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Review Article

Perioperative Nociception and Pain in Dogs and Cats - Part II: Nociception Assessment, Therapeutic Strategies and Multimodal Analgesia

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Abstract

Optimal perioperative analgesia in dogs and cats depends on the appropriate selection and combination of analgesic agents based on pain mechanisms and accurate pain assessment. Building on the physiological and assessment principles discussed in Part I, this review focuses on therapeutic strategies for perioperative pain management in small animals. Commonly used pharmacological agents, including opioids, non-steroidal anti-inflammatory drugs, local anesthetics, and adjunctive analgesics, are reviewed with respect to their mechanisms of action, clinical applications, and roles in perioperative care. An exhaustive literature search was conducted using Scopus, Google Scholar, and ScienceDirect, including randomized studies evaluating perioperative analgesic interventions in dogs and relevant literature in cats. Keywords included nociception, pain pathways, peripheral and central sensitization, multimodal analgesia, pre-emptive analgesia, electroencephalography, algometry, ketamine, lidocaine, and other analgesics. This review is presented in two complementary parts. Part I focuses on pain pathophysiology and assessment, forming the foundation for Part II, which focuses on pharmacological analgesic modalities and the clinical application of pain management strategies ranging from unimodal techniques to pre-emptive and multimodal analgesia, with emphasis on achieving balanced intraoperative and postoperative pain control. The integration of multimodal approaches targeting different components of the nociceptive pathway is highlighted as a cornerstone of modern veterinary anesthesia, aiming to enhance analgesic efficacy while minimizing adverse effects.

Keywords: Cat, Dog, Nociceptive pathways, Pain assessment, Perioperative pain, Sensitization

Introduction

Based on the foundational understanding of pain mechanisms and assessment outlined in Part I, effective perioperative pain management in dogs and cats requires timely, targeted, and multimodal therapeutic interventions. Appropriate analgesic strategies not only mitigate nociceptive input but also attenuate neuroendocrine stress responses, support physiological stability, and promote recovery and patient welfare. This second part of the review focuses on contemporary pharmacological and non-pharmacological approaches to perioperative analgesia, emphasizing multimodal protocols, species-specific considerations, and patient-centered decision-making. By integrating accurate pain assessment with tailored therapeutic strategies, this review aims to provide clinicians with practical guidance to optimize analgesic efficacy, minimize adverse effects, and reduce the risk of pain chronicity and perioperative complications.

Assessment of Nociception

Parasympathetic Tone Activity Index

Parasympathetic tone activity (PTA) has been used as an objective method to assess nociception intraoperatively [1,2] and postoperatively [3] in dogs. Parasympathetic tone activity (PTA) is an index to assess the nociception/analgesia balance in anaesthetised animals. This is an objective method and is similar to the analgesia nociception index in humans, a validated method for the detection of intraoperative nociception [4]. This index has been derived based on the heart rate variability (HRV) and reflects parasympathetic tone and sympathovagal balance of the patient [1].

A monitor displaying PTA index (PhysioDoloris®; Mdoloris Medical Systems, Lille, France) has been developed and used to assess nociception intraoperatively. This monitor displays an index score from 0 to 100. The lower index values reflect low parasympathetic tone indicating any potential nociception as a result of increased sympathetic tone. While a higher value indicates high parasympathetic tone, reflecting the absence of nociception due to adequate analgesia. This monitor uses ECG signals to assess HRV with low and high frequency variations. Low frequency (LF) ranges from 0.004 to 0.15 Hz, whereas high frequency (HF) range from 0.15 to 0.5 Hz. High frequency reflects predominance of the parasympathetic activity, mainly influenced by respiratory sinus arrhythmia. Low frequency is associated activation of both the sympathetic and parasympathetic systems. Surface ECG is recorded using a 3-lead system. The monitor detects R wave and calculates RR interval from 250 Hz digitized EEG signal. The RR series are filtered in real time using a non-linear artefact removal algorithm preventing artefact-induced inaccurate measurement of these series. After mean centering, RR series are resampled at 8 Hz and normalised using the vectorial norm of the RR series over 64 s for inter subject comparability. The mean centered and normalised RR series are then band pass filtered from 0.15 Hz to 0.5 Hz using a 4 coefficient Daubeuchies wavelet-based filter. This provides RRhf in order to keep only HF variations and display the influence of respiratory sinus arrhythmia in the RR series, which corresponds to the parasympathetic tone of the patient. The amplitude of the normalised and filtered RR series is comprised between 0 and 0.2 (normalised unit). Parasympathetic tone is assessed from the high-frequency component of the RR interval (RRhf). Local maxima and minima of the RRhf signal are identified to construct upper and lower envelopes. The area between these envelopes is calculated within four consecutive 16-second subwindows, yielding areas A1, A2, A3, and A4. The minimum area under the curve (AUCmin) is then determined as the smallest of these four values (AUCmin = min[A1, A2, A3, A4]). This parameter reflects the lowest level of parasympathetic activity observed during the analyzed recording period. [1,2].

The PTA index is then calculated in order to express a fraction of the total window surface, based on formula, $PTA = (100 * [\alpha * AUCmin + \beta]/12.8) * 100/161$, where $\alpha = 5.1$ and $\beta = 1.2$ have been determined in order to keep the coherence between the visual effect of respiratory influence on RR series and the quantitative measurement of ANI; 100/12.8 and 100/161 are coefficients determined to obtain PTA values between 0 and 100, with 100/161 being specific for the dog. The PhysioDoloris® monitor continuously displays an average measurement of PTA made over the previous 4 min. Like ANI, PTA values are scored between 0 and 100 [1].

Parasympathetic tone activity index has been reported to be very useful to monitor nociception intraoperatively [2] as well as postoperatively [3] in dogs. Although very few studies have been reported on PTA index for nociception/analgesia balance in dogs, these studies have demonstrated its usefulness in monitoring for analgesia. Future studies are warranted in other species to prove its effectiveness in clinical setup.

Plethysmography Index

Plethysmography or surgical pleth Index (SPI) has been used in humans to detect and anticipate perioperative nociception and antinociception. It is an objective nociception-monitoring device that assesses nociception using photo-plethysmographic signals [5]. Surgical pleth Index detects the degree of nociception during surgery under general anaesthesia with great accuracy, consequently, provides better guidance for administration of various opioids, faster recovery and lower pain scores [5].

The Surgical Pleth Index monitor uses photo-plethysmographic signals of finger arterioles and balances the nociception and antinociception during general anaesthesia. This monitor uses the equation, $SPI = 100 - (0.33 \times HBI + 0.67 \times PPGA)$, where HBI is the heartbeat interval and PPGA is the photo-plethysmographic waveform amplitude. This monitor requires only a pulse oximeter attached to a finger. The values for the SPI range from 0-100; the lower the values less the nociception there is and vice versa. For adequate intraoperative analgesia, recommended values are 20-50 [5].

The additional advantage of SPI is to help predict the intensity of postoperative pain and analgesic requirement, immediately before patient arousal. The values before consciousness toward the end of surgery had close association with pain in the post anaesthesia care unit [6-8]. Lower incidence of delirium was observed in post anaesthesia care unit, after SPI guided analgesia, in elderly patients [9]. However, in children SPI might not be useful due to higher blood vessel distensibility and baseline heart rates than adults, making SPI values less valid in children than in adults [10]. Age is a factor that confounds the SPI monitoring, since the HBI and PPGA, the main determinants of SPI are directly related to age. Thus, the reference values for heart rate variability for paediatric, young and older age groups vary, for example <20 years vs >60 years. Since vascular elasticity and arterial stiffness vary with age, PPGA depends on vascular wall distensibility and intravascular pulse pressure. Leading to more variation in the values among age groups. In children SP value of <40 has been recommended as a target for adequate intraoperative analgesia [5]. Besides age, a few other factors such as, underlying diseases, different anesthetic and analgesics, may have an impact on SPI results. This warrants further research.

In veterinary medicine, the use of PSI has been reported recently in one study in dogs [11]. These dogs were of ASA class I and II, with testicular tumours, 3 months to 12 years of age and 6 to 50 kg. Acepromazine and methadone were used as premedication. The baseline SPI values were 63-65 in the absence of nociception, higher than SPI values for humans [5]. The authors concluded that analgesics and nociceptive perioperative events caused variation in SPI values. Its ability to predict a hemodynamic reaction was limited by high specificity but low sensitivity. They suggested modification of the algorithm to specifically accommodate for the canine species. The results of this one study in dogs warrant further research for the search of perfect method to assess nociception-antinociception in veterinary species.

Subjective Methods of Pain Scoring

Behaviour

Behavioural response has been recognised as a good indicator of pain in dogs and cats. In general, the behavioural changes to be considered in dogs and cats include response to call, posture (arched back, cornering at one side), vocalisation, aggression, attention to wound, reaction to touch near incision, self-mutilation, interaction with people and ability to walk. It is very important for a clinician to observe the particular animal´s normal behaviour (when not in pain) after admission of the patient at the clinic or hospital and before surgery and use this as a baseline (authors practice) in order to differentiate between the normal and abnormal behaviour (due to pain) of that animal postoperatively to properly treat pain. In addition to general behavioural characteristics, each species exhibits distinct behaviours that are not necessarily applicable to other species, for example cats have been reported to reduce activity, tend to hide and avoid interaction, may perform excessive licking, interfering with their normal grooming, rigid posture and loss of appetite [12,13], especially when cats are alone; however, they mask these behaviours when interacting with other individuals [14]. Dogs show refusal to move, vocalisation, excessive tears, licking and guarding the affected site and, more commonly depression; however, aggression has been reported as well [15,16].

