Tremaine. Preparation of the manuscript was 70% V.L.H. Roberts, 10% N.K. Patel and 20% W.H. Tremaine and all approved the final version.

Manufacturers' addresses

a. Algotec Research and Development Ltd, Crawley, West Sussex, UK.
b. Dechra Ltd, Stoke-on-Trent, Staffordshire, UK.
c. BCF Technology Ltd, Bellshill, Scotland, UK.

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6.3 Paper Seven

Safety and efficacy of EquiPENS™ neuromodulation for the management of trigeminal mediated headshaking in 168 horses.

Roberts VLH, Bailey M, The EquiPENS™ Group, Patel N.K.

Equine Veterinary Journal 2020 ISSN 0425-1644 DOI: 10.1111/evj.13174

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Safety and efficacy of EquiPENS™ neuromodulation for the management of trigeminal mediated headshaking in 168 horses.

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Summary

Background: Early results from the use of neuromodulation by percutaneous electrical nerve stimulation for the management of trigeminal-mediated headshaking in horses were promising but lacked sufficient case numbers and long-term follow-up. The neuromodulatory procedure has since been established as EquiPENS™.

Objectives: The aim of this study was to report long-term results from a larger number of cases and to investigate for predictors of outcome.

Study design: Prospective case series using international, multi-centre data.

Methods: Eligible cases were horses with a veterinary diagnosis of trigeminal-mediated headshaking, which received EquiPENS™ neuromodulation at trained centres between August 2013 and November 2017. The standard protocol was an initial three-procedure course, with additional procedures should a horse go into remission but then relapse. Data collected included signalment, history, diagnostic tests performed, details of any complications, whether horses had gone into remission and the length of remission.

Results: Results were obtained from 168 horses, with 530 procedures. The complication rate was 8.8% of procedures. In all but one case, complications were mild and transient, without self-trauma. Remission of headshaking following the initial course occurred in 53% (72/136) of horses. Median length of time recorded in remission was 9.5 weeks (range 2 days to 156 weeks ongoing). Where signs recurred, most horses went back into remission following additional procedures, usually for longer than from the previous procedure. No predictors for outcome were determined.

Main limitations: No placebo or control group, owner-assessed results.

Conclusions: EquiPENS™ neuromodulation can be an effective and safe treatment for the management of trigeminal-mediated headshaking in some horses. An increased understanding of neuromodulation could help optimise the technique. Advances in treatment

for trigeminal-mediated headshaking will remain limited until there is a greater understanding of the aetiopathogenesis of the condition.

Keywords: horse; headshaking; trigeminal-mediated; neuromodulation; percutaneous electrical nerve stimulation

Introduction

Trigeminal-mediated headshaking is an idiopathic neuropathic facial pain condition of the horse. The condition can have important welfare implications [1]. It carries a poor prognosis, with published treatments lacking consistent efficacy, and in some instances, safety and practical application [2–5]. The use of a nose-net improves clinical signs by 70% or greater in one-third of horses [6]. A nose-net is non-invasive and cheap and is usually the first-line of treatment but its use in competition is not accepted by all equestrian organisations. Medical treatment with carbamazepine and/or cyproheptadine [2,7] can be effective in some individuals. However, in general, results are inconsistent, and the use of these pharmaceuticals can be expensive, associated with side effects of drowsiness and would not usually be permitted in competition. The surgical placement of platinum coils within the infraorbital canal was reported to have a 49% remission rate [5] but resulted in adverse effects of enough severity as to result in euthanasia in 4/58 horses.

Advances in the treatment for trigeminal-mediated headshaking will remain limited until the aetiopathogenesis of the condition is understood. The most recent advance was that the trigeminal nerve of affected horses is sensitised, having a reduced threshold for activation, which is thought to result in neuropathic pain [8]. The nerve is functionally abnormal but appears to be structurally normal [9] which could mean that the sensitisation is reversible. Following on from this, percutaneous electrical nerve stimulation, a repeatable, minimally invasive neuromodulatory therapy with some application for the management of neuropathic pain in people, was trialled in seven horses [10]. All horses tolerated the procedure well. Three horses developed a haematoma at the site on one occasion and two had increased clinical signs suspected to be due to a transient neuritis, for up to 3 days following one of the procedures. All horses underwent a minimum of three procedures, with two horses having four procedures. Following their last procedure, remission, classed as ridden work at their previous level, was obtained in five horses, with a median remission time of 15.5 weeks from the third procedure and 20 weeks from the fourth. These early results were promising for management of the condition but lacked sufficient case numbers and long-term follow-up. Following this, the use of electroacupuncture, which uses a different electrical algorithm,

equipment and technique, gave positive results in a small number of suspected trigeminal-mediated headshakers [11].

The percutaneous electrical neuromodulatory procedure has since been established as EquiPENS™ and various centres across the UK and Europe have been trained by the first author in the technique, using the same equipment[a], ensuring consistency. The aim of this study is to report long-term results for treatment with EquiPENS™ and to identify any predictors for outcome from a larger number of cases, using international, multi-centre data.

Materials and methods

Eligible cases were horses with a veterinary diagnosis of trigeminal-mediated headshaking, which received EquiPENS™ neuromodulation at trained centres between August 2013 and November 2017. Centres were issued with guidelines for reaching a diagnosis of trigeminal-mediated headshaking. These are detailed in Appendix Three. Horses could have previously received, but responded insufficiently to, other treatments for headshaking, but were not receiving any other treatment at the time of enrolment. In order to assess response to treatment, horses were in ridden or lunge work prior to the onset of clinical signs of headshaking. EquiPENS™ neuromodulation was performed as described previously [10]. The protocol was for each horse to receive an initial course of three procedures. The second procedure was performed 3–7 days after the first procedure, and the third procedure was performed 10–14 days after the second procedure. Intervals were extended if a horse went into remission after a procedure, until it relapsed. If the horse went into remission after three procedures but then relapsed, additional procedures could be performed.

A standard recording form was available to each centre for prospective collection of data regarding each horse's signalment, history and the diagnostic tests they performed. The information requested included whether signs were known to be spring/summer seasonal only or present all year round. Seasonality of signs was recorded as unknown in those cases which were reported to have been affected for less than a year. The diagnosis of trigeminal-mediated headshaking was made by exclusion. If during investigation abnormalities were detected, these were judged to not be clinically relevant, sometimes after treatment with no response. Examples would include sharp dental arcades and iris cyst.

Centres were also asked to record the following information for each EquiPENS™ procedure performed for each case: the date of the procedure; whether any complications were experienced during or after the procedure and the nature of those complications; whether the horse went into remission; and if so, for how long. Remission was defined as return to

ridden exercise (or if not trained, lunge exercise) at, or above, the level of performance prior to the onset of clinical signs, within 3 weeks from the last procedure. This was an assessment made by the owner. Follow-up on each case was obtained by the centre responsible for that case by telephone questionnaire (Appendix Four). The longest-term available follow-up was used in this study. Where horses had been initially classified as going into remission with an initial follow-up performed prior to March 2016, follow-up was repeated between July and November 2017. Where horses could no longer be classified as being in remission, whether this was due to recurrence of headshaking signs or because horses could no longer be assessed as they were out of ridden work for other reasons, was recorded. Otherwise, remission was recorded as being on-going at the time of follow-up.

Data analysis

Statistical analysis was performed using the survival and survminer packages for the R statistical program (Version 3.4.4)b and R Studio (Version 1.1.423)[b] running on Ubuntu 17.10c. Censored survival objects were created using the Surv function of the survival package and Kaplan Meier plots created using the survfit and ggsurvplot functions. Probabilities for differences in length of remission after third or final treatment dependent on response to first or second treatments were calculated using log-rank methods. Cox proportional hazards for presence of and differences in length of remission dependent on management, centre and history prior to treatment were calculated using the coxph function. Variables tested were: the time for which the horse had been affected with clinical signs prior to presentation; whether use of a nose-net had, judged by the owner, no effect on clinical signs, insufficient effect or aggravated clinical signs; whether diagnostic local anaesthesia had been performed, the location of that anaesthesia and the result; seasonality.

Results

Population statistics

There were 168 horses fitting the inclusion criteria. The median age at presentation was 9 years (range 2–21 years, n = 163, 5 not recorded). The most common groups of breeds were sports horses (49/160, 31% 8 not recorded) and warmbloods (42/160, 26%). Age ranges appeared evenly distributed across the breeds (Figure 1).

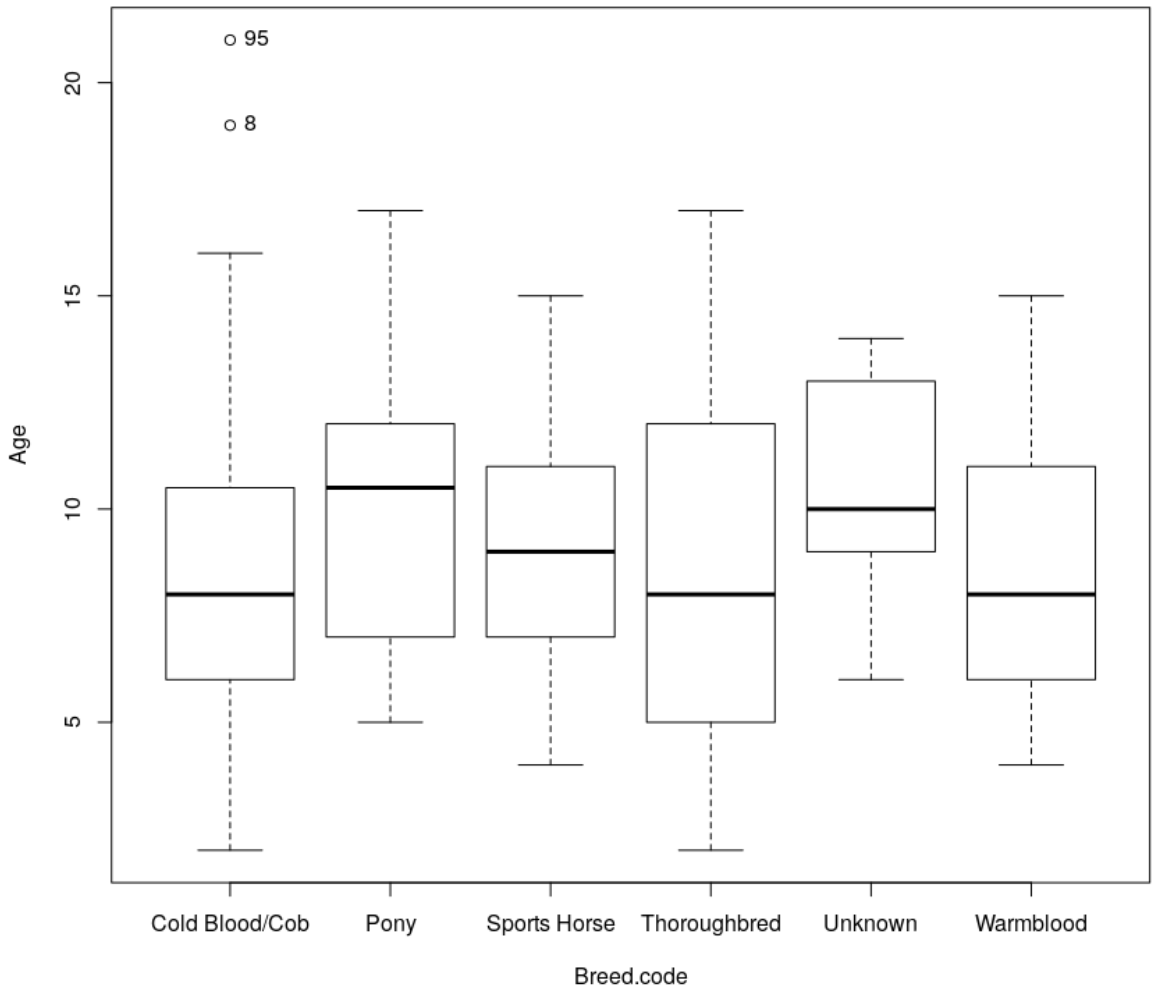

Figure 1: Age distribution across breeds.

