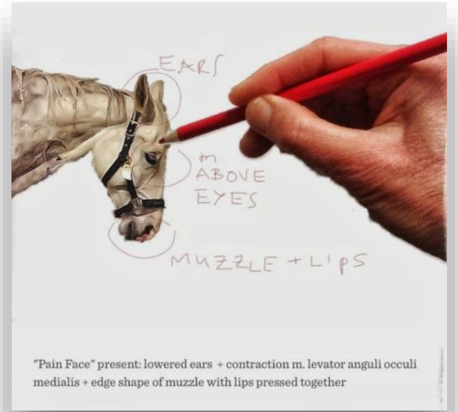
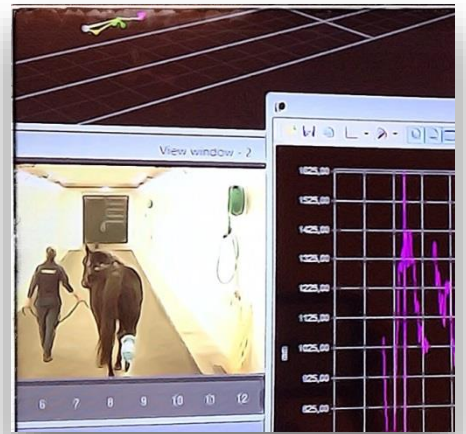
Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Veterinary Medicine and Animal Science
Department of Clinical Sciences

No Pain, More Gain? Evaluating Pain Alleviation Post Equine Orthopedic Surgery Using Subjective and Objective Measurements





Britt Alice Coles

Uppsala
2016

Degree Project 30 credits within the Veterinary Medicine Programme

ISSN 1652-8697
Examensarbete 2016:41

No Pain, More Gain? Evaluating Pain Alleviation Post Equine Orthopedic Surgery Using Subjective and Objective Measurements

En utvärdering av smärtlindring post ekvin ortopedisk kirurgi genom subjektiva och objektiva mätmetoder

Britt Alice Coles

Supervisor: *Pia Haubro Andersen, Department of Clinical Sciences, SLU*

Assistant Supervisor: *Marie Rhodin, Department of Clinical Sciences, SLU*

Examiner: *Karin Holm Forsström, Department of Clinical Sciences, SLU*

Degree Project in Veterinary Medicine

Credits: *30*
Level: *Second cycle, A2E*
Course code: *EX0736*

Place of publication: *Uppsala*
Year of publication: *2016*
Number of part of series: *Examensarbete 2016:41*
ISSN: *1652-8697*
Online publication: *http://stud.epsilon.slu.se*

Key words: *horse, equine, pain evaluation, pain face, arthroscopy, NSAID*
Nyckelord: *häst, ekvin, smärtutvärdering, smärtansikte, Artroskopi, NSAID*

Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Veterinary Medicine and Animal Science
Department of Clinical Sciences

"One of the psychological curiosities of therapeutic decision making is the withholding of analgesic drugs, because the clinician is not absolutely certain that the animal is experiencing pain. Yet the same individual will administer antibiotics without documenting the presence of a bacterial infection. Pain and suffering constitute the only situation in which I believe that, if in doubt, one should go ahead and treat."

Dr. Lloyd Davis (1983: p. 175) *Animal Pain: Perception and Alleviation*

Fig. 1. *Location of horse indicative of a high pain score.*
(Textures graphically altered to lessen identifiable features.)

SUMMARY

As “you can’t manage what you can’t measure,” there has been a quest to identify the best measures of pain to effectively and timely manage equine pain. Adequate pain management after a surgical procedure is imperative to address postoperative pain that negatively affects numerous organs. Arthroscopy is a frequently used surgical procedure: making an evaluation of equine post-arthroscopic pain cardinal. Furthermore, an evaluation of such pain using subjective pain scoring *and* objective four beat gait analysis scoring had yet to be explored.

The objectives of this case study series were to: study a potential varying degree of pain after equine arthroscopy in relation to varying intra-articular tissue damage; survey the pain relief of systemic NSAID analgesics post equine arthroscopy; and to observe a possible difference in equine pain behavior in human presence vs. absence. This observational unmatched paired cross-sectional qualitative case study series included six horses. The study used three subjective modalities and one objective modality to score pain: a composite Equine Pain Scale (EPS) score based on blinded-rated video footage; an Arthro and a VAS score as proxies for tissue damage; and an objective optical symmetry measurement (OS) score to evaluate low-grade lameness at walk. These modalities were used to compare potential pain states 12 hours before and 8-48 hours after surgery before and after NSAID administration. During the two months collection period, 277 individual video segments were recorded and 40 OS-readings were collected and analyzed. The results are illustrated in descriptive graphics.

The contradictory Arthro/VAS score findings illustrate the complexity of pathology and subsequent pain expression as well as the difficulty of designing a general tool to foresee individual future pain scenarios. However, both the subjective EPS and the objective OS scores seem to illustrate a common undulating pattern that could be a mirroring of an increased pain state before NSAID-administration and a decreased pain state post NSAID-administration, with the one caveat that there were two differing OS parameters of interest. This study also raised questions in relation to a differing efficacy of the analgesic and the duration of a postsurgery pain state. These findings could point to a potential clinical need for an alternate multi-modal medical approach and/or prolonged medication duration/increased intervals as needed for certain cases. Finally, in regard to hidden pain behaviors, there were examples of an equine increase in gross pain behavior, restless activity, and horses positioning themselves towards the back of the stall when there were no humans present.

Overall, this case study series seems to suggest the usefulness of a simple and cheap subjective pain score measuring system such as the EPS as it is possibly reflected by a high-tech complex objective optical symmetry measurement system. The results of the latter are among the first reported for the use of this new algorithm of fall 2015. As there is no golden standard for uncovering the true equine pain state, there might be added power in attempting to describe pain states using differing but complimentary pain modalities. Nevertheless, any suggested findings of this highly limited case study series should primarily be regarded as potential seeds for future hypotheses generation for future large targeted quantifying studies to validate or refute this study’s suggested findings and possible clinical relevance. No pain, more gain?

SAMMANFATTNING

Idag finns det ett behov av att identifiera dem bästa sätten att mäta smärta för att i tid kunna effektivt behandla smärta hos häst. Tillräcklig smärtlindring efter kirurgiska ingrepp är nödvändigt för att adressera postoperativ smärta som påverkar flera organ negativt. Artroskopi är en frekvent använd kirurgisk procedur, vilket gör en utvärdering av ekvin post-artroskopisk smärta av yttersta vikt. Dessutom hade en smärtutvärdering med hjälp av både en subjektiv värdeskala och ett objektivt optiskt rörelseanalyssystem i skritt ännu inte utforskats.

Syftet med studien var att: studera en potentiell varierande grad av smärta efter ekvin artroskopi i relation till varierande intra-artikulär vävnadsskada; undersöka smärtlindring av en systemisk administration av NSAID analgesi efter ekvin artroskopi; och att observera en möjlig skillnad i ekvint smärtbeteende i människors närvaro vs. frånvaro. Denna observerande parade kvalitativa fallstudie inkluderade sex hästar. Studien använde tre subjektiva och en objektiv modalitet för att poängsätta smärta: ett Equine Pain Scale (EPS) värde baserat på videomaterial; ett Arthro och ett VAS värde för vävnadsskada; och ett objektivt optiskt symmetrimätningssystemvärde (OS) för att utvärdera låg-gradig hälta vid skritt. Dessa modaliteter användes för att jämföra potentiella smärtförhållanden 12 timmar innan och 8-48 timmar efter kirurgi samt före och efter NSAID administrering. Under en två månader lång insamlingsperiod spelades 277 individuella videosegment in och 40 OS-mätningar samlades in och analyserades. Resultaten illustreras med hjälp av deskriptiv grafik.

De motsägelsefulla Arthro/VAS fynden illustrerar komplexiteten av patologin med påföljande smärtuttryck så väl som svårigheten i att utveckla ett generellt redskap för att förutse individuella framtida smärtscenarier. Både dem subjektiva EPS och objektiva OS värdena verkar illustrera ett vågmönster som skulle kunna tolkas som en spegling av ett ökat smärttillstånd före NSAID administration och ett sänkt smärttillstånd efter NSAID administration, med ett caveat: det fanns två olika OS parametrar av intresse. Studien väcker också frågor i relation till en möjlig varierande effektivitet av analgesin och duration av smärta efter det kirurgiska ingreppet. Dessa fynd skulle kunna peka på ett potentiellt kliniskt behov av ett alternativt multi-modalt medicinskt smärtprotokoll och/eller förlängd medicinering/ökade intervaller vid behov för vissa fall. Slutligen, hos hästpatienter fanns det exempel på en ökning av kraftigt synliga smärtbeteenden, rastlös aktivitet och att hästarna positionerade sig i bakre delen av boxen av när människor inte var närvarande.

Denna fallstudieserie verkar stödja användandet av ett enkelt och billigt subjektivt smärtutvärderingssystem som EPS som verkar reflektera ett högteknologiskt komplext objektivt optiskt rörelseanalyssystem. Dessa resultat är bland dem första att rapporteras för denna nya algoritm hösten 2015. Eftersom det inte finns något facit för att mäta det sanna smärttillståndet kan det finnas en styrka i att försöka beskriva smärttillstånd med hjälp av olika men kompletterande smärtmodaliteter. Alla föreslagna fynd måste dock tolkas utifrån kontexten av en högst begränsad fallstudieserie. Fynden borde därför betraktas som potentiella frön för framtida hypotesgeneration för större riktade kvantitativa studier som skulle kunna validera eller förkasta dessa fynd och deras möjliga kliniska relevans.

CONTENT

LIST OF ABBREVIATIONS

NSAID –Non-Steroidal Anti-Inflammatory Drugs

CPS - Composite Pain Scale

EPS – Equine Pain Scale

VAS – Visual Analagous Scale

IRT – Intermediate Ridge of Tibia

BID – “bis in die” to administer (medicine) two times a day

QD – “quaque dies” to administer (medicine) once a day

INTRODUCTION

Background

There is a saying that "you can't manage what you can't measure." Due to the complex nature of pain, measuring equine symptoms of pain has in the past - at worst - been ignored or - at best - been reduced to quickly identifiable and easily quantifiably physiological numerical measures such as heart rate, respiratory rate, and blood pressure. However, these readily made measurements are not the most relevant indicators to identify, evaluate, and thus effectively manage pain in horses (Raekallio *et al.,* 1997; Valverde & Gunkel, 2005; Driessen, 2007; Bussieres, 2008; Gleerup & Lindegaard, 2015; de Grauw & van Loon 2015).

Today, there is a growing interest towards advancing the science of pain evaluation and subsequent pain management in equine veterinary medicine (Muir, 2010). Withholding pain relief due to old dogmas such as: pain having a protective component; pain being preferable to any possible drug side effects; pain control masking concurrent pathologies; and pain control being too expensive, is now being questioned point by point by emphasizing continuous assessment of dosage, administration path, short-term analgesic solutions, affordable alternatives, and client communication about animal comfort (Taylor *et al.,* 2002).

This advancement and interest in adequate pain relief has been heavily dependent upon the discovery and testing of various composite pain scoring systems (Pritchett *et al.,* 2003; Bussières *et al.,* 2007; Driessen, 2007; Loon *et al.,* 2010; Wagner, 2010; Sutton *et al.,* 2012; de Grauw *et al.,* 2015) to study both colic and orthopedic associated pain. The latter is the focus of this study, with the particular aim of looking at post-operative pain after arthroscopic procedures. Arthroscopy is a frequently used diagnostic as well as therapeutic surgical tool that has greatly transformed orthopedics in horses (McIlwraith *et al.,* 2005). Therefore, evaluating the potential degree of equine post-operative pain after arthroscopy is imperative to addressing possible improvements needed for optimal pain management.

Why is postoperative pain management important? Postoperative pain affects a number of organs through neuroendocrine and metabolic responses to pain sensation. These responses interfere negatively on the healing patient through various catabolic mechanisms (Hellyer *et al.,* 2007; Gaynor & Muir, 2015). In human medicine, postoperative pain management is regarded an important investment that pays off through greater patient comfort as well as reducing morbidity and hospital duration (Stoelting, 2007). Similar concerns have been raised in regard to animals (Mathews, 2000; Baller *et al.,* 2002; Taylor *et al.,* 2002; Goodrich, 2009; Berry, 2015). Pain management in horses can be challenging, however, as researchers have noted that horses tend to hide gross pain behavior in the presence of human observers (Price *et al.,* 2003; Gleerup, 2014).

While evaluations of post-operative pain of arthroscopic equine patients using behavior-based systems (Rice, 2003) or subjective lameness scores at trot (Walliser *et al.,* 2015) have previously been investigated, an evaluation of equine post-operative pain following arthroscopic procedures using a combined subjective pain scoring *and* objective four beat gait analysis system had yet to be explored.

Finally, this study offered an opportunity to evaluate current standard analgesic protocols in a particular context and location with the potential to offer recommendations for preventative as well as palliative treatment to address possible un-addressed orthopedic pain states.

Research objectives

A review of seminal literature on the various manifestations and alleviation of animal pain - with an emphasis on the equine species - set the stage for this study. Subsequently, this review formed the foundation from which the following objectives below were drawn.

1. *Objective*: to study the possibility of foreseeing the degree of pain after arthroscopy by contrasting intra-articular tissue damage scores (Arthro score and VAS score) produced during surgery with postsurgery subjective EPS scores and objective optical symmetry measurements (OS scores).

2. *Objective*: to survey the efficacy of a systemic routine NSAID analgesic administration during a time frame of up to 48 hours post equine arthroscopy by comparing presurgery EPS and OS scores with postsurgery scores before and after NSAID administration.

   This second objective is based on the assumption that a horse will exhibit levels of pain scores postsurgery and preNSAID administration that were not present at the intake of that patient, one day prior to surgery.

3. *Objective*: to observe the pain behavior of equine post orthopedic patients when there are humans present as well as seemingly absent from the immediate stall environment by juxtaposing EPS scores from video footage shot by research student at stall with that of remotely operated recorded video footage.

The set-up of these objectives can be compared to that of peeling an onion. The first objective can be seen as equivalent to using the initial spread of outer layers laid out on the table, by using multiple pain modalities, as a point of departure. The last objective can be likened to the last standing core as it makes use of only one pain modality to conclude the investigation. Successional presentation of results and discussion will follow this same order of unraveling.

LITERATURE REVIEW

Understanding the physiology of pain

Definition of pain

What is pain? In trying to answer this question as it relates to animals, key animal pain researchers have used the definition provided by the International Association for the Study of Pain as a starting point: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage…The inability to communicate verbally does not negate the need for appropriate pain-relieving treatment” (Gaynor & Muir, 2015: p. 63). In short, a veterinarian have a duty to attend to the pain of a patient not based on an animal’s ability to successfully express pain but based on the medical knowledge of an animal’s ability to fully experience pain.

Neurophysiological mechanisms of pain

The ability to experience pain is based on neurophysiological wiring processes of nociception that are shared by humans as well as non-human mammals (Gaynor & Muir, 2015). Nociception is the term used to describe a physical response that includes detection, transduction, transmission, and perception of the message of encountered tissue-damaging stimuli. These stimuli of tissue damage activate peripheral sensory nociceptors, specialized sensory nerve receptors, found at the peripheral end of fast-conducting myelinated A-delta and slow-conducting unmyelinated C nerve fibers. These nerve fibers recognize and transform the incoming message of tissue damage before sending it on as an electrical signal. The electrical signal is then sent from the peripheral nerve ending to the dorsal horn of the spinal chord where the peripheral nerve turns over the signal of tissue-damage to the next neuron in line of messenger nerve fibers. In these synapses of information exchange between nerve fibers exist neurotransmitters and neuromodulators that have the potential to change the signal volume of the message transmitted in the nerve fibers. These second set of nerve fibers then, in turn, continue the transmission of the stimuli message to the headquarters of neuronal messaging, the sensory cortex of the brain, via the thalamus. It is here in this last station, the sensory cortex, that the transmitted signal is processed to create the concept of perceived conscious pain response. As the signal travels from the brainstem to the cortex, there is a parallel process where the signal of tissue damage is sent to various locations in the brainstem for unconscious responses, including certain autonomic responses (Hellyer *et al.*, 2007; Stoelting, 2007; Gaynor & Muir, 2015). To complement the afferent sensory pathway just described, there are known efferent pathways. One of these efferent pathways is inhibitory, with the periaquaductal grey in the brain stem playing an important part as it modulates descending pain signals with the help of endogenous opioids (Gaynor & Muir, 2015).

Neurological basis of articular pain

Joints are wired with two kinds of nerves to help communicate changes related to trauma and/or tension of articular structures. They are primary and accessory articular nerves containing both myelinated and unmyelinated nerve fibers with nerve endings that communicate through four different kinds of receptors (mechanical or nociceptive) in different locations of the joint. Type 4 endings are unique in that they are polymodal and thus can respond to chemical as well as thermal stimuli in addition to mechanical stimuli, where they are distributed (Fig. 2).

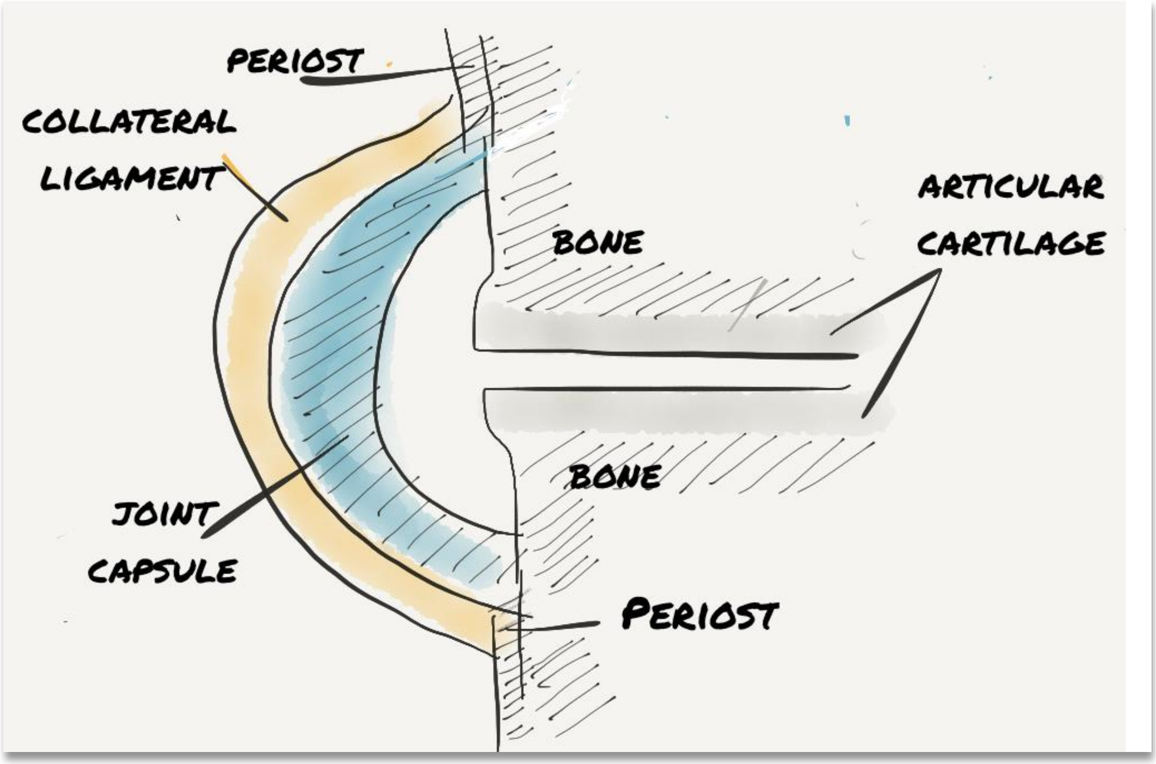


Fig. 2. *Articular location of type 4 nerve endings marked with overlaying diagonal striped pattern. Illustration created based on Caron, 1996.*

In terms of distribution, of all the structures of the joint, articular cartilage is the one structure that is not innervated by any of the four receptors mentioned above, as opposed to the subchondral bone, joint capsule, intra- and periarticular ligament and menisci (Caron, 1996; Weeren *et al.,* 2010).