Unidimensional Pain Scales

Assessment of pain and evaluation of the efficacy of analgesics is the major purpose of the pain scoring scales [17]. Various pain scales have been developed and used for pain measurement in veterinary practices, such as, simple descriptive scale, numerical rating scale, and visual analogue scale [17-23]. The principle of all these scales is based on subjective assessment of behaviour, as a consequence, significant interobserver variations in pain scores have been reported [21]. One of the factors for the variation among these scales is lack of clarity of definition for the particular descriptor used. For instance, the same “term” may be interpreted differently by two observers, such as “uncomfortable” [24], “frequent” [23], “responds to calm voice” [23,25]. Similarly, lack of linearity in scores (unequal difference in pain with each increment), inter-observer variability and requirement of more knowledge and skills are the disadvantages of these systems *(https://doi.org/10.5281/zenodo.20612885)*.

Visual Analogue Scale (VAS)

This numerical scale has been described extensively in human practice [26]. However, this is also used in veterinary medicine for postoperative pain measurement [18,19,22,23,25,27]. The VAS consists of a straight 100 mm line starting with 0 as no pain to 100 as worst possible pain. The researcher or observer draws a line intersecting the 100 mm straight line at various intervals, which best describes the estimated level of animal pain. The VAS pain score is then calculated by measuring the distance (in millimeters) between the left end of the line and the intersection. Similarly, VAS can also be used for the sedation score [18,22]. The advantage of VAS is that it is more sensitive and is not labelled to categories. However, lack of linearity in scores (unequal difference in pain with each increment), inter-observer variability and requirement of more knowledge and skills are the disadvantages of the VAS system.

Simple Descriptive Scale

This scale describes different levels of pain intensity with the help of four or five expressions. These expressions are given a number that describes the pain score for that animal. For example, 0 = no pain, 1= mild pain, 2 = moderate pain, and 3 = severe pain [21]. The advantage of this scale is that it is very simple to use. The disadvantages are interobserver variability, which may result in over- or underestimation of pain due to a lack of more pain descriptors [21].

Numerical Rating Scale

This scale works with the same simple descriptive scale principle except that it comprises multiple categories of descriptive definitions for pain behaviours in each category. The observer decides a number which represents the pain score of the animals. Its advantages are easy score tabulation and detailed assessment of the patient due to more categories. Disadvantages include lack of specificity with descriptive pain behaviours. The distribution of the results is not normal, leading to inappropriate statistical analysis [21].

These unidimensional pain scales, despite their limitations, are useful for subjective pain assessment in animals post-operatively and clinical settings. These can be used with other pain scales to improve accuracy.

Multidimensional Pain Scales

The multidimensional pain scales are more advance in a way that, they assess pain more comprehensively than unidimensional pain scales. Unlike unidimensional scales, multidimensional scales assess behavioural and physiological parameters, such as, vocalisation, posture, response to palpation, heart and respiratory rates *(https://doi.org/10.5281/zenodo.20612885)*.

Glasgow Composite Measure Pain Scale

The Glasgow composite measure pain scale has been described as the most validated scale [28], consisting of six behavioural categories with 30 pain descriptors. Based on the intensity of pain, descriptors are ranked numerically. Observer assigns the pain score after selecting the appropriate descriptor in response to the patients' discomfort in each category; sum up of the scores in each category gives the total score. The maximum possible pain score is 24 or 20 if the patient is immobile. It has been shown that the total score of the CMPS-SF is a useful indicator of analgesic requirements. An analgesic intervention has been recommended at 6/24 or 5/20 [29]. The advantage of this scale is that it evaluates multiple aspects for signs of pain in the animal, and does not require any specialized skill or experience to use because the pain descriptors were taken from practicing veterinary surgeons, frequently assessing dogs and cats for acute pain behavior [29]. Each descriptor is well defined to avoid misinterpretation and takes a few minutes to perform. This scale is considered a reliable tool for assessing pain and provides an objective means to quantify pain scores, guiding clinical decision-making during postoperative pain management.

University of Melbourne Pain Scale (UMPS)

The UMPS is a categorized ordinal scale developed by Firth and Haldane [19] in 1999. This system consists of behavioural and physiological parameters, which are divided into six categories: physiological data (heart and respiratory rate), response to palpation, activity, mental status, posture, and vocalization. Each of the categories has been assigned a score for pain. The advantage of this system is that multiple parameters result in better sensibility and accuracy, whereas the disadvantage is the requirement of extensive knowledge of pain demonstration in animals. It can only be used postoperatively and is unable to detect subtle behavioural changes [30].

Colorado Canine and Feline Acute Pain Scale

The Colorado State University Canine and Feline Acute Pain Scales (CSU-CAP and CSU-FAP) are composite pain scales developed at Colorado State University. They incorporate behavioral and psychological indicators, along with responses to wound palpation and body tension, and are influenced by earlier multidimensional pain scales developed at institutions such as the University of Glasgow and the University of Melbourne [32]. The overall numeric pain score is 0 – 4. Patients are scored a quarter per ticked box. A minimum score of 2 or more requires analgesic intervention [31]. The advantages of the CSU pain scale are easy to use, and minimal interpretation is required. The major disadvantage of this scale is the lack of validation by clinical studies [33-36]. In a recent feline study, this scale showed moderate to good inter-rater reliability to assess pain in an ovariohysterectomy model. Although its validity still fell short of current guidelines for correlation coefficients, further refinement is warranted to improve its performance [34].

The UNESP - Botucatu Multidimensional Composite Pain Scale (UNESP - Botucatu MCPS)

This scale encompasses behavioural observations, physiological measurements and intervention levels [36]. This is the first scale that has been validated for post-operative pain in cats [37,38]. Ten items are divided into three subscales. Each scale item is ranked numerically and is assigned a score from 0 to 3. A score of ≥7/30 requires intervention [39]. Drugs such as ketamine and gabapentin, demeanours such as shy, fearful and aggressive behaviours can influence the actual score of the UNESP – Botucatu MCPS and Glasgow composite measure pain scale-feline [40].

Feline Grimace Scale

The Feline Grimace Scale (FGS) was developed and validated as a tool for assessing acute pain in cats. Ear position, head position, muzzle tension, orbital tightening, and whisker change are five action units (AU) identified to record (0-2 for each AU) for this scale. Overall, excellent intra-rater reliability with excellent internal consistency and very strong correlation with another validated instrument for pain assessment have been observed in cats [41]. Furthermore, a trend is increasing to validate this scale in different pain models. Recently, this scale has been validated reliably in a feline dental extraction model [42].

Since these scoring scales rely on observable behavioral responses and interaction with animals, they are suitable for pain assessment during the postoperative period to evaluate the animal's level of comfort and guide decisions regarding analgesic intervention.

Frontline Drugs Used to Manage Surgical and Non-Surgical Pain

The most effective way of properly addressing postoperative pain would be pre-emptive multimodal analgesia [43-45]. This method involves using different classes of drugs acting on various pain pathways involved in nociception and subsequent central sensitization, thus preventing or blocking changes in the central nervous system. Opioids are often considered a cornerstone in acute analgesia. In addition to that, NSAIDs inhibit cyclooxygenase enzymes *(Fig. 1)*, and have the ability to relieve mild to moderate and even severe pain with relatively longer duration of action and offer a great synergistic action with opioids. As research into the multimodal aspects of pain management in veterinary medicine has evolved, various additional drug classes such as alpha-2 adrenergic agonists [46,47], local anesthetics *(Table 1)* [48-52], and NMDA receptor antagonists *(Table 2)* [53-55] have been reported to be effective. *Table 3* serves as a concise reference summarizing commonly used analgesics, anti-inflammatory drugs, anesthetics, and their reversal agents in dogs and cats, particularly from the perspective of pain management and analgesia [56-58].

Perioperative Pain Management Strategies

Why and How to Control Perioperative Nociception?

Surgery instigates a cascade of inflammatory events in the immune system and subsequent changes in the central nervous system (CNS), leading to peripheral and central sensitization. This sensitization of the CNS leads to the development of a condition known as allodynia (pain due to a stimulus that would not normally provoke pain) and hyperalgesia (increased pain from a stimulus that normally provokes pain) (IASP, 2020) [59]. This is the stage that needs to be addressed properly. If this stage is untreated or improperly managed and the pain is maintained, the changes in the CNS may lead to abnormal processing of nociceptive stimuli, and acute pain may lead to chronic pain [60]. Severe acute pain is strongly associated with the development of chronic pain. Therefore, efforts should be made to adequately manage acute pain [61].

Impact of Postoperative Pain on the Health of Animal: Animal Welfare

Perioperative Nociception and Postoperative Pain: Impact of Perioperative Nociception on Postoperative Pain

It is worthwhile to mention, that a clinician must have knowledge of the events which are taking place during the surgical procedure. As discussed above, it is understood from the established knowledge of the nociception, peripheral and central sensitization (see section 1.6) that these phenomena occur as a result of surgical insult and subsequent continuous surgical manipulation as well as duration of the procedure. This intense surgical injury stimulates the C fibers to fire at a very high frequency and speed [62] resulting in the expression of all the receptors and channels involved in nociception, and if not addressed properly, this can lead to the development of central sensitisation. This also includes recruiting silent nociceptors [62,63], which are normally not involved in the process of pain; this is responsible for the enhanced pain during the postoperative period. Therefore, it is of utmost importance that analgesia be provided continuously throughout the procedure, starting before the surgical incision, continuing during the surgery, and extending into the postoperative period to prevent the development of severe acute pain. This could be done with continuous monitoring of HR, BP and RR intraoperatively, and monitoring of behavioural indicators along with HR, BP and RR postoperatively. The selection of antinociceptive agents and their dosages is based on clinical experience, professional judgment, and the individual patient's physiological status and response at a given time.