There were 120/165 (73%) geldings, 42/165 (25%) mares and 3/165 (2%) stallions. The sex of 3 horses was not recorded. Procedures were performed at 13 trained centres across the UK and Europe. On occasion, diagnostics and the first one or two procedures were performed at one centre, with other procedures performed at a different centre. In these instances, the first centre only was attributed the case. The distribution of cases across the centres is displayed in Figure 2.

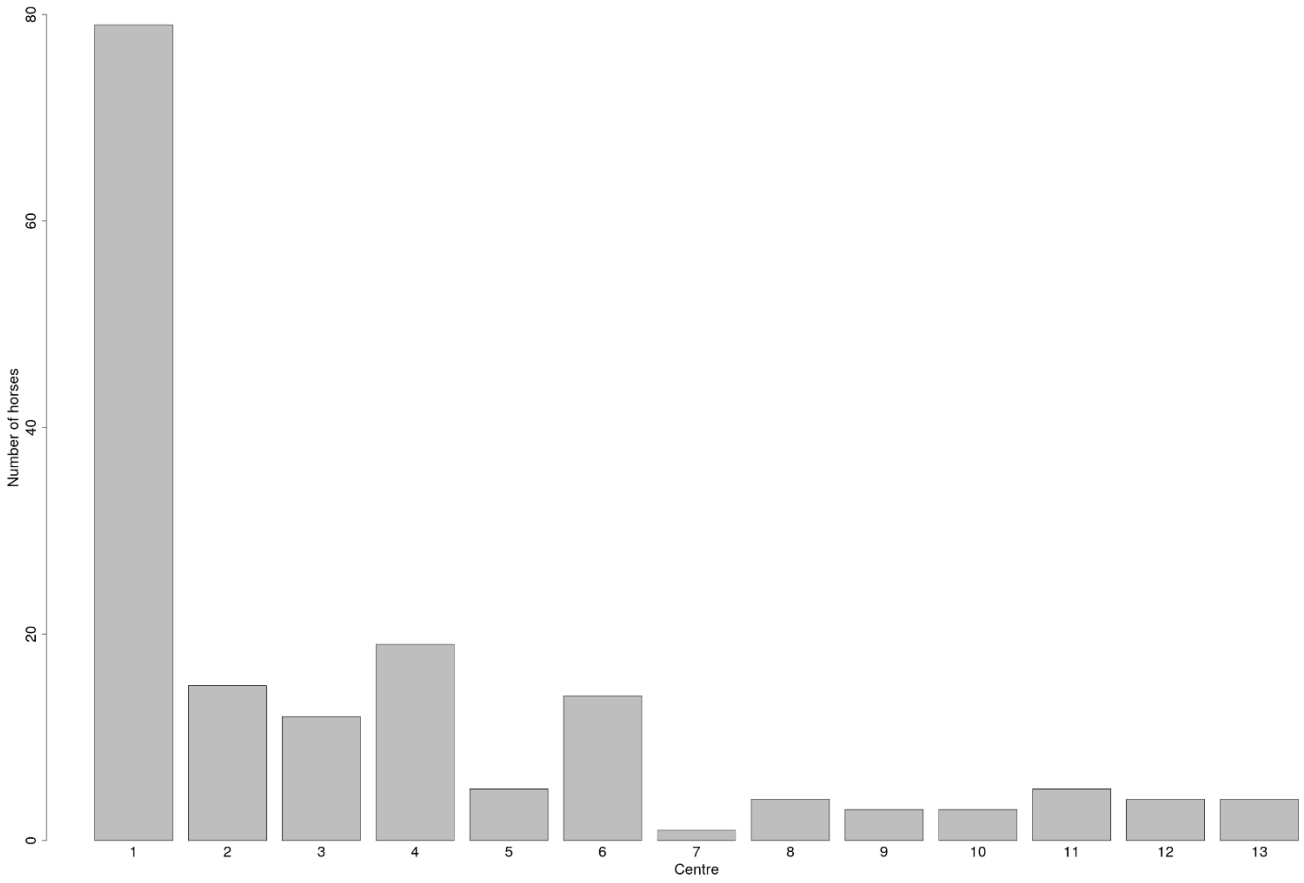

Figure 2: Distribution of cases across centres.

Most horses (94/166, 57%, 2 not recorded) were used for general riding. Distribution of use is displayed in Figure 3.

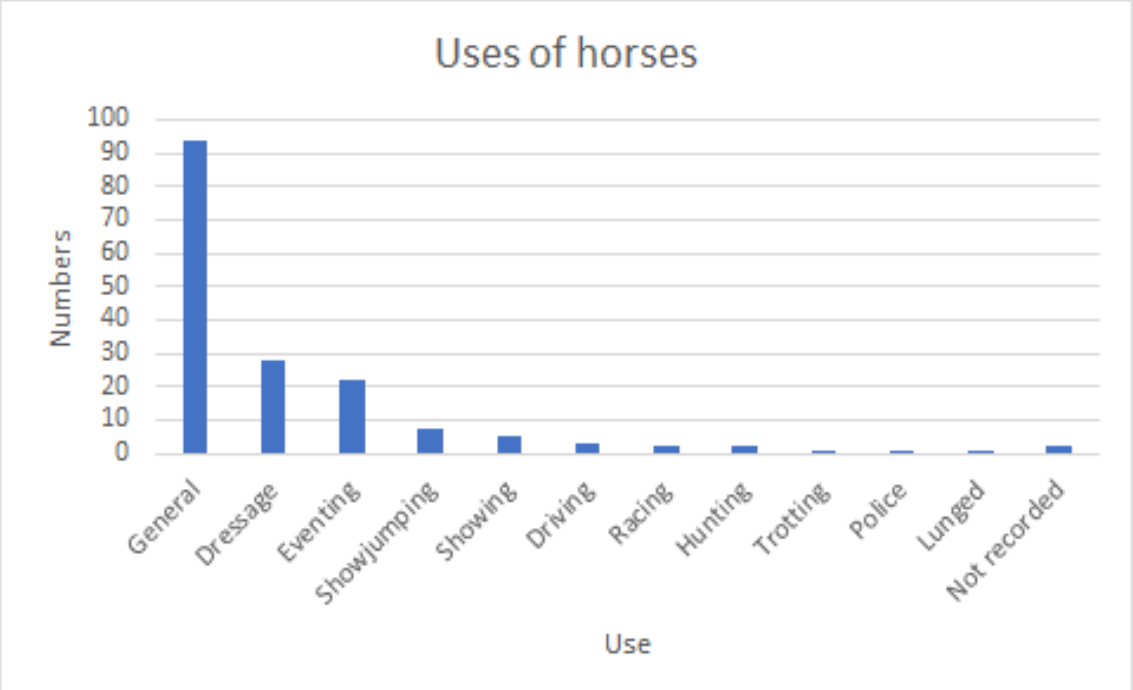

Figure 3: Uses of horses.

Prior treatment

Nose-nets had been trialled for treatment in 128 horses and it was reported by the owner to have no, or insufficient, effect in 109/128 (84%) cases and worsen clinical signs in 16/128 (12%) cases. Three horses whose clinical signs were alleviated by use of a nose-net were presented for treatment because they were unable to compete in their discipline with a nose-net.

Distribution of the main other attempted treatments are shown in Figure 4. None of these treatments were reported by the owners to have been effective or sufficiently effective. Less commonly used, attempted but failed, treatments reported by owners are detailed in Appendix Five.

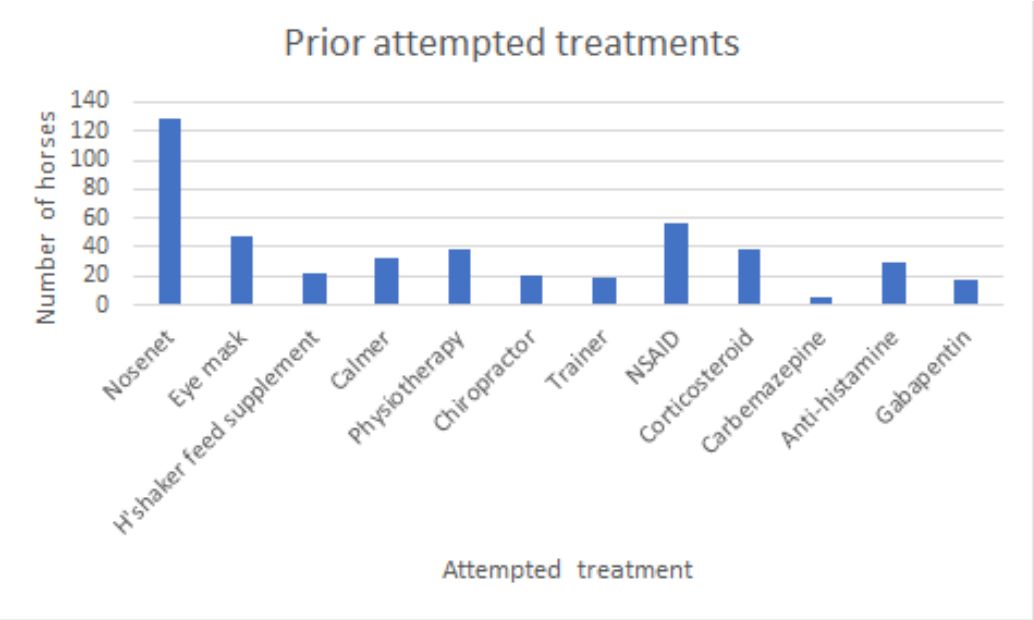

Figure 4: Main prior attempted treatments in the study cases.

