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Perioperative pain treatment

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Introduction

Successful perioperative treatment of pain in horses is an important goal of the equine veterinary practitioner, as it improves the final surgical outcome. Pain management in the perioperative settings refers to actions before, during and after a surgical procedure that are intended to minimize post-operative pain. By reducing the occurrence of physical and psychological pain related side effects it is possible to improve the animal wellbeing, to speed up the healing process and to facilitate postoperative rehabilitation. Knowledge of basic principles of pain physiology and pathology as well of pharmacology of pain control are fundamental for a correct approach to perioperative pain therapy.

What is pain?

An official definition of “pain” is offered by the International Association for the Study of Pain: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective…Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus [which is usually defined as nociception (author’s note)] is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.”

According to the official definition it is clear that assessing pain in animals would imply knowing their affective state, their subjective feelings and emotions, which they cannot communicate. All the physiological measures of pain described so far in animals are actually a direct or indirect measure of nociception more than pain.
Acute pain due to nociceptive pathways activation has an important protective function, it appears early in ontology and represents an adaptive response to damaging or potentially damaging stimuli. This is the pain that causes a horse to try to escape a painful stimulus (for example during branding) or situation (for example refusal to be ridden in case of back pain). The biological and behavioral reactions to pain are evident not only in adults but also in term neonates and even in extremely premature newborns and fetuses. The importance of newborn and fetal pain has been completely neglected until recent times. The common concept of “no need to treat pain in newborns or very young animals” due to the weaker physiological and behavioural responses to pain observed in these age categories, is no longer actual (even if the smaller amount of tissue damage has still to be considered an important issue). Indeed in humans it has been shown that early pain experience predisposes the individuals to increase pain perception later in life, as the nociceptive system is highly plastic and able to increase its gain.

In contrast to acute nociceptive pain, pathological pain is a non-functional (non-useful) pain that occurs when the intensity or duration of the experience is not appropriate for the damage sustained and when physiological and behavioral responses are unsuccessful in alleviating it.

Pain is a complex phenomenon, with sensory-motor, sympatho-adrenal, hemodynamic and behavioural components, which can have important systemic consequences. Immobility, for example, can retard bone healing and decrease pulmonary function. Catecholamine release stimulates the sympathetic nervous system, increasing myocardial work and oxygen consumption. Stress hormone release, loss of appetite and insomnia all lead to an overall catabolic state, decrease quality of life and lengthen the time required for healing. Reducing pain will have consequences on the overall wellbeing and healing capabilities of the animals, consistently contributing to animal welfare in the perioperative period.

**Neurophysiology of pain**

The neurophysiological processes involved in the transduction, transmission, modulation and perception of noxious inputs are essentially similar in all
mammals, even if individual variation in pain sensitivity and interspecies differences are known from the clinical practice.

Acute pain is detected in the periphery by a set of specialized peripheral sensory neurons, called nociceptors, which density varies depending on the tissue. The nociceptors are free nerve endings of thin myelinated Aδ and unmyelinated C fibres that respond to one or more (polymodal) type of noxious stimuli (thermal, mechanical, chemical) generating action potentials. This first peripheral event is termed “nociceptive transduction”. The generated action potentials travel along the afferent axons via bundles of sensory nerves to the dorsal horn of the spinal cord or to cranial nerve nuclei. The organization of the afferents makes it possible to localize the source of information on the basis of a spatially ordered neural architecture. The primary neuron synapses in the dorsal horn (or cranial nerve nuclei) with second order neurons, which relay the stimulus up the spinal cord to the brain, and with spinal motor neurons responsible for nociceptive reflexes. Transmission to higher centers leads to suprasegmental and cortical responses. Suprasegmental responses include increases in sympathetic tone and catecholamine release, hypothalamic stimulation with increases in metabolism and oxygen consumption, cortisol release and an overall increase in "fight or flight" arousal mechanisms.