Effective management of nociception during the perioperative period can prevent the development of central

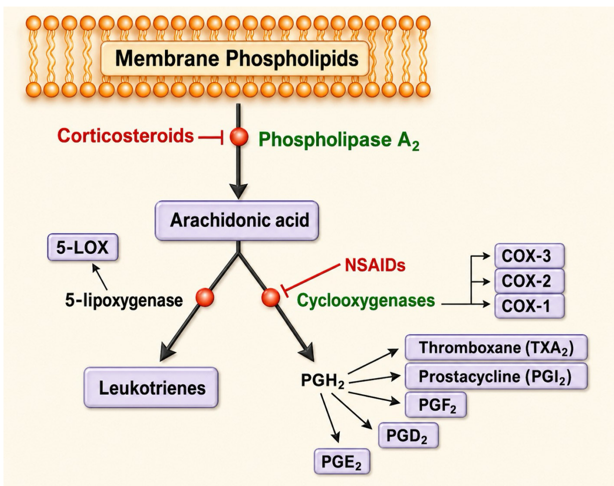

Fig 1. Schematic illustration of NSAIDs' mode of action

Table1. *Summary of various studies on the antinociceptive effects of IV lidocaine in dogs*					
Pain Models	**Pain Scoring Methods**	**Dose**	**Timing**	**Conclusion**	**References**
Intraocular surgery (*)	Categorized Numerical behavioural scale	1) Morphine 0.15 mg/kg IV + 0.1 mg/kg/h CRI, 2) Lidocaine 1 mg/kg IV + 0.025 mg/kg/min CRI, 3) Saline 0.3 ml/kg IV + 0.2 mL/kg/h CRI	15 min pre-surgery until end of anaesthesia	Analgesic effect similar to that of morphine	[49]
Electric Stimulus in conscious dogs	Behavioral reactions	1) Lidocaine 2 mg/kg IV + 10, 25, 50, 75 and 100 µg/kg/min CRI 2) Saline equal volume	CRI for 12 h	No antinociceptive effect of lidocaine compared to saline	[50]
Soft tissue and orthopedic surgery (**)	20% increase in intra-operative HR & BP than previous readings taken as indicators of nociceptive responses due to surgery	1) Lidocaine 2 mg/kg IV + 50 µg/kg/min CRI 2) Saline equal volume	15 min pre-surgery	Inclusion of lidocaine as part of balanced anaesthesia reduced the intraoperative use of opioid compared to saline group	[51]
Ovariectomy (*#)	Categorized numerical behavioral scale	1) Lidocaine 2 mg/kg IV + 50 µg/kg/min CRI + Buprenorphine 0.02 mg/kg IV 2) Lidocaine 2 mg/kg IV + 50 µg/kg/min CRI + Fentanyl 4 µg/kg IV + 8 µg/kg/h CRI 3)Saline + Buprenorphine equal volume/dose 4) Saline + Fentanyl equal volume/dose	Pre-surgery up to skin closure	Systemic lidocaine infusion did not improve the quality of anesthesia. No effect on hemodynamic and respiratory function, peri-operative and post-operative pain relief	[52]
Ovariohysterectomy surgery (*)	Categorized numerical behavioral Scale and plasma cortisol level	1) Lidocaine 1 mg/kg IV + 0.025 mg/kg/min CRI 2) Meloxicam 0.2 mg/kg IV + LRS 10 mL/kg/h CRI 3) Lidocaine + Meloxicam (same dose as above)	5 min pre-surgery until end of anaesthesia	Lidocaine infusion provided similar analgesic effects to meloxicam up to 12 h	[48]

CRI: Continuous rate infusion; IV: Intravenous route; HR: Heart rate; BP: Blood pressure; LRS: Lactated ringer solution; (*): Acepromazine used as premedication, induced with propofol and maintained on isoflurane; (**): Premedication (acepromazine + buprenorphine), induction (propofol + midazolam) and maintenance with isoflurane; (#): premedication (Ketoprofen + diazepam), induction (Diazepam + Ketamine), maintenance with sevoflurane*

sensitization; consequently, animals experience improved comfort in the postoperative period compared with those in which intraoperative nociception is inadequately controlled. As a consequence, less frequent dosing would be required during subsequent days of postoperative pain management, ultimately resulting in lower costs and reduced hospital stay.

Table 2. *Summary of various studies on the antinociceptive effects of IV ketamine in dogs*					
Pain Model	**Pain Scoring Method**	**Dose**	**Timing**	**Conclusion**	**Ref.**
Electric stimulus	Withdrawal reflexes, electromyography	Ketamine 0.5 mg/kg IV + 10 µg/kg/min CRI	Infused pre-stimulus for 1 h	No effects on withdrawal reflexes	[53]
Mastectomy (*)	French multiparametric scoring scale	1) Morphine 0.1 mg/kg IM + Ketamine 150 µg/kg IV + 2 µg/kg/min LCRI, 2) Morphine 0.1 mg/kg IM + Ketamine 700 µg/kg IV + 10 µg/kg/min HCRI 3) Morphine 0.1 mg/kg IM + Saline 0.09 ml/kg IV followed by 0.5 ml/kg/h CRI	Post-operative for 6 h	No effect of ketamine on postoperative morphine requirement. HCRI improved feed intake at 20^{th} h postextubation	[54]
Forelimb amputation (**)	UMPS	1) Ketamine 0.5 mg/kg IV + 10 µg/kg/min CRI during surgery and 2 µg/kg/min CRI for 18 h after surgery 2) Saline same volume Note: Both groups received fentanyl 1-5 µg/kg/min CRI for the first 18 h post-surgery	Starting from pre-surgery, CRI during and 18 h after surgery	Dogs administered ketamine had lower pain scores at 12 h and 18 h and were more comfortable than control group	[55]

LCRI: Low continuous rate infusion; HCRI: High continuous rate infusion; CRI: Continuous rate infusion; UMPS: University of Melbourne pain scale; IV intravenous route; IM: Intramuscular route; (*): Premedicated with acepromazine and morphine; (**): Premedicated with glycopyrrolate and morphine, induction with propofol and maintained on isoflurane

Table 3. *Commonly used analgesics, anti-inflammatory drugs, and anaesthetics especially from the perspective of pain and analgesia and their reversal agents in dogs and cats*

Drugs	**Class**	**Dose in Dogs**	**Dose in Cats**	**Duration of Effect**	**Reference**
Opioids					
Morphine	μ-agonist	0.1-1.0 mg/kg IM, SC 0.1-0.34 mg/kg/h CRI 0.1 mg/kg **Epidural	0.1-0.25 mg/kg IM, SC 0.05-0.1 mg/kg/h CRI	3-4 h	[56-58]
Meperidine (Pethidine)	μ & κ-agonist	2-10 mg/kg IM, SC	2-5 mg/kg IM, SC	1-2 h	[56-58]
Hydromorphone	μ-agonist	0.05 to 0.2 mg/kg IV, IM, SC 0.02-0.04 mg/kg/h CRI	0.1 mg/kg IV, IM, SC 0.02-0.03 mg/kg/h CRI	3-4 h	[56-58]
Oxymorphone	μ-agonist	0.1 mg/kg IV, IM, SC 5-12 μg/kg/h CRI	25-50 μg/kg IV, IM, SC 2.5-5 μg/kg/h CRI	2-4 h	[56-58]
Methadone	μ, κ- and σ-agonist	0.1-0.5mg/kg IV, SC, IM	0.1-0.3 mg/kg IV, SC, IM	3-4 h	[56-58]
Fentanyl	μ-agonist	5-20 μg/kg bolus followed by 3-20 μg/kg/h IV Transdermal: 2.5-5 μg/kg/h DD with selected patch size (25-100 μg/h) according to total body weight, q72h	5-10 μg/kg bolus followed by 2-5 μg/kg/h IV Transdermal: 5.8-10.9 μg/kg/h DD with 25 μg/h patch size for cats ≥2 kg, q120h	0.5-2 h CRI dosing builds up in circulation	[56-58]
Remifentanil	μ-agonist	0.15-0.6 μg/kg/min CRI	0.2-0.4 μg/kg/min CRI	~10 min CRI dosing does NOT build up in circulation	[56-58]
Sufentanil	μ-agonist	3-5 μg/kg bolus followed by 2.6-3.4 μg/kg/h CRI	2-5 μg/kg IV titrated to effect	10-20 min	[56-58]
Alfentanil	μ-agonist	1-5 μg/kg IV followed by 0.5-2.5 μg/kg/min CRI	1 μg/kg IV to effect followed by 1 μg/kg/min CRI	10-20 min	[56-58]
Butorphanol	μ-anatgonist & κ-agonist	0.2-0.4 mg/kg IV, SC, IM	0.2-0.4 mg/kg IV, SC, IM	1-2 h	[56-58]
Buprenorphine	Partial μ-agonist	10-20 μg/kg IV, IM, SC	10-20 μg/kg IV, IM, SC, *OTM	6-8 h	[56-58]
Tramadol	μ-agonist (atypical)	2-4 mg/kg IV, IM, PO	2-4 mg/kg IV, IM, PO	6-12 h	[56-58]
Naloxone	Non-selective, competitive neutral opioid antagonist	0.004-0.04 mg/kg IV, IM, SC	0.005-0.02 mg/kg IV, IM, SC	40 min	[56-58]
Nalmefene	Non-selective, competitive neutral opioid antagonist	0.03 mg/kg IV	0.03 mg/kg IV	8-12 h	[56-58]
Naltrexone	Non-selective, competitive neutral opioid antagonist	0.003-0.1 mg/kg IV, use lowest dose for opioid antagonism and higher dose for reversal of overdose	0.003-0.1 mg/kg IV, q60sec, to effect	12-24 h	[56-58]
Non-steroidal Anti-inflammatory Drugs (NSAIDs)					
Acetaminophen (Paracetamol)	Non-selective COX inhibitor	10-15 mg/kg PO	Contraindicated in cats	8-12 h	[56-58]
Aspirin	Non-selective COX inhibitor	10-25 mg/kg PO q12h 0.5 mg/kg PO q24h for IMHA	10-25 mg/kg PO q48h 81 mg/cat PO q48-72h for TED	12-24 h (dogs) 48-72 h (cats)	[56-58]
Carprofen	Moderately selective COX-2 inhibitor	4 mg/kg PO q24h for 7 days followed by 2 mg/kg PO q24h if needed 4-4.4 mg/kg IV, SC q24h for 3 days followed by 2-2.2 mg/kg q12h if needed	4 mg/kg IV, SC q24h once only	24 h	[56-58]
Deracoxib	Selective COX-2 inhibitor	1-2 mg/kg PO for chronic pain 3-4 mg/kg PO for 7 days followed by 1-2 mg/kg PO for acute pain	1 mg/kg PO	24 h	[56-58]