In addition, the nociceptors can interact with mechanoreceptors as in the case of orthopedic pain originating from chronic degenerative joint disease (osteoarthritis/osteoarthrosis). This pain originates from two different kinds of stimuli: mechanic stimuli (due to changes such as outer physical force) picked up by mechanoreceptors and chemical stimuli (due to inflammatory mediators in the tissue) picked up by nociceptors. The two different receptors can interact as in when a mechanical receptor is chemically sensitized by an inflammatory soup of endogenous pain-related mediators, leading to possible hyperalgesi with high threshold sensory nociceptors being activated by low intensity stimuli (Weeren *et al.,* 2010).

Pharmaceutical interventions of neuronal pathways

Depending on the pain state, pharmaceutical interventions such as analgesics can modify a message of painful stimuli in one or several locations as it travels to (the afferent sensory pathway) or from the CNS back to the spinal chord (the efferent inhibitory pathway). For example, peripherally, the signal of tissue injury is augmented (or sensitized) to the sensation of pain, with the help of inflammatory mediators. NSAIDs can block the production of these inflammatory mediators at the local site of tissue damage, thus changing the sensation of pain by ”turning down the volume” of the peripheral signal. It has been suggested that the major analgesic component of NSAIDs is this local anti-inflammatory response and reduction of local swelling as opposed to a more central function (Moses & Bertone, 2002). Systemic opioids work centrally, however. In the spinal chord and brain, such a systemic pharmaceutical intervention modify afferent pain transmission and effect efferent pain-modulating transmission from the brainstem back to the spinal chord through the three opioid receptors (Hellyer *et al.,* 2007; Stoelting, 2007). In addition, if applied intra-articularly, locally administered opioids lower the volume of nociceptive input peripherally in the articular afferent sensory pathway (Baller, 2002) as peripherally opioid μ-receptors have been found in the equine synovial membrans (Sheehy *et al.,* 2001). These receptors are upregulated in the case of articular inflammation and a selective administration can therefore potentially be more effective (Valverde & Gunkel, 2005). An experimentally induced synovitis pharmacokinetic study documenting the local anti-inflammatory and analgesic effects of deposited intra-articular opioids supports such a peripherally mediated effect (Lindegaard *et al.,* 2010a). Subsequently, the knowledge and application of a range of pharmaceutical targets point to the strength of multi-modal pain control.

Evaluating pain

The need for postoperative pain assessment

A number of researchers have pointed to the need for adequate postsurgery pain relief to support anabolic healing processes, a positive energy balance, and overall client comfort as well as minimize the risk of a wind-up pain response and prolonged hospital duration for animal patients (Bonica *et al.,* 1992; Mathews, 2000; Baller *et al.,* 2002; Taylor *et al.,* 2002; Goodrich, 2009; Berry, 2015). In the specific case of orthopedic patients, Goodrich point to the risk of support-limb laminitis in the face of insufficient perioperative pain alleviation (2009). She writes: “Poorly planned pain management may obviate the best and most elegant orthopedic surgical procedure” (Goodrich, 2006: p. 611).

According to Hall (1992), pain-relief related to most surgery procedures is valid for a majority of animal individuals within a time window of 24-48 hours after surgery. However, finding the right indirect external parameters that adequately mirror the internal mental experience of an animal makes for a challenging process (Hansen, 1997). One would be remiss if one would not touch briefly upon the emotional facet of pain perception: suffering (Taylor *et al.,* 2002). In addition, Hellyer and his colleagues point to neuroanatomical evidence of wiring between the limbic system – responsible for the brain’s emotional filter – and the afferent pain pathways of humans and animals (2007). Consequently, the need for pain alleviation needs to be framed in a neurophysiological context of physical as well as emotional well-being. Finally, there is also the issue of intra-species variation in response to pain as well as to administered pain relief drugs that further complicate the evaluation of post-operative pain needs (Raekallio *et al.,* 1997b).

Pain assessment of orthopedic pain through physiological parameters

In the 1990s, pain evaluation of post-orthopedic states concentrated on physiological parameters that reflected metabolic and hormonal changes (Robertson *et al.,* 1990; Raekallio *et al.,* 1997). Robertson’s earlier study found a variance in plasma β-endorphins that differed during intra-articular manipulation (high levels) vs. suturing and bandaging (low levels). A few years later, Raekallio's study found that the levels of plasma β-endorphins stayed higher 6 to 12 hours after surgery, a much longer time period than that reported by Robertson's study (1997a). The latter study findings suggested that subjective pain scores had the best correlation with only one of the parameters collected, β-endorphins, a few days after surgery, but not immediately after (Raekallio *et al.*, 1997a). However, in another study that same year, the authors deduce, that this time, β-endorphins did not correlate to the subjective pain parameters as they returned to baseline measures 2 hours after surgery (Raekallio *et al.*, 1997b).[1] As noted by the varying results above, physiological parameters of hormone substances are often found to have varying correlation to pain (de Grauw & van Loon, 2015). In addition, these physiological parameters are problematic in that that they can be influenced by other treatments or concurrent pathologies (dehydration, cardiovascular compromise etc) and the testing itself is invasive with possible delay in turn-around time for test results being counter-productive for daily decision-making (Gleerup & Lindegaard, 2014).

Composite pain scales: incorporating behaviors in pain scoring

As several researchers discovered that physiological parameters were inferior to behavioral measures to correlate internal pain states, comprehensive studies were performed to identify certain behaviors that could be connected to post-operative orthopedic pain with the goal of developing a more effective evaluation tool. One such study used repeated behavioral observations (2x1 minutes at 5 minutes intervals) and a subjective pain score to create a total post-operative pain severity index (Raekallio *et al.*, 1997b) that also included physiological parameters such as heart rate and plasma humoral readings for evaluating pain post arthroscopy. Nevertheless, the researchers concluded that their behavioral assessment had failed to add any additional pain evaluation value to the subjective pain score and physiological parameters.

A later study complemented physiological parameters (heart rate) with a more time-intensive method of videotaped activity time budgets, starting 24 hours prior to surgery and lasting up to 48 hours post arthroscopic surgery (Price *et al.*, 2003). The Price study suggested the possibility of having identified pain-related behaviors of interest such as restlessness, changes in exploratory movement and locomotion. Furthermore, they note that certain expressive pain behaviour – such as weight shifting of legs as well as restlessness - could only be gathered from watching time-lapse video footage but not when researchers were present in person. However, these researchers did not share the current interest in an equine facial pain expression. As they discuss not being able to register facial expressions on tape from afar, they argue that such expressions ”may not be particularly useful for evaluation of post-operative pain in horses” (Price, 2003:p. 136). A few years later, Driessen looked at a number of studies and compiled a list of behaviors that differed between musco-skeletal pain vs. abdominal pain (2007). The list for the former category included behaviors such as restlessness, increased weight shifting of limbs, abnormal gait, change of head positions, abnormal posture in stall, and reduced locomotion.

[1] β-endorphins are endogenous opioids peptides that can produce analgesia through a suppresion of nociception (Gaynor & Muir, 2015).

Looking for a pain evaluation tool that was academically sound in a systematic consistency as well as high in reproducibility, Bussières and his fellow researchers claim to have explored the first *multifactoral* composite pain scale (CPS) to evaluate and numerically grade pain in the context of an experimentally induced acute pain (2008). This pain scale incorporated various behaviors (interactive behaviour, response to palpation of painful area, kicking, pawing, posture, head movement and appetite) as well as physiological parameters (heart rate, respiratory rate, digestive sounds, rectal temperature) to evaluate the pain alleviation offered by the analgesic offered. They found that the physiological parameters investigated had a poor correlation to orthopedic pain (except for noninvasive blood pressure) but that with the help of the behavioral parameters (with the most valid parameters being posture, pawing, kicking, head movement and response to palpation), they were able to confidently assess three different levels of pain. Bussières' model was validated by van Loon two years later, including postoperative pain states, with van Loon suggesting that such a CSP tool could be supportive of sound objective evidence-based analgesic treatments and follow-ups as it produced high intra-observer reliability to compare the efficacy of pain control at different times (van Loon *et al.,* 2010).

The possible advantages of a composite pain scoring are several, they: raise awareness of pain and the need for alleviation; train practitioners' ability to register and quantify pain; augment intra-observer quality for validity and follow-up of pain alleviation; and aid in medical documentation purposes (Wagner, 2010).

Adding to the CSP work performed earlier, Gleerup and Lindegard suggest that Bussieres model could be improved, however, to avoid the stress of invasive testing of physical parameters and to shorten the time it takes to complete the CSP and (2015). As a case in point, the authors question not only the feasibility but also the use-ability aspect of a pain score fulfilling all of Ashley's classic animal pain scoring system that ”needs to be linear, weighted, sensitive to pain type, breed-and species-specific” (Ashley, 2005: p. 567).

Therefore, they suggest a condensed version of a CSP, the Equine Pain Scale (EPS) that omits physiological parameters altogether to focus on the following behavioral categories for all pain types: “gross pain behaviour, activity level, position in the stall, posture/demeanor, weight bearing, head position, head movement, attention towards painful area, interactive behavior, and appetite.” The two researchers add to past work by also investigating characteristics of an equine pain face, uncovering the following features as possible signs of pain: “asymmetric/low ears, angled eye/tension above the eye, withdrawn and tense stare, square-like nostrils, tension of the muzzle/strained mouth and tension of the mimic muscles” (Gleerup & Lindegaard, 2015).

In their overall review of equine composite pain scales over the last decade, de Grauw and Loon agree on the importance of a pain face as well as reducing the number of parameters in a composite pain scale to those most sensitive and specific for pain, thus producing an instrument of higher validity and of better time management use in the daily clinic work (2015).

Lameness as a behavioral indicator for pain

Lameness is a clinical sign characterized by an aberration from a normal gait pattern due to locomotor dysfunction or structural pathology caused by pain, mechanic dysfunction or both. For example, when the horse experiences pain in a hindlimb it will try to shift its weight towards the non-ailing side to minimize vertical movement of the ailing side by a combined translational/rotational movement (Fig. 3) of *tuber coxae* and *sacrale* (Buchner *et al.*, 1996).

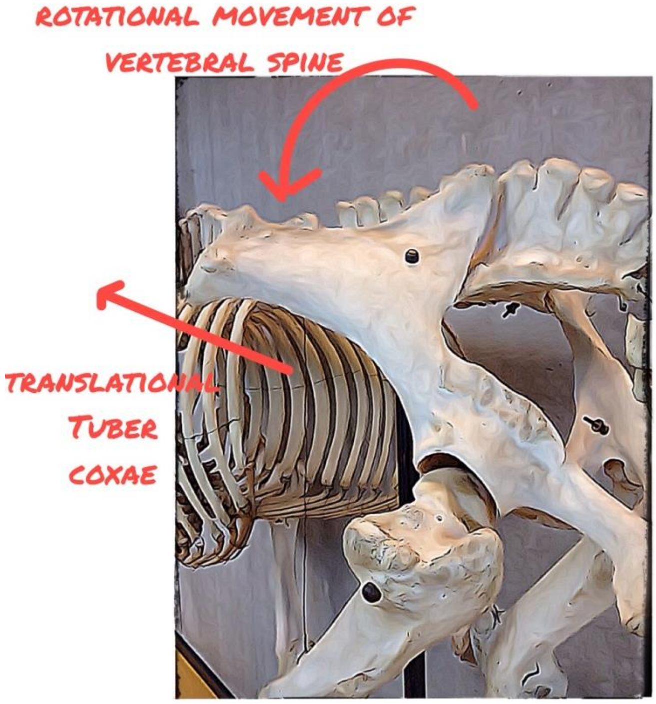


Fig. 3. *Graphic illustrating trans-rotational movement based on Buchner (1996).*

Thus creating a rear asymmetri in the form of a "pelvic hike" characterized by what is visually conceived as an increase in the pelvic area amplitude when the ailing leg hits the ground and a decrease in amplitude when the non-ailing leg hits the ground (Peham, 2001; Ross & Dyson, 2011).

Similarly, the highest and lowest points of *tuber sacrale* will also lessen in vertical amplitude on the same side as the ailing leg (Buchner, 1996). However, the amplitude of the ailing leg's *tuber coxae* will increase on the side of the ailing leg (Church *et al.*, 2009). Finally, there is a change of head movement for both front- and hindlimb lameness, though much more pronounced for the former (Buchner *et al.*, 1996).

As part of a larger welfare context, a team of researchers explored the connection between lameness and pain in a study of pathological abnormalities in working draught horses in India and Pakistan (Broster *et al.*, 2009). In this study, the researchers suggested a finding of higher lameness scores with a positive correlation to intense pain responses during digital pressure and joint manipulation of a number of regions of the affected extremities. The researchers admit, however, to the limited field circumstances of the lameness examination, devoid of further pain testing with the help of local diagnostic analgesia.

For consistency of an evaluation of lameness severity, the American Association of Equine Practitioners has established a scoring system from 0 to 5. The lowest score is representative of no lameness at all and the highest represents lameness so severe that horse is non-weight bearing of the pathological limb (Ross & Dyson, 2011).

A lameness study of subjective evaluations suggested that the evaluation of low-grade lameness can be particularly problematic to identify, with there being less consensus amongst participating veterinarians for low-grade lameness than an evaluation of lameness of a higher degree (Keegan, 2010). As with the systematic composite pain scoring described above, similar concerns have therefore been raised for the need of a systematic objective evaluation system to improve measurement and quantification of lameness for better record keeping, consistency of results, continued evaluation of treatment, and to avoid confounding factors such as individual traits, environment, and subjective bias (Keegan, 2007).

There are two types of objective evaluation methods that have been developed: kinematic (measuring movements) based systems and kinetic (measuring forces) based systems. Keegan describes these two differences accordingly: ”Kinematics describes motion, and kinetics explains motion” (2007:p. 407). An example of the former is the 4-beat gait analysis that will be described further in the methods section.

Managing pain

Comparative orthopedic postoperative analgesia

Several equine researchers (Baller, 2002; Goodrich, 2009) have advised against the old misconception to withhold analgesics as a protective mechanism post orthopedic surgery, urging instead for adequate pain relief to ensure a speedier recovery not only physically but in a larger welfare context. Horses are a particular species in that they have an innate flight response to stress, including the stress caused by pain from surgical procedures. Therefore, Valverde and Gunkel make a point of how ”a rough/violent recovery related to pain can upset hours of surgical and anesthetic efforts in a matter of seconds” (2005: p. 295), advocating not only polypharmacy but also possible polyadministration of such substances as needed. Subsequently, Goodrich advocates adjunctive perioperative protocols such as epidural analgesia, regional perineural anaesthesia or local intra-articular anaesthetics, depending upon orthopedic procedure (2009).

Nevertheless, perioperative analgesic protocols for horses lag behind those of small animal practice (Taylor *et al.*, 2002), with perioperative multimodal analgesia for arthroscopy being a case in point. NSAIDs are routinely administered before and after orthopedic surgery (Moses & Bertone, 2002) but the concurrent administration of opioids - as in human and small animal arthroscopic surgery - is not part of the standard equine surgery protocol. An equine study of Meloxicam suggested that the sole use of NSAID was adequate for pain alleviation after a particular arthroscopic intervention of addressing splint bones that had been fractured (Walliser *et al.*, 2015). The method used to ascertain degree of pain was a subjective lameness score of horses trotting and walking raising two concerns: the critique of subjective scoring of lameness as discussed earlier as well as the issue of relying on this one and only pain measure modality.[2] In addition, the question is how effective sole NSAID administration is to more invasive procedures of weight-bearing structures.

As early as in 1991, in human medicine, Stein and his colleagues published a seminal article in the New England Journal of Medicine, describing the positive effect of a low dose of intra-articular morphine after surgery in order to reduce local post-operative pain, a practice that is today is common practice in human medicine. For dogs, studies followed shortly after, documenting post-operative intra-articular morphine administration suggesting a positive effect compared to an epidural (Day *et al.*, 1995) and albeit a positive effect was shown it was found to be inferior to that of bupivacaine in another study (Sammarco *et al.,* 1996).

The administration of morphine to equine patients has been controversial due to its possible negative behavioral and ileus side effects (Bennet & Steffey, 2002; Mircica *et al.,* 2003). Feeling the need to review opioid use in the equine species back in 2002, the researchers write that, due to possible side effects such as excitation systemic ”routine, indiscriminate administration of opioids for pain relief in horses is not justified” (Bennet & Steffey, 2002:57). In regard to regional administration, the same authors write back in 2001, “However, the evidence of local opioid receptors legitimately encourages work to substantiate the value of intra-articular opioid administration to relieve joint-associated pain in horses (Bennet & Steffey, 2002: 56-57).

A retrospective case record analysis looking at the use of morphine perioperatively suggested that this substance could possibly offer a rather inexpensive alternative perioperative analgesic solution as there were no findings of differences in post-operative complications (such as colic and box-walking) in comparing those receiving morphine after induction but before surgery started at a dose of 100-170 μg/kg intravenously and those not receiving morphine when used in horses anaesthetized with romifidine, ketamine, diazepam, and halothane (Mircica *et al.,* 2003). Of the few studies up to date looking at the potential analgesic effects of intra-articular morphine they have all been in connection with alleviating pain from experimentally LPS-induced synovitis (Bussieres *et al.,* 2007; Santos *et al.,* 2009; Lindegaard *et al.,* 2010b; van Loon *et al.,* 2010). The only study up to date that looks at the effect of morphine in a perioperative setting is a study where morphine was administered with detomidine as an epidural to effectively decrease hind limb lameness following bilateral stifle arthroscopy procedures (Goodrich *et al.,* 2002).

One joint, a complexity of pain management

To conclude, as there are a number of structures in the joint with a variety of nerves of different classes, serving multiple receptors in different locations and distributions, the particular anatomical locations serving as the origin of an articular pain state can be difficult to pin down (Caron, 1996). The clinical application of such a complexity points to the need of an individual case-by-case evaluation of an administered treatment for this area (arthroscopy, lavage etc.) with the potential of applying synergistic analgesia in a variety of administrative ways to address a possible variety of different mechanisms causing an articular pain state. In

[2] The authors disclose that their 2015 study was funded by the pharmaceutical company Boehringer Ingelheim Vetmedica, Germany.

addition, the concurrent use of NSAIDs and opioids has a synergistic effect and the added advantage of individual smaller dosages and thus less side effects (Moses & Bertone, 2002).