At the level of the dorsal horn of the spinal cord, the incoming pain information may be modified by inputs from both excitatory and inhibitory interneurons before the incoming information is relayed to higher centers in the brain or to spinal motor neurons. Various neurotransmitters are important for transmitting information across synapses in the spinal cord, including excitatory amino acids (as glutamate), peptides (as substance P) and cyclooxygenase products of arachidonic acid metabolism (as prostaglandin E2). Repetitive noxious stimulation, including that associated with surgery or trauma, results in a change in the response properties of the dorsal horn neurons such that neuronal activity of the dorsal horn cell progressively increases throughout the duration of the stimulus. This phenomenon is called “wind-up”. Temporal and spatial summation of repeated or multiple parallel nociceptive inputs also occur in second order neurons, so that the final pain perception is much higher than expected from the intensity of each single applied stimulus. Furthermore, activity within the spinal cord is strongly influenced by descending inhibitory (opioidergic, serotonergic and noradrenergic pathways) or facilitatory pathways originating in higher centres of the brain, and able to depress or increase incoming nociceptive inputs.
Finally, the electrochemical events linked to nociception have to be integrated in the central nervous system (so called pain matrix), where it’s the unique psychology of the individual that determine the subjective experience of pain perception.

**Pain pathology**

The nociceptive system, as other systems in the body, can undergo pathological changes that alter its function and produce unusual, often persistent forms of pain. In fact, the perception of pain cannot anymore be viewed as a static process. Long-term changes might occur within the peripheral and central nervous system following stimulation, which could alter the body's response to further input. Neuronal plasticity is crucial to the development of the hypersensitive states associated with inflammatory and neuropathic pain. Hypersensitivity to pain occurs both at the level of peripheral sensory neurons and centrally at the level of the spinal cord. This might be the phenomenon responsible for the increase sensitivity to a later occurring painful event if a first pain has been experienced early in life.

Inflammatory pain typically develops in the post-operative period or in acute conditions like septic arthritis. Tissue damage and the ensuing inflammatory response promote peripheral sensitization, through a number of substances released peripherally at the site of injury to increase transduction of the noxious stimulus. Release of these substances increases the excitability of sensory and sympathetic nerve fibers, causes vasodilation and extravasation of plasma proteins, and results in further release of chemical mediators from inflammatory cells. Nociceptors that were previously “silent” are activated, overall further contributing to the lowering of the pain threshold.

Furthermore, any injury to the nervous system (peripheral and central) can potentially provoke a peculiar form of pain defined as neuropathic, often not responding to conventional analgesic therapy. This is typically the case for post-amputation pain and for chronic post-surgical pain. In fact during surgery small peripheral nerves might be damaged; recent studies have shown that the occurrence of chronic post-operative pain in humans is much higher than it could be expected, following very different kinds of interventions. The net result of pathological pain is sensitization of the peripheral nociceptors such that low intensity signals not normally causing pain are perceived as painful (allodynia), and an increase in the pain response to noxious stimulation.
(primary hyperalgesia). In addition, these changes spread to adjacent non-
injured tissue (secondary hyperalgesia).

Sustained nociceptors activation caused by nerve injury and inflammation,
accompanied by activation of glial cells and cells of the immune system, leads
to the so-called central sensitization, where spinal neurons augment their
responsiveness provoking chronic hyperalgesia and allodynia. Reduced
descending inhibition or enhanced facilitation can further sustain the central
sensitization state, thus making pain persistent and possibly completely
independent from ongoing peripheral inputs.
The presence of persisting pain or discomfort in horses can increase the
occurrence of aggressive or violent behaviour, and should be seriously
considered as it constitutes a common source of accidents involving
veterinarians or caretakers.

**General concepts for pain treatment**

Understanding pain pathways and the mediators responsible for transduction,
transmission and modulation allows a tailored approach to pain management.
For example, analgesia may be directed at inhibiting transduction or
transmission of the nociceptive signal (e.g., by using a local anesthetic) and/or
at modulating pain processing at spinal or supraspinal level (e.g., by using
alpha-2 agonists or opioids) or at minimizing inflammatory changes at the site
of injury (e.g., by using steroids or non-steroidal anti-inflammatory agents).

Furthermore, if a neuropathic pain component can be suspected or anticipated,
drugs able to inhibit or reduce neuropathic pain specifically should be selected
and the dose titrated to the individual need of the patient. Regular pain
assessment will have to be performed in any case to optimize the therapy and
avoid overdosing and side effects.