Table 3. *Continue*					
Drugs	**Class**	**Dose in Dogs**	**Dose in Cats**	**Duration of Effect**	**Reference**
Etodolac	Selective COX-2 inhibitor	5-15 mg/kg PO	Not used in cats	24 h	[56-58]
Firocoxib	Highly selective COX-2 inhibitor	5 mg/kg PO (Puppies <7 months age is very sensitive to >5 mg/kg dose)	1.5 mg/kg PO	24 h	[56-58]
Ketoprofen	Non-selective COX inhibitor	1-2 mg/kg IV, SC, IM for 3 days 1 mg/kg PO for 5 days 0.25 mg/kg PO for 30 days	1-2 mg/kg IV, IM, SC for 3 days 1 mg/kg PO up to 5 days	24 h	[56-58]
Mavacoxib	Selective COX-2 inhibitor	2 mg/kg PO q14d for first 2 doses then q1month for a total of maximum 7 doses	Not used in cats	2-4 weeks For dogs 12 month of age or older	[56-58]
Meloxicam	Preferential COX-2 inhibitor in dogs and cats	0.2 mg/kg IV, SC, PO once followed by 0.1 mg/kg IV, SC, PO	0.1-0.2 mg/kg IV, SC, PO once followed by 0.05 mg/kg PO up to 5 days	24 h	[56-58]
Nimesulide	Selective COX-2 inhibitor	5 mg/kg PO up to 5 days	Not used in cats	24 h	[56-58]
Piroxicam	Non-selective COX inhibitor	0.3 mg/kg PO q24h first 2 doses then q48h	1 mg/cat PO q24h for maximum 7 days	24-48 h	[56-58]
Robenacoxib	Highly selective COX-2 inhibitor	1-2 mg/kg PO 2 mg/kg SC maximum 2 doses	1 mg/kg PO maximum 3-6 days 2 mg/kg SC maximum 2 doses	24 h	[56-58]
Tepoxalin	Non-selective COX and LOX inhibitor	10-20 mg/kg PO on day one followed by 10mg/kg PO	Not used in cats	24 h	[56-58]
Tolfenamic acid	Non-selective COX inhibitor	4 mg/kg IM, SC q24h x two treatments 4 mg/kg PO q24h for 4 days a week and 3 days off (can be repeated on weekly basis)	4 mg/kg SC q24h x two treatments 4 mg/kg PO q24h for 3 days (cannot be repeated on weekly basis)	24 h	[56-58]
Alpha-2 adrenergic agonists and their reversal agents					
[#]Medetomidine	α_2 adrenergic agonist	10-30 µg/kg IM, IV, SC (light sedation) 30-80 µg/kg IM, IV, SC (moderate to deep sedation and analgesia) 2-4 µg/kg CRI (perioperative analgesia particularly as an adjunct to opioid)	100-150 µg/kg IM, SC (deep sedation) 50-100 µg/kg IM, SC (Moderate sedation) 40-80 µg/kg IM (sedation and analgesia) 10-40 µg/kg IV (sedation and analgesia) CRI same as dog for perioperative analgesia 10 µg/kg epidurally (epidural analgesic)	Duration of analgesia is almost 1 h at the dose rate of 10 µg/kg. Better analgesia achieved when combined with opioids	[56-58]
Dexmedetomidine	α_2 adrenergic agonist	2-20 µg/kg IM, IV for sedation and analgesia Perioperative analgesia and rousable sedation 1-2 µg/kg/h CRI	20-40 µg/kg IM, IV for sedation and analgesia Perioperative analgesia and rousable sedation 1-2 µg/kg/h CRI	Duration of analgesia is almost 1 h at the dose rate of 5 µg/kg. Better analgesia achieved when combined with opioids	[56-58]
Xylazine	α_2 adrenergic agonist	1.1 mg/kg IV (Sedation, analgesia, preanesthetic) 2.2 mg/kg IM (Sedation, analgesia, preanesthetic)	1.1 mg/kg IV (Sedation, analgesia, preanesthetic) 2.2 mg/kg IM (Sedation, analgesia, preanesthetic)	~30 min (analgesia) 1-2 h sedative effect	[56-58]
Atipamezole	Selective α_2 adrenergic antagonist	0.1-0.3 mg/kg IM	Same as dogs	Rapid effect: onset of arousal occurs within 5-10 min of IM injection	[56-58]

Table 3. Continue

Drugs	Class	Dose in Dogs	Dose in Cats	Duration of Effect	Reference
Yohimbine	Selective α_2 adrenergic antagonist	0.1-0.2 mg/kg IV, IM (start at low dose, titrate up if needed)	Same as dogs	Reversal of xylazine within 1-3 min of IV injection	[56-58]
Naloxone	Non-selective, competitive neutral opioid antagonist	0.02 mg/kg IM, IV (in severely hypotensive or comatose patients if specific alpha-2 antagonist is not available)	Same as dogs	40 min; Onset of action is within 1-2 min of IV and 2-5 min of IM or SC administration	[56-58]
Miscellaneous					
Gabapentin	Alpha-2- delta subunit of voltage gated calcium channels blocker	10-20 mg/kg PO q8h Cancer pain: 10-20 mg/kg PO q12-24h	5 mg/kg PO q24h Ramp up or taper to effect (range 5-20 mg/kg) Cancer pain: 2-10 mg/kg PO q12-24h	8-24 h in dogs 12-24 h in cats	[56-58]
Amantadine	NMDA-antagonist	3-5 mg/kg PO q12-24h	2-5 mg/kg PO q24h	24 h	[56-58]
Ketamine	NMDA-antagonist	0.25-0.5 mg/kg loading dose followed by 0.01 mg/kg/min CRI intraoperative or 0.002-0.005 mg/kg/min CRI postoperatively	Doses are same as dogs	Dogs: 15±8 min Cats: 20-40 min	[56-58]
Lidocaine	Sodium channel blocker	1 mg/kg loading dose (very slow IV) followed by 0.02-0.04 mg/kg/min CRI intraoperative and postoperatively if needed. Beware of drug accumulation	Avoid lidocaine for analgesia in cats due to the risk of drug accumulation	Systemic lidocaine is best used in combination with other analgesics drugs to achieve balanced analgesia	[56-58]

*Note: Use of some drugs may be considered "off label". Approval of use varies country to country. IV: Intravenous route; IM: Intramuscular route; SC: subcutaneous route; CRI: Continuous rate infusion; OTM: Oral transmucosal route; PO: per os or by mouth; DD: Delivered dose; **Preparation should be preservative free; IMHA: Immune-mediated haemolytic anaemia; TED: Thromboembolic disease; *indicates maximal effect obtained in 15 to 20 minutes; COX: Cyclooxygenase; LOX: lipoxygenase*

Pre-Emptive and Preventive Analgesia

The idea to prevent or "pre-empt" pain was introduced by Crile [64]; he blocked the regional nerves along with general anaesthesia. With increasing knowledge of the subject of pain, it can be considered that there are several factors that play a role in the development of central sensitization during the pre-, intra- and post-operative (peri-operative) periods. However, the extent to which each period contributes to central sensitization is not yet clear [60]. Pre-emptive analgesia has been defined as "administration of antinociceptive agent that inhibit setting up central sensitisation of the CNS" [45]. Although the terms "preventive" and "pre-emptive" are frequently used interchangeably, they represent distinct concepts. Pre-emptive analgesia refers to the administration of analgesic interventions prior to the onset of the surgical stimulus [41,65,66]. In contrast, preventive analgesia is not limited by timing relative to surgical incision and instead involves the use of analgesic interventions throughout the perioperative period, including preoperative, intraoperative, and postoperative phases [66].