Overview of NSAIDs

Surgical trauma induces an inflammatory response postsurgery (Valverde *et al.,* 2005). NSAIDs, highly protein bound weak organic acid substances, address this inflammatory response by impeding the production of prostaglandin and thromboxane production by inhibiting the rate-limiting metabolizing enzym cyclooxygenas (COX) that is a part of the arachidonic acid cascade (Blikslager & Jones, 2002). There are two main isoforms of COX enzymes (in addition to the newly discovered COX-3): COX-1 regulates standard body function such as gastrointestinal protection, plateletet aggregation and renal perfusion while COX-2 is more inflammation specific (Blikslager & Jones, 2002; Moses & Bertone, 2002). The older version arrest both COX-1 and COX-2, thus compromising gastrointestinal protection by affecting the mucosal barrier negatively (Moses & Bertone, 2002). The newer version, the more selective COX-2 inhibitor, is potentially gentler to this system of organs, although the comparative long-term effects between the two could be similar (Blikslager & Jones, 2002). The main side effects of NSAIDs include not only gastric ulceration but a negative effect on renal blood perfusion as well (Blikslager *et al.,* 2002). Consequently, stress and dehydration are two conditions that will augment the risk for such adverse side effects (Moses & Bertone, 2002). Finally, in addition to being antiinflammatory, NSAIDs are also antipyrrhetic and antiendotoxic (Moses & Bertone, 2002).

Flunixin meglumine

Even though phenylbutazone has generally been regarded as superior for muscusceletal pain in the past, more recent research point to similar efficacy of flunixin (Foreman *et al.,* 2012).[3] The study executed by Foreman and colleagues looked at the varying clinical efficacy of a titration of Flunixin for a pressure-induced reversible foot lameness. They found that a single dose (1.1mg/kg) of Flunixin reduced the lameness score from one to twelve hours after intravenous administration (Foreman *et al.,* 2012) for this specific orthopedic condition. This same dose-titration study did not produce findings to support a single-dose higher than the recommended 1.1mg/kg. The study did find, however, that a lower dose did not produce as consistent results for orthopedic pain at the recommended dose. The clinical application of such a finding is the recommendation for veterinary practitioners to be attentive to possible ineffective pain relief at the anti-endotoxin half- and quarter dose administration of flunixin to colic horses with laminitis (Foreman *et al.,* 2012).

According to the Saunders Handbook of Veterinary Drugs this non-selective COX has a half-life of about 2 hours and should primarily be used for short-term treatment of moderate pain and inflammation once or twice a day during a time period of up to five days (2011). As a

[3] Phenylbutazone is reported as having a more toxic safety profile than Flunixin (Papich, 2011). Even though some researchers have suggested a possible beneficial use of a combination of flunixin and phenylbutazone (Keegan *et al.* 2008) a later study did not support such a finding of combined efficacy (Foreman & Ruemmler, 2011). A more recent study indicated that combining phenylbutazone with a coxib could lead to potential renal adverse effects after 10 days (Kivett et al, 2013).

clinical application caveat in regard to switching from intravenous to oral administration as the equine patient returns home, Goodrich writes that veterinary practitioners need to consider a potential lag of 12-24 hours accommodation period, with subsequent pain (2009).

Meloxicam

This COX-1 sparing NSAID is recommended for pain relief in the context of orthopedic procedures, including pain relief and treatment of inflammation perioperatively with a suggested dose of 0.6mg/kg intravenously or orally once a day, exhibiting a half-life averaging 8.5 hours (Papich, 2011). A study from 2012 showed that there were no adverse effects at the recommended single oral dose of 0.6mg/kg during an investigative period of six weeks (Noble *et al.*, 2012). Of interest in a general orthopedic context, a cross-over study with the aim of exploring the *in vivo* effects of Meloxicam suggest that the substance not only reduces lameness and joint swelling in experimentally induced synovitis but may suppress inflammatory-induced catabolic cartilage turnover as well (de Grauw *et al.*, 2009).[4]

Overview of opioids

Opioid receptors can be divided into three different categories: μ, κ, and δ. Opiods are categorized according to their affinities and efficacy to the different categories: agonist, agonist-antagonist, antagonist. Opioid receptors within the CNS are the main target of this substance, although these receptors can be found in various locations of the body, including the equine synovial membranes (Sheehy *et al.*, 2001). Across species, opioids differ in effect and equine use has been curtailed by concerns about the behavioral effects as well as the limited duration of analgesia (Bennett & Steffey, 2002). If administered to pain-free animals or in animals mildly sedated, possible side effects of excitation have been noted (Valverde & Gunkel, 2005). Some of these possible systematic effects can be avoided, however, by administration through an epidural or articular administration (Baller, 2002; Bertone & Horspool, 2004). Morphine can also be applied intramuscularly as well as transdermally (Valverde & Gunkel, 2005). For controlling orthopedic pain, μ-receptor agonist substances such as morphine or fentanyl are considered more effective than κ agonist substances such as butorphanol (Valverde & Gunkel, 2005).

Morphine

Morphine is indicated for moderate to severe musculoskeletal pain. With intra-articular administration morphine provide animals with both anti-nociceptive and anti-inflammatory relief without the side effects typical of systemic administration or loss of motor inervation, making it a favorable postoperative option (Bertone & Horspool, 2004). The recommended dose for intra-articular administration in patients is 0.05mg/kg diluted in saline to 5mg/mL administered at 1mL per joint per 100kg of body weight (Papich, 2011). Morphine can also be administered as an epidural at 0.1mg/kg with sterile 0.9%NaCl to make 10 ml for 500kg horse or 0.05-0.1mg/kg + detomidin 30μg/kg (Knottenbelt, 2006).

[4] The authors disclose that their 2009 study was partly funded by the pharmaceutical company Boehringer Ingelheim BV, Netherlands.

MATERIAL AND METHODS

Population and sampling

Population and sample size

The reference population was the general population of horses undergoing arthroscopy. The study population was horses admitted to Uppsala Universitetsdjursjukhus (UDS) October through November 2015. The total number of patients included for this cases series was six.

Recruitment procedure

The research student, Britt Alice Coles, recruited equine patients by talking to the owners over the phone after examining the schedule of incoming patients or in person when owners arrived with the horse in the evening prior to arthroscopy. A written letter of consent was obtained from all owners after confirmation of eligibility of inclusion for study (see appendix at the end of this protocol).

Inclusion criteria for arthroscopy patients

Horses admitted to UDS in the evening before arthroscopy procedure with informed consent from owners were included in the study. In terms of joint pathology, only horses with a unilateral pathology of carpal, tarsal, fetlock or hoof joints being investigated and suited for a 4 beat gait analysis were included. The following horses were excluded from the study: patients with intra-articular fractures, pathology on more than one leg, yearlings and/or other horses who appeared to be temperamental, aggressive or unused to handling, and severely diseased horses.

Design and randomisation

This was an observational unmatched paired cross-sectional case series study. There was no randomization: all horse owners admitting their horses for arthroscopy procedures from October through November of 2015 were asked if they wanted to participate. None of the owners who were asked declined. As the horses were observed before and after arthroscopy, they were their own fall-control case.

Instrumentation

The Equine Pain Scale Composite Scoring

The Equine Pain Scale (EPS) contains nine different categories, including the Equine Pain Face, with differing individual maximum score for each category, from 2-4, to measure intensity of pain parameter. The maximum total score of all categories is 30 (see appendix).

The Equine Pain Face

A systemic observation of an undisturbed horse in the stall, without a holster on, was made to note any facial expressions that might be indicative of pain. Such expressions include a lowering of the ears, possible contraction of m. *levator anguli occuli medialis*, dilated nostrils, a more edge-shaped muzzle (as opposed to a relaxed rounded shape when not in pain), and tension of facial muscles located caudally/aborally of the muzzle. A rating of no pain face, present pain face or intense pain face is then entered into the EPS (see appendix).

Arthroscopy score as a proxy for tissue damage

This general score was created based on general pathology categories that could be applicable to any of the joints. As a first source of inspiration, the research student studied a scoring system created for arthroscopies of the metacarpal joints (Boyce, 2013). However, as there would be a wide range of joints to be examined (none of them being a metacarpal joint) the score was revised to cover a range of general categories based on a number of different pathologies of different joints as described in general equine arthroscopy literature (McIlwraith *et al.*, 2005).

The first half of the score contained notations on the id of horse, date of surgery, anatomical joint to be examined, duration of procedure, notes on any deviations from standard anesthesia/analgesia protocol, number of portal holes in the skin, position of patient, any notes on complications, surgeons VAS score of tissue damage (0-100, with 100 being the worst overall tissue damage he had encountered), prognosis (0-100%), any intra-articular administration towards the end of surgery (usually antibiotics only). The second half of the list contained 11 unweighted categories that rated pathology from 0 (absent) to 3 (severe). Pathologies noted included invasiveness of procedure, hemorrhage during or before procedure, cartilage pathology, depth of cartilage lesion, extent of cartilage damage, soft tissue pathology, synovial pathology, granuloma, and other pathology of note. The maximum total score of all categories was 33 (see appendix at the end of this protocol).

Objective motion analysis

Kinematic motion analysis systems can be divided into optical-or sensor based depending on measuring technique. For the present study an optical based motion capture system (Qualisys) was used. Numerous spherical reflective markers with a diameter of 25 mm were placed on anatomical landmarks on the head, withers, and croup of the horse. Marker positions were registered by twelve infrared cameras with a frame rate of 200 Hz.

Recordings took place indoor when the horse walked in a straight line for 20 m on asphalt. The coordinate system in the calibrated measuring volume (2x2x20m) was oriented with the x-axis horizontal and positive in the horse’s direction of motion, the Y-axis horizontal and positive to the left and the Z-axis vertical and positive upwards.

The Qualisys system was chosen out of a convenience since a joint research group of the Swedish University of Agricultural Sciences and Utrecht University (Marie Rhodin, Lars and Christoffer Roepstorff and Filipe Bragança) was already working on developing an algorithm for a 4 beated gait analysis.

Data processing

The walk of a horse is a 4-beat (number of feet hitting the ground in one stride) natural gait where the horse is never suspended in air. Lameness evaluation is usually performed in walk and trot, with the latter usually being the focus. As the horses participating in the study could only be walked right after surgery, a new algorithm was developed in the late fall by the founders of the Qualisys Track Manager to detect possible low-grade lameness in a 4 beat gait analysis.

The statistical analysis was performed by Filipe Serra Brancaga who used Matlab® (2015) to process the data generated from the motion capture system (Qualisys) collected by the research student. The reconstruction of the 3D position of each marker was based on a direct linear transformation algorithm (Q-track). The raw x-, y- and z-coordinates were exported into Matlab for further analysis. Stride split was performed and the vertical head and pelvic motion for each stride were analyzed. Local maxima and minima in the signal were identified and different variables and symmetry indexes (n=40) were calculated. The resulting numerical values were then returned to the student in Excel sheet format as well as JPEG stride split images.

For the sake of simplicity, this case study series concentrated on three of the pelvic motion variables produced by the statistical analysis. Needless to say, a horse is an one-unit locomotion where head and wither movements are affected by hindlimb pathology as well (with markers placed all on all three areas as described in the methods section) but as the primary focus of the study was to evaluate the objective motions scores in comparison with recorded EPS scores for hindlimb pathology, the choice was to narrow down the parameters with this anatomical single-minded focus for initial simplicity and expediency.

Consequently, the three paramers that were compared with the individual EPS scores and across the different case study horses were: Hip hike difference, Pelvic maximum difference, and Pelvic minimum difference. Hip hike difference calculates the difference in amplitude of right vs left *tuber coxae* in the ascending movement of the this particular area. With an ailing leg, the amplitude increases on this side. The Pelvic maximum/minimum difference calculates the difference between the two top/bottom points of the signal produced by the vertical movement of this area as the horse touches the ground with alternately the right and left hindlimb's hoof (Starke *et al.*, 2012).

Left-sided asymmetries will produce negative values whereas right-sided symmetries produce positive values. For the ease of visualization, all values were turned into absolute values, however, for a comparison with the positive EPS score numerical values. A value of 0 indicates perfect symmetry.

Study procedures

Time schedule of study

Patients were included in the study from October to November of 2015. The total duration of the study was four months (Fig. 4).

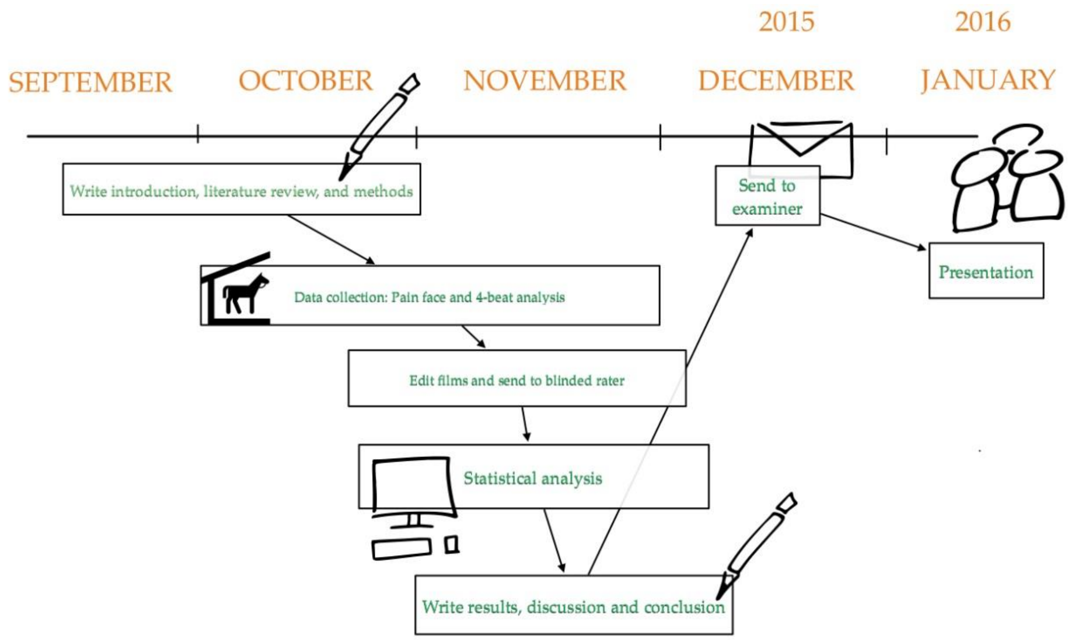


Fig. 4. *Illustration of study time schedule.*

Timeline of procedure

The patient was in the study for four days: arriving on day 0, arthroscopy procedure on day 1 and being observed postop for another 24-48 hours.

Day 0 (day of arrival):
Upon arrival, owners were asked if they wanted to participate with their horse. If they agreed, they were asked to fill in an informed consent form (see appendix at the end of this protocol). Once the horse was settled in the evening, prior to arthroscopy and prior to preop NSAID in the following morning, all equine patients in the study were videotaped in their stall to investigate whether they were exhibiting pain faces as part of a composite EPS. The patients were then walked in the calibrated measuring area for a 4-beat gait analysis. A temporary bandage was put on the location/joint to be operated on, as applicable, for the walk during measurement and then removed before leaving the horse to rest for the night.

Day 1 (day of arthroscopy):
Directly after the arthroscopy, the attending surgeon was interviewed to complete an arthroscopic score of the procedure (see appendix at the end of this protocol). The same surgeon performed all arthroscopic procedures that took place between 10:00 and 15:00. In the evening, the horses were filmed before and after administration of postop routine NSAID administration, the process starting around 90 minutes after administration.

Day 2-3 (after arthroscopy):
In the morning and evening after arthroscopy, the horses were again filmed before and after NSAID administration scheduled at 8am and 8pm. Starting in the morning after arthroscopy, the horses were also filmed and motion analysis was performed in walk before and after routine NSAID administration.

Treatment and examinations in the study

The following parameters were recorded: age, gender, breed, bodyweight and diagnosis. Other clinical parameters noted from the general medical record were: body temperature, heart rate, respiratory rate, auscultation of gastro-intestinal tract and food intake recorded daily by hospital staff. If there were any complications after surgery, these too were noted.

Standard protocol for arthroscopy

First, horses were premedicated with a single dose of acepromazin (0.03 mg/kg intramuscularly). They were then given additional premedications in the form of romifidin (0.1 mg/kg intravenously) and butorphanol (0.025 mg/kg intravenously). All horses were also administered a preoperative single dose of flunixin meglumine (1.1 mg/kg intravenously) as well as a systemic perioperative antibiotica (benzylpenicillin 10 mg/kg intravenously). Then anesthesia was induced with ketamine (2.2 mg/kg intravenously) and bensodiazepin (0.03 mg/kg intravenously). Maintenance of anesthesia was upheld with isoflurane (MAC 1.3%) and oxygen in closed-circuit system. The joint of interest as well as surrounding area was clipped, scrubbed, cleaned and prepared aseptically. All horses were positioned in a dorsal position. Standard arthroscopy procedures were then executed. At the end of the procedure, joints were lavaged and evacuated. Skin portal incisions were then closed with nonaborbable 2-0 Prolene ® using a cruciate pattern. At the end of the surgery, an intra-articular deposit of amikacin (Biklin®) was administered when the surgeon felt there was an indication based upon pathology. Intra-articular analgesics were never administered. Sutures were then protected with an application of sterile bandage, cotton wool, gauze and adhesive bandage. Postsurgery, flunixin meglumine was re-administered (1.1 mg/kg intravenously) as a post-op analgesic in the evening of the surgery and then 8am in the morning and 8pm the next day. If the horse spent another day in the clinic postsurgery, flunixin was administered once a day. Horses were usually discharged the day after the surgery. Home-care recommendations included a prescription of oral meloxicam (0.6 mg/kg) to be given once a day for 10 days.

Video filming procedure

Initially, for the overall pain composite scoring, the horse was first videotaped in an overall wide full shot and then approached and fed a snack at the end. The patient was then left alone again for a few minutes before the face was filmed without a holster. However, it became apparent that the administration of a snack would get the horse to start foraging again directly after, delaying the filming of a potential pain face. The order was therefore switched after the first three horses, with a close-up filming of a potential pain face being first recorded and then the wide shot was executed. If the face had a wound or other distinguishing features, filming was done of the other side. For the face, the horse was shot from the side and slightly from the front so eye, nostrils, ears and facial side muscles could be seen, for a duration of 2-3 minutes. For the remotely controlled footage only a wide shot was possible. The small portable camera with a Bluetooth connection was mounted to the stall. The horse could then be observed and recorded about 10 meters away from the stall.[5] The remotely controlled video footage (Fig 5)

[5] Signage was clearly posted on the stall close the camera to inform staff that the remote camera was not there to monitor neither record anyone tending to the horse.

of the undisturbed horse took place 10-20 minutes prior to the regular video footage with the research student present by the stall.