Diagnosis

All horses were diagnosed with trigeminal-mediated headshaking by veterinary surgeons. European or American board-certified specialists were responsible for case management at 9/13 centres. The median length of time for which horses were affected prior to presentation was 4 months (range 0.5–84 months, n = 153, 15 not recorded). There were 21/158 (13%, 10 not recorded) horses known to be Spring/Summer seasonally affected and 62/158 (39%) horses known to be affected all year round. Seasonality was unknown i.e. horses having been affected for less than a year, in 75/ 158 cases (48%).

The diagnostic techniques performed included computed tomography of the head in 124/168 (85%) cases (21 not performed, 23 not recorded). Diagnostic local anaesthesia was performed bilaterally at the caudal point of the infraorbital canal in 51 cases, giving a positive result in 35/51 (68%). Bilateral diagnostic local anaesthesia of the infraorbital nerve at the level of the infraorbital foramen was performed in a further three cases, giving a positive result in two cases. Diagnostic local analgesia was not performed in 79/133 (59%) cases.

Procedure information

A total of 530 procedures were performed. Of the 168 horses which began the initial three-procedure course, 156 horses had completed the course at the time of follow up. Details regarding non-completion are in Table 1.

If horses had gone into remission following the initial three-procedure course, they were eligible for an additional procedure should signs return. Of these eligible horses, 26 underwent a fourth procedure, 11 underwent a fifth procedure and 4 underwent a sixth procedure.

The median interval between the first and second procedures was 6 days (range 3–36 days) due to long remission from the first procedure, n = 133, interval not recorded in 32 horses, three horses did not continue to a second procedure or had not done so by the time of follow-up (Table 1) and the second and third was 14 days (range 4–165 days) due to long remission from the second procedure, n = 125, interval not recorded in 31 horses, 9 horses did not continue to a third procedure or had not done so by the time of follow-up (Table 1).

		Reason for non-completion					
Procedure number	Number of horses	In remission	Withdrawn due to developing other medical condition	Horse compliance	Owner compliance	Course not yet completed at time of follow up	Unknown
1	168						
2	165			2		1	
3	156	2	1	1	1	3	1

Table 1: Details of numbers of cases undergoing initial three procedure course.

Complications

Complications were reported in 47/530 procedures (8.8%, Table 2). In all but one case, complications were transient. Of these, worsening of signs presumed to be secondary to neuritis was the most frequent complication occurring in 18/530 (3.4% procedures). No self-trauma was reported. All but one horse's signs returned at least to pre-treatment baseline in a few days and this occurred more rapidly if dexamethasone was administered intravenously at 0.1 mg/kg. One horse, treated soon after the onset of headshaking, showed a worsening of signs after each of two procedures. The horse's compliance was also poor, so it was decided not to perform the third procedure and that horse's clinical signs continued to progress. It is unclear whether this progression was a direct result of the neuromodulatory therapy, or the natural disease course in this horse. Suspected neuritis was reported more than once over the treatment course in four cases, which accounted for 9/18 (50%) of episodes. This was reported on two occasions in three cases; in one case with the first and third procedures and in the others with the first and second. One of these is the horse detailed above which had also complied poorly with the procedures, so a third procedure was not attempted. In the other case, dexamethasone was given prior to the third procedure

and no subsequent neuritis was observed. Suspected neuritis occurred after all three procedures in one case.

	Complication					
Procedure number	Suspected neuritis	Horse compliance	Haematoma	Dermatitis	Catheter complication	Colic
1	7	2	6	4	3	1
2	6	1	4	2	0	0
3	5	0	5	0	0	0
4	0	0	0	0	0	0
5	0	0	1	0	0	0
6	0	0	0	0	0	0

Table 2: Complications recorded for each procedure.

Success rates

The proportion of horses going into remission following the initial three-procedure course was 53% (72/136) with follow-up data which includes two horses which remained in remission after two procedures and did not complete the third, 64/136 were non-responders, 20/156 were lost to follow-up or could not be evaluated due to being out of work because of other conditions). The median duration of remission was 9.5 weeks (range 2 days to 156 weeks and ongoing). This calculation of the duration of remission included not only the length of time until signs returned (36/72, 50%) but also the time to follow-up for those still in remission at the end of the study (33/72, 46%). There was a small number of horses (3/72, 4%) which, having gone into remission were then out of work for reasons other than headshaking. For these horses, the duration of remission was taken to be until the last date the horses could be assessed i.e. when still in ridden work. Figure 5 displays how remission was sustained over time. At 56 weeks following the third procedure, 15% of cases remained in remission and these then remained in on-going remission at the last follow up at 156 weeks, with no further horses relapsing.

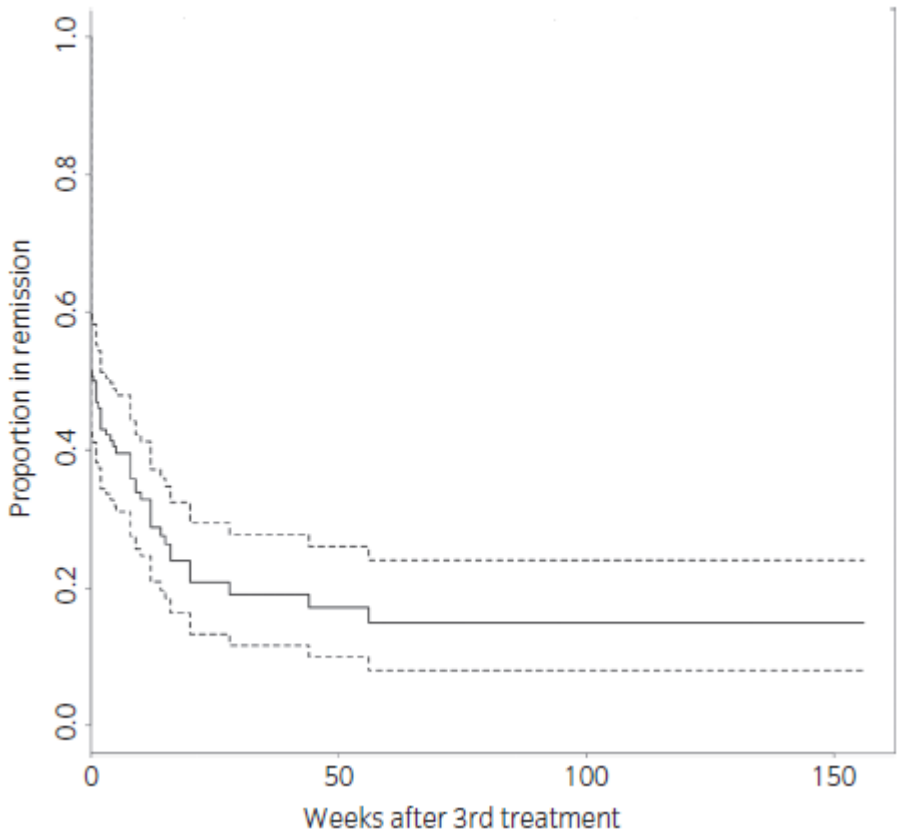

Figure 5: Kaplan-Meier survival plot demonstrating the proportion of horses entering remission at the end of the initial three-procedure course and the maintenance of remission over time. The dotted lines are 95% confidence intervals.

Within the initial three-procedure course, 35% (46/130) of horses went into remission after the first procedure (84/130 not in remission, 38/168 not recorded) with a median length of remission of 3 days (range, 1–14 days) before relapsing prior to the second procedure. Following the second procedure, 43% (60/137) of horses went into remission (77/137 not in remission, 28/165 not recorded) before relapsing prior to the third procedure. The median length of remission was 2 weeks (range, 2 days to 61 weeks) before relapse.

	Status at time of follow-up of horses which went into remission after each procedure		
Procedure number	Remission on-going	Headshaking recurred	Out of work for another reason
2	2	0	0
3	30	35	2
4	7	9	1
5	3	5	0
6	2	0	0

Table 3: Status at time of follow-up of horses which went into remission after each procedure.

A Cox proportional hazards regression model was performed to assess for significant predictors of remission after the initial three-procedure course. Nerve blocks, centre and seasonality were all non-significant (P>=0.15) and are displayed in Table 4. However, horses were significantly (P<0.001) more likely to go into remission at the end of the first three-procedure course if they went into remission after the first procedure and second procedures, but horses could still respond if the first procedure was unsuccessful.

Variable	Coef	Exp(coef)	Se(coef)	z	p
Duration of clinical signs prior to presentation	-2.322e-02	9.770e-01	1.700e-02	-1.366	0.17
Caudal infra-orbital nerve block, negative result	4.373e-01	1.549e+00	4.936e-01	0.886	0.37
Rostral in infra-orbital nerve block, negative result	-1.723e+01	3.288e-08	4.143e+03	-0.004	0.99
Caudal infra-orbital nerve block, positive result	2.777e-01	1.320e+00	3.469e-01	0.800	0.42
Rostral in infra-orbital nerve block, positive result	1.906e+00	6.724e+00	1.139e+00	1.673	0.09
Nosenet – no response	-1.361e+00	2.565e-01	1.149e+00	-1.185	0.23
Nosenet – insufficient response	-1.551e+00	2.121e-01	1.183e+00	-1.311	0.19
Nosenet – worse signs	-1.423e+00	2.409e-01	1.219e+00	-1.167	0.24
Seasonal signs	-8.198e-02	9.213e-01	5.636e-01	-0.145	0.88
Seasonality unknown	-7.643e-02	9.264e-01	3.500e-01	-0.218	0.83
Centre 2	-8.944e-01	4.088e-01	1.047e+00	- 0.854	0.39
Centre 3	8.620e-01	2.368e+00	8.560e-01	1.007	0.31
Centre 4	-4.572e-03	9.954e-01	5.147e-01	- 0.009	0.99
Centre 5	1.323e-01	1.141e+00	6.398e-01	0.207	0.84
Centre 6	7.549e-02	1.078e+00	1.043e+00	0.072	0.94
Centre 7	NA	NA	0.000e+00	NA	NA
Centre 8	NA	NA	0.000e+00	NA	NA
Centre 9	2.912e-01	1.338e+00	6.403e-01	0.455	0.65
Centre 10	1.007e-01	1.106e+00	1.062e+00	0.095	0.92
Centre 11	-1.023e+00	3.596e-01	7.896e-01	-1.295	0.19
Centre 12	1.142e+00	3.132e+00	7.822e-01	1.460	0.14
Centre 13	2.298e-01	1.258e+00	6.207e-01	0.370	0.71

Table 4: Results of Cox proportional hazards regression model for predictors from history on outcome of remission or not after the initial three procedure course.