Often a so-called multimodal approach to pain management will give the best
results. The combination of 2 or more analgesic drugs or analgesic procedures,
like acupuncture or physiotherapy, more effectively reduces pain than one
drug/procedure alone because different families of analgesics act through
different receptors and at different sites along pain pathways. Analgesics
administered together might have an additive or synergistic effect thus allowing
the dose of each drug used to be reduced while still providing adequate
analgesia. In addition to improved analgesia, there is a reduction in drug side
effects that are more common when higher doses are required.

**Treating perioperative pain**
Preoperative evaluation and anticipated pain

Preoperative patient evaluation is integral to perioperative pain management planning. Patient factors to consider in formulating a plan include type of surgery, anticipated severity of postoperative pain, underlying medical conditions or presence of preoperative pain and the risk–benefit ratio of available treatment modalities.

Pain history, pain-specific physical examination and pain treatment plan should be included in the anaesthetic evaluation prior to surgery. Available procedure-specific pain scoring system should be applied whenever possible and a preoperative score should be assigned.

Preoperative preparation

In equine patients, premedication before surgery is mandatory and should be regarded as first part of a multimodal pain management plan, including treatment of pre-existent pain, or preoperative initiation of therapy for postoperative pain management.

Alpha-2 agonists are a must for equine premedication, both for standing procedures and for surgeries in general anaesthesia. Administered systemically as a bolus they provide powerful analgesia and sedation. The extent and duration of analgesic action is dose and substance dependent. Among the classical alpha-2 agonists approved for equine use (xylazine, romifidine and detomidine) romifidine provides the longest lasting modulation of spinal nociception when equipotent sedative doses are administered

Combining alpha-2 agonists with opioids allows strengthening and stabilizing sedation while substantially improving analgesia. Their peripheral, spinal and central actions in inhibiting pain transmission make them a very important category of analgesic drugs in horses as well as in other species. The well-known excitation observed in horses when opioids are administered alone is dose dependent and occurs only in pain-free subjects. The combination with alpha-2 agonists prevents this side effect and is highly suggested during premedication.

Most commonly used opioids in horses at present are methadone, morphine (most powerful, pure mu agonists), butorphanol (k agonist, mu antagonist) and buprenorphine (partial mu agonist).
Before surgery, non-steroidal anti-inflammatory drugs (NSAIDs) are also commonly administered. While their preventive anti-inflammatory effects are surely of strong interest to obtain a multimodal analgesia, it is important to consider their side effects (on kidneys, gastric mucosa, platelets) which consequences can be exacerbated during general anaesthesia, mostly if tissue perfusion cannot be maintained at optimal levels. Benefit/risk ratio has to be evaluated for each single patient and the decision can be made to postpone the use of NSAIDs to the postoperative phase.

Multimodal intraoperative pain management

Whenever surgery is performed in general anaesthesia, including ketamine in the induction protocol allows to obtain from the very beginning a powerful analgesia. Ketamine, a dissociative anaesthetic, is a NMDA receptor antagonist useful to prevent "wind-up" through inhibition of glutamatergic transmission. As distribution and elimination of the drug after bolus administration are quick, it is necessary to administer the drug further as a sub-anaesthetic CRI during surgery to prolong its analgesic effects throughout the procedure, as adjunct to inhalation anaesthesia or during standing surgeries. Alpha-2 agonists, alone or combined with ketamine and/or lidocaine, can also be administered as a CRI during surgery in general anaesthesia to reduce inhalants MAC or for standing procedures to provide analgesia. Several protocols have been proposed and evaluated, the drugs mostly cited at present being romifidine, medetomidine and dexmedetomidine.

Systemic lidocaine became in the last decade also common part of balanced anaesthesia protocols, as adjunct to inhalants, with the purpose to provide supplemental analgesia and to reduce MAC. Lidocaine also seems to protect tissues against ischemic and reperfusion injuries, endotoxaemia to reduce inflammation and promote gut motility. It is known to suppress development of peripheral hyperalgesia as well as central nociceptive sensitization and allodynia. Classically in colic horses it is used intraoperatively during laparotomies, as a slow bolus followed by CRI.