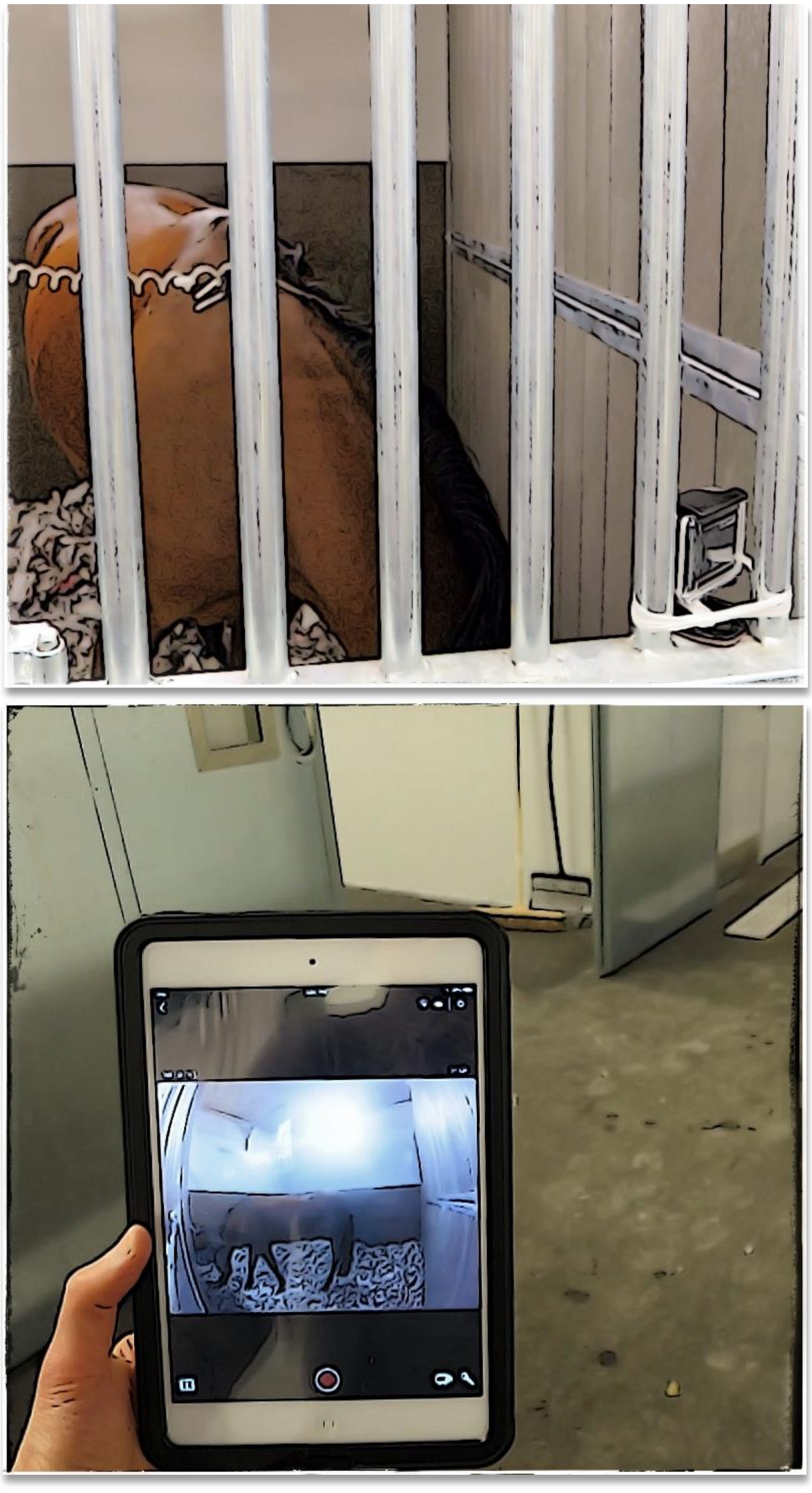


Fig. 5. *Illustration of remote video set-up. Note small camera in bottom right corner in top picture.*

Blinding and rating procedure

Each video clip, of one to three minutes long, was examined by the research student who then selected a 30-50 seconds segment of continuous representative footage. As the objective was to ascertain whether there were expressions of pain or not present, representative footage is thus here defined as any signs of pain behavior that could refute a non-interrupted pain-free state.

The selected shorter representative clips of the various patients, shot pre- and postsurgery, pre- and postNSAID administration, were then randomly organized into a powerpoint presentation, with each clip being assigned a number of reference. The powerpoint and an excel sheet for input according to number of reference were then sent to the rater.

The rater - an experienced rater with high qualifications in equine behavior as well as the EPS scoring system - was chosen by convenience sampling. Subsequent rating of all the clips was blinded. That is, the rater scoring the clips was not familiar with any of the horses included in the study, scoring each film clip without knowledge of whether the clip was shot before or after surgery, before or after NSAID administration. Upon completion of examining all the clips, the scores were then returned to the student.

Qualisys procedure

The Qualisys system was calibrated every morning and each horse had its own folder where every individual trial was noted in terms of date, time and whether the walk was pre- or postsurgery, pre- or postNSAID administration.

When the horse was walked prior to arthroscopy, bandaging similar to that to be put upon horse after surgery was applied to the leg about to be examined for consistency of possible influence of bandage on the walk, before and after surgery.

The horse was then walked from the stall to the room with the optical sensors where markers were attached to the horse as described earlier. After the markers were attached, the horse was walked back and forth in a locale where stationary cameras in the ceiling registered the movements of the markers. The surface of the room consisted of a hard flat non-slip surface. After the walk was registered, the markers were removed and the horse was returned to the stall.

Ethical considerations

As the study was an observation study of routine procedures, with neither a withholding of analgesics (negative control) nor any changing of treatment, no ethical protocol was needed.

RESULTS

Overall description of case study participants and EPS scores

There were six horses that underwent arthroscopy/tenoscopy and that met the inclusion criteria to be in this case study series. All horses included in the study presented with clinical pathology in the hindlimb. Table 1 describes the various characteristics of these horses.

Table 1. *Demographics and diagnoses of horses participating in case series study*

Case ID	Breed	Age	Gender	Weight	Diagnosis
E01	Warmblood	14 years	Gelding	482 kg	Ruptured manicura flexorica, chronic tenosynovitis in digital flexor tendon sheath area and proximal annular ligament constriction in fetlock area of right hindlimb
B02	Warmblood	13 years	Mare	582 kg	Chronic cartilage degeneration and hemarthros in femoral joint of left hindlimb
M03	Warmblood Trotter	8 years	Mare	505 kg	Tendovaginitis and peritendinitis with secondary acute osteomylitis in tibiotarsal joint of left hindlimb
C04	Warmblood	11 years	Gelding	674 kg	Traumatic/mechanic pathology of femur in left hindlimb
Z06	Warmblood Trotter	2 years	Mare	352 kg	Osteochondros dissecans in tibia(IRT)/fibula of right hindlimb
D07	Warmblood Trotter	5 years	Stallion	530 kg	Osteochondros dissecans in tibia(IRT)/fibula of right hindlimb

All horses in the case study series could be studied with the help of the core EPS scoring system. Unfortunately, M03 presented acutely in the evening and therefore there was no presurgery EPS score recorded. In addition, there were no readings collected of E01 in the evening after surgery, thus the lack of data between intake and day 2. A basic quartile statistical overview of EPS values was calculated in Microsoft Excel (Table 2).

Table 2. *EPS score quartile statistics of horses participating in case series study*

	Value of the five short-term cases preop n=5	Value of the five short-term cases postop preNSAID administration n= 14	Value of the five short-term cases plus first two days of long-term case postop preNSAID administration n=18	Value of the five short-term cases postop postNSAID administration n= 13	Value of the five short-term cases plus first two days of long-term case postop postNSAID administration n=18
Median	0	9	10,5	6	7
25% quartile	0	7,25	8	5	5
75 % quartile	0,75	11	12,75	8	8
Max	2	14	17	8	17
Min	0	4	4	1	1

All four horses with presurgery recorded EPS scores started at very low scores in the evening of the intake evaluation. There seems to be a subsequent higher pain score premedication followed by a lower pain score postmedication. The latter statistics, representing readings 8-48 hours after surgery, stay at a higher level of pain postsurgery than presurgery (Table 2). One of the short-term case patients was rated with an EPS score of 11 before NSAID administration and then an EPS score of 8 after NSAID administration, more than 24 hours postsurgery (Fig. 6).

Fig. 6. *Still from video footage of horse with prolonged high EPS score.*
(Textures graphically altered to lessen identifiable features.)

The quartile statistics also include an additional column where a long-term case was included. As this long term case study showed continued gross pain behavior after NSAID administration, alternative analgesics to the NSAID administration were tried. First methadone was administered but as it did not seem to produce adequate pain relief, a morphine epidural was administered, with resulting EPS scores (Fig. 7).

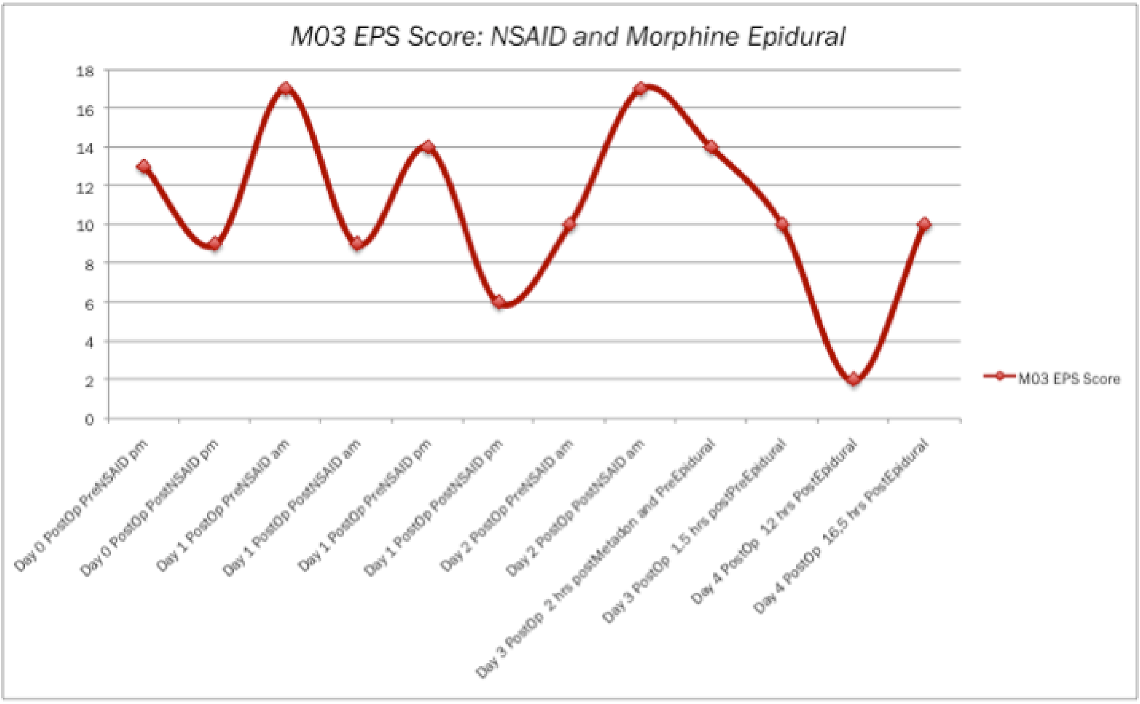


Fig. 7. *EPS scores before and after administration of different analgesics.*

Overall description of what pain modalities were used and for which horses

Motion analysis was performed for four out of the six horses. For one of these four horses, the research student was unable to collect presurgery motion analysis readings as the stable section the horse was located in was put momentarily in quarantine shortly after the horse's arrival (due to another horse in this same section developing a high fever).

The fifth horse performed exemplary during the intake in regard to general handling and the subsequent motion analysis evaluation in the evening before surgery. Nevertheless, the research student elected to abort further motion analysis postsurgery to keep risk-taking at a minimum and decrease further stress (with possibilities of augmented "fight/flight" reactions) as the expressive young horse with postoperative pain would have had to be led to/from the optical symmetry measurement system in the main transit area in the daytime during which there were extensive loud and busy construction work going on in the equine clinic.

The sixth horse was not stable enough to be walked to/from the optical sensor system due to its serious orthopedic pathology. As an optical sensor evaluation was not applicable to this horse, an additional pain evaluation modality was performed during its long-term stay: remote video recordings to document possible augmented pain behavior when no humans were present. This additional module was also tested for a subsequent horse that was also included in the optical symmetry measurement system group.

Presentation of the resulting optical symmetry output and parameters of interest

The visual statistical analysis output of the optical symmetry measurement system collected moving equine coordinates can be visualized in a Matlab graphical output display (Fig. 8) to better visualize the origin of the numerical scoring system presented later on in this case study series. This is the only instance where these graphs will be presented for one horse. For the remainder of the results section, three parameters will be presented at a time for expediency in comparing the different values with the collected EPS score. Consequently, the three paramers to be compared with the individual EPS scores and across the different case study horses are: Hip Hike Difference, Pelvic Maximum Difference, and Pelvic Minimum Difference.

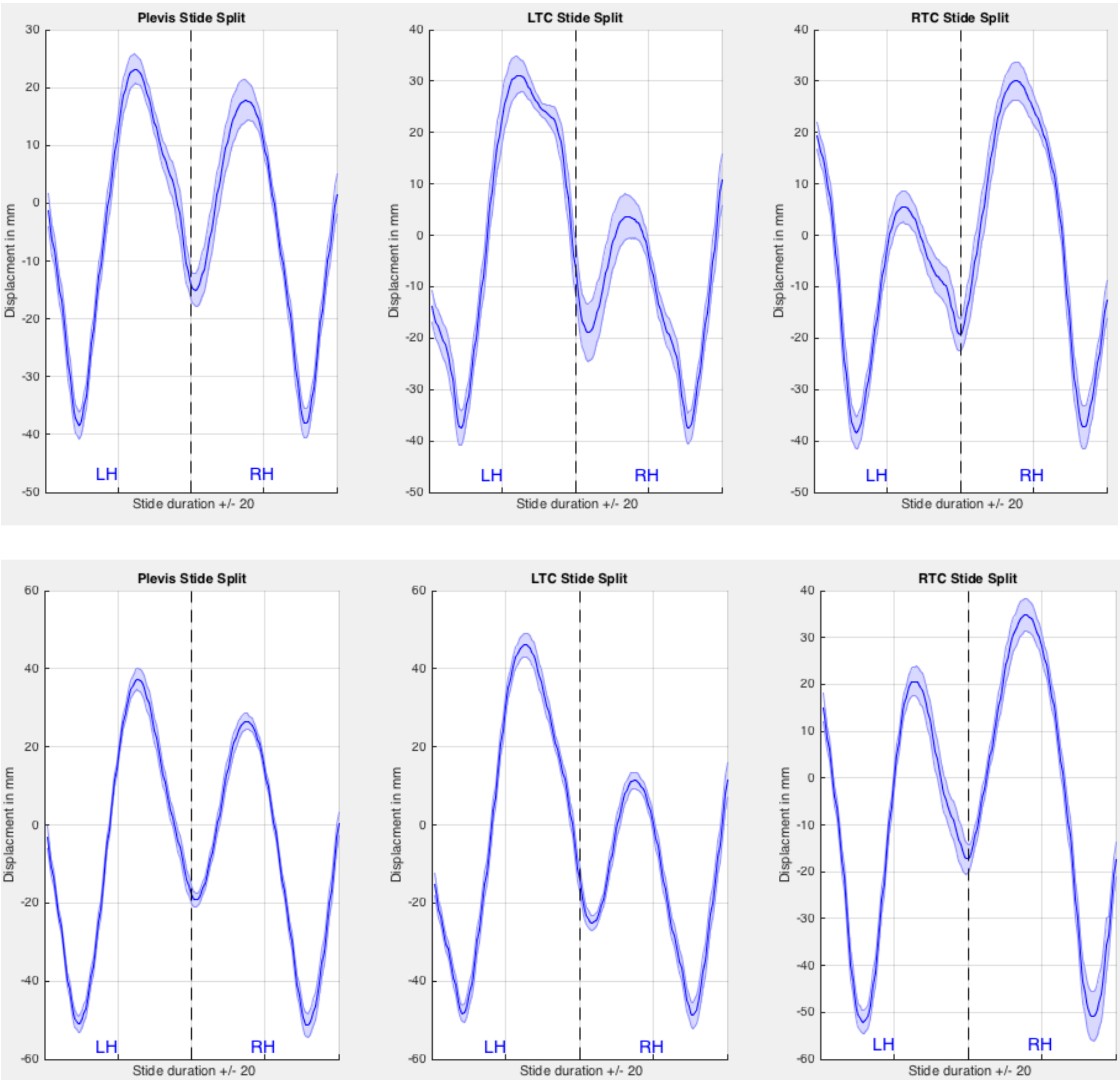


Fig. 8. *Illustration of vertical displacement of tuber sacrale ("Plevis"), left tuber coxae ("LTC") and right tuber coxae ("RTC") before (upper row) and after surgery (lower row) for E01. Matlab®*

The three different visual representations (Fig. 8) present stride splitted data for the vertical displacement of *tuber sacrale*, left *tuber coxae* and right *tuber coxae*. The change in *tuber sacrale* (one point-of view graph to the far left) is the bases for Pelvic maximum and minimum difference parameters where as the change in *tuber coxae* (a view from the left side and the right side as represented by the middle graph and the graph to the far right) creates the basis for Hip Hike Difference parameter.

As can be shown in the far left of Fig. 8, there is a marked increased displacement difference in the right side (RH) vs left side (LH) of the pelvic stride split after surgery (lower row) in comparison with the graph from before surgery (upper row) for E01 that presented with a right hindlimb pathology. The far right images illustrate a displacement difference in the right *tuber coxae* (RTC) movement after surgery that creates a greater asymmetry when comparing the right and left *tuber coxae* views.

Objective 1: All case study participants' EPS scores in relation to Arthro and VAS scores

The results of the EPS scores based on video footage recorded by the research student being present as well as corresponding Arthro scores are shown in Fig. 9. This graph shows the development of the pain scores (Y-axis) over time (X-axis) and, in the right panel, varying values of Arthro scores (used as a proxy for tissue damage and invasiveness of procedure) next to the far right legend.

Note that for this and subsequent graphs, this case study series' data mining approach of descriptive statistics presents the individual values measured in subsequent days as connected with lines rather than individual columns to better visualize differences in trends over time.

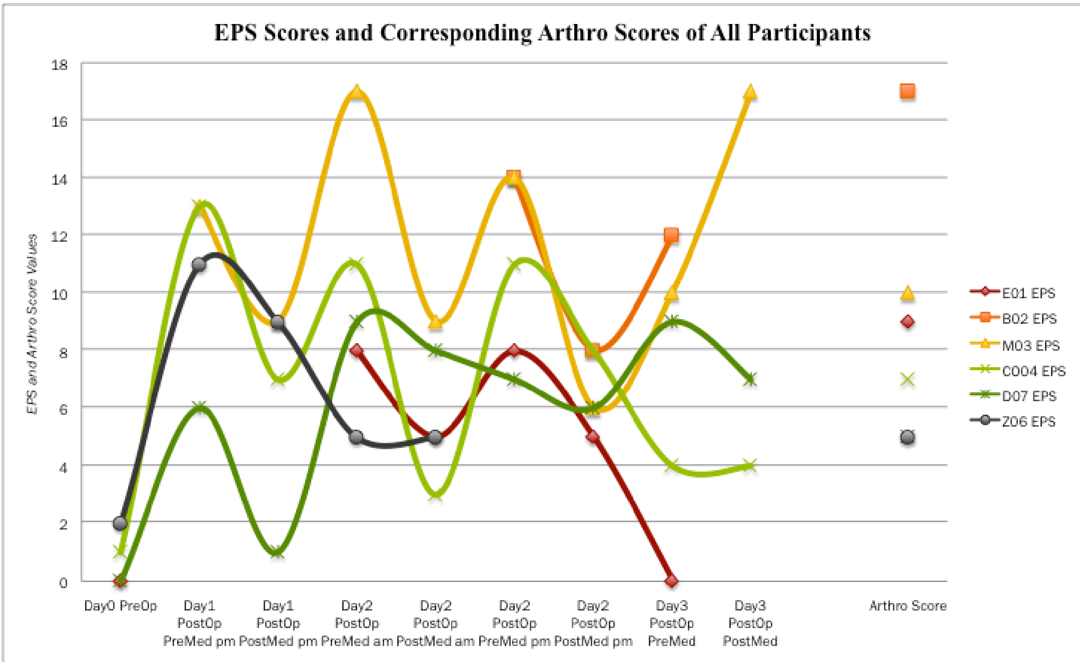


Fig. 9. *Illustration of difference in EPS and Arthro scores (Z06 and D07 have the same Arthro scores).*

There seems to be a general pattern of the subjective EPS scoring system illustrating no to mild amounts of pain presurgery with a subsequent higher pain score pre-medication and a subsequent lower pain score post-medication. E01 illustrates a singular case where the EPS ratings imply that the horse returns to the no-pain intake state two days after surgery before returning home (Fig. 9).