There were 26 horses which, following recurrence after remission from the initial course, received a fourth procedure. Of these initial responders, 69% (18/26) went back into remission. There were 32% of horses still in remission 12 weeks after the fourth procedure and these remained in on-going remission with up to 140 weeks' follow-up.

There were 11 horses which received a fifth procedure. Of these, 82% (9/11) went back into remission. There were 30% of these horses still in remission 14 weeks after the fifth procedure and these horses remained in on-going remission with up to 140 weeks' follow-up. Figure 6 demonstrates the proportion of horses in remission after the last procedure they received and the maintenance of remission over time. There were four horses which went on to have a sixth procedure following recurrence of signs after a fifth procedure. Two went back into remission, which was ongoing at 28 and 56 weeks after this sixth procedure.

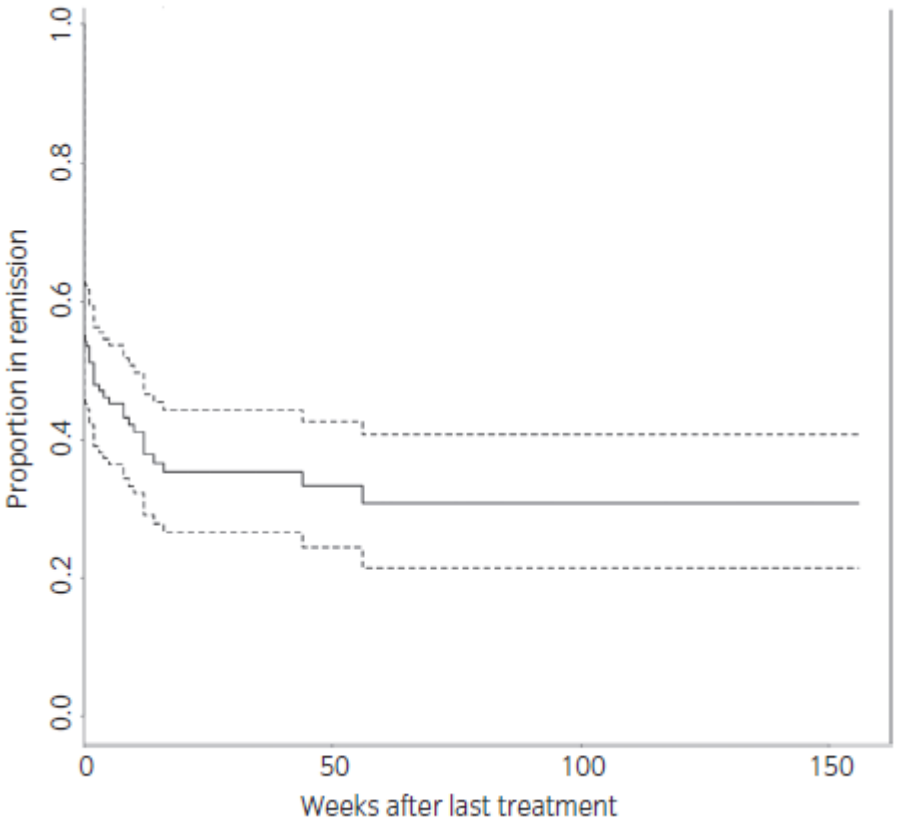

Figure 6: Kaplan-Meier survival plot demonstrating the proportion of horses entering remission after their last procedure and the maintenance of remission over time.
The dotted lines are 95% confidence intervals.

Discussion

This study demonstrates that EquiPENS™ neuromodulation can be an effective and safe treatment for the management of trigeminal-mediated headshaking in some horses. The data suggest that approximately 50% of cases will respond to the initial three-procedure course. Crucial, however, is whether remission is sustained and if not, how long until signs can be expected to recur and whether further treatment will result in remission again. Our results suggest that should a horse remain in remission for longer than 56 weeks from the initial course, the remission might last for years. However, for most horses, it can be expected that remission will be shorter. The median length of remission was 9.5 weeks. However, it should be noted that almost half of the cases were still in remission at the time of follow-up, so a longer study would be likely to show a longer median remission time. When signs recur, most but not all, horses can be expected to return to remission following additional procedures. This return to remission was usually but not always, longer-lasting than from after the previous procedure.

There was wide individual variation in how horses responded and no predictors of response were identified. Whilst horses were more likely to go into remission at the end of the initial three-procedure course if they had gone into remission following the first and second procedures, this was not exclusively the case. The only way to know if a horse will respond is to attempt treatment. Where horses responded to the initial course it was not possible to predict length of remission. Although most horses which responded but then relapsed did respond again to additional procedures, this was not the case for all. Even in a successful case, this uncertainty would impact on a horse's re-sale value.

The numbers of horses going into remission increased with each subsequent treatment within the initial course. Horses were more likely to go into remission at the end of the course if they had responded during the course. This suggests a minimum of three procedures should be undertaken. There may be benefit in continuing to pursue treatment in horses which have not responded to the third procedure, but with reducing odds of success. It is, therefore, the authors' recommendation that the protocol of performing an initial three-procedure course be continued with a fourth procedure only being offered to responders which have then relapsed.

A further advantage of EquiPENS™ is the short competition detection time for pharmaceuticals used during the procedure, namely sedation and local anaesthetic. This allowed several horses in this study to compete at a high level whilst their clinical signs were managed with EquiPENS™.

Studies of headshaking are at risk of a placebo effect and false positive results due to spontaneous remission. There are two studies on headshaking treatments which were designed in such a way as to be able to quantify the placebo effect on owners of treatments for this condition [12,13]. The study by Pickles et al. [12] investigated an effect of a gonadotrophin-releasing hormone vaccine in trigeminal-mediated headshakers. One-third of owners reported a subjective improvement in headshaking signs, but no real improvement was detected when considering results of serial scoring of signs on a visual analogue scale made by the same owners. The study by Talbot et al. [13] was a double-blinded placebo-controlled trial of a commercially available feed supplement for headshaking. Videos taken at set time-points within the study were assessed by veterinary surgeons with no significant difference found across the study, contrasting with the owners' positive subjective impression of effect on headshaking signs of both the supplement and the placebo. Ideally, our study would have included a placebo or control group. The data from our study suggests that for a control to be valid, the horse should be monitored for clinical signs for 1 year. During this year, no other treatments could be administered and the horse not euthanased. It would not be ethical to enrol horses into this study to leave them without treatment for a painful condition. A sham treatment course could be used, inserting the probes under sedation but not performing electrical stimulation. The sham treatment would have to be performed first and the real treatment 6 weeks later. Government ethical approval would have to be obtained for this study and it would be unlikely to be obtained, given the considerable time-period where no other treatment could be administered if horses were showing clinical signs of pain. The results of this study, relying on owner reports at follow-up, must be considered in the light of a lack of a placebo or control group. However, steps were taken in study design to reduce a placebo effect. All horses were showing clinical signs at the time of treatment. Remission was taken as return to ridden exercise at the previous level, in all but one case which was not yet in ridden work and so was assessed on the lunge, within 3 weeks of the last procedure.

The practical nature of the definition given to remission was chosen as being less likely to result in a false positive result than the owners' subjective interpretation of improvement in signs [12,13].

There is a risk of false positive results, with headshaking signs having resolved due to a change of season, or to spontaneous resolution of the condition. To reduce this risk, signs had to resolve within 3 weeks of the last procedure for that resolution to be attributed to the neuromodulation. There was no effect of seasonality on chances of, or length of, remission. Spontaneous remission, considered to be where signs resolved for 1 year or greater, to

differentiate from seasonal remission, is reported from an owner survey to occur in 5% of headshakers [3]. The median length of time for which horses were affected prior to presentation was 4 months, range 0.5-84 months. It would seem unlikely that the 50% of horses going into remission within 3 weeks of neuromodulation would all have recovered spontaneously.

It is possible that some of the horses in this study were mis-diagnosed, which would confound results. The diagnosis of trigeminal-mediated headshaking is currently one of exclusion, making misdiagnosis more likely than for a condition where there is a specific test. Furthermore, the diagnoses were made by several different veterinary surgeons at different centres and in different countries. All centres were provided with guidelines for reaching a diagnosis. These guidelines had to accommodate some variation between centres, for example computed tomography of the head was not available at the time in all the countries. It may be possible in the future to further develop a technique measuring somatosensory evoked potentials as a definitive test for trigeminal nerve sensitisation, which alongside the guidelines issued to centres, would improve accuracy of diagnosis.

Complication rates were low, and in all but one case, all side-effects were transient. This is of importance for a technique which must be repeated and has far from a guarantee of success. Where horses exhibited signs consistent with suspected neuritis, there was a strong tendency for these signs to occur again following the next procedure. In these cases, there may be some merit to considering administration of dexamethasone prior to the next procedure. This may reduce the risk of recurrence of suspected neuritis, although this is based on only one horse. There may also be merit to local administration of corticosteroid, although the authors have not trialled this yet. Even in horses where dexamethasone was not administered for suspected neuritis, signs did not result in self-trauma and resolved in a few days in all but one case, so the risk to benefit ratio of corticosteroid administration should be considered on an individual basis.

Advances in treatment for trigeminal-mediated headshaking will remain limited until the aetiopathogenesis of the condition is understood. It is certainly possible that there is more than one cause with the same clinical manifestation, leading to different response rates to treatment. It is recognised in human medicine that response to treatment for neuropathic pain varies amongst individuals, even with the same diagnosis [14]. Therefore, even if all trigeminal-mediated headshakers have the same underlying condition, response to the same treatment may vary. Also, the mechanism of action of any neuromodulatory therapy is not well understood. There is a need for research into neurophysiology pre- and post-

neuromodulation in any species. The lack of knowledge in this area limits our ability to determine whether adaptations of the EquiPENS™ technique could lead to remission in non-responders and longer remission times in responders. It also limits our ability to compare the technique to electroacupuncture [11], leaving the only way to make a comparison being to compare the use of a uniform electroacupuncture technique over a similar number of appropriately diagnosed horses.

In conclusion, based on these results, we recommend that at present, EquiPENS™ neuromodulation be considered for the management of trigeminal-mediated headshaking in horses where a nose-net is unsuitable. Further advances in the understanding of the aetiopathogenesis of trigeminal-mediated headshaking are vital for there to be real progress in treating the condition. In the shorter term, a greater understanding of neuromodulation could aid refinement of the EquiPENS™ technique.

Authors' declaration of interests

The University of Bristol receives a fee for training centres in the procedure, part used to cover professional time and part used to fund research into headshaking.

Ethical animal research

The study received University of Bristol ethics approval, registered with Veterinary Investigation Number 18/011.

Owner informed consent

Informed consent was obtained from horse-owners.

Source of funding

The Academy of Medical Sciences and the Wellcome Trust's Inspire Research Studentship funded a 1-month student post to help with data collection.