Timing of Administration of Analgesics

A thorough understanding of drug pharmacokinetics is crucial for achieving effective analgesia. Factors including the onset of action, duration of effect, plasma concentration, and their relationship to the duration of the surgical procedure must be carefully considered. For example,

1. An intravenous fentanyl bolus administered 30 minutes prior to the start of surgery is generally inadequate for preoperative antinociceptive management, given its relatively short duration of action of about 20 minutes [67]. Consequently, its effects may dissipate before the onset of surgical stimulation. Furthermore, administration of a single fentanyl bolus during an orthopaedic procedure of 2–3 hours duration is insufficient to provide continuous nociceptive control for optimal pain management.
2. The peak plasma concentration of commonly used NSAIDs following subcutaneous administration occurs within 0.5 to 2.4 hours [68,69]. Likewise, buprenorphine has an onset of action of approximately 30–45 minutes [61]. Consequently, if surgical stimulation occurs during this interval, pre-emptive analgesia may not be achieved. This supports Woolf's assertion [70] that the timing of analgesic administration is a critical determinant of effective postoperative pain management.

The concept of pre-emptive analgesia was taken from the strategy that post-operative abnormal sensibility could be prevented by reducing the stimulation of central neurons by the bombardment of afferent activity during surgery by pre- or intra-operative analgesic(s) administration [43]. Therefore, once central sensitization has developed, it cannot be reduced immediately [71]; hence, the traditional method of post-operative analgesic administration may not be sufficient to control pain, and high doses of the drugs would be required to counteract this phenomenon [72]. Thus, the evidence suggests that the timing of the administration of analgesia is the crucial factor for successful postoperative pain control [73].

Multimodal Analgesia

In multimodal analgesia, two or more analgesic agents that act on different pain pathways and neurotransmitter systems are used in combination to prevent nociception and reduce hyperalgesia *(Table 4, Table 5)* [74-77,79]. Since postoperative pain is the result of five major steps of nociception, transduction, transmission, modulation, projection and perception [83], it would not be possible to obtain the optimum analgesia with a single drug or method without potential side effects [73,83]. The rationale of multimodal analgesia should therefore be to prevent transduction and transmission at the periphery by agents acting on sodium channels, preventing nociceptive activity at the level dorsal horn of the spinal cord, such as opioids, and preventing central sensitization by inhibition of NMDA receptors through the use of NMDA antagonists. Thus, optimizing analgesic management during the acute phase is essential for improving patient comfort and reducing the risk of chronic pain development *(Fig. 2)* [49].

Pre-Emptive Multimodal Analgesia

"Pre-emptive multimodal analgesia" is the administration of multimodal analgesic therapy before surgical stimulation. An effective pre-emptive multimodal analgesia may raise the nociceptive threshold and decrease or block stimulation of nociceptors [45]. Pre-emptive multimodal analgesia is thought to be more efficient in treating post-operative pain than traditional unimodal (single drug) analgesia because of its enhanced efficacy, potential for drug synergism, decreased drug-related side effects [43], and decreased amount of inhalant anaesthetic required for maintaining general anaesthesia, thus minimizing cardiorespiratory depression [43,78]. The synergism between alpha-2-agonists and opioids [84] and NSAIDs and opioids has been reported in dogs [22,85]. Dose and the side effects (e.g., nausea, vomiting, sedation, respiratory depression, urinary retention, constipation and pruritus) can be minimized by using a non-opioid adjunct [44,86].

Although there are positive results of multimodal analgesia from the available literature, some studies have failed to observe the beneficial effects of multimodal analgesia compared with conventional unimodal analgesia [44,87]. This may be due to the small sample size and insensitive pain assessment tools.

The benefits of pre-emptive multimodal analgesia have been well established in human medicine. The trend in veterinary medicine has also increased recently and research has been carried out. However, there is an increase in the trend of investigation of various combinations for the purpose of optimum pain management. So far, an ideal, free of side effects protocol for postoperative pain management is not available. The availability of various analgesic agents

Table 4. *Summary of the studies conducted in dogs using various pre-emptive analgesic agents*

Model of Pain	Drug/Dose	Timing	Conclusion	References
Ovariohysterectomy surgery	Pethidine 5 mg/kg IM; Saline control	Pre versus post-operative	Preoperative pethidine group showed significantly lower pain scores than other two groups.	[74]
Ovariohysterectomy surgery	Carprofen 4mg/kg SC; Saline control	Pre versus post-operative	Greater analgesic effect was shown by carprofen given preoperatively than given postoperatively.	[75]
Tibial fracture surgery	Epidural 2% lidocaine 4 mg/kg, ketamine 3 mg/kg and saline (for control group)	Pre-operative	Higher wound swelling and hyperalgesia in saline group compared with lidocaine and ketamine group. Ketamine group had less wound hyperalgesia and swelling than lidocaine group	[79]
Ovariohysterectomy surgery	Pre ketamine 2.5 mg/kg IM; Post ketamine 2.5 mg/kg IM; Saline 0.025ml/kg	Pre versus post-operative	Saline group had significant hyperalgesia and required more rescue analgesia, while pre-surgery ketamine treatment was more beneficial than post-surgery treatment	[76]
Tibial fracture surgery	Epidural pethidine 2 mg/kg, ketamine 3 mg/kg and saline (for control group)	Pre-operative	Less wound swelling, hyperalgesia, pain and early weight bearing in ketamine compared with pethidine group	[77]

IM: Intramuscular route; SC: subcutaneous route

Table 5. *Summary of the studies using multimodal analgesic therapy for pain management*

Model of pain	Drug/Dose	Conclusion	References
Ovariohysterectomy surgery	Pethidine alone; Carprofen alone; Pethidine + Carprofen	Combination of carprofen and pethidine provided good postoperative analgesia than pethidine alone	[18]
Toe pinching response	Medetomidine 20 μg/kg IV; Medetomidine + Hydromorphone 20 μg/kg + 0.1 mg/kg IV; Medetomidine + Butorphanol 20 μg/kg + 0.2 mg/kg IV	Combination of medetomidine with hydromorphone and butorphanol resulted in better analgesia but longer sedation and had cardiopulmonary effects compared with medetomidine alone	[46]
Ovariohysterectomy surgery	Epidural ketamine 1 mg/kg; Ketamine + Morphine 0.5 mg/kg + 0.05 mg/kg; Ketamine + Morphine 1 mg/kg + 0.025 mg/kg	All 3 groups provided adequate analgesia up to 8h. Combining morphine with ketamine did not improve the analgesic effects of ketamine	[87]
Elective orthopedic surgery of pelvic limb	Epidural morphine + bupivacaine 0.2 mg/kg + 1 mg/kg; Morphine 0.2 mg/kg alone; Saline 0.21 mL/kg	Morphine-bupivacaine combination induced better analgesia than morphine alone	[88]
Ovariohysterectomy surgery	Buprenorphine 0.02 mg/kg IM; Carprofen 4 mg/kg SC; Buprenorphine + Carprofen	Wound swelling and pain scores in buprenorphine + carprofen group were lower to buprenorphine alone at 6 h	[22]
Ovariohysterectomy surgery	Epidural morphine 0.1 mg/kg alone; Neostigmine 10 μg/kg alone; Morphine + Neostigmine 0.l mg + 10 μg/kg; Saline control	Adding neostigmine to epidurally administered morphine did not potentiate opioid-induced analgesia	[89]
Orchiectomy	Epidural lidocaine + tramadol 6 mg/kg + 1 mg/kg; Lidocaine + Morphine 6 mg/kg + 0.1 mg/kg; Lidocaine + Saline 6mg/kg + 0.01 mL/kg	Both combinations provided better analgesia for initial 12h compared to lidocaine alone	[80]
Deep pin prick into skin and muscles of thorax and forelimbs	Epidural lidocaine 3.8 mg/kg alone; Ketamine 3 mg/kg alone; Lidocaine + Ketamine	Ketamine provided analgesia for 30 min, lidocaine for 40 min and combination of Ketamine and lidocaine up to 90 min	[81]
Ovariohysterectomy surgery	IV bolus followed by CRI throughout anesthesia, then a CRI at a decreased dose for a further 4 h for all groups. Control group was butorphanol 0.4 mg/kg and infusion rate of 0.9% saline was 2 mL/kg/h. Test groups were: Fentanyl 5 μg/kg, 10 μg/kg/h, then 2.5 μg/kg/h; Ketamine 1 mg/kg, 40 μg/kg/min, then 10 μg/kg/min; Lidocaine 2 mg/kg, 100 μg/kg/min, then 25 μg/kg/min; Dexmedetomidine 1 μg/kg, 3 μg/kg/h, then 1 μg/kg/h; Combination of LKD at the afore mentioned doses	Fentanyl and combination of LKD resulted in adequate postoperative analgesia. Lidocaine, butorphanol, ketamine and dexmedetomidine alone were not effective for treatment of postoperative pain	[47]
Ovariohysterectomy surgery	Both groups received intravenous tramadol 4 mg/kg body weight as premedication. Immediately after induction, the KLT group received ketamine and lidocaine at 0.5 and 2 mg/kg loading dose, followed by continuous rate infusion of 50 and 100 μg/kg/min, respectively, for 2 h. Dogs in T group received saline bolus and continuous rate infusion at equi-volume	Addition of pre-emptive ketamine-lidocaine infusion to single intravenous dose of tramadol enhanced attenuation of central sensitization and improved intra- and postoperative analgesia	[82]

IV: Intravenous route; IM: Intramuscular route; SC: subcutaneous route; CRI: Continuous rate infusion; LKD: Lidocaine + Ketamine + Dexmedetomidine;KLT: Ketamine+Lidocaine+Tramadol

provides an opportunity to evaluate their use within pre-emptive multimodal analgesia approaches to identify the most suitable protocols with minimal side effects.