The intraoperative use of opioids in equine is increasing based on positive clinical experience but its clinically observed efficacy is still not confirmed by strong scientific evidence.

Whenever possible, loco-regional anaesthesia/analgesia should be provided, both in general anaesthesia or in standing surgeries, to effectively prevent pain transduction/transmission in the periphery or at spinal level.
Local anaesthetics like lidocaine, mepivacaine and bupivacaine are amides frequently used in horses. These drugs act by blocking the sodium channel in the neuronal membrane and by inhibiting action potential generation and propagation. When used topically, by local infiltration or for regional nerve blocks, they block transduction and transmission of primary afferent signals. Opioids may also be administered epidurally or intrathecally where they act to block transmission of the nociceptive signal from the dorsal root of the spinal cord to higher centers. Recent evidence suggests that there is also an up-regulation of peripheral opioid receptors (e.g., within the joint capsule) during acute inflammatory states, and that local administration may provide analgesia. Thus, intraarticular administration of opioids (mainly morphine) at the end of the surgery can be used to reduce joint pain\textsuperscript{14,15}.

**Postoperative pain control**

NSAIDs are routinely administered for postoperative pain treatment in horses. They are effective analgesics, especially in case of inflammatory pain. NSAIDs inhibit the cyclooxygenase (COX) enzyme of arachidonic acid metabolism, resulting in a number of antiinflammatory, antipyretic, and analgesic effects. COX products of arachidonic acid metabolism include the "classic" prostaglandins (e.g., prostaglandin E2), prostacyclin and thromboxane. Many of these metabolites are important mediators of the peripheral inflammatory response that contributes to peripheral hypersensitization. It is now apparent that the COX enzyme exists in at least two isoforms, COX-1 and COX-2. COX-1 is always present in tissues (i.e., constitutive), including the gastric mucosa, liver, kidneys and platelets. COX-2 activity, both peripherally and centrally, increases following peripheral inflammation. Until recently, inhibition of peripheral COX activity was believed to be the primary mechanism of action through which NSAIDs provided analgesia. However, it is now recognized that much of their analgesic effect is due to inhibition of the cyclooxygenase enzyme centrally.

Phenylbutazone and flunixin, COX non-selective inhibitors, are still commonly employed with good success by equine practitioners. More recent advances in the field of NSAIDs are represented by the oxicams and coxibs families, with preferential (meloxicam) or selective COX-2 activity (Firocoxib). While the COX-2 preferential or selective NSAIDs are theoretically advantageous in animals with kidney, liver and intestinal problems, non-selective COX drugs seem to provide better control of central hyperalgesia sustained by ongoing peripheral inflammation. This could theoretically explain
the better clinical outcomes obtained with non-selective drugs like phenylbutazone for the treatment of pain in chronic laminitis. Ketoprofen, a slightly COX-1 preferential NSAID, exerting antinociceptive activity through mechanisms other than COX inhibition, might represent a very powerful alternative for pain therapy in horses.

Lidocaine CRI is nowadays commonly used following laparotomic surgery, up to days after the intervention, to provide postoperative analgesia. It prevents reflux and improves quality of life in the first post-operative days. It can also be used in case neuropathic pain components are known to be present or suspected. In general care should be taken to recognize its side-effects as muscle weakness and recumbency can occur in case of overdose or reduced metabolism and should not be falsely interpreted as progressing disease. Ketamine can be provided as a sub-anaesthetic CRI in the postoperative phase to control severe pain. Besides providing visceral and somatic analgesia, ketamine decreases the occurrence of opioid-induced hyperalgesia during prolonged opioids treatment. Butorphanol administered as a CRI has also been demonstrated to reduce postoperative pain and hospital stay following laparotomy surgeries. Continuous administration of epidural or perineural local anaesthetics via catheter can be used for treatment of severe pain, as in case of podal or distal limb pain.

Gabapentin, an anticonvulsant acting on voltage gated calcium-channels in the spinal cord and the brain, has been proposed as specific anti-neuropathic pain treatment in horses. The pharmacokinetics profile of the drug administered to horses has been reported, thus allowing an optimization of therapeutic regimens for the treatment of neuropathic pain syndromes in equines.