Acknowledgements

Julie Hillman for her help with data collection under the Academy of Medical Sciences and the Wellcome Trust's Inspire Research Studentship.

Authorship

V. Roberts contributed to study design, study execution, data analysis and interpretation, and preparation of the manuscript. N. Patel contributed to study design, and data analysis and interpretation. M. Bailey contributed to study design, and data analysis and

interpretation. The EquiPENS™ group contributed to study execution and preparation of the manuscript. All authors gave their final approval of the manuscript.

Manufacturers' addresses

a. Algotec Reseach and Development UK, Crawley, West Sussex, UK.
b. The R Project for Statistical Computing, Vienna, Austria.
c. Canonical Ltd, London, UK.

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Chapter Seven

General discussion and options for future research

7.1 General discussion

This thesis draws together my original research work furthering the understanding of equine trigeminal-mediated headshaking. Alongside this is my own personal research journey. I have learned an enormous amount, starting with a small retrospective study and building up to a large, international, multi-centre prospective study. I have learned, amongst other things, about study design, grant writing, ethics, informed consent for enrolment, questionnaire use, operator bias, placebo effect, the need for and challenges of controls and placebo groups, working with collaborators, handling datasets, paper writing and supervising research students. I have learned that my future studies should be prospective, with control or sham groups where possible, to work with collaborators and use an objective measure of assessment where possible. I have a lot more to learn, in particular with regard to statistics and am very grateful to the support of Professor Mick Bailey for his work on this in Paper Six. This journey is one on which I intend to continue for the rest of my career.

7.2 Research findings

i. Prevalence (Paper One)

This work provides evidence of the prevalence of owner-reported headshaking in the UK equine population (4.6 – 6.2%). This statistic will include horses with a range of causes for their headshaking, which would include head tossing from musculoskeletal pain. If a similar study was repeated, a more detailed description of what type of headshaking the horses had demonstrated could help identify the proportion of horses within that group which were likely to be showing signs consistent with neuropathic facial pain. Information on prevalence in other countries is required. Avoiding bias in an owner survey is very challenging. Efforts were made to avoid bias, by placing the headshaking specific questions within a general health questionnaire to avoid a predominance of owners with an interest in headshaking. The horse owner population which answered the survey was deemed to be representative of a general population as their responses for laminitis correlated with those found in other studies. However, laminitis as headshaking, is a condition where owners may consult other owners or para-professionals rather than their veterinary surgeons. Very few owners in our study had sought veterinary attention for their horses. Of those, only one horse was reported by the owner to have been diagnosed with trigeminal-mediated headshaking. There may be a lack of owner understanding of their horse's diagnosis however, as two horses had received EquiPENS ™ neuromodulation and both had been reported to have gone into

complete remission. A future study could be made more robust by asking for videos of the horse's headshaking, although then this would reduce responses as this information would be limited to those horses currently showing signs and to very engaged owners. Asking for access to the veterinary records for affected cases would give more reliable data as to the nature of the headshaking, its investigation, diagnosis and treatment but would be limited to the small proportion of cases where veterinary attention had been sought.

To avoid some of these challenges, it can be possible to consider data on horses seen by veterinary surgeons for headshaking. Determining the proportion of cases that are seen over a year's time period for headshaking as opposed to other complaints would help to determine prevalence within a population where veterinary attention is sought. It would be necessary to compare numbers presented for headshaking against numbers presented for investigation of other suspected disease processes rather than those presented for routine care. However, our study revealed that many horses which headshake do not receive veterinary attention and so this proportion, likely to include mildly affected trigeminal-mediated headshakers who respond to a nose-net, would not be detected. Furthermore, a diagnosis might not be reached by a first-opinion veterinary surgeon and indeed, diagnosis of trigeminal-mediated headshaking should ideally include advanced imaging and referral to a hospital so some information would remain missing.

The proportion of horses presenting to hospitals for investigation for headshaking could be compared to that if the general population for that hospital. Whilst this is useful data, it biases results towards a referred population. Some hospitals would see a biased proportion of cases due to being particular centres of excellence for the condition so several hospitals would have to be enrolled in the study.

A study from 1987, before advanced imaging was used in equine practice, found that up to 98% can be expected to receive a diagnosis of trigeminal-mediated headshaking (Lane and Mair, 1987). This study could be repeated, with the proportion now likely to be lower, at 90% (unpublished data).

Prevalence constitutes one aspect of impact. The impact of a condition is considered when prioritising research and so is vital to establish.

7.2.ii Aetipathogenesis (Paper Two)

This research found no evidence of trigeminal nerve root demyelination in a limited number of horses affected by trigeminal-mediated headshaking. Many sufferers of human trigeminal neuralgia have this demyelination, which suggests a different mechanism underlying

trigeminal-mediated headshaking. This implies that translational research may be more applicable to managing the clinical condition and to seeking an alternative aetiopathogenesis.

There are, however, a number of improvements to this study which could be made in future studies. The controls could be horses with a known history, euthanased for reasons other than headshaking, rather than an unknown abattoir sample. The entirety of the nerve should be studied, and also the brainstem, whereas this study sectioned nerves from brainstem to parallel with the 6th cheek tooth. The nerve can be frozen immediately on removal, prior to sectioning to give better samples than our obtained by formalin-fixing. Further stains, mostly heavy metal staining and using thicker sections can be better for a more thorough examination of long axons. Special stains used for investigation of axonopathies can include Bielschowsky silver impregnation and de Olmos amino cupric silver. There are genetic axonpathies in people where there is a lowered threshold potential. Histological comparison would be interesting, although all nerves are affected in these individuals, from birth. Pathologists should be blinded and independent in their assessment of slides, whereas in our study they were not blinded and reviewed the slides independently but then reached agreement together. They focussed on demyelination and then a more general assessment of whether there was any structural change to the nerve. Establishing pre-defined criteria to consider, such as reviewing slides for evidence of Renaut bodies which can occur at sites of nerve impingement would make the examination of slides more robust.

The apparent structural normality of the nerve may be a positive finding as a functional rather than structural abnormality holds potential to be reversible. The potential for the condition to be reversible is supported by several clinical factors. These include that many cases may show seasonal remission and there is a likely 5% spontaneous remission rate. A condition which is reversible may be more amenable to treatment and it opened the option of trying management through neuromodulation.

7.2.iii Diagnosis (Paper Three)

This paper clarified which nerve branches are likely affected when local anaesthetic is deposited near the round foramen. A strong influence of experience on accuracy of the technique was documented, which therefore affects interpretation of the result. The work could be expanded to better consider the clinical application of the technique. In clinical practice, the volume of local anaesthetic solution is several times greater than the volume of contrast medium used in the study. Expanding the study to observe the deposition pattern of a clinically applicable volume of contrast medium would improve the applicability of results.

This should be imaged at various time points after the injection to mimic the use of diagnostic local anaesthesia in a clinical situation and follow likely diffusion patterns for the solution. Trigeminal-mediated headshaking is currently diagnosed by exclusion and any work which refines this process is beneficial.

7.2.iv Treatment (Papers Four, Five, Six and Seven)

The first two of these papers demonstrated a treatment which could have fair results but proved to have a high risk of very serious complications. Papers six and seven document the development of a neuromodulatory treatment with improved success rates and far lower complications and severity of those complications. Whilst it is progress to be able to offer this neuromodulatory treatment, we are still far from finding a cure for most cases.

Considering papers four and five, there are a number of improvements which could be made to the studies, beyond those considered in the discussion sections of those papers. There is one horse in Paper Four which was treated only unilaterally due to unilateral signs. Now that more is known about the condition, I would consider this horse to have been mis-diagnosed. Had CT been available at that time, we may have been able to make a different diagnosis. This highlights the challenge where a diagnosis is made by exclusion. The complication of self-trauma from the surgery reported in Papers Four and Five is a major concern. Although management of these complications was reported, efficacy of this medication was not and would be required to inform any future use of the procedure. The possibility of recording whether or not coil migration was involved in surgical success or failure was considered but not performed and this would also improve our understanding and potentially allow refinement of the technique.

Considering Papers Five and Six, it was not discussed why the site for neuromodulation was selected to be at the infra-orbital formen when the response to diagnostic local anaesthesia is much better when performed further caudally. The reasoning was ability and safety of access. However, use of radio-frequency ablation at the sphenopalatine ganglion is considered in the next section with options for future research. In Paper Six, there were multiple centres and veterinary surgeons involved. Although all were trained and given guidelines to follow when making a diagnosis of trigeminal-mediated headshaking, this inevitably increases the variables and risk of mis-diagnosis in a condition where diagnosis is by exclusion. If diagnostic local anaesthesia was more reliable then this could be a required step. Certainly, it would have been possible to require having had CT scan in order to be included in the study but this would have limited numbers. The possibility of developing the use of somatosensory evoked potentials in the standing sedated horse is considered in the

section on future options for research and if possible to perform, could further refine diagnostics and case-selection for treatment. Ideally, horses would be enrolled onto a study where a blinded sham course of treatment could be performed initially. This, however, is unlikely to be possible practically as it carries welfare implications and would need Home Office licensing. Furthermore, a delay in providing treatment to allow sham treatments to be performed and evaluated could risk confusing response to treatment with a natural seasonal remission in some horses. It would also reduce numbers of owners willing to enrol in the study due to extra inconvenience and expense. However, the possibility of including a control or sham group must be considered when planning studies into headshaking treatment.

In Paper Four, follow-up information was obtained mostly from the owner but on some occasions from the referring veterinary surgeon. It was not recorded which method of follow-up was obtained for each case. It would be of particular interest to obtain follow-up by both methods for each horse and then compare the owner's report of the horse's response with that of their vet as this may reveal incidences of placebo effect. There was a short median follow-up time, with the shortest cases excluded. A long follow-up time is particularly important where clinical signs may be shown seasonally. The later papers considering treatment all used owner reports for follow-up. This could be improved by asking referring veterinary surgeons for their reports also, viewing videos and competition results where possible. Another improvement would be asking owners if they would opt to repeat the treatment if they were to own another horse with the same condition, as a measure of owner satisfaction. Ultimately, the best way to improve the quality and reliability of feedback will be to develop an objective measure of headshaking, which we hope to do using an accelerometer.

7.3 Future options for research

There is very little known about trigeminal-mediated headshaking. Further research is vital, with greater understanding of the condition being key to improving its treatment and potentially, to preventing it. Further research is required in all the areas covered by this thesis; impact, aetiopathogenesis, diagnosis and treatment.