On the other hand, there are some factors that can be considered when comparing the results of multimodal analgesia with unimodal analgesia:

a) Use of opioids as pre-medication or as part of general anaesthesia in the control groups may mask pain scores and affect the results [88,89].

b) Testing pre- and post-operative analgesia during various trials, when comparing the tested drug with saline as a control, does not consider that

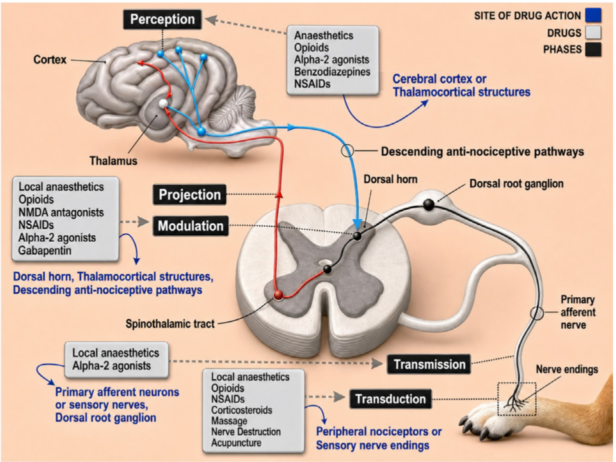

Fig 2. Illustrative summary of the drugs according to their anatomical site of action and phases of pain pathway

the comparison results are not positive. However, comparing the same drug in the pre- and post-injury or stimulus groups is ideal [45,46].

c) Selection of the analgesic agent should depend on the type and severity of the surgery, and it should cover the time from starting before surgery until the last suture is placed [89].

d) The choice of the dose, route and type of analgesic agent are also important factors to be considered to achieve successful analgesia without side effects [89].

The selection of drugs for pre-emptive multimodal analgesia should be based on their efficacy, ease of administration, cost-effectiveness, and additional benefits associated with clinical outcomes [90]. The choice of drug, dosage, and route of administration should be tailored to the type of surgery to achieve maximum benefit.

Successful Pre-Emptive Multimodal Analgesia

Irrespective of the outcomes of the clinical and experimental studies discussed above, a comprehensive understanding of the molecular mechanisms of nociceptive pathways is fundamental to the effective application of pre-emptive multimodal analgesia. This strategy targets multiple stages of nociception, including transduction, transmission, modulation, projection, and perception.

Agents such as lidocaine (sodium channel blockade), opioids (opioid receptor agonism), and ketamine (NMDA receptor antagonism), along with NSAIDs and alpha-2 adrenergic agonists, act at different sites within the nociceptive pathway and constitute effective components of multimodal pain management *(Table 3, Table 4, Table 5)* [18,22,46,47,56-58,74-77,79-82,87-91]. Moreover, continuous administration of antinociceptive agents during the postoperative period is essential and should be maintained until adequate pain control is achieved [47]. Agents with a short duration of action may be administered as a CRI to maintain therapeutic plasma concentrations and ensure consistent antinociceptive effects, such as ketamine, lidocaine, and fentanyl CRIs [47].

Conclusion

Since animals can not communicate verbally, objective evaluation of pain is a major challenge in the assessment of pain for both clinicians and researchers. Pain assessing scales such as feline grimace scale, Glasgow pan scale, UNESP – Botucatu MCPS, and VAS along with algometer offer a useful option and can be successfully used for post operative pain measurement and pain management.

Pre-emptive multimodal analgesia works on the principles of using more than one drug, with various modes of action, acting on different pathways. Thus, the rationale of pre-emptive multimodal analgesia should be targeting transduction, transmission, modulation, projection and perception. To date, there is no single ideal protocol, free of side effects; therefore, drugs acting on sodium channels, NMDA, COX and opioid receptors can be good options to be used to provide multimodal analgesia. In recent years, gabapentin and pregabalin have emerged as agents which may open new avenues for research into their role in pain management protocols. However, further studies are warranted to fully evaluate their efficacy and safety in veterinary medicine.

Declarations

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References

1. **Mansour C, Merlin T, Bonnet-Garin JM, Chaaya R, Mocci R, Ruiz CC, Junot S:** Evaluation of the Parasympathetic Tone Activity (PTA) index to assess the analgesia/nociception balance in anaesthetised dogs. *Res Vet Sci,* 115, 271-277, 2017. DOI: 10.1016/j.rvsc.2017.06.022

2. **Mansour C, El Hachem N, Jamous P, Saade G, Boselli E, Allaouchiche B, Bonnet JM, Junot S, Chaaya R:** Performance of the Parasympathetic Tone Activity (PTA) index to assess the intraoperative nociception

using different premedication drugs in anaesthetised dogs. *Int J Vet Sci Med,* 8 (1): 49-55, 2020. DOI: 10.1080/23144599.2020.1783090