B02 and M03 are the two horses with the highest EPS scores as well as the highest Arthro scores. A comparison of the Arthro score with the VAS score (Fig. 10) reveals that B02 and M03 have among the highest scores in both categories.

Nevertheless, as opposed to the Arthro score distribution, the highest VAS score belongs to a third horse, E01, a horse with a suggested lower EPS than both of them. Three horses C04, Z06 and D07 have the lowest Artro and VAS scores. However, it is of note that C04 has consistently higher EPS scores than higher-ranking Arthro and VAS scoring E01.

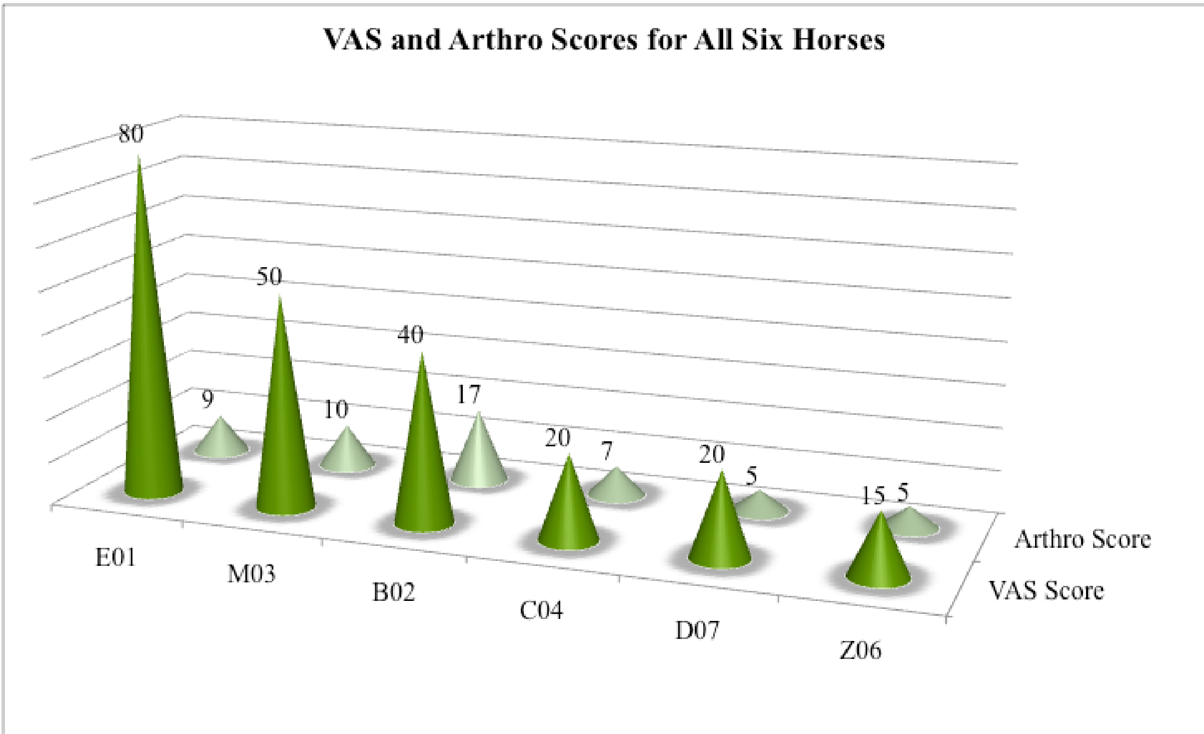


Fig. 10. *Illustration of difference in Arthro and VAS scores.*

The two different scores can be simply described as one being a shortcut to evaluate overall damage (VAS score) whereas the other illustrates the extent of a variety of parallel pathology categories being present at the same time (Arthro score).

Objective 1: OS parameters across case study cases in relation to Arthro and VAS scores

Mean Pelvic Maximum/Minimum Difference. The top graph displays the different mean Pelvic Maximum Difference values of all horses (Y-axis) over time (X-axis), with the varying values of Arthro scores in the right panel, next to the far right legend (Fig. 11). The two highest Arthro scores E01 and B02 also have high mean Pelvic Maximum Differences for Day 2 and Day 3, with D07 intermittently shuffling in between the two despite having the lowest Arthro score. The OS scores values of C04 in this category are consistently the lowest. (The minimum OS score graphic (Fig. 12) does not seem to produce any valuable information).

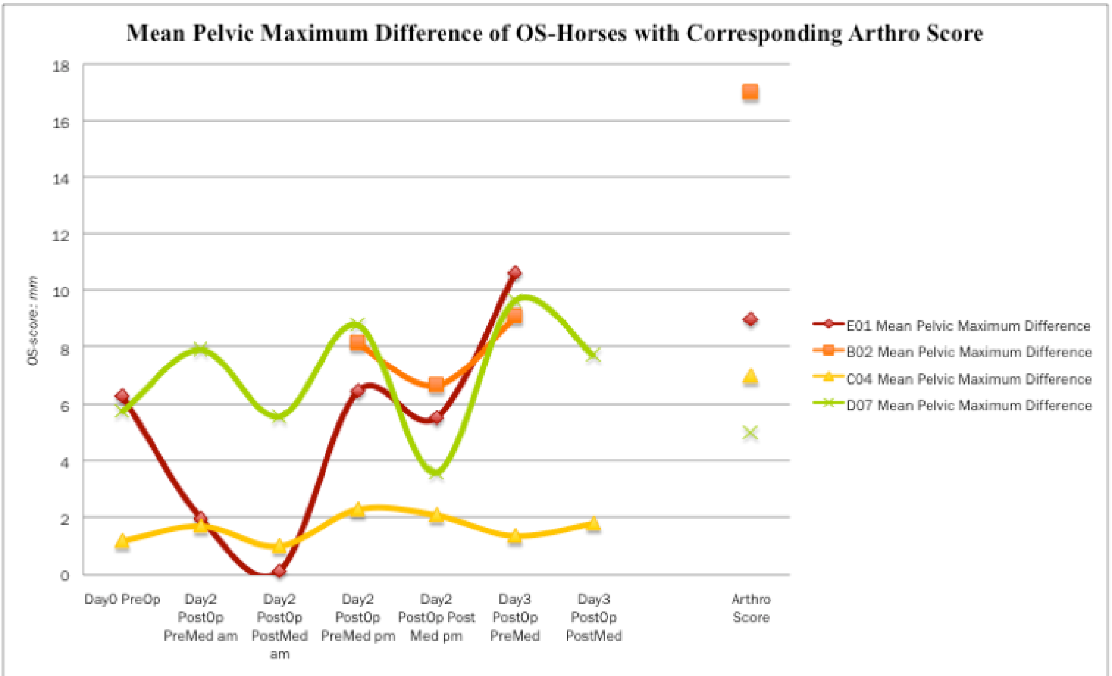


Fig. 11. *Change in mean Pelvic Maximum Difference scores over time and Arthro scores.*

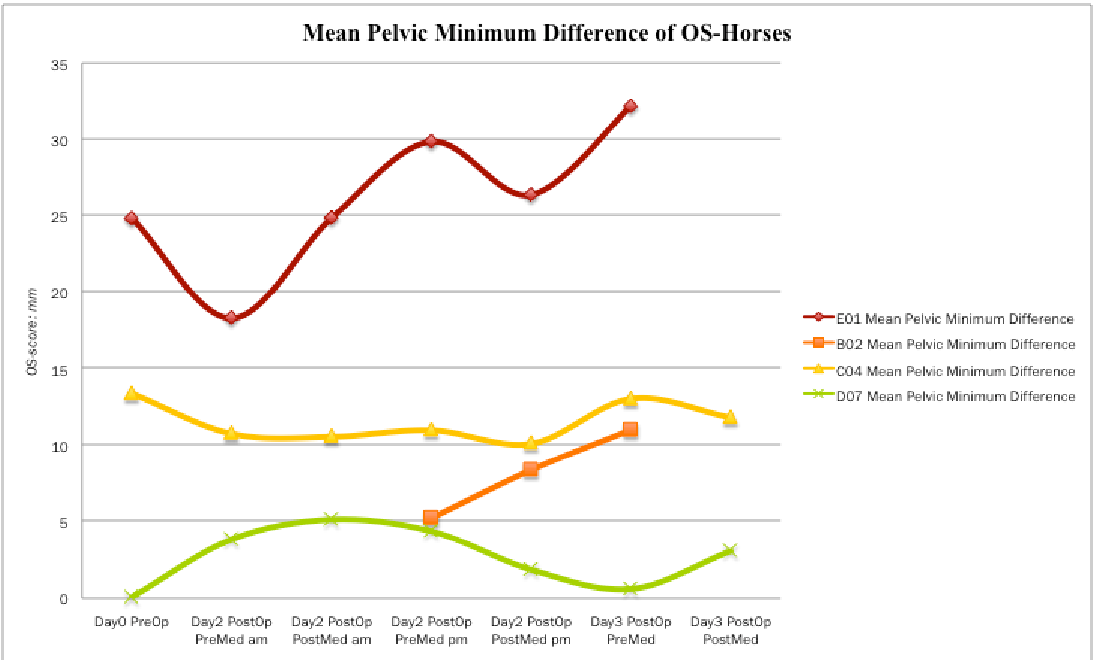


Fig. 12. *Change in mean Pelvic Minimum Difference.*

Mean Hip Hike Difference. For this OS score, the values for the four case study horses are contrasted with the VAS score in the right hand side for comparison (Fig. 13). For this parameter, there seems to be a suggested relationship of VAS score and the degree of mean Hip Hike Difference across the four cases: E01 having the highest score, B02, having the next to highest score, and C04 as well as D07 - with identical VAS scores - being fairly close to each other in terms of having the lowest Hip Hike Difference values of the four horses.

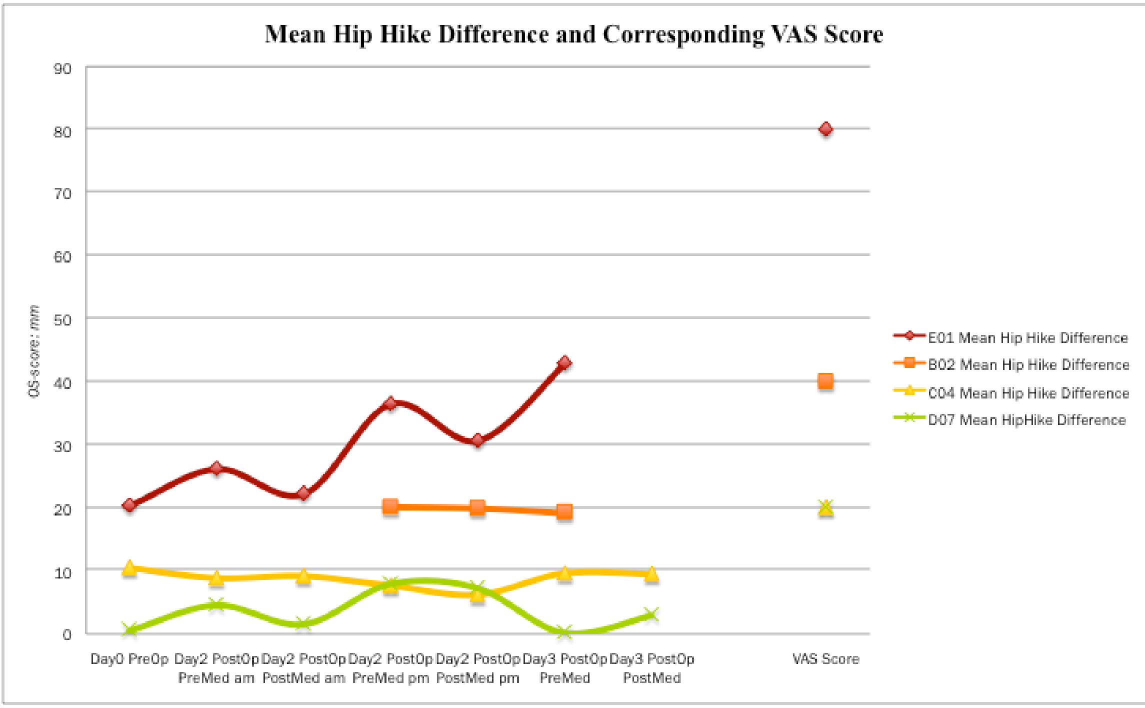


Fig. 13. *Change in mean Hip Hike Difference Scores compared to VAS scores.*

Objective 2: Comparing EPS score of individual case study participants with their OS scores

Horse E01. This graph (Fig. 14) shows the development of the varying OS scores as well as the one EPS score (Y-axis) over time (X-axis), with the legend to the far right. By comparing the composite EPS score with the three different parameters, the mean Hip Hike Difference of E01 is the lameness parameter that seems to reflects the pre and post medication administration the EPS score the most. All three parameters show a continued increase on Day 2 and 3, however, in comparison with the EPS score that returns to the preop state on Day 3.

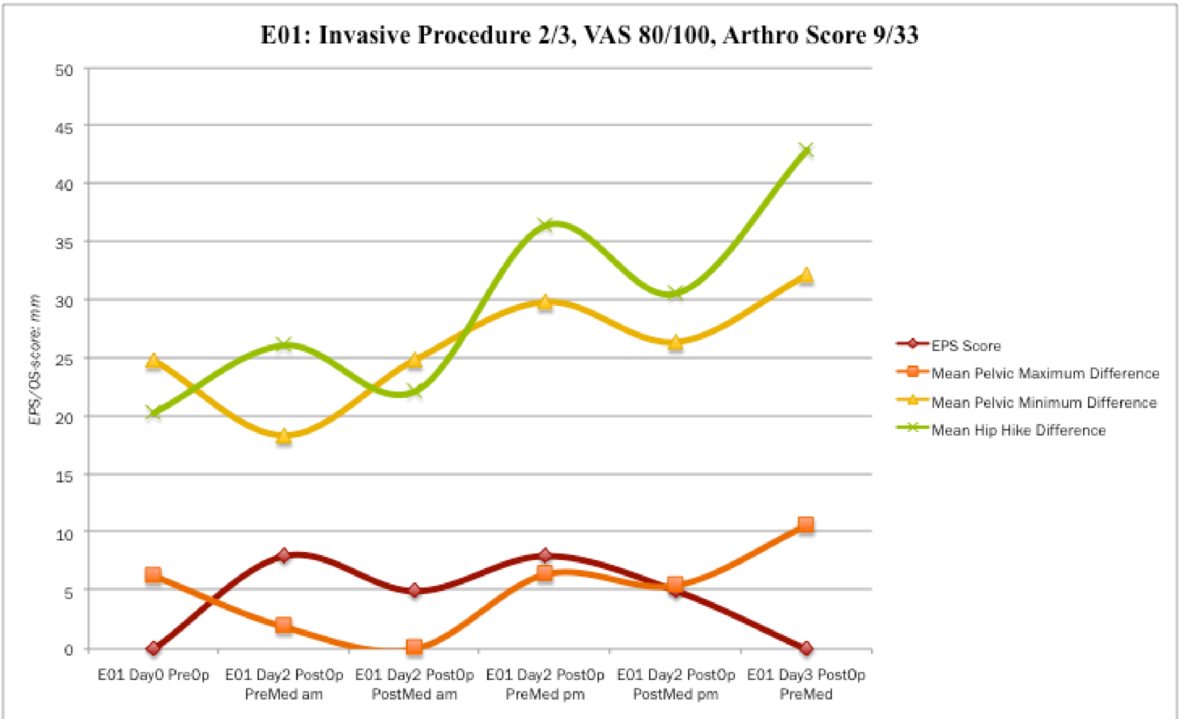


Fig. 14. *OS three values and EPS score of E01with diagnosis: ruptured manicura flexorica, chronic tenosynovitis in digital flexor tendon sheath area and proximal annular ligament constriction in fetlock area of right hindlimb.*

Horse B02. The Mean Pelvic Max Difference seems to best mirror the EPS score (Fig. 15).

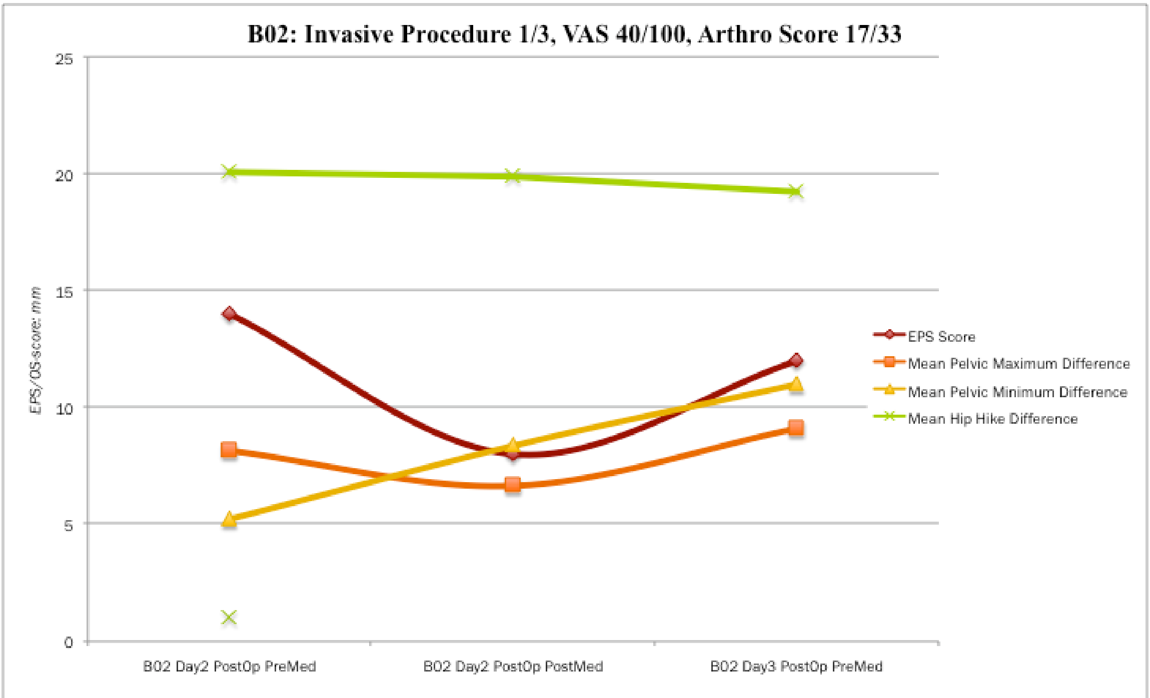


Fig. 15. *OS values and EPS scores of B02 with diagnosis: Chronic cartilage degeneration and hemarthros in femoral joint of left hindlimb.*

Horse C04. For this horse as well, mean Pelvic Maximum Difference seems to be the parameter that most accurately reflects the EPS trajectory (Fig. 16). However, the OS score values for this horse are rarely above the 2 mm asymmetry threshold used to determine lameness of clinical significance.

In addition, for Day 3, this curve for C04 also shows a slight increase of lameness (as an indicator of pain) as opposed to the stagnant values of the EPS. A similar pattern, albeit more dramatic, was shown for E01 (Fig. 14) where the mean Pelvic Maximum Difference hinted at a continued increase in pain where the EPS score decreased.