The priority given to research into trigeminal-mediated headshaking should be influenced by the impact of the condition. This thesis covers some work into prevalence, which forms just one part of the impact of a condition. While figures on wastage to the equine industry due to trigeminal-mediated headshaking can be estimated, a true population calculation is preferable. Animal welfare influences impact and determining the proportion of horses

whose clinical signs are manageable, those which are manageable only if retired, those euthanased as they cannot be used, and those euthanased on welfare grounds should be the aim. Additionally, these statistics, and those for prevalence, should be determined in countries other than the UK. There seems to likely be a complex environmental role in the aetiopathogenesis of trigeminal-mediated headshaking and this requires research. Determination of prevalence in countries with different climates and different management practices and comparison with already established data may add to understanding of aetiopathogenesis and indeed to understanding of impact. Anecdotally, prevalence in the UK is increasing. This may be due to greater awareness of the condition and indeed, an acceptance that headshaking may occur due to a medical condition. Comparison of prevalence in the UK over time may reveal if this is the case and if so, why it is the case.

The key to treating and potentially preventing, this condition, will be to understand the pathophysiology and how, and why, it occurs. Given that there are no changes at a microscopic level in the nerves a functional disorder is presumed, therefore research at cell physiology level, such as ion channel function, should be considered. This could focus on axonal transport initially, given that there may be reduction of clinical signs with magnesium and boron supplementation (boron given to enhance magnesium uptake). There are specific axonopathies in people where threshold potential is reduced but these affect all nerves rather than seemingly, one branch of one cranial nerve. However, potential parallels could be explored by investigating ion channel function.

It seems likely that there is a complex role of environment in the development of this acquired condition. Determining more information as to local climate, pollen types, diet and management practices may reveal a pattern although would be challenging when there are so many variables. It is not unusual for signs to be relived in a new environment, although often temporarily or for signs to resolve temporarily whilst competing (personal observation) which could be a short-term local environmental effect and perhaps interaction with neurotransmitters such as adrenaline. Further work here could help uncover underlying interactions. There must also be a role of individual susceptibility. The author is currently exploring the possibilities of comparing RNA expression of axon channel genes, to compare affected with unaffected horses. This work is in its early stages but is in collaboration with the University of Bristol Genomics facility and the Avon Longitudinal Study of Parents and Children (ALSPAC, ‘Children of the 90s’) who bring extensive experience and knowledge.

There are also some horses seasonally affected, some not so. It should be determined whether these horses have a different clinical manifestation of the same condition, or in fact

have different conditions with similar clinical signs. This would be possible to determine once aetiopathogenesis is determined in either seasonal or non-seasonal groups.

Once aetiopathogenesis has been determined, this would open options not just for treatment but for diagnosis. A diagnosis of exclusion as it is currently, carries limitations. However, there is potential to improve diagnostic sensitivity and specificity should more data determine whether a reduced threshold potential is a consistent finding for all horses with trigeminal-mediated headshaking. If this is confirmed to be the case, exploring whether the procedure can be tolerated or modified to allow performing under standing sedation, and whether such measurements remain accurate, is required. At present it has only been performed under general anaesthesia which presents a patient risk, and a cost, both of which could be reduced if it could be performed under standing sedation, making this an achievable gold standard for diagnosis in a clinical setting.

The lack of an objective measure of headshaking is a consistent challenge to determining efficacy of treatment. The author is currently exploring validation of an accelerometer device to give an objective measure.

Consideration must be also be given in any study of treatment as to whether a control and/or placebo group is possible. It should be aimed for but may not be possible as usually welfare would be compromised.

The early work published on electroacupuncture is promising in that it may provide a more accessible treatment with similarities to neuromodulation. However, the published study on electroacupuncture is on a small number of horses and reports results poorer than the first small study on neuromodulation (Paper Five). A larger study of electroacupuncture is required to make a comparison to the results of neuromodulation. A blinded study comparing the two techniques or with a sham or control group would be ideal. As for Paper Six, the same challenges exist in reaching as reliable a veterinary diagnosis as possible, needing multiple centres to give numbers but then increasing variables, using the same equipment and protocols, and the challenges of follow-up.

Further work into neuromodulation in any species may increase our understanding of how it works, allowing refinement of the technique. There is potential to explore the use of an implant to facilitate repeated neuromodulation in cases with a short remission time and there has been some success in unpublished cases (personal communication, Dr. K. Pickles). Recent changes in rules for some equestrian competitions mean that it may be possible to compete a horse with an implant in place, if it is switched off during competition and this

change enables further work to be done with implants with a potentially practical outcome. Further translational work into treatment of neuropathic pain in any species may be useful. The author is exploring the possibility of radio-frequency stimulation of the sphenopalatine ganglion of the trigeminal nerve. Ganglia are aggregations of nerve cell bodies outside the central nervous system. Thus, specifically targeting this area could result in a more effective treatment for neuropathic pain.

The sphenopalatine ganglion has been targeted in human neuropathic pain patients, using radiofrequency. Pulsed radiofrequency of the sphenopalatine ganglion (SPG-PRF) in patients with chronic head and face pain of various aetiologies has been reported to give complete pain relief in 21% of patients and partial relief in 65% of patients (Bayer et al, 2005). Twenty percent of these required repeat treatment within a four to 52 month follow-up period. No side effects were reported. In patients with refractory cluster headaches treated with SPG-PRF (Fang, et al, 2015), 11/13 episodic cluster patients and 1/3 chronic cluster headache patients were completely relieved of pain an average of 6 days after treatment (range 1-20 days). Only one patient suffered a relapse during the study period (mean 17 months, range 12-30 months). Remission time between episodes was increased from an average of 8.7 months (range 5.8 – 11.6 months) to 16.6 months (range 11 – 21.6 months). One patient was treated with SPG-PRF again following return of pain at 9 months and this again induced remission for a further 11 months. Remission from a third procedure was on-going at the time of publication. Since no side effects were reported, this study shows that the procedure can be repeated safely and can give repeatable remission.

Radiofrequency has similarities to PENS neuromodulation in that it uses an electrically conductive probe with a current which alternates between frequencies. Whereas the PENS probe is wholly conductive and placed over the nerve bundle, with SPG-RF the tip of the probe only is conductive. It is placed into the SPG under intra-operative guidance of computed tomography or radiography. Heat is produced around the electrode tip. The exposure has a biological effect with induction of early gene expression demonstrated in the dorsal horn in cell culture studies (Sluijter et al, 1998). Permanent damage to the ganglion is not expected, unlike if continuous radiofrequency is employed. In animal studies of the sciatic nerve, oedema, cell and myelin pathology changes were not significantly different between sham and pulsed radiofrequency, but significantly different with continuous radiofrequency (Vatansever et al, 2008). Our study has so far identified the location of the sphenopalatine ganglion in the horse and external landmarks. We have obtained magnetic resonance images and CT images of the head and determined likely location of the ganglion. The study is ready to move to the cadaver phase.

To conclude there is an enormous amount of research still required in the field of trigeminal-mediated headshaking. Whilst determining aetiopathogenesis is expected to bring a break-through in management, it is likely that, as with human neuropathic pain, even with the same underlying condition, different individuals experiencing neuropathic pain may respond to different treatments. Finally, once the condition is better understood, research towards prevention would be the goal.

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Appendix One

Equine Veterinary Journal

Supplementary Item 1:

Horse Health Questionnaire

Introduction

Thank you for your interest in this survey on equine health. In order to complete the survey we ask that you are 18 years of age or over, live in the United Kingdom (UK) and currently own or have owned a horse within the last year. A survey can still be filled in for any horse which may have passed away or been sold within the last year. This aim of this survey is to allow veterinary researchers to establish how common certain diseases are within the horse population in the UK. Your participation is greatly appreciated. If you have more than one horse, please complete the survey for the horse whose name comes first in the alphabet. Completion of this survey indicates your consent for us to use your data for research purposes, however please note that questionnaires are completed anonymously.

The survey does not take long to complete, we anticipate less than 5 minutes for most people and a maximum of 10 minutes. Please note that we are using the term "horse" throughout however this form can be completed for a horse or pony. We also refer to the present tense throughout however we do realise that some horses may be sold or deceased.

Are you completing this survey for a horse that you currently own?

- ○ Yes
- ○ No

If you answered "no" to the question above, is this a horse you have sold or did he/she die whilst in your ownership?

- ○ Yes, the horse has been sold
- ○ Yes, the horse died whilst in my ownership

If your horse was sold or has died, how old was he/she when you last owned him/her?

General Information

How old is your horse this year?

What sex is your horse? ✱ *Required*

- Mare/Filly
- Stallion/Colt
- Gelding

What breed or type is your horse? *"x" refers to crossbreed.*

- Arab
- Arab x
- Cob
- Cob x
- Irish Draught
- Irish Draught x Thoroughbred
- Irish Sports Horse
- Thoroughbred
- Thoroughbred x
- Thoroughbred x Warmblood
- Warmblood
- Warmblood x
- Native
- Unknown horse breed
- Unknown pony breed
- Other

If you selected Other, please specify:

How old was the horse when you got him or her?

During what season of the year did you purchase this horse?

Which UK region is this horse kept in for most of the year?

Did you have a pre purchase examination (vetting) performed prior to purchase?

- Yes
- No
- Not applicable (homebred)

If Yes, what form of vetting was carried out?

- Two stage
- Five Stage (includes evaluation at exercise)
- Five Stage (includes evaluation at exercise) and X-rays

Which of the following options best describes the usual management of this horse during the Summer?

- Lives in 24/7
- Stabled during the day only
- Stabled during the night only
- Stabled for part of the day or night only
- Turned out 24/7

Which of the following options best describes the usual management of this horse during the Winter?

- ○ Lives in 24/7
- ○ Stabled during the day only
- ○ Stabled during the night only
- ○ Stabled for part of the day or night only
- ○ Turned out 24/7

Does your horse display any of the following behaviours? *Please tick all that apply.*

- ☐ Weaving
- ☐ Box walking
- ☐ Crib biting
- ☐ Windsucking
- ☐ Self mutilation
- ☐ None of the above

Veterinary Conditions and Definitions

We are interested in finding out how many horses or ponies in the UK are affected by the following conditions:- laminitis, headshaking and sarcoids.

Definitions

Laminitis is inflammation of the sensitive laminae of the hoof. For the purposes of this survey, laminitis is an episode of lameness which was either;

a) diagnosed by a vet as laminitis (or)

b) laminitis was strongly suspected based upon the following; lameness was present in all four limbs **and** the horse or pony stood with an altered stance **and**/**or** the horse or pony was reluctant to move **and**/**or** there was increased heat in all four hooves **and**/**or** laminitis was diagnosed by a farrier.

For the purposes of this survey, **headshaking** is characterised by unexplained and uncontrollable movements of the head and neck that may affect the horse either at rest or during exercise.

For the purposes of this survey, **sarcoids** are fibroblastic tumours of the equine skin that have been diagnosed by a vet, either based upon appearance or biopsy results.