3. **Hernández-Avalos I, Valverde A, Ibancovichi-Camarillo JA, Sánchez-Aparicio P, Recillas-Morales S, Rodríguez-Velázquez D, Acevedo-Arcique CM:** Clinical use of the parasympathetic tone activity index as a measurement of postoperative analgesia in dogs undergoing ovariohysterectomy. *J Vet Res,* 65 (1): 117-123, 2021. DOI: 10.2478/jvetres-2021-0020
4. **Boselli E, Bouvet L, Bégou G, Torkmani S, Allaouchiche B:** Prediction of hemodynamic reactivity during total intravenous anesthesia for suspension laryngoscopy using Analgesia/Nociception Index (ANI): A prospective observational study. *Minerva Anestesiol,* 81, 288-297, 2015.
5. **Oh SK, Won YJ, Lim BG:** Surgical pleth index monitoring in perioperative pain management: Usefulness and limitations. *Korean J Anesthesiol,* 77 (1): 31-45, 2024. DOI: 10.4097/kja.23158
6. **Ledowski T, Sommerfield D, Slevin L, Conrad J, von Ungern-Sternberg BS:** Surgical pleth index: Prediction of postoperative pain in children? *Br J Anaesth,* 119, 979-983, 2017. DOI: 10.1093/bja/aex300
7. **Park M, Kim BJ, Kim GS:** Prediction of postoperative pain and analgesic requirements using surgical pleth index: An observational study. *J Clin Monit Comput,* 34, 583-587, 2020. DOI: 10.1007/s10877-019-00338-4
8. **Hung KC, Huang YT, Kuo JR, Hsu CW, Yew M, Chen JY, Sun CK:** Elevated surgical pleth index at the end of surgery is associated with postoperative moderate-to-severe pain: A systematic review and meta-analysis. *Diagnostics,* 12 (9):2167, 2022. DOI: 10.3390/diagnostics12092167
9. **Won YJ, Oh SK, Lim BG, Kim YS, Lee DY, Lee JH:** Effect of surgical pleth index-guided remifentanil administration on perioperative outcomes in elderly patients: A prospective randomized controlled trial. *BMC Anesthesiol,* 23:57, 2023. DOI: 10.1186/s12871-023-02011-5
10. **Lim BG:** Nociception monitoring tools using autonomic tone changes for intraoperative analgesic guidance in pediatric patients. *Anesth Pain Med,* 14 (4): 380-392, 2019. DOI: 10.17085/apm.2019.14.4.380
11. **Gavet M, Cardinali M, Bernady A, Ruiz CC, Allaouchiche B, Junot S:** Evaluation of the Surgical Pleth Index (SPI) for the monitoring of the nociception-antinociception balance in dogs undergoing castration: A prospective clinical trial. *Res Vet Sci,* 171:105320, 2024. DOI: 10.1016/j.rvsc.2024.105320
12. **Reid J, Nolan AM, Scott EM:** Measuring pain in dogs and cats using structured behavioural observation. *Vet J,* 236:72-79, 2018. DOI: 10.1016/j.tvjl.2018.04.013
13. **Brondani JT, Luna SP, Padovani CR:** Refinement and initial validation of a multidimensional composite scale for use in assessing acute postoperative pain in cats. *Am J Vet Res,* 72, 174-183, 2011. DOI: 10.2460/ajvr.72.2.174
14. **Brondani JT, Mama KR, Luna SP, Wright BD, Niyom S, Ambrosio J, Vogel PR, Padovani CR:** Validation of the English version of the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats. *BMC Vet Res,* 9:143, 2013. DOI: 10.1186/1746-6148-9-143
15. **Franzini de Souza CC, Dias DPM, Souza RN, Salgado BS, Carreira L, Molento CFM:** Use of behavioural and physiological responses for scoring sound sensitivity in dogs. *PLoS One,* 13:e0200618, 2018. DOI: 10.1371/journal.pone.0200618
16. **Landa L:** Pain in domestic animals and how to assess it: A review. *Vet Med (Praha),* 57, 185-192, 2012. DOI: 10.17221/5915-VETMED
17. **Mathews KA:** Pain assessment and general approach to management. *Vet Clin North Am Small Anim Pract,* 30, 729-755, 2000. DOI: 10.1016/S0195-5616(08)70004-4
18. **Lascelles BD, Butterworth S, Waterman AE:** Postoperative analgesic and sedative effects of carprofen and pethidine in dogs. *Vet Rec,* 134, 187-191, 1994.
19. **Firth AM, Haldane SL:** Development of a scale to evaluate postoperative pain in dogs. *J Am Vet Med Assoc,* 214, 651-659, 1999. DOI: 10.2460/javma.1999.214.05.651
20. **Slingsby LS, Taylor PM, Waterman-Pearson AE:** Effects of two doses of buprenorphine four or six hours apart on nociceptive thresholds, pain and sedation in dogs after castration. *Vet Rec,* 159, 705-711, 2006. DOI: 10.1136/vr.159.21.705
21. **Holton LL, Scott EM, Nolan AM, Reid J, Welsh E, Flaherty D:** Comparison of three methods used for assessment of pain in dogs. *J Am Vet Med Assoc,* 212, 61-66, 1998.DOI: 10.2460/javma.1998.212.01.61
22. **Shih AC, Robertson S, Isaza N, Pablo L, Davies W:** Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy. *Vet Anaesth Analg,* 35, 69-79, 2008. DOI: 10.1111/j.1467-2995.2007.00352.x
23. **Conzemius MG, Hill CM, Sammarco JL, Perkowski SZ:** Correlation between subjective and objective measures used to determine severity of postoperative pain in dogs. *J Am Vet Med Assoc,* 210, 1619-1622, 1997. DOI: 10.2460/javma.1997.210.11.1619
24. **Vesal N, Cribb PH, Frketic M:** Postoperative analgesic and cardiopulmonary effects in dogs of oxymorphone administered epidurally and intramuscularly, and medetomidine administered epidurally: A comparative clinical study. *Vet Surg,* 25, 361-369, 1996. DOI: 10.1111/j.1532-950X.1996.tb01428.x
25. **Grisneaux E, Pibarot P, Dupuis J, Blais D:** Comparison of ketoprofen and carprofen administered prior to orthopedic surgery for control of postoperative pain in dogs. *J Am Vet Med Assoc,* 215, 1105-1110, 1999.
26. **McQuay HJ, Moore RA:** Methods of therapeutic trials. **In,** Wall PD, Melzack R (Eds): Textbook of Pain. 4th ed., 1125-1138, Churchill Livingstone, Edinburgh, 1999.
27. **Budsberg SC, Cross AR, Quandt JE, Pablo LS, Runk AR:** Evaluation of intravenous administration of meloxicam for perioperative pain management following stifle joint surgery in dogs. *Am J Vet Res,* 63, 1557-1563, 2002. DOI: 10.2460/ajvr.2002.63.1557
28. **Holton L, Pawson P, Nolan A, Reid J, Scott EM:** Development of a behaviour-based scale to measure acute pain in dogs. *Vet Rec,* 148, 525-531, 2001. DOI: 10.1136/vr.148.17.525
29. **Reid J, Nolan A, Hughes JML, Lascelles D, Pawson P, Scott EM:** Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Anim Welf,* 16 (S): 97-104, 2007. DOI: 10.1017/s096272860003178x
30. **Mich PM, Hellyer P:** Objective, categoric methods for assessing pain and analgesia. **In,** Gaynor JS, Muir WW (Eds): Handbook of Veterinary Pain Management. 2nd ed., 78-109, Mosby, St. Louis, 2008.
31. **Hellyer PW, Uhrig SR, Robinson NG:** Canine acute pain scale and feline acute pain scale. *Colorado State University-CSU Veterinary Medical Center*, 2006.
32. **Beilin B, Bessler H, Mayburd E, Smirnov G, Dekel A, Yardeni I, Shavit Y:** Effects of preemptive analgesia on pain and cytokine production in the postoperative period. *Anesthesiology,* 98, 151-155, 2003. DOI: 10.1097/00000542-200301000-00024
33. **Han ZA, Song DH, Oh HM, Chung ME:** Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. *Ann Neurol,* 79, 569-578, 2016. DOI: 10.1002/ana.24609
34. **Shipley H, Guedes A, Graham L, Goudie-DeAngelis E, Wendt-Hornickle E:** Preliminary appraisal of the reliability and validity of the Colorado State University Feline Acute Pain Scale. *J Feline Med Surg,* 21, 335-339, 2019. DOI: 10.1177/1098612X18777506
35. **Mich PM, Hellyer PW, Kogan L, Schoenfeld-Tacher R:** Effects of a pilot training program on veterinary students' pain knowledge, attitude, and assessment skills. *J Vet Med Educ,* 37, 358-368, 2010. DOI: 10.3138/jvme.37.4.358
36. **Reid J, Nolan AM, Scott EM:** Measuring pain in dogs and cats using structured behavioural observation. *Vet J,* 236, 72-79, 2018. DOI: 10.1016/j.tvjl.2018.04.013
37. **Brondani JT, Luna SPL, Padovani CR:** Refinement and initial validation of a multidimensional composite scale for use in assessing acute postoperative pain in cats. *Am J Vet Res,* 72, 174-183, 2011. DOI: 10.2460/ajvr.72.2.174

38. **Brondani JT, Mama KR, Luna SPL, Wright BD, Niyom S, Ambrosio J, Vogel PR, Padovani CR:** Validation of the English version of the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats. *BMC Vet Res,* 9:143, 2013. DOI: 10.1186/1746-6148-9-143

39. **Della Rocca G, Catanzaro A, Conti MB, Bufalari A, De Monte V, Di Salvo A, Minicucci L, Lacava G, Vignoli M:** Validation of the Italian version of the UNESP-Botucatu multidimensional composite pain scale for the assessment of postoperative pain in cats. *Vet Ital,* 54, 49-61, 2018. DOI: 10.12834/VetIt.567.2704.2

40. **Steagall PV, Monteiro BP:** Acute pain in cats: Recent advances in clinical assessment. *J Feline Med Surg,* 21, 25-34, 2019. DOI: 10.1177/1098612X18808103

41. **Evangelista MC, Watanabe R, Leung VSY, Monteiro BP, O'Toole E, Pang DSJ, Steagall PV:** Facial expressions of pain in cats: The development and validation of a Feline Grimace Scale. *Sci Rep,* 9:19128, 2019. DOI: 10.1038/s41598-019-55693-8

42. **Watanabe R, Doodnaught GM, Evangelista MC, Monteiro BP, Ruel HLM, Steagall PV:** Inter-rater reliability of the Feline Grimace Scale in cats undergoing dental extractions. *Front Vet Sci,* 7:302, 2020. DOI: 10.3389/fvets.2020.00302

43. **Woolf CJ, Chong MS:** Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg,* 77, 362-379, 1993. DOI: 10.1213/00000539-199377020-00026

44. **Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D:** Acute opioid tolerance: Intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology,* 93, 409-417, 2000. DOI: 10.1097/00000542-200008000-00019

45. **Kelly DJ, Ahmad M, Brull SJ:** Preemptive analgesia II: Recent advances and current trends. *Can J Anesth,* 48, 1091-1101, 2001. DOI: 10.1007/BF03020375

46. **Kuo WC, Keegan RD:** Comparative cardiovascular, analgesic, and sedative effects of medetomidine, medetomidine-hydromorphone, and medetomidine-butorphanol in dogs. *Am J Vet Res,* 65, 931-937, 2004. DOI: 10.2460/ajvr.2004.65.931

47. **Gutierrez-Blanco E, Victoria-Mora JM, Ibancovichi-Camarillo JA, Sauri-Arceo CH, Bolio-González ME, Acevedo-Arcique CM, Moles-Mora M, Rodríguez-Vivas RI:** Postoperative analgesic effects of either a constant rate infusion of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine after ovariohysterectomy in dogs. *Vet Anaesth Analg,* 42, 309-318, 2015. DOI: 10.1111/vaa.12215

48. **Tsai TY, Chang SK, Chou PY, Yeh LS:** Comparison of postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing ovariohysterectomy. *Vet Anaesth Analg,* 40, 615-622, 2013. DOI: 10.1111/vaa.12064

49. **Smith LJ, Bentley E, Shih A, Miller PE:** Systemic lidocaine infusion as an analgesic for intraocular surgery in dogs: A pilot study. *Vet Anaesth Analg,* 31, 53-63, 2004. DOI: 10.1111/j.1467-2995.2004.00142.x

50. **MacDougall LM, Hethey JA, Livingston A, Clark C, Shmon CL, Duke-Novakovski T:** Antinociceptive, cardiopulmonary, and sedative effects of five intravenous infusion rates of lidocaine in conscious dogs. *Vet Anaesth Analg,* 36, 512-522, 2009. DOI: 10.1111/j.1467-2995.2009.00480.x

51. **Ortega M, Cruz I:** Evaluation of a constant rate infusion of lidocaine for balanced anesthesia in dogs undergoing surgery. *Can Vet J,* 52, 856-860, 2011.