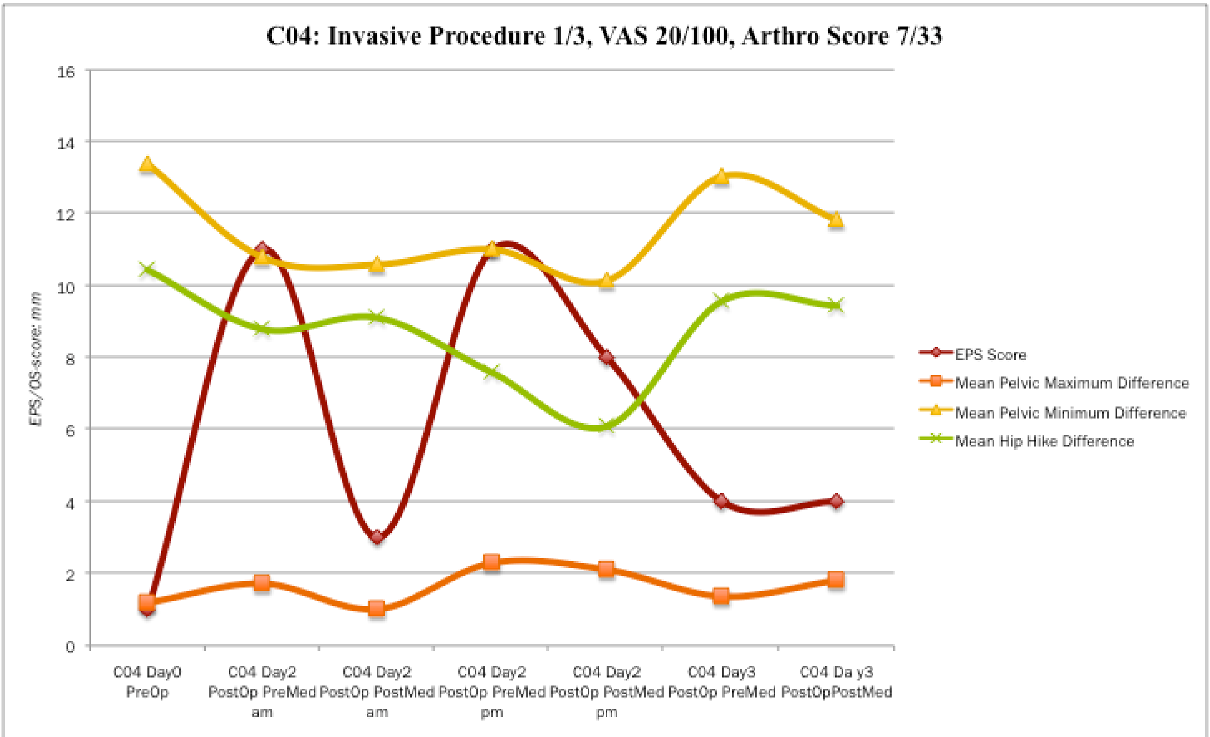


Fig. 16. *C04 Diagnosis: Traumatic/mechanic pathology of femur in left hindlimb.*

Horse D07. Here is an additional case where the graphic representing the OS-parameters illustrates how mean Pelvic Maximum Difference seems to be the most reflective of the EPS pain score (Fig. 17). Of the three OS score parameters, two out of them display a rise at the end where the EPS pain score declines. The OS score that shows a mirroring decrease is mean Pelvic Maximum Difference, the one parameter seemingly more reflective of the overall EPS pattern for this horse.

However, note that there is an increase in *all* OS scores but mean Pelvic Minimum Difference (the parameter that seems to be the least reflective of the three parameters for all four horses) on "Day 2 PostOp PreMed" where the EPS score - based on video footage with the research student being present - shows a continued decrease before increasing again in the "Day 2 PostOp PreMed" state. This will be commented on further, with contrasting additional observations from remotely shot footage, later in this results section (Fig. 19).

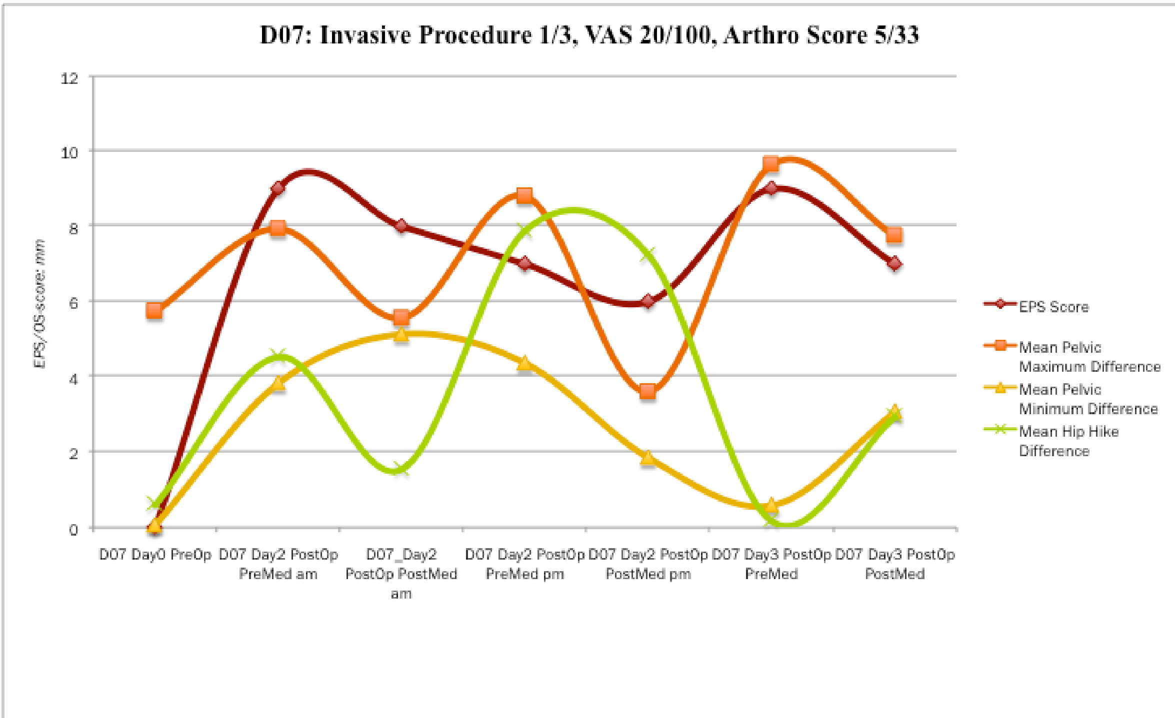


Fig. 17. *D07 Diagnosis: Osteochondros dissecans in tibia(IRT)/fibula of right hindlimb.*

Objective 3: Presentation of remotely shot video footage

The remotely controlled video footage documented behaviors that were seemingly either higher in frequency (such as *continuous* shifting of all four legs) than with a human present by the stall or showed behaviors not present (such as circling) with a human present by the stall (Fig. 18).

Consequently, such remotely recorded behaviors caused higher pain scores in the following individual categories of the EPS: “Gross Pain Behaviors,” “Location in the Stall,” “Activity,” and “Posture/Weight Bearing” for the two horses used for this modality. (See appendix for presentation of complete scoring system for all categories of the EPS scoring system).

The seemingly most frequent difference in EPS values for this remotely recoded footage were observations falling in the category of “Gross Pain Behavior.” Blinded rated scorings of openly shot material such as “none” (value of 0) changed to “occasional” (value of 2) or “continuous (value of 4) with blinded rated scoring of remotely shot footage recorded only 10-15 minutes prior to openly shot footage.

In addition, there were also often noted changes in the EPS “activity” category from “no movement” (value of 1) in the openly recorded category to “restlessness” (value of 3) or “depressed” (value of 4) in remotely shot footage. Occasionally, there were also changes in location of horse in the stall, with the horse facing or standing in the back of the stall when shot with remote footage.

Fig. 18. *Digitally altered stills from footage recorded by remotely operated portable camera. (Textures graphically altered to lessen identifiable features.)*

Earlier in the results section for D07 (Fig. 17), there was an EPS decline (based on openly shot footage) for the "Day 2 PostOp PreMed state" yet a concurrent increase in all OS scores. For this horse, the research student also tested the remote camera for the PreMed states (but not PostMed states). The difference in PreMed states (with the same PostMed states being used for both patterns for ease of visualization) is shown in Fig. 19. Also, a corresponding OS score is added to illustrate how the "hidden" EPS scores are seemingly more consistent with the mean Pelvic Maximum Difference score.

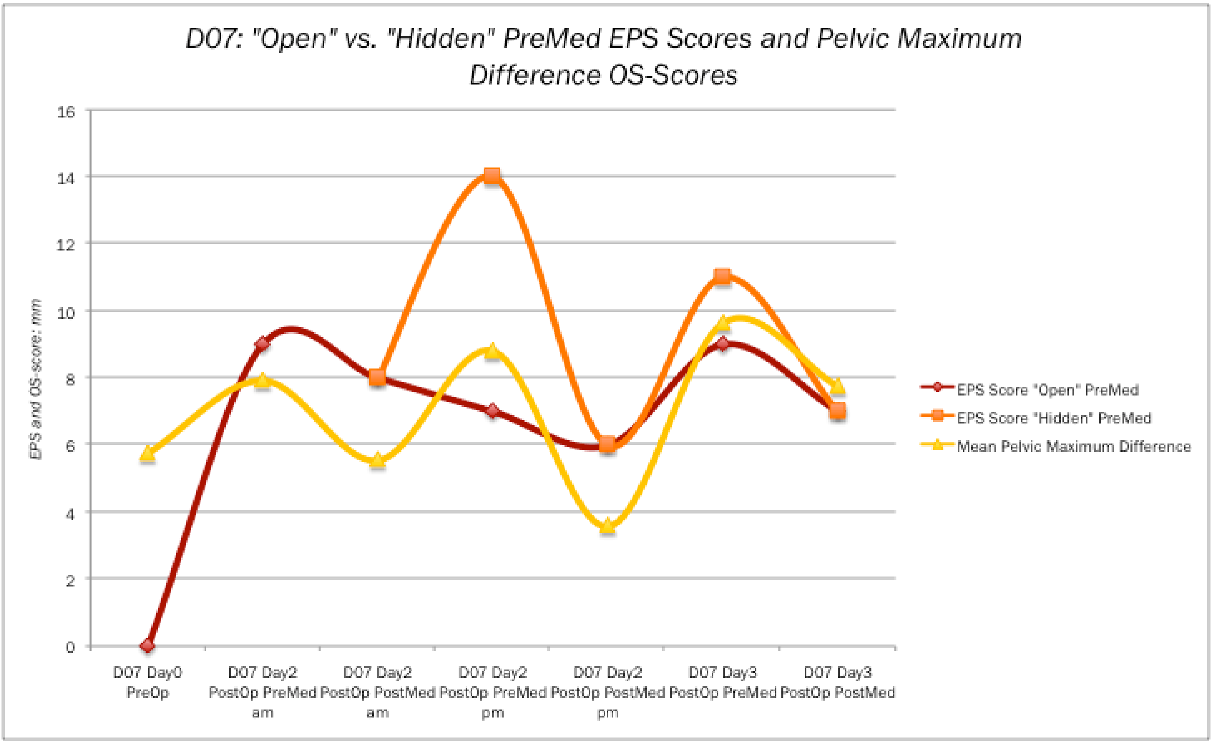


Fig. 19. *D07: illustrating difference in PreMed EPS scores for "Open" vs. "Hidden" EPS scores in relation to mean Pelvic Maximum Difference OS score.*

Finally, for M03 where both PostOp PreMed and PostMed states were shot with an "open" cand "hidden" camera, there is a similar increase in EPS values for the latter (Fig. 20).

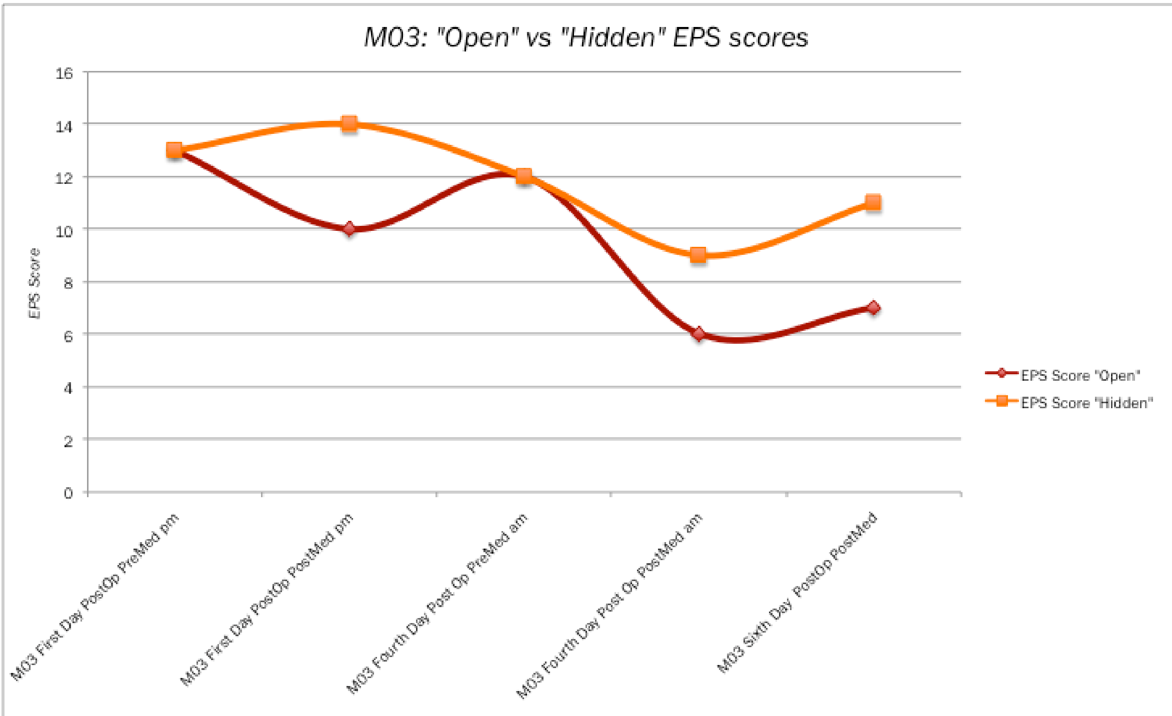


Fig. 20. *MO3: difference in PreMed and PostMed EPS scores for open vs. hidden footage.*

DISCUSSION

First of all, these qualitative case study findings are limited by the small number of patients included, in addition to using a non-randomized selection, all from the same clinic in the same location. Ideally, this study would have had the opportunity to examine more patients but the exclusion criteria, coupled with a smaller number of arthroscopies than expected for certain weeks, in a short amount of time, proved to be a trial of inclusion. The subsequent discussion of findings, in the context of the presented introductory objectives, should therefore be viewed as a possible starting point for further large quantitative investigations with highly targeted aims.

Objective 1: potential to foresee degree of pain with Arthro/VAS scores?

This objective made use of all four pain modalities covered in the methods section – EPS, OS, Arthro and VAS scores - to look at possible findings when comparing behaviors observed in the stall or the results of an optical symmetry analysis with both proxies noted for tissue trauma during surgery.

A quick glance at the EPS scores of all six horses, compared to the Arthro scores and VAS scores, could support the use of such complimentary proxies of prediction for horses with high Arthro scores, ie. ≥ 9 (Figs 9, 10 and 21). Such a threshold would include the two horses B02 and M03 with the highest values in all three categories (EPS, Arthro, and VAS) but would also include E01 that has a high VAS score but lower EPS scores.

However, even though the need for a valuable cheap tool for predicting pain is great, the inconclusive mixed findings of this case study series does not seem to support further testing of the Arthro and VAS scores. Because if one would predict pain solely based on high-scoring Arthro and VAS scores, one would miss the potential pain alleviation needs of the two Arthro and VAS low-scoring horses C04 (that exhibited high EPS scores but a low mean Pelvic Maximum Difference OS score) and D07 (that exhibited fairly high EPS scores and a high mean Pelvic Maximum Difference OS score) (Fig. 9, 10 and 11). Therefore, even though the Arthro score was constructed with the hope of potentially becoming a friend of effective initial postsurgery tailored pain alleviation, it could potentially, and unfortunately, be a foe as it is designed now. The OS score parameter Hip Hike Difference did seem to reflect the varying amplitude of the simple VAS score but this sole finding does not seem to be enough to support an overall recommendation (Fig. 13).

Nevertheless, further testing of a new and improved Arthro score could be of future interest since this study has been limited by not only the small size of participants but also with using a novel proxy instrument that has neither been tested nor validated by other studies. A modified future version could include the weighting of certain included categories, such as the invasiveness of procedure. The particular joint of pathological focus could also possibly be included as part of the scoring process.

Fig. 21. *One of the case study horses before surgery (left) and after surgery but before pain medication (right) with two different Pain Face scores (0 vs. 2) presented in the results section as part of composite EPS scores. Note the dilation of nostrils, changed position of the ears, contraction of muscle above the eye, tensed facial muscles caudally to the muzzle (in addition to the horse facing the wall) in the picture to the right. (Textures of these photographs have been graphically altered to lessen identifiable features.)*

These inconclusive findings have been a valuable addition to this study, nevertheless, as they have illustrated the complex relationship of pathology and subsequent pain expression as well as the difficulty of creating a general tool to foresee individual future pain scenarios. The latter difficulty highlights the main limitations of the study: the issue of individual variability in pain expression and response to pain accrued postsurgery in addition to variability in individual response to NSAID administrated.

Nevertheless, one might also conclude that the findings presented here propose that an individual sensitivity to pain could be more significant than the nociception produced by joint pathology. In a recent article, behavioral scientists explored the importance of such an individual equine pain sensitivity, referring to this variation as a consequence of "personality and coping style" (Ijichi *et al.*, 2014:38). Even though the Ijichi study's use of a subjective lameness evaluation performed by only one person can be problematic, the use of an equine owner based pain questionnaire could be a welcome and valuable addition to veterinarians in their daily clinical work.

Objective 2: possible efficacy of systemic NSAID postsurgery in this study?

This second objective was based on the assumption that a horse will exhibit levels of pain scores postsurgery preNSAID administration that were not present at the intake of that patient, one day prior to surgery. This did seem to be the case for all horses where presurgery testing was possible. EPS scores started at very low values (0-2) in the evening of the intake, prior to surgery (Table 2). These presurgery EPS scores were followed by a general undulating pattern of seemingly higher pain scores preNSAID administration and subsequent lower pain scores postNSAID administration (Fig. 9).

Many of the OS scores of the four individual horses (Figs 14-17) appear to mirror the EPS undulating waves of pain states according to pre- and postNSAID administration. Therefore, the two pain scoring modalities – one subjective and one objective – could be pointing in the same direction of unraveling possible traces of an equine postsurgery pain state responding to NSAID administration in varying degree. The one caveat to this suggested reflection of EPS and OS scores is that mean Pelvic Maximum Difference seems to be the parameter of interest for only three out of the four cases. For the last one, mean Hip Hike Difference appears to echo the EPS score much better, however. As there are only a very limited number of cases, further studies would be needed to give additional clues whether it is the one or the other (or none of the above). As a complimentary parameter, one could have added optical symmetry parameters related to the head in a wider investigation of OS scores of interest.

In addition, there was one case where there were high EPS scores concurrent with a low mean Pelvic Maximum Difference OS score for CO4 (Fig. 16). Even though this parameter does have an undulating quality that mirrors the EPS of this horse, the OS score value itself is ≤ 2mm, considered the threshold of clinical significant lameness. This OS score is low compared to the other horses (Fig.11), displaying individual variability in pain expression. One reason for a discrepancy between the EPS and the OS score could be that the two pain states – one noted while the patient is standing and/or moving around in a confined environment whereas the other is noted while the horse is walking – could be quite different in nature from each other.