Laminitis

Reminder- laminitis is inflammation of the sensitive laminae of the hoof. For the purposes of this survey, laminitis is an episode of lameness which was either;

a) diagnosed by a vet as laminitis (or)

b) laminitis was strongly suspected based upon the following; lameness was present in all four limbs **and** the horse or pony stood with an altered stance **and**/**or** the horse or pony was reluctant to move **and**/**or** there was increased heat in all four hooves **and**/**or** laminitis was diagnosed by a farrier.

Has your horse had laminitis? ✱ *Required*

- Yes in the last year
- Yes more than a year ago
- Not since I have had him/her
- My horse/ pony is no longer alive as a result of laminitis

Laminitis questions

Which of the following best describes how easy your horse is to feed?

- He/she is a very "good doer" and gets fat easily
- He/she is uncomplicated to feed and to keep weight on
- He/she is a fussy eater and/ or is difficult to keep weight on

Body condition scores help us estimate the condition of animal without the use of weigh scales. The body condition scoring system devised by Carroll and Huntington (1988) is based on a grading system of 0 (emaciated) to 5 (obese). Based on this grading system (link below) what score is most applicable to your horse or pony? http://www.bris.ac.uk/vetscience/media/images/conditionscoringleaflet.pdf

- 0
- 1
- 2
- 3
- 4
- 5

With thanks to the British Horse Society for the body condition scoring leaflet used above.

Which, if any, of the following methods do you use to monitor your horse's condition? *Tick all that apply.*

- [ ] None (I don't worry about this)
- [ ] Weight tape
- [ ] Weigh scales
- [ ] Body condition score
- [ ] By eye
- [ ] Based on how tight or loose the girth is
- [ ] Other

If you selected Other, please specify:

In which month did your horse first have laminitis?

In which year did your horse first have laminitis?

How many episodes of laminitis has your horse had since you have owned him or her?

- [ ] Just one
- [ ] 2-3
- [ ] 4 or more
- [ ] My horse has chronic laminitis and management is ongoing

What was your horse **mainly** used for before his or her laminitis? *Select one box only.*

If you selected Other, please specify:

Which of the following best decribes the level of use your horse returned to after the most recent bout of laminitis?

- ○ Same or higher level of use
- ○ He/ she has dropped down a level
- ○ He/ she still has laminitis and is out of work
- ○ He/ she has another problem
- ○ He/ she was put to sleep (euthanased)

Was laminitis diagnosed by a vet?

- ○ Yes
- ○ No

Have these possible underlying causes of laminitis been tested for by this vet?

	Has your horse been tested for this disease?			
	Yes and positive	Yes and negative	Yes but can't remember results	No
Equine Metabolic syndrome (EMS)	○	○	○	○
Pars Pituitary Intermedia Dysfunction (PPID or Cushing's)	○	○	○	○

Which if any of the following drugs been given for treatment or control of laminitis? *Please select all that apply.*

- ☐ Bute (phenylbutazone) e.g. equipalazone
- ☐ Suzibuzone e.g. danilon
- ☐ Flunixin e.g. finadyne paste
- ☐ Meloxicam e.g metacam
- ☐ Metformin
- ☐ Pergolide e.g. prascend
- ☐ None of these

Which if any of the following options have you tried for managing weight in your horse or pony? *Please select all that apply.*

- ☐ Restricting grazing using a grazing muzzle
- ☐ Restricting grazing by stabling or increasing time spent indoors
- ☐ Restricting grazing by fencing off small areas or strip grazing
- ☐ Turn out into poorer quality grazing
- ☐ Avoiding grass turnout completely
- ☐ Soaking hay
- ☐ Using double haynets or small holed haynets
- ☐ Increasing exercise
- ☐ Cutting out treats
- ☐ None of these
- ☐ Other

If you selected Other, please specify:

How often does your farrier usually attend to your horse's feet?

- [ ] Every 4-6 weeks
- [ ] Every 7-8 weeks
- [ ] Every 9-12 weeks
- [ ] As required
- [ ] Only when my horse has a problem

Has your farrier performed corrective farriery for laminitis on this horse or pony?

- ○ Yes
- ○ No

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Headshaking

Reminder- for the purposes of this survey **headshaking** is characterised by unexplained and uncontrollable movements of the head and neck that may affect the horse either at rest or during exercise.

Has your horse shown signs of headshaking? ✱ *Required*

- Yes in the last year
- Yes more than a year ago
- Not since I have had him/ her
- My horse is no longer alive as a result of headshaking

Headshaking questions

In which month did headshaking first begin?

In which year did headshaking first begin?

How would you describe the onset of headshaking?

- ○ Headshaking came on gradually
- ○ Headshaking came on suddenly
- ○ My horse or pony has been headshaking since I've owned him/ her

At which times of the year does your horse tend to show signs of headshaking? *Indicate all that apply.*

- ☐ Spring (March, April, May)
- ☐ Summer (June, July, August)
- ☐ Autumn (September, October, November)
- ☐ Winter (December, January, February)
- ☐ Unknown (started less than a year ago)

Which weather conditions, if any, do you associate with headshaking in your horse? *Tick all that apply.*

- ☐ Sunshine
- ☐ Rain
- ☐ Wind
- ☐ Cold
- ☐ Heat
- ☐ Other

If you selected Other, please specify:

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Which of these best describes your horse whilst headshaking? *Tick all that apply.*

- ☐ Vertical (up and down) head movements
- ☐ Horizontal (side to side) head movements
- ☐ Rotational (circular) head movements
- ☐ Acting as though an insect has flown up the nose
- ☐ Excessive rubbing of the muzzle
- ☐ Striking at the nose with the forelimbs
- ☐ Excessive and persistent snorting
- ☐ Low head carriage
- ☐ An anxious expression
- ☐ Submerges muzzle in water
- ☐ Other

If you selected Other, please specify:

Does your horse headshake at the following times?

	Head shaking seen			
	Yes	No	Don't know	Not applicable
When lunged	○	○	○	○
When ridden	○	○	○	○
When turned out	○	○	○	○
In the stable	○	○	○	○

The following practical grading system has been devised to help classify the severity of headshaking.

Grade 0 - there is no headshaking.

Grade 1 - there is headshaking, only at exercise but sufficiently mild that the horse may be ridden.

Grade 2 - there is headshaking at exercise to a severity as to make ridden exercise unsafe or impossible.

Grade 3 - there is headshaking even at rest.

Based on the above grading system, please indicate the usual severity of headshaking under the following circumstances:

	During the day	At night	Indoors	Outdoors	Without a nose net	With a nose net	In open spaces	Next to hedgerow
Grade 0	☐	☐	☐	☐	☐	☐	☐	☐
Grade 1	☐	☐	☐	☐	☐	☐	☐	☐
Grade 2	☐	☐	☐	☐	☐	☐	☐	☐
Grade 3	☐	☐	☐	☐	☐	☐	☐	☐

Based on the above grading system, please indicate how severe your horse's headshaking usually is at the following times of the year:

	Season			
	Spring (March, April, May)	Summer (June, July, August)	Autumn (September, October, November)	Winter (December, January, February)
Unsure	○	○	○	○
Grade 0	○	○	○	○
Grade 1	○	○	○	○
Grade 2	○	○	○	○
Grade 3	○	○	○	○

Based on the above grading system, please grade how severe your horse's headshaking is, or has been, when at its worst.

- ○ Grade 0
- ○ Grade 1
- ○ Grade 2
- ○ Grade 3

Has your horse been seen by a vet for the complaint of headshaking?

- ○ Yes
- ○ No

If yes, which of the following tests were performed? *Select all that apply.*

- ☐ Dental examination
- ☐ Radiographs (x-rays) of the head
- ☐ Endoscopy of the head (camera up nose)
- ☐ Ophthalmologic (eye) examination
- ☐ Ear examination
- ☐ Computed tomography (CT) of the head
- ☐ Nerve blocking
- ☐ Other

If you selected Other, please specify:

Has a cause been diagnosed? If so, please tick the **main cause** from the list below or add other if unlisted.

- ○ The cause remains unknown
- ○ Dental disease
- ○ Sinus problem
- ○ Neck pain
- ○ Ocular (eye) problem
- ○ Problem associated with the guttural pouch(es)
- ○ Allergy
- ○ Trigeminal mediated (Idiopathic) headshaking
- ○ Temperomandibular joint (jaw) pain
- ○ Behavioural
- ○ Other

If you selected Other, please specify:

Which, if any, of the following treatments were trialled?

- ☐ Eye mask
- ☐ Nosenet
- ☐ Phenylbutazone (bute)
- ☐ Steroids
- ☐ Antihistamines e.g. periactin, cyproheptadine, carbamazepine
- ☐ Gabapentin
- ☐ Surgery for placement of coils
- ☐ EquiPENS
- ☐ Other

If you selected Other, please specify:

Thinking about the effects of these treatments please grade the average severity of headshaking signs seen whilst on treatment. Grade for applicable treatments only. As a reminder the grading scheme is as follows:- Grade 0 - there is no headshaking. Grade 1 - there is headshaking only at exercise but sufficiently mild that the horse may be ridden. Grade 2 - there is headshaking at exercise to a severity as to make ridden exercise unsafe or impossible. Grade 3 - there is headshaking even at rest.

	Eye mask	Nosenet	Phenylbutazone (bute)	Steroids	Antihistamines	Gabapentin	Surgery for placement of coils	EquiPENS	Other
Grade 0	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grade 1	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grade 2	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grade 3	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sarcoids

Reminder- for the purposes of this survey **sarcoids** are fibroblastic tumours of the equine skin that have been diagnosed by a vet; either based upon appearance or biopsy results.

Has your horse ever had sarcoids? ✱ *Required*

- Yes, in the last year
- Yes, more than a year ago
- Not since I have had him/ her
- My horse/pony is no longer alive as a result of sarcoids

Sarcoid questions

What age was your horse when you first noticed a sarcoid or sarcoids?

At what time of year did you first notice a sarcoid or sarcoids on your horse or pony?

What colour is your horse?

- Grey
- Chestnut
- Bay
- Black
- Roan
- Palomino
- Skewbald
- Piebald
- Brown
- Dun
- Spotted
- Other

If you selected Other, please specify:

Are you aware whether your horse has any relatives that also suffer from sarcoids? *Tick all that apply.*

- Unsure
- The dam (mother)
- The sire (father)
- Half brother

- [ ] Half sister
- [ ] Full brother
- [ ] Full sister

What is the distance to the closest cattle farm from where your horse is kept?