52. **Columbano N, Secci F, Careddu GM, Sotgiu G, Rossi G, Driessen B:** Effects of lidocaine constant rate infusion on sevoflurane requirement, autonomic responses, and postoperative analgesia in dogs undergoing ovariectomy under opioid-based balanced anesthesia. *Vet J,* 193, 448-455, 2012. DOI: 10.1016/j.tvjl.2011.12.005

53. **Bergadano A, Andersen OK, Arendt-Nielsen L, Theurillat R, Thormann W, Spadavecchia C:** Plasma levels of a low-dose constant-rate infusion of ketamine and its effect on single and repeated nociceptive stimuli in conscious dogs. *Vet J,* 182, 252-260, 2009. DOI: 10.1016/j.tvjl.2008.06.003

54. **Sarrau S, Jourdan J, Dupuis-Soyris F, Verwaerde P:** Effects of postoperative ketamine infusion on pain control and feeding behaviour in bitches undergoing mastectomy. *J Small Anim Pract,* 48, 670-676, 2007. DOI: 10.1111/j.1748-5827.2007.00362.x

55. **Wagner AE, Walton JA, Hellyer PW, Gaynor JS, Mama KR:** Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *J Am Vet Med Assoc,* 221, 72-75, 2002. DOI: 10.2460/javma.2002.221.72

56. **Plumb DC:** Plumb's Veterinary Drug Handbook. 7th ed., 1-1208, Wiley-Blackwell, Ames, 2011.

57. **Ramsey I:** BSAVA Small Animal Formulary. 8th ed., 1-480, British Small Animal Veterinary Association, Gloucester England, 2014.

58. **Kuehn NF:** North American Companion Animal Formulary. 12th ed., North American Compendiums, Inc., Port Huron, 2018.

59. **International Association for the Study of Pain:** IASP terminology. https://www.iasp-pain.org/resources/terminology/; *Accessed:* 08.01.2026.

60. **Gurney MA:** Pharmacological options for intra-operative and early postoperative analgesia: An update. *J Small Anim Pract,* 53, 377-386, 2012. DOI: 10.1111/j.1748-5827.2012.01243.x

61. **Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J:** Acute Pain Management: Scientific Evidence. 4th ed., 1-647, Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, Melbourne, 2015.

62. **Muir WW, III, Woolf CJ:** Mechanisms of pain and their therapeutic implications. *J Am Vet Med Assoc,* 219 (10): 1346-1356, 2001. DOI: 10.2460/javma.2001.219.1346

63. **Willis WD, Westlund KN:** Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol,* 14 (1): 2-31, 1997. DOI: 10.1097/00004691-199701000-00002

64. **Crile G:** The kinetic theory of shock and its prevention through anoci-association (shockless operation). *Lancet,* 182, 7-16, 1913. DOI: 10.1016/s0140-6736(01)65552-1

65. **Grape S, Tramèr MR:** Do we need preemptive analgesia for the treatment of postoperative pain? *Best Pract Res Clin Anaesthesiol,* 21, 51-63, 2007. DOI: 10.1016/j.bpa.2006.11.004

66. **Monteiro BP, Lascelles BDX, Murrell J, Robertson S, Steagall PVM, Wright B:** 2022 WSAVA guidelines for the recognition, assessment and treatment of pain. *J Small Anim Pract,* 64 (4): 177-254, 2023. DOI: 10.1111/jsap.13566

67. **Ramsey I (Ed):** *Small Animal Formulary*. 7th ed., 1-600, BSAVA, Gloucester, 2011.

68. **Busch U, Schmid J, Heinzel G, Schmaus H, Baierl J, Huber C, Roth W:** Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug Metab Dispos,* 26, 576-584, 1998.

69. **Jung M, Lees P, Seewald W, King JN:** Analytical determination and pharmacokinetics of robenacoxib in the dog. *J Vet Pharmacol Ther,* 32, 41-48, 2009. DOI: 10.1111/j.1365-2885.2008.01035.x

70. **Woolf CJ (Ed):** Central mechanisms of acute pain. **In,** *Proceedings of the 6th World Congress on Pain.* Elsevier, Amsterdam, 1991.

71. **Woolf CJ:** Evidence for a central component of post-injury pain hypersensitivity. *Nature,* 306, 686-688, 1983. DOI: 10.1038/306686a0

72. **Woolf CJ, Wall PD:** Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neurosci Lett,* 64, 221-225, 1986. DOI: 10.1016/0304-3940(86)90104-7

73. **Dobromylskyj P, Flecknell PA, Lascelles BD, Pascoe PJ, Taylor P, Waterman-Pearson A:** Management of postoperative pain and other acute pain. **In,** Flecknell P, Waterman-Pearson A (Eds): Pain Management in Animals. 81-145, WB Saunders, London, 2000.

74. **Lascelles BDX, Cripps PJ, Jones A, Waterman-Pearson AE:** Post-operative central hypersensitivity and pain: The pre-emptive value of pethidine for ovariohysterectomy. *Pain,* 73, 461-471, 1997. DOI: 10.1016/S0304-3959(97)00141-3

75. **Lascelles BD, Cripps PJ, Jones A, Waterman-Pearson AE:** Efficacy and kinetics of carprofen, administered preoperatively or

postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Vet Surg,* 27, 568-582, 1998. DOI: 10.1111/j.1532-950X.1998.tb00533.x

76. **Slingsby LS, Waterman-Pearson AE:** The post-operative analgesic effects of ketamine after canine ovariohysterectomy: A comparison between pre- or post-operative administration. *Res Vet Sci,* 69, 147-152, 2000. DOI: 10.1053/rvsc.2000.0406

77. **Raj H, Amarpal, Singh GR, Aithal HP:** Comparison of preemptive analgesia with epidural pethidine and ketamine for the management of postoperative pain in dogs. *Indian Vet J,* 79, 1059-1062, 2002.

78. **Kehlet H, Dahl JB:** The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg,* 77, 1048-1056, 1993. DOI: 10.1213/00000539-199311000-00030

79. **Raj H, Amarpal, Singh GR, Aithal HP:** Postoperative pain management in dogs: Efficacy of pre-emptive analgesia with lignocaine and ketamine. *Indian J Anim Sci,* 70, 362-365, 2000.

80. **Almeida RM, Escobar A, Maguilnik S:** Comparison of analgesia provided by lidocaine, lidocaine-morphine or lidocaine-tramadol delivered epidurally in dogs following orchiectomy. *Vet Anaesth Analg,* 37, 542-549, 2010. DOI: 10.1111/j.1467-2995.2010.00563.x

81. **DeRossi R, Frazílio FO, Jardim PHA, Martins ARC, Schmidt R, Negrini-Neto JM:** Evaluation of thoracic epidural analgesia induced by lidocaine, ketamine, or both administered via a lumbosacral approach in dogs. *Am J Vet Res,* 72, 1580-1585, 2011. DOI: 10.2460/ajvr.72.12.1580

82. **Kaka U, Rahman NA, Abubakar AA, Goh YM, Fakurazi S, Omar MA, Chen HC, Ebrahimi M:** Pre-emptive multimodal analgesia with tramadol and ketamine-lidocaine infusion for suppression of central sensitization in a dog model of ovariohysterectomy. *J Pain Res,* 11, 743-752, 2018. DOI: 10.2147/JPR.S152475

83. **Kehlet H:** Surgical stress: The role of pain and analgesia. *Br J Anaesth,* 63, 189-195, 1989. DOI: 10.1093/bja/63.2.189

84. **Grimm KA, Tranquilli WJ, Thurmon JC, Benson GJ:** Duration of nonresponse to noxious stimulation after intramuscular administration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. *Am J Vet Res,* 61, 42-47, 2000. DOI: 10.2460/ajvr.2000.61.42

85. **Slingsby LS, Waterman-Pearson AE:** Analgesic effects in dogs of carprofen and pethidine together compared with the effects of either drug alone. *Vet Rec,* 148, 441-444, 2001. DOI: 10.1136/vr.148.14.441

86. **Mao J:** Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain,* 100, 213-217, 2002. DOI: 10.1016/S0304-3959(02)00422-0

87. **Acosta AD-P, Gomar C, Correa-Natalini C, Bopp S, Polydoro A, Sala-Blanch X:** Analgesic effects of epidurally administered levogyral ketamine alone or in combination with morphine on intraoperative and postoperative pain in dogs undergoing ovariohysterectomy. *Am J Vet Res,* 66, 54-61, 2005. DOI: 10.2460/ajvr.2005.66.54

88. **Kona-Boun JJ, Cuvelliez S, Troncy E:** Evaluation of epidural administration of morphine or morphine and bupivacaine for postoperative analgesia after premedication with an opioid analgesic and orthopedic surgery in dogs. *J Am Vet Med Assoc,* 229, 1103-1112, 2006. DOI: 10.2460/javma.229.7.1103

89. **Marucio RL, Luna SPL, Neto FJT, Minto BW, Hatschbach E:** Postoperative analgesic effects of epidural administration of neostigmine alone or in combination with morphine in ovariohysterectomized dogs. *Am J Vet Res,* 69, 854-860, 2008. DOI: 10.2460/ajvr.69.7.854

90. **Kehlet H:** Postoperative pain relief - What is the issue? *Br J Anaesth,* 72, 375-378, 1994. DOI: 10.1093/bja/72.4.375

91. **Gassel AD, Tobias KM, Egger CM, Rohrbach BW:** Comparison of oral and subcutaneous administration of buprenorphine and meloxicam for preemptive analgesia in cats undergoing ovariohysterectomy. *J Am Vet Med Assoc,* 227, 1937-1944, 2005. DOI: 10.2460/javma.2005.227.1937