Furthermore, for C04, all of the OS score lameness scores show an increase in varying degrees when the EPS score starts to decline on day 3 (Fig. 16). This pattern of increase was even more dramatic for all OS scores for E01 (Fig. 14) and for two of the three OS scores for D07 (Fig. 17). Again, these are moderate suggestions of findings in a limited study. Yet they could potentially be seeds for future idea generation: is there a potential lag of pain-related lameness expression in some horses? Transitioning to the next objective to be discussed – covert pain behavior – the OS system thus suggests possible delayed instances of heightened pain as it relates to lameness in walk in three of the four OS cases where the human observed registered EPS notes a decline on the second and/or third day. Another explanation could be that the horse has habituated itself to a more asymmetrical walk to avoid discomfort. As a consequence, once the horse is forced to change the habituated pattern of locomotion once back home when the owner gets back in the saddle, this could lead to a new pain state.

Even if the EPS scores did decline, as noted above, the questions that follows are: did these EPS scores decline sufficiently and/or in a time-effective manner?

The question of degree of pain alleviation offered is an important one. How much pain is acceptable after administered analgesics? According to Table 2, the maximum total score of the postsurgery postNSAID administration EPS for the five short-term cases was 8. According to the designers of the EPS, a total score of 8-10 is a reason to consider further diagnostics and/or additional analgesic treatment as the EPS system has been set up to offer numerical end-points of acceptable pain levels to help guide the practitioner. The long-term case study is a case in point for why these end-points matter: the postop postNSAID administration maximum EPS score for this case was 17 (Table 2). When the systemic NSAID treatment failed to produce satisfactory results, an alternate analgesic (a morphine epidural) was administered. The highly differing postanalgesic EPS values illustrate the potential power of charting a new analgesic course as needed (Fig. 7).

This long-term case study also raises the question of the influence of the pain state of the horse prior to surgery. An EPS presurgery evaluation was done of all horses except for this horse that presented acutely in the evening. For comparison purposes, the initial postsurgery analgesic plan was originally the same as for the other horses though, before attempting other protocols (Fig. 7). In cases like this, it could be of interest to perform additional pain diagnostics of the pathology area of interest presurgery to test whether any potential pre-existing pain has produced a wind-up effect that demands alternate multi-modal analgesia postsurgery. For example, such a test could be as basic as palpating the area around the pathology of interest to see if there are any signs of hyperalgesia in areas distant to the pathology.

The other question that follows is, how long should an equine patient stay in a heightened postsurgery pain state before it returns to its presurgery non pain state? Of all the horses with presurgery evaluations, only E01 seemed to return to its intake no-pain state before returning home, according to the EPS score (Fig. 9). The others stay at a higher level of pain postsurgery than the recorded presurgery level for the following 8-48 hours after surgery while residing at the clinic. Consequently, is there a need for a better vigilance with the possibility of adding a multimodality approach and/or entertaining the idea of prolonging medication duration and/or intervals beyond the first 24 hours?

How much pain do veterinary practitioners sub/consciously expect an animal to tolerate, for how long following a surgical procedure, and what are the consequences for the patients? The EPS is a useful tool in that it offers practitioners a hands-on materialized system of shared end-points as an alternative to individual mental unofficial endpoints that are neither easily shared nor systemically organized to allow for subsequent follow-ups.

Before moving on to the next and final objective one must address how the lack of a negative control – as in a placebo group – to compare with the active treatment of NSAID is another limitation of this self-paired test. Such a negative control is needed to be able to truly ascertain that the difference in pain is due to treatment only. However, such a withholding of pain treatment would have raised serious ethical concerns.

Objective 3: do the horses exhibit pain differently with no humans present?

The third objective dwells upon perhaps the most burning question of all: can we truly evaluate the potential gain of analgesic treatments without, literally, fully committing to unraveling the hidden aspects of pain? This study has made use of two technologies, one more high-end (the OS system) and one more consumer-oriented low-tech (a portable remote video recording unit) to help uncover pain behaviors that are hard to observe by the naked eye. Fig. 19 illustrates how remotely operated “hidden” footage seems to reflect an OS score (mean Pelvic Maximum Difference) more accurately than the openly recorded video clip for D07. Examples of such altered ”hidden” gross pain behaviors are graphically illustrated in Fig. 18. In addition, an ”open” and ”closed” difference in pre- and postNSAID administration EPS scores was also suggested for the long-term case study, M03 (Fig. 20).

Herein lies the heart of the true and perhaps most challenging limitation of any pain study: most equine patients are hesitant to exhibit expressive pain behaviors in the presence of humans. Yet another limitation is that the focused eyes of the observer is active only in short periods of time throughout the duration of the hospital stay as opposed to non-stop filming 24 hours before surgery to 48 hours after surgery. Going through such vast amounts of footage would not be realistic or time-effective, however, in a clinical setting. Thus, using live remotely operated video footage could be an effective and time-efficient compromise to help uncover hidden pain behaviors.

The analysis of the last testing module of this study, the blinded scoring of remotely shot footage, reveal high-scoring disturbing gross pain behavior in the shape of continuous weight shifting of all four legs, horses moving to the back of the box to stare into the wall, or restless circling. Incorporating these additional covert pain behaviors made for a substantial increase in the EPS scores. Thus, any such scores noted by the human observer present at the stall might be the tip of an iceberg if considering this hidden additional material.

If attaching a piece of EPS scoring document (as the one shown in the appendix) to the stall of a newly operated equine patient is an extremely cheap and easy way to monitor a patient’s degree of pain, using remote video equipment might not be. Nevertheless, as technology gets cheaper, smaller, and more user-friendly, the remote surveillance of equine patients does not have to be the obstacle it used to be. In addition, a number of equine veterinary facilities already have certain stalls with remotely operated cameras to monitor pregnant mares. These stalls can easily be used for pain monitoring as well.

In the absence of technology, the great art of observation should be coupled with a professional foresight of possible (gross) pain scenarios based on the veterinary practitioners medical knowledge of when, how, where and why an animal might experience pain. Then, regardless of access to the latest technology, there is always the advice from Dr Lloyd Davis, cited in the 1983 quote that opened this research study: “*Pain and suffering constitute the only situation in which I believe that, if in doubt, one should go ahead and treat*” (1983:175). The one caveat to this advice is to take the important consideration of side effects into the equation.

CONCLUSIONS

Summary of objectives and related findings

This study offered the opportunity to look at the possibility of foreseeing the degree of pain after arthroscopy by contrasting intra-articular tissue damage scores (Arthro Score and VAS Score proxies) during surgery with postsurgery subjective EPS scores and OS scores. Even though there is a great need for effective scoring proxies of intra-articular damage, the inconclusive mixed findings of this study does not seem to support further testing of an Arthro/VAS score of the current design. The inconclusive findings illustrate the complexity of pathology and subsequent pain expression as well as the difficulty of creating a general tool to foresee individual future pain scenarios.

In addition, this study surveyed the potential efficacy of a systemic routine NSAID analgesic administration during a time frame of up to 48 hours post equine arthroscopy by comparing presurgery EPS scores and OS scores with postsurgery scores before and after NSAID administration. In doing so, both the subjective and objective scores seemed to suggest a common undulating pattern that could be interpreted as a reflection of an increased pain state before NSAID-administration and decrease in pain state post NSAID-administration. The one important caveat was that this pattern was illustrated by one and the same OS parameter for three out of the four horses, yet another OS parameter for the fourth horse. Further differences in compared amplitude of EPS vs. OS scores could point to the differing pain nature of standing vs. walking. This survey also raised new questions in relation to differing efficacy of the analgesic as well as the duration of a postsurgery pain state. The former question calls for more studies on quantifying the varying degree of pain responses to analgesics and the latter question calls for more studies quantifying the duration of postoperative pain. What can be gained with even more effective analgesics to get equine patients back to their original presurgery state more quickly?

The last objective was to observe the pain behavior of equine post orthopedic patients when there were no humans present as well as seemingly absent from the immediate stall environment by juxtaposing EPS scores from video footage shot by research student at the stall with that of remotely operated recorded video footage. As a result, there was a suggested increase in gross pain behavior and restless activity as well as positioning towards the back of the stall for the latter. As any behavior noted in person could therefore be the top of an iceberg, this study calls for more quantifying studies using continued methodological ingenuity to help unravel pain behaviors hidden out of clear sight. The use of smaller, cheaper, and user-friendly portable technological equipment could be a useful aid.

Finally, in addition to the objectives above, this case study series suggests the potential usefulness of a subjective pain measuring system such as the EPS as it seems to be reinforced by the parameters produced by the high-tech complex OS system. As there is no golden standard for uncovering the true pain state of the horse, there could be added power in attempting to describe pain states using differing but complimentary pain modalities. Any suggested findings of this limited case study should be regarded, however, as potential seeds for future hypotheses generation for large quantifying studies with very specific goals.

Clinical implications

Even though this study is clearly limited by the small number of cases, the amount of material collected for each patient during a short but pain-behavior eventful period of time might offer practitioners additional material from which to draw future hypotheses testing to study the function of pain and the need for timely, effective and adequate pain alleviation.

In order to attempt to estimate the level of postsurgery pain, rather than putting energy into an improved Arthro score during surgery, one could consider adding an additional pain component during the noting of the equine patient history as described by Ijichi and her research collagues (2014). Has the owner of the equine patient made any note of the horse's possible pain personality or tolerance in the past? In regard to presurgery clinical examinations, there is also the possibility of exploring additional palpation pain diagnostics to explore if there is any existing presurgery wind-up effect, especially in cases of chronic pain.

As discussed earlier, the increased OS readings could be a suggestion of a continued increase in pain response on the second and third day. If this response is due to a wind-up effect, this possible finding could support a suggested multi-modal medical approach for the first 24 hours postsurgery. As an example, with horses with severe pathology and/or invasive arthroscopies procedures, the veterinary surgeon could consider the administration of intra-articular morphine to prevent a possible wind-up effect of pain, a multi-modal pain control approach currently being practiced in small animal medicine. This needs to be proven in the clinical situation in horses.

In addition to a multi-modal approach, there is also the possibility of considering the option to continue the BID administration of NSAIDs beyond the first 24 hours to an additional 24 hours for certain patients, depending upon the procedure and/or pathology, as opposed to the standard QD as is often the case at UDS today, 8-48 post standard arthroscopic procedures.

A multi-modal approach and/or prolonged BID administration might also address the case study finding of how many of the horses failed to return to their pre-op state prior to going home. Even though a realistic goal might not be for the horse to be painless within this time period, the question is: are there any possible easy adjustment to be made that can lessen the postoperative pain sensation further and thus speed up the convalescence?

The efficacy of the suggested protocols above could be investigated and documented with the help of the cheap and quick EPS tool for routine hospital use with minor effort. A small limitation is that foraging behavior puts some serious limitations to the use of this tool. One cannot judge pain face effectively when the horse is eating, which it must do regularly, being the grazer it is. Also, compulsive eating may be seen as a certain pain behavior. In the video footage, almost all horses ate the food offered by the research student, even the horse that had a very high EPS score of 17. Such film clips suggest that if even if a horse is eating, this does not preclude it from being in a moderate to high pain state. This finding merits further investigation.

The OS system offers another remote tool of recording data to aid veterinary practitioners in their daily practice as the new logarithm developed seems to be able to successfully pick up low-grade lameness in walk. These results are among the first reported for this use.

PERSPECTIVES

Further research is clearly needed for complementary comparative studies incorporating simple and cheap subjective pain scoring systems and high-tech kinematic objective lameness scoring systems such as the OS-system. For the former, a scoring system using both human-present video recorded observations with remotely controlled footage would be of essence to unravel the hidden complex pain behaviors of the equine species. This hidden complex pain behavior calls upon researchers to use their ingenuity to come up with an ever-expanding toolbox of pain recognition modalities. The reticence shown by not only horses but a variety of other species in pain points to a perpetual need to question the role and influence of our human presence when observing the possible pain behavior of an animal. Have we adequately reflected upon this influence on the animal that is the focus of our probing gaze, with the observer sometimes needing to take a step back literally and figuratively?

In addition, there is a need for more self-reflective research to probe the mind of the veterinary practitioner’s view of the true role of pain and its adversary companion, pain alleviation. How does one define functional vs. malfunctioning pain in an ethical, clinical, as well as biological evolutionary perspective? Are signs of pain a beacon of failure or a signal that there is room for improvement of the current analgesic protocol? For what patient, and/or at what point, is pain alleviation a friend or a foe (as in too many side effects)?

Finally, the methodological question that follows a qualitative study like this is: can veterinary practitioners suffice with using simple and cheap tools such as the EPS in their daily practice to monitor and manage post orthopedic pain? Judging by the modest findings of this limited case study series, the response could be affirmative.

Nevertheless, as we continue to work side by side with e other professionals in a never-ending multidisciplinary endeavor to create technologies to help veterinarian excel in their diagnostic and therapeutic day-to-day clinical work, this study also seems to suggest that the two tool sets – cutting edge objective technology and the subjective scoring based on the mind of an acute observer – might be two complementary methods, with the caveat, again, that this study is based on a very small selection. These results may contribute to the generation of new hypotheses to be investigated in the future in quantitative studies with highly targeted aims. This process of uncovering is part of an overall veterinary ongoing quest for plausible answers to what methods of pain assessment can one seemingly trust the most, and why?

To conclude, this study's exploration of a combined subjective evaluation of the EPS and the objective use of a 4 beat gait analysis recognizes that to manage the dynamic nature of pain in animals more effectively, we must address the art *and* science of identifying, measuring, and recording such varying subtle symptoms. Therefore, one could argue that the art of focused observation demands an open, inquisitive and creative mind to be able to document signs of pain where and when one might not first have noted them. Science then offers the tools needed to subsequently objectively and methodologically analyze these signs to better evaluate the outcome of a chosen analgesic protocol. Addressing subsequent potential un-addressed pain states is critical to meeting one of the basic tenets of the so-called five freedoms of optimal animal welfare: freedom from pain.

No pain, more gain?

ACKNOWLEDGEMENTS

Writing acknowledgements is an uplifting task, remembering all who offered inspiration:

- First of all, I would like to thank my four-legged colleagues that patiently and most gently accompanied me through this whole process from start to finish. In doing so, they reminded me that there are two kinds of people in this world: those who love horses and those who love horses but don't know it yet. I entered the veterinary program belonging to the latter but exit this program belonging to the former.

- Then there is Emelie Smith: a dear friend, classmate, and sister-in-arms who always inspire to greater courage, integrity, and sincerity in veterinary medicine. Her taking me on a joyous surprise visit to meet new feisty fourlegged friends during tough times.

- In addition, I express my immense gratitude to the many UDS veterinary technicians. They are the unsung heroes of veterinary medicine, yet have rockstar quality as they are incomparable key players in a team-oriented approach to more effective and timely pain management. Thank you for your sincere interest and help during this project.

- In a wider context of veterinary equine research, more thanks goes out to head equine surgeon Tamás Tóth who graciously made time to offer his VAS scores and surgical impressions in order for me to create the Arthro Scores. This research was also made possible thanks to the helpful advice offered by Marie Rhodin, biomechanic processing by Filipe Serra Bragança, and the permission of supportive horse owners.

- At the UDS/KV equine clinic, I thank Kia Nostell for tough, honest, but supportive advice, even as she had to plow through my initial tortuous attempts at writing medical records. I also sincerely thank Karin Holm Forsström, Lena Ström, Kerstin Bergvall, Ylva Hedberg Alm, Jenny Hedenby, and with a special thanks to Sara Larsdotter Davey for always offering generous, patient, and non-judgmental teaching to an equine neophyte as myself.

- Finally, as all good things, surgeon/orthopedic role models usually come in groups of three. In the UDS small animal operating suites I found Mia Norell invariably amiable, jocular, encouraging, energetic, and always stressing the importance of local analgesics. And Annika Bergström, perpetually calm, present, effective, succinct, and witty, even in the face of complexity and uncertainty. Last, but never least, I end this page with the being that – along with the horses I mentioned first – truly made this specific research process a reality: large animal surgeon Pia Haubro Andersen. She never ran out of enthusiastic advice or sharp editing suggestions, evermore instilling a sense of personal strength in her students as well as trust in the great unknown yet to be discovered.

APPENDIX

Informed consent forms

Vill du delta i ett forskningsprojekt om hur hästar kommunicerar sin smärta?

Professor Pia Haubro Andersen (pia.haubro.andersen@slu.se) och hennes medarbetare utför just nu en forskningsstudie gällande hur hästar kan kommunicera sin smärta via ansiktsuttryck och/eller hälta.

Finns det några nackdelar med att min häst deltar i studien?

Nej, att din häst deltar i studien påverkar *inte* kvalitén på eller längden av vård före, under eller efter artroskopin. Det enda som skiljer din hästs vistelse från andra hästars är att din häst kommer att filmas i boxen för att se om den visar smärta via ansiktsuttryck. Din häst kommer även att skrittas före och efter artroskopin i hältgången för att upptäcka ev. hälta med hjälp av ett 3-D program.

Videofilmningen utförs med en liten digitalkamera utan artificiellt ljus. Filmningen kommer därför inte att påverka behandlingen av hästen negativt eller orsaka annan skada. Notera att din häst får samma smärtlindring som alla andra hästar - varken mer eller mindre - under den tid din häst vårdas hos oss.

Finns det några direkta fördelar med att min häst deltar i studien?

Nej, på UDS är vi måna om att ge alla våra patienter samma höga standard av vård, oavsett om dem deltar i en studie eller ej. Din häst kommer därför inte att särbehandlas på något sätt. Vi kan inte heller erbjuda någon finansiell ersättning för deltagandet i studien.

Däremot hoppas vi att din hästs deltagande i studien kommer att hjälpa oss besvara frågan om huruvida dagens rutiner för smärtlindring under och efter artroskopin är den mest ultimata. Din hästs deltagande i studien skulle därför potentiellt kunna bidra till att UDS har ett forskningsunderlag som bidrar till ännu bättre vård av hästpatienter i framtiden.

Jag ger härmed min tillåtelse till att Pia Haubro Andersen och hennes medarbetare videofilmar min häst i ca fem minuter samt skrittar min häst för hältutvärdering med hjälp av ett 3-D dataprogram vid ankomst samt före och efter smärtlindring under hästens vistelse på Uppsala Universitetsdjursjukhus. Videofilmen/bilderna kommer bara att användas för forskning och utbildning: de kommer ej att publiceras. Om publicering skulle bli aktuell kommer jag först att tillfrågas för separat tillåtelse.

Datum:________________ Patient och Journalnr.____

Ägare/Ansvarig:________________________________Körkortslegitimation:______________________

Tillåtelse till publicering av bilder från videos tagna under forskningsprojekt

Professor Pia Haubro Andersen (pia.haubro.andersen@slu.se) och hennes medarbetare utför just nu en forskningsstudie gällande hur hästar kan kommunicera sin smärta via ansiktsuttryck och/eller hälta.

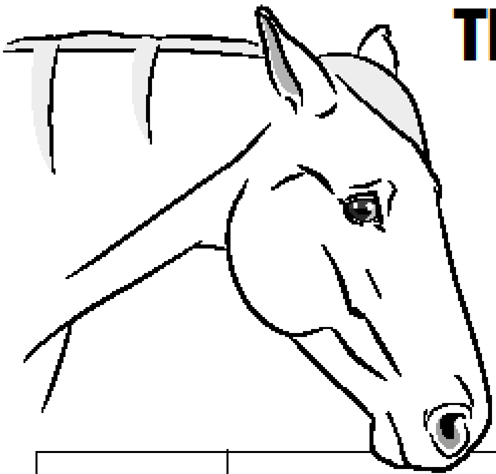
Publiceringskomplement till tidigare undertecknat intyg om deltagande

Jag ger härmed även min tillåtelse till att bilder publiceras från de videofilmer som Pia Haubro Andersen och hennes medarbetare filmat vid min hästs ankomst samt före och efter smärtlindring under hästens vistelse på Uppsala Universitetsdjursjukhus.