Please indicate which part of the body is, or has been affected. *Select as many options as apply.*

- [ ] Around or close to the eye
- [ ] Face (but not close to the eye)
- [ ] Ear
- [ ] Neck
- [ ] Sternum/ chest
- [ ] Girth
- [ ] Flank
- [ ] Sheath
- [ ] Mammary
- [ ] Axillary (armpit region of front leg)
- [ ] Inginual (groin region)
- [ ] Upper limb (on or above the knee or hock)
- [ ] Lower limb (below the knee or hock)
- [ ] Other

If you selected Other, please specify:

Which of the following best applies to your horse? *Tick all that apply*

- [ ] My horse has sarcoids but these do not cause us a problem at present
- [ ] My horse has sarcoids and these are unsightly/ cause a cosmetic problem
- [ ] My horse has sarcoids and these interefere with where I want to put tack
- [ ] My horse has sarcoids and these are causing a problem through bleeding or ulceration
- [ ] My horse has sarcoids and I believe this will affect his or her resale value

☐ Other

If you selected Other, please specify:

Have you had a vet examine your horse for sarcoids?

- ○ Yes
- ○ No

If yes, was a biopsy taken to confirm diagnosis?

- ○ Yes
- ○ No
- ○ Don't know

Have any treatments been tried? If so please indicate response to treatment

	Outcome					
	Not tried	Complete success	Some success	No improvement	Made things worse	Other
Traditional surgery	○	○	○	○	○	○
Laser surgery	○	○	○	○	○	○
Ligation (tying off or use of rubber bands)	○	○	○	○	○	○
Cryotherapy (freezing)	○	○	○	○	○	○
AW4-LUDES (Liverpool) cream	○	○	○	○	○	○
Xtterra cream	○	○	○	○	○	○
Iridium wires	○	○	○	○	○	○
High Dose Radiation (HDR) therapy	○	○	○	○	○	○
Photodynamic therapy (PDT)	○	○	○	○	○	○
Strontium therapy	○	○	○	○	○	○
BCG vaccine	○	○	○	○	○	○

Intra-lesional injection of chemotherapy e.g. mitomycin	○	○	○	○	○	○

Feel free to list any additional treatments not included in the list above, and response to treatment here.

Final question

How did you **first** hear about this survey?

- Through a friend
- Via an online equestrian forum
- Advertised in "Horse and Hound" magazine
- Advertised in "Your Horse" magazine
- Advertised in another magazine
- Via social media (facebook or twitter page)
- Other

If you have any brief comments regarding the survey that you would like to leave, please feel free to do so below.

Free prize draw

https://svs.onlinesurveys.ac.uk/prize-draw-details

Thank you for completing this suvey. Your help is greatly appreciated. If you would like to be entered into a free draw for an iPad pro, follow the link above to enter your details.

Key for selection options

1.a.i - If your horse was sold or has died, how old was he/she when you last owned him/her?

A foal 0-5 months of age
A foal 6-11 months of age
1 year of age
2 years of age
3 years of age
4 years of age
5 years of age
6 years of age
7 years of age
8 years of age
9 years of age
10 years of age
11 years of age
12 years of age
13 years of age
14 years of age
15 years of age
16 years of age
17 years of age
18 years of age
19 years of age
20 years of age
21 years of age or older

2 - How old is your horse this year?

1 year
2 years
3 years
4 years
5 years
6 years
7 years
8 years
9 years
10 years
11 years
12 years
13 years

14 years
15 years
16 years
17 years
18 years
19 years
20 years
21 years or older

5 - How old was the horse when you got him or her?

Home bred
Less than 1 year
1 year
2 years
3 years
4 years
5 years
6 years
7 years
8 years
9 years
10 years
11 years
12 years
13 years
14 years
15 years
16 years
17 years
18 years
19 years
20 years
21 years or older

6 - During what season of the year did you purchase this horse?

Spring (March, April, May)
Summer (June, July, August)
Autumn (September, October, November)
Winter (December, January, February)
Don't remember
Not applicable (homebred)

7 - Which UK region is this horse kept in for most of the year?

Northern Ireland
Scotland
Wales
North East England
North West England
Yorkshire and the Humber

East Midlands
West Midlands
South East England
South West England
Greater London
East Anglia

15 - In which month did your horse first have laminitis?

January
February
March
April
May
June
July
August
September
October
November
December
Don't know

16 - In which year did your horse first have laminitis?

2016
2015
2014
2013
2012
2011
2010
2009
2008
2007
2006
More than 10 years ago
Don't know

18 - What was your horse mainly used for before his or her laminitis? ***Select one box only.***

Eventing (affiliated)
Show jumping (affiliated)
Dressage (affiliated)
Hacking
General riding/ unaffiliated competition
Hunting
Showing
Polo
Dressage
Racing (includes flat, national hunt and point to point)
Endurance

Breeding
Youngstock
Non- ridden companion
Other

26 - In which month did headshaking first begin?

January
February
March
April
May
June
July
August
September
October
November
December
Don't know

27 - In which year did headshaking first begin?

2016
2015
2014
2013
2012
2011
2010
2009
2008
2007
2006
More than 10 years ago

37 - What age was your horse when you first noticed a sarcoid or sarcoids?

Less than 1 year of age
1 year of age
2 years of age
3 years of age
4 years of age
5 years of age
6 years of age
7 years of age
8 years of age
9 years of age
10 years of age
11 years of age
12 years of age
13 years of age

14 years of age
15 years of age
16 years of age
17 years of age
18 years of age
19 years of age
20 years of age
21 years of age or older
At purchase

38 - At what time of year did you first notice a sarcoid or sarcoids on your horse or pony?

Spring (March, April, May)
Summer (June, July, August)
Autumn (September, October, November)
Winter (December, January, February)
Can't remember
Unsure - they were present when I bought him or her

41 - What is the distance to the closest cattle farm from where your horse is kept?

My horse is kept on a cattle farm
Less than 1 mile
Between 1 and 5 miles
Between 6 and 10 miles
Greater than 10 miles
Unsure

Appendix Two

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Appendix Three

Guidelines issued to centres for diagnosis.

Horses should have been diagnosed with trigeminal-mediated headshaking.

i. **Gold standard:** The gold standard for this is likely to be proof that the trigeminal nerve is sensitised, obtained by performing somatosensory-evoked potentials. However, these must be performed under general anaesthesia.

ii. **History, signalment, observation:** History, signalment and observation are likely to give you your index of suspicion for trigeminal-mediated headshaking. Headshaking is often acute in onset although some cases will be insidious in onset. Onset typically occurs between the ages of 5 and 12 years. About one quarter of trigeminal-mediated headshakers will improve when wearing a nose-net, so improvement with a nose-net is consistent with trigeminal-mediated headshaking, although a failure to improve with a nose-net does not rule out this diagnosis. I would not expect trigeminal-mediated headshakers to respond to administration of phenylbutazone or systemic or inhaled corticosteroids. They might respond to medication such as carbemazapine or gabapentin. Headshaking is usually predominantly vertical and often accompanied by sharp, vertical twitches. There are usually signs of nasal irritation, such as snorting, rubbing the nose on surfaces or legs and sometimes striking at the nose. Signs may be seen at rest in the stable and or field but are usually worse at exercise. Although they may be worse when ridden than on the lunge, signs would usually be seen at exercise without a rider. About one third of cases are seasonally affected, and if so these are usually Spring/Summer affected. Some horses will show signs when outside, but not inside, on the same day.

iii. **Are signs of headshaking due to facial pain?** If possible, demonstrate that the horse is headshaking due to facial pain. This would be demonstrated if the horse shows a positive response to diagnostic local anaesthesia of the trigeminal nerve. Only two sections of this nerve are practically accessible for infiltration of local anaesthetic. The most rostral part of the infraorbital nerve may be anaesthetised, which is best accessed as far caudally as possible as it emerges at the infraorbital foramen. It is relatively simple to perform but there is evidence to suggest that response is usually poor. The poor response may be that only a small portion of the nerve is affected by the local anaesthetic in this position. Trigeminal-mediated headshakers usually show signs of nasal irritation.

Innervation to the nasal mucosa is from the caudal nasal nerve, a branch of the infraorbital nerve which runs parallel to this nerve before branching in the caudal nasal foramen, usually caudal to the rostral aspect of teeth 109/209. Infiltration of local anaesthetic at the infraorbital foramen would not involve the caudal nasal branch and involvement of this branch may be important. It is perhaps because of this that results from diagnostic local anaesthesia of the caudal portion of the infraorbital nerve, before it enters the infraorbital canal, are better. A positive response to diagnostic local anaesthesia of the infraorbital nerve would be consistent with headshaking due to facial pain, although a negative result would not refute it as there are many limitations to the technique.

iv. **Is there gross pathology which could be responsible for causing facial pain?** The next stage is to look for any gross pathology which could be responsible for the facial pain. Where an abnormality is found, it could be treated and then the horse observed to see if signs of headshaking are resolved, as abnormalities may be incidental. I perform upper respiratory tract and guttural pouch endoscopy, oral examination, basic ophthalmic examination. Where possible, computed tomography of the head should be performed and, if not, radiographs of the head performed.

v. **Grade the severity of headshaking.** This may be graded as: 0/3 = no headshaking; 1/3 = headshaking at exercise but insufficiently severe as to interfere with ridden exercise; 2/3 = headshaking at exercise, of a severity sufficient to make riding impossible or dangerous; 3/3 = headshaking even at rest, in the stable and/or field. Please contact me to discuss suitability for treatment, if you have any cases which do not meet these diagnostic criteria.

Appendix Four

Data collected from owners at follow-up.

Centres were asked to complete the following information during telephone follow-up to owners:

Number of procedure	Date	Complications? If so, details	Remission (back to ridden work at previous level or above)?	Length of remission	Date of last follow-up
1			Yes / No		
2			Yes / No		
3			Yes / No		
4			Yes / No		
5			Yes / No		
6			Yes / No		

Appendix Five

Other treatments attempted prior to referral for EquiPENS™

TREATMENT	NUMBERS OF HORSES
Omeprazole	1
Suspension of powdered Sarracenia purpurea (Sarapin[2]) injected subcutaneously at the infra-orbital foramina	1
Cellulose based nostril powder spray 'Nostril Vet[3]'	3
Application of petroleum jelly to the inside of the nostrils	3
Acepromazine[4]	1
Valerian	1
Melatonin	1
Salt supplementation	2
Feeding spirulina	1
Feeding a low starch diet	1
Taurine supplementation	1
Allergen immunotherapy	1
Fly repellent	1
Ceratohyoidectomy	1
Extraction of the first pre-molars	1
Extraction of a molar and supranummerary tooth	1
Diastema treatment	1
Medication of the temporomandibular joint with corticosteroid	3
Medication of the nuchal bursa with corticosteroid	1
Cranial therapy	2
Acupuncture	6
Laser treatment	1
Ultrasound treatment	1
Sinus lavage	1
Riding in the dark	1
Ear covers	3
Riding in a headcollar	1
Padding the poll under the bridle	1
Application of magnets to the headcollar	2
Bitless bridle	6
'Micklem'[5] bridle	7
Bucket nose muzzle	1