Postoperative pain management in companion animals: an update

Author: Alberto Palella Gómez

Categories: Companion animal, Vets

Date: February 27, 2017

ABSTRACT

Adequate postoperative pain control is very important to reduce complications and hospital stay. This also relies on a correct pain assessment of the patient. Pain score tools, such as behavioural pain scales, help us identify the appropriate time and level of intervention. Pre-emptive and multimodal analgesia have a key role in the correct management of pain. Multimodal analgesia comprehends pharmacological drugs, such as opioids, NSAIDs, local anaesthetics, analgesic adjuncts and non-pharmacological methods, such as cold compress therapy, manual therapy and good nursing.

Pain is a complex, multidimensional experience involving sensory and affective (emotional) components, which can be classified as acute or chronic.

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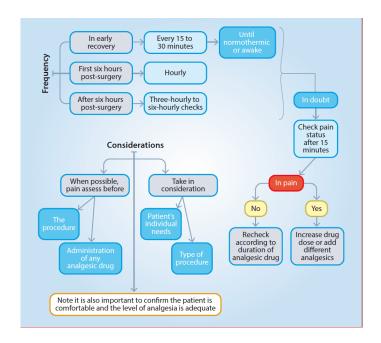


Figure 1. Frequency of pain assessments and considerations.

Acute pain is generally associated with tissue damage or the threat of this, altering the animal's behaviour and, if left untreated, increasing morbidity and mortality. Adequate analgesia is necessary to reduce these deleterious effects.

To be adequate, postoperative pain management should encompass pre-emptive and multimodal analgesia.

Pre-emptive analgesia is the practice of preventive pain management by the principle of preventing upregulation of pain pathways and the development of central and peripheral sensitisation (Katz et al, 2011). This involves the use of analgesic drugs before the noxious stimulus occurs (or as soon as possible if it has already occurred) and continued use of these drugs afterwards for an appropriate period.

Data from studies on acute postoperative pain indicate it is greater in the first 24 hours following surgery, although persistent pain is present in a considerable percentage of individuals – even after common operations. For instance, in dogs and cats undergoing ovariohysterectomy, behavioural changes were observed for at least three days, suggesting pain relief is required following this procedure (Fox et al, 2000; Brondani et al, 2009).

Multimodal analgesia consists of administrating a combination of drugs belonging to different classes. These mainly include opioids, NSAIDs, local anaesthetics, alpha-2 agonists and non-pharmacologic analgesic techniques. Most drugs have a synergistic action and their combination will allow the use of lower doses to minimise side effects. The latest data suggests multimodal analgesia strategies – such as the combination of an opioid and NSAID – are already widely used

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for routine surgeries in the UK (Hunt et al, 2015).

Table 1. Acute pain scales validated in companion animals				
Cats	Dogs			
 The UNESP-Botucatu Multidimensional Composite Pain Scale only within the context of post- ovariohysterectomy (Brondani et al, 2013) 	The short form of the Glasgow Composite Measure Pain Scale (Morton et al, 2005)			
 The Glasgow Composite Measure Pain Scale (Calvo et al, 2014) 				

Table 1. Acute pain scales validated in companion animals.

This article aims to present the latest thinking on postoperative pain management in small animal practice.

Pain assessment and recognition

Effective management of pain relies on the ability to recognise it. For this purpose, pain assessments should be performed at intervals to judge whether the management is adequate and to avoid the underuse or overuse of analgesic drugs. The frequency of pain assessments and considerations are represented in **Figure 1**.

Objective measurements, including heart rate, arterial blood pressure, plasma cortisol, have been associated with pain in dogs (Hansen et al, 1997). However, these are unreliable as stress, fear, disease and anaesthetic drugs may affect these parameters in the same way as pain (Srithunyarat et al, 2016).

Scoring tools, such as pain scales based on behavioural changes, are very useful to record changes in pain over time or after intervention. Few pain scales are validated to assess acute pain in companion animals (**Table 1**).

Pharmacological management

Different analgesic drugs are available to manage postoperative pain. It is important to be aware of

local licensing regulations and, if in the UK, to follow the VMD's prescribing cascade.