Datum:_______________ Patient och Journalnr.____

Ägare/Ansvarig:________________________________Körkortslegitimation:_____________________

The Equine Pain Scale (EPS) scoring system



The Equine Pain Scale

For the specific definitions of each grade of each of the categories please refer to the "Equine pain scale".

To obtain a pain score of any given horse, start observing the horse from a distance to score the first 7 categories of the Equine Pain Scale then approach the horse in the box stall, open the door and evaluate the horse' response to this followed by the horse' response to the approaching observer. Finally, offer the horse some hay or other feed that it would normally eat and observe the horse' response to this. After scoring all 9 categories, sum up the result to yield a final pain score for the specific time point.

Interpretation of the result: Any horse scoring 4 at any parameter and/or having a total pain score of 8-10 or above should be considered in pain and thereby in need for further diagnostic work up, immobilization and/or additional analgesic treatment.

Behaviour category	Patient name:			Patient J.no.:	
	Time:	Time:	Time:	Time:	Time:
Pain face					
Gross pain behaviour*					
Activity					
Location in the stall					
Posture/ weight bearing					
Head position					
Attention towards the painful area					
Interactive behaviour					
Response to food					
SUM					

**Gross pain behaviour includes all readily visible behaviours like, excessive head movements (vert/lat), flehmen, kicking, pawing, rolling, tail swishing, mouth playing, repeated stretching etc.*

Ref. From Bech Gleerup and Lindegaard 2015. Recognition and quantification of pain in horses – a tutorial review, Equine Veterinary Education, In press. Gleerup et al., An equine pain face, Veterinary Anaesthesia and Analgesia, 2015, 42, 103-114. Illustrator: Andrea Klintbjer.

SLU

The Equine Pain Scale Scoring (cont.)

Behaviour category	Score 0	1	2	3	4
Pain face	No pain face		Pain face present	Intense pain face	
Gross pain behaviour*	None		Occasional		Continuous
Activity	Exploring, attention towards surroundings or resting	No movement		Restless	Depressed
Location in the stall	At the door watching the environment	Standing in the middle, facing the door	Standing in the middle facing the sides	Standing in the middle facing back or standing in the back	
Posture/weight bearing	Normal posture and normal weight bearing	Foot intermittent of the ground/ occasional weight shift	Pinched (groove between abd. muscles visible)	Continuously taking foot off the ground and trying to replace it.	No weight bearing. Abnormal weight distribution
Head position	Foraging, below withers or high	Level of withers	Below withers		
Attention towards the painful area	Does not pay attention to painful area		Brief attention to painful area (e.g. flank watching)		Biting, nudging or looking at painful area (e.g. flank watching)
Interactive behaviour	Looks at observer or moves to observer when approached	Looks at observer does not move	Does not look at observer or moves away avoids contact	Does not move, not reacting/introverted	
Response to food	Takes food with no hesitation	Looks at food		No response to food	

**

**Gross pain behaviour includes all readily visible behaviours like, excessive head movements (vert/lat), flehmen, kicking, pawing, rolling, tail swishing, mouth playing, repeated stretching etc.*

Gleerup, K.B. (2014). *Pain evaluation in cattle and horses – a study of behavioural responses to pain.* Diss: Copenhagen: University of Copenhagen.

Arthro score

ARTHROSCOPY SCORE PATIENT PROJECT CODE XXX

Date of surgery:

Anatomical name of joint:

Duration of procedure:

Anesthesia notes if not standard protocol:

Analgesia notes if not standard protocol:

Number of portals:

Position of patient during procedure:

Complications (leakage of fluid, iatrogen injury, difficulty inserting instruments etc):

Surgeons VAS score of tissue damage (0-100):

Prognosis (0-100%):

Intra-articular deposit at end of procedure (analgesic, antibiotic etc):

*Description procedure: (*shaving, recession, suture repair)
1 Mildly invasive
2 Moderately invasive
3 Severely invasive

Hemorrhage during procedure?
0 Absent
1 Mild
2 Moderate
3 Severe

Signs of past hemorrhage (blood clots, hematoma)
0 Absent
1 Mild
2 Moderate
3 Severe

Joint capsule affected (tearing, adhesion etc)?
0 Absent
1 Mild
2 Moderate
3 Severe
Cartilage pathology. Comments: degeneration/erosion

0 Absent
1 Mild
2 Moderate
3 Severe

Depth of cartilage lesion (non-chip/fragment)
0 Absent
1 Mild
2 Moderate
3 Severe

Extent of cartilage damage on articular surface.
0 Absent
1 Mild swelling/softening
2 Moderate: circumscribed areas of prominent fibrillation
3 Severe: generalized fibrillation extending over large areas w/ thinning of articular cartilage
4 Highly severe: exposure of subchondral bone

Tendon/ligament/other soft tissue affecd
0 Absent
1 Mild: fibrillation
2 Moderate: tearing without separation
3 Severe: avulsion/complete tear

Other tearing, rupture and/or adhesion of note?
0 Absent
1 Mild
2 Moderate
3 Severe

Extensive granuloma formation?
0 Absent
1 Mild
2 Moderate
3 Severe

Synovia pathology.
0 Absent
1 Mild
2 Moderate
3 Severe

Copy and paste surgeon operating narrative here

REFERENCES

Ashley, F.H., Waterman-Pearson, A.E. & Whay, H.R. (2005). Behavioral assessment of pain in horses and donkeys: application to clinical practice and future studies. *Equine Veterinary Journal*, 37(6): 565-575.

Bennet, R.C. & Steffey, E.P. (2002). Use of opioids for pain and anesthetic management in horses. *The Veterinary Clinics of North America: Equine Practice*, 18:47-60.

Berry, S.H. (2015). Analgesia in Perioperative Period. *Veterinary Clinics of North America: Small Animal Practice*, 1013-1027.

Bertone, J.J. & Horspool, L.J.I. (2004). *Equine Clinical Pharmacology*. Edinburgh: Saunders.

Blikslager, A. & Jones, S. (2005). NSAIDs. *Journal of Equine Veterinary Science*, March 98-102.

Bonica, J.J. (1992). Pain Research and Therapy: History, Current Status, and Future Goals. In: Short, C.E. & van Poznak, A. (eds) *Animal Pain*. New York: Churchill Livingstone, 1-29.

Boyce, M.K. (2013). Non-terminal animal model of post-traumatic osteoarthritis induced by acute joint injury. *Osteoarthritis and cartilage*, 21(5):746-755.

Broster, C.E, Burn, C.C., Barr, A.R.S. & Whay, H.R. (2009). The range and prevalence of pathological abnormalities associated with lameness in working horses from developing countries. *Equine Veterinary Journal*, 41(5):474-481.

Buchner, H.H.F., Savelberg, H.H.C.M., Schamhardt, H.C., & Barneveld, A. (1996). Head and trunk movement adaptations in horses with experimentally induced fore-or hindlimb lameness. *Equine Veterinary Journal*, 28:71-76.

Bussières G., Jacques C., Lainay O., Beauchamp G., Leblond A., Cadoré J-L, Desmaizières L-M, Cuvelliez S.G. & Tronzy E. (2008). Development of a composite orthopedic pain scale in horses. *Research in Veterinary Science*, 85:294-306.

Caron, J.P. (1996). Neurogenic factors in joint pain and disease pathogenesis. In: McIlwraith C.W. & Trotter G.W. (eds.) *Joint Disease of the Horse*, Philadelphia: Saunders and Company, 70-77.

Davis, L.E. (1983). Species Differences in Drug Disposition as Factors in Alleviation of Pain. In: Kitchell, R.L. & Erickson, H.H. (eds.) *Animal Pain: Perception and Alleviation*. Bethesda: American Physiological Society, 161-178.

Day, T.K., Pepper, W.T., Tobias, T.A., Flynn, M.F., & Clarke, K.M. (1995). Comparison of intra-articular and epidural morphine for analgesi following stifle arthrotomy in dogs. *Veterinary Surgery*, 24:522-530.

Dennis, S.G. & Melzack, R. (1983). Perspectives on Phylogenetic Evolution of Pain Expression In: Kitchell, R.L. & Erickson, H.H. (eds.) *Animal Pain: Perception and Alleviation*. Bethesda: American Physiological Society, 151-160.

Driessen, B. (2007). Pain: From Diagnosis to Effective Treatment. *Clinical Techniques in Equine Practice*, 6:126-134.

Foreman, J.H. & Ruemmler, R. (2011). Phenylbutazone and flunixin meglumine used singly or in combination in experimental lameness in horses. *Equine Veterinary Journal,* 43 (suppl) 40:12-17.

Foreman, J.H., Bergstrom, B.E., Golden, K.S., Roark, J.J., Coren, D.S., Foreman, C.R. & Schumacher, S.A. (2012). Dose titration of the clinical efficacy of intravenously administered flunixin meglumine in a reversible model of equine foot lameness. *Equine Veterinary Journal,* 44 (suppl 43):17-20.

Gaynor, J. S. and Muir, W. W. (2015). *Handbook of Veterinary Pain Management.* St. Louis: Elsevier.

Gleerup K.B. & Lindegaard C. (2015). Recognition and quantification of pain in horses: A tutorial review. *Equine Veterinary Education*, doi:10.1111/eve.12383 [2015-09-20]

Gleerup, K.B. (2014). *Pain evaluation in cattle and horses – a study of behavioural responses to pain.* Diss: Copenhagen: University of Copenhagen.

Goodrich, L.R. (2009). Strategies for Reducing the Complication of Orthopedic Pain Perioperatively. *Veterinary Clinic of North America: Equine Practice*, 611-620.

Goodrich, L.R., Nixon, A.J., Fubini, S.L., Ducharme, N.G., Fortier, L.A., Warnick, L.D. & Ludders, J.W. (2002). Epidural Morphine and Detomidine Decreases Postoperative Hindlimb Lameness in Horses After Bilateral Stifle Arthroscopy. *Veterinary Surgery*, 31:232-239.

de Grauw J.C., van de Lest, C.H.A., Brama, P.A.J., Rambags, B.P.B. & van Weeren, P.R. (2009). In vivo effects of meloxicam on inflammatory mediators, MMP activity and cartilage biomarkers in equine joints with acute synovitis. *The Equine Veterinary Journal*, 41(7):693-699.

de Grauw J.C. & van Loon J.P.A.M. (2015). Systematic pain assessment in horses. *The Veterinary Journal*, doi: 10.1016/j.tvjl.2015.07.030. [2015-09-30]

Hall, L.W. (1992). Postoperative Pain Control in Hospitalized and Out-patient Animals. In: Kitchell, R.L. & Erickson, H.H. (eds.) *Animal Pain: Perception and Alleviation*. Bethesda: American Physiological Society, 353-357.

Hansen, B. (1997). Through a glass darkly: using behavior to assess pain. *Seminars in Veterinary Medicine Surgery*, 12:61-74.

Ijichi, C., Collins, L.M. & Elwood, R.W. (2014). Pain expression is linked to personality in horses. *Applied Animal Behavior Science*, 152:38-43.

Keegan, K.G. (2007). Evidence-Based Lameness Detection and Quantification. *Veterinary Clinics of North America: Equine Practice*, 403-423.

Keegan, K.G., Messer, N.T., Reed, S.K., Wilson, D.A. & Kramer, J. (2008). Effectiveness of administration of phenylbutazone alone or concurrent administration of phenylbutazone and flunixin meglumine to alleviate lameness in horses. *American Journal of Veterinary Research,* 69(2):167-173.

Keegan K.G., Dent, E.V., Wilson, D.A., Janicek, J., Kramer, J., Lacarrubba, A., Walsh, D.M., Cassells, M.W., Esther, T.M., Schiltz, P., Frees, K.E., Wilhite, C.L., Clark, J.M., Pollit, C.C., Shaw, R. & Norris, T. (2010). Repeatibility of subjective evaluation of lameness in horses. *Equine Veterinary Journal*, 42:92-97

Keegan, K.G. (2011) Objective assessment of lameness. In: Baxter, G.M., Adams, O.R. & Stashak, T.S. (eds.) *Adam and Stashak's Lameness in Horses.* Iowa: Wiley-Blackwell.

Kivett, L., Taintor, J. & Wright, J. (2013) Evaluation of the safety of a combination of oral administration of phenylbutazone and firecoxib in horses. *Veterinary Pharmacology and Therapeutics*, 37:413-416.

Lindegaard C., Frost, A.B., Thomsen M.H., Larsen, C., Hansen, S.H., & Andersen P.H. (2010a). Pharmacokinetics of intra-articular morphine in horses with lipopolysaccharide-induced synovitis. *Veterinary Anaesthesia and Analgesia,* 37:186-195.

Lindegaard C., Thomsen M.H., Larsen, C. & Andersen P.H. (2010b). Analgesic efficacy of intra-articular morphine in experimentally induced radiocarpal synovitis in horses. *Veterinary Anaesthesia and Analgesia*, 37:171-185.

McCracken, M.J., Kramer, J., Keegan, K.G., Lopes, M., Wilson, D.A., Reed, S.K., LaCarrubba, A., & Rasch, M. (2012). Comparison of an inertial sensor system of lameness quantification with subjective lameness evaluation. *Equine Veterinary Journal*, 44:652-656.

Mathews, K.A. (2000). Pain Assessment and General Approaches to Management. *Veterinary Clinics of North America: Small Animal Practice*, 30:4 729-755.

McIlwraith C. W., Nixon, A. J., Wright, I. M., & Boening, K. J. (2005). *Diagnostic and surgical arthroscopy in the horse.* Edinburgh: Mosby Elsevier.

Mircica, E., Clutton, R.E., Kyles, K.W. & Blissitt, K.J. (2003). Problems associated with perioperative morphine in horses: a retrospective case analysis. *Veterinary Anasthesia and Analgesia*, 30:147-155.

Moses, V.S. & Bertone, A.L. (2002). Nonsteroidal anti-inflammatory drugs. *The Veterinary Clinics of North America: Equine Practice*, 18:21-37.

Muir, W. (2010). Pain: Mechanisms and Management in Horses. *The Veterinary Clinics of North America: Equine Practice*, 26:467-480.

Noble, G., Edwards, J., Lievaart, J., Pippia, J., Boston, R. & Raidal, S.L. (2012). Pharmacokinetics and Safety of Single and Multiple Oral Doses of Meloxicam in Adult Horses. *Journal of Veterinary Internal Medicine*, 26:1192-1201.

Papich, M.G. (2011). *Saunders Handbook of Veterinary Drugs: Small and Large Animal.* Edinburgh: Saunders Elsevier.

Peham, C., Licka, T., Girtler, D., & Scheidl, M. (2001). Hindlimb lambness: clinical judgement versus computerised symmetry measurement. *Veterinary Record*, 148:750-752.

Price, J., Catriona, S., Welsh, E.M. & Waran, N.K. (2003). Preliminary evaluation of a behaviour-based system for assessment of post-operative pain in horses following arthroscopic surgery. *Veterinary Anasthesia and Analgesia*, 30:124-137.

Pritchett L.C., Ulibarri C., Roberts C.M., Schneider R.K. & Sellon, D.C. (2003). Identification of potential physiological and behavioral indicators of postoperative pain in horses after exploratory celiotomy for colic. *Applied Animal Behavior Science*, 80:31-43.

Raekallio, M., Taylor, P.M. & Bloomfield, M. (1997a). A comparison of methods for the evaluation of pain and distress after orthopedic surgery in horses. *Journal of Veterinary Anaesthesia and Analgesia*, 24(2):17-20.

Raekallio, M., Taylor, P.M., & Bennett, R.C. (1997b). Preliminary Investigations of Pain and Analgesia Assessment in Horses Administered Phenylbutazone or Placebo After Arthroscopic Surgery. *Veterinary Surgery*, 26:150-155.

Robertson, S.A, Steele, C.J., and Chen, C-L. (1990). Metabolic and hormonal changes associated with arthroscopic surgery in horses. *Equine Veterinary Journal*, 22(5):313-316.

Ross, M.W. & Dyson, S.J. (2011). *Diagnosis and management of lameness in the horse.* St. Louis: Saunders Elsevier.

Sammarco, J.L., Conzemius, M.G., Perkowski, S.Z., Weinsten, M.J., Gregor, T.P. & Smith, G.K. (1996). Postoperative analgesi for stifle surgery: a comparison of intra-articular bupivacaine, morphine or saline. *Veterinary Surgery*, 25:59-69.

Santos Pereira L.C., de Moraes, A.N. & Mere, E.S. (2009). Effects of intraarticular ropivacaine and morphine on lipolysaccharide-induced synovitis in horses. *Veterinary Anaesthesia and Analgesia*, 36:280-286.

Sheehy, J.G., Hellyer, P.W. & Sammonds, G.E. (2001). Evaluation of opioid receptors in synovial membranes of horses. *American Journal of Veterinary Research*, 62:1408-1412

Starke, S.D., Willems, E., May, S.E. & Pfau, T. (2012). Vertical head and trunk movement adaptations of sound horses trotting in a circle on a hard surface. *The Veterinary Journal*, 193:73-80.

Stein, C., Comisel, K., Haimeri, E., Yassouridis, A., Lehrberger, K., Herz, A. & Klaus, P. (1991). Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *New England Journal of Medicine*, 325(16):1123-1126

Taylor, P.M., Pascoe, P.J. & Mama, K.R. (2002) Diagnosing and treating pain in the horse. Where are we today? *Veterinary Clinics of North America: Equine Practice*, 18:1-19.

Walliser, U., Fenner, A., Mohren, N., Keefe, T., deVries, F. & Rundfeldt, C. (2015). Evaluation of the efficacy of meloxicam for post-operative management of pain and inflammation in horses after orthopaedic surgery in a placebo controlled clinical field Trial. *BMC Veterinary Research*, 11:113 doi: 10.1186/s12917-015-0427-4. [2015-09-20]

Valverde, A. & Gunkel, C.I. (2005). Pain management in horses and farm animals. *Journal of Veterinary Emergency and Critical Care*, 15(4):295-307.

Van Loon J., Back W., Hellebrekers L.J. & van Weeren P.R. (2010). Application of a Composite Pain Scale to Objectively Monitor Horses with Somatic and Visceral Pain under Hospital Conditions. *Journal of Equine Veterinary Science*, 30 (11): 641-649.

Van Loon, J.P.A.M, de Grauw, J.C., Dierendonck, M., L'Ami, J.J., Back, W. & van Weeren, P.R. (2010). Intra-articular opioid analgesia is effective in reducing pain and inflammation in an equine LPS induced synovitis model. *Equine Veterinary Journal*, 42(5): 412-419.

Visser, E.K., van Reenen C.G., van der Werf J.T.N., Schilder M.B.H., Knapp J. H., Barnevald A. & Blokhuis H.J. (2002). Heart rate and heart rate variability during a novel object test and handling test in young horses. *Physiology and Behavior*, 76: 289-296.

Wagner, A.E. (2010). Effects of Stress on Pain in Horses and Incorporating Pain Scales for Equine Practice. *Veterinary Clinics of North America: Equine Practice*, 26:481-492.

Weary, D.M., Niel, L., Flower, F.C. & Fraser, D. (2006). Identifying and preventing pain in animals. *Applied Animal Behaviour Science*, 100:64-76.

Van Weeren, P.R. & de Grauw J.C. (2010). Pain in Osteoarthritis. *Veterinary Clinics of North America: Equine Practice*, 26;619-642.