Opioids

Opioid analgesic	Dogs	Cats	Receptor	Receptor action	Route of administration	Duration of action	Comments
Methadone	0.1mg/kg to 0.4mg/kg	0.1mg/kg to 0.4mg/kg	Mu	Full agonist	SC/IM/IV	2 to 6 hours	Has N-methyl-D-aspartate receptor antagonist properties
Morphine	0.3mg/kg to 0.5mg/kg	0.1mg/kg to 0.3mg/kg	Mu	Full agonist	IM/IV	2 to 6 hours	Caution with IV administration due to histamine release
Buprenorphine	0.01mg/kg to 0.02mg/kg	0.02mg/kg to 0.04mg/kg	Mu	Partial agonist	SC/IM/IV (oral transmucosal in cats)	4 to 8 hours	Moderate pain
Butorphanol	0.2mg/kg to 0.4mg/kg	0.2mg/kg to 0.4mg/kg	Mu and kappa	Mu antagonist, kappa agonist	SC/IM/IV	1 to 2 hours	Mild to moderate pain
Pethidine	3mg/kg to 5mg/kg	5mg/kg to 10mg/kg	Mu	Full agonist	SC/IM	90 minutes	Do not administer IV due to histamine release Mild pain
Fentanyl	0.002mg/kg to 0.005mg/kg (bolus)	0.001mg/kg to 0.003mg/kg	Mu	Full agonist	IV (bolus)	20 to 40 minutes	Can be used as an initial loading dose previous to CRI
	Constant rate infusion (CRI) 0.003mg/kg/hr to 0.006mg/kg/hr	CRI 0.002mg/ kg/hr to 0.003mg/ kg/hr			IV (CRI)	Can cause accumulation after prolonged CRI	Can be used for significant minimum alveolar concentration reduction during anaesthesia
Tramadol	2mg/kg to 5mg/kg	2mg/kg to 4mg/kg	Mu	Agonist	By mouth	8 hours	Mild to moderate pain as an adjunctive
Naloxone (antagonist)	0.01mg/kg to 0.02mg/kg	0.01mg/kg to 0.02mg/kg		Antagonist	IV		Reversal of both agonist and agonist/antagonist opioids

Table 2. Suggested doses and dosing frequencies of opioid analgesic drugs in cats and dogs.

Opioids are already widely used in clinical practice in the UK, hence they will not be described in depth in this article. Opioids are the cornerstone of effective postoperative pain treatment as they have high efficacy and are remarkably safe (Pascoe, 2000). They vary in their receptor specificity, potency and efficacy, resulting in different clinical effects.

Several opioids are licensed for veterinary use, but it is necessary to be aware of indications and species variations (**Table 2**). Full μ agonists elicit greater and more predictable analgesia than partial μ agonists or k agonists. When choosing which opioid is the most appropriate to use, the factors shown in **Table 3** should be considered.

The most common side effects of opioids are usually associated with excessive doses. These include vomiting (mostly with morphine administered in the premedication period), nausea, dysphoria, panting (atropine-responsive), bradycardia and respiratory depression. Any of these adverse effects can be prevented with careful titration of the drug and, if necessary, can be reversed with naloxone administered to effect. It must be kept in mind naloxone will also antagonise the analgesic effects of the first opioid.

In cats, buprenorphine administered via the oral transmucosal (OTM) route has been proven to be as effective as the IV route (Robertson et al, 2003; Robertson et al, 2005), but later clinical studies have given rise to some controversy on this matter and, where possible, the IV and IM administration routes are preferred to SC and OTM (Steagall et al, 2006; Giordano et al, 2010).

Table 3. Factors to consider when choosing the most appropriate opioid			
Duration of action	Long acting opioids, such as methadone or buprenorphine, are primarily used for the postoperative management of pain to avoid frequent redosing		
Level of pain	Pain assess the patient to decide whether it is experiencing mild, moderate or severe pain		
Other analgesic drugs administered	Administering local anaesthetics at the time of surgery might allow the use of opioids of lower efficacy, such as buprenorphine instead of methadone		

Table 3. Factors to consider when choosing the most appropriate opioid.

Fentanyl is a potent, synthetic? agonist opioid with a rapid onset and short duration of action when administered IV. It is a Schedule 2 narcotic – approximately 100 times more potent than morphine. Its use as boluses or constant rate infusion (CRI) should be considered for its potent analgesia and minimum alveolar concentration-sparing effects.

A transdermal fentanyl solution was licensed for use in dogs, but has been removed from the market (although, at the time of writing this article, it may still be found). For this reason, the off-licence use of fentanyl patches – specifically designed for relief of chronic pain in humans – is becoming popular again.

A review article on transdermal fentanyl patches in small animals showed effective plasma concentrations were achieved in dogs approximately 24 hours after patch application and produced analgesia for up to 72 hours. In cats, effective plasma concentrations were achieved 7 hours after patch application and produced analgesia equivalent to intermittent butorphanol administration for up to 72 hours (Hofmeister and Egger, 2004).

NSAIDs

NSAIDs exert antipyretic, anti-inflammatory and analgesic effects. Unless contraindicated, NSAIDs are the mainstay of most analgesic protocols – being administered on their own in mild pain states or as part of a multimodal approach in more severe cases.

No data exists showing one NSAID is superior to another, and if one fails to provide analgesia, another type of NSAID can be considered. Caution should be taken when switching between

NSAIDs and should follow a washout period of several days (Goodman et al, 2009).

Many NSAIDS are licensed for veterinary use with variations in species and condition indications. It is particularly important to check the product datasheets as some preparations may not be licensed in the perioperative period, where a reduction in systemic blood pressure related to anaesthesia and combined with constitutive cyclo-oxygenase (COX) inhibition (mostly those related with the kidneys and the intestinal tract) may increase the risk of adverse events (Monteiro-Steagall et al, 2013).

Table 4. NSAIDs used in the perioperative period in dogs and cats			
Drug	Indication	Species	Dose/route/frequency
Meloxicam	Surgical pain/acute musculoskeletal	Dogs	0.2mg/kg SC, IV as first loading dose 0.1mg/kg by mouth (PO) once daily
		Cats	0.2mg/kg SC once 0.05mg/kg PO once per day for up to 4 additional days
Carprofen	Surgical pain	Dogs	4mg/kg SC, IV, PO once per day for up to 4 days2mg/kg SC, IV, PO every 12 hours for up to 4 days
		Cats	2mg/kg to 4mg/kg SC, IV – one dose only; DO NOT follow up with additional dosing
Firocoxib	Surgical pain	Dogs	5mg/kg PO once daily for up to 3 days
Paracetamol	Perioperative adjunctive analgesia	Dogs	10mg/kg IV, PO every 12 hours
		Cats	DO NOT USE

Table 4. NSAIDs used in the perioperative period in dogs and cats.

Although the use of NSAIDs is contraindicated in patients with kidney disease, a retrospective study on the effects of meloxicam on the longevity of old-aged cats with degenerative joint disease, and with or without chronic kidney disease (CKD), suggested meloxicam should be considered as a part of the therapeutic regime in cats with chronic painful conditions (titrated to the lowest effective dose – 0.02mg/kg in this particular study). Meloxicam did not appear to reduce the lifespan in patients with pre-existing stable CKD, nor for cats in International Renal Interest Society stages two and three (Gowan et al, 2012).

During the perioperative period the recommendation must be the patient is not dehydrated or hypovolaemic and that blood pressure is maintained. When administered before anaesthesia in healthy animals with controlled modest hypotension, no adverse reaction on renal function was detected (Crandell et al, 2004; Boström et al, 2002). However, in these studies, some dogs developed changes in renal parameters, underlining the importance of maintaining a normotensive state during anaesthesia when considering NSAIDs in the preoperative period.

A summary of NSAIDs available in companion animals is presented in **Table 4**.

Paracetamol

Paracetamol's mechanism of action is complex and includes effects on both the peripheral (COX

inhibition), and central (COX, serotoninergic descending neuronal pathway, L-arginine/nitric oxide pathway, cannabinoid system) antinociception pathways.

Paracetamol is generally used alongside NSAIDs as part of a multimodal approach, or instead of NSAIDs when these are contraindicated. It has analgesic and antipyretic effects, but little, if any, anti-inflammatory activity.

A licensed formulation of paracetamol for dogs is available, which is a mixture of codeine and paracetamol. However, because in dogs the bioavailability of codeine is low (Kukanich, 2010), this drug does not contribute to the analgesia. Paracetamol should not be given to cats (Mathews, 2010). Doses and indications are included in **Table 4**.

Adjunctive drugs

Drug	Dose	Comments		
Ketamine	Doss: 0.2mg/kg to 1mg/kg IV bolus followed by 0.002mg/kg/min (0.12mg/kg/hr) to 0.01mg/kg/min (0.6mg/kg/hr) Cats: 0.2mg/kg to 1mg/kg IV bolus followed by 0.002mg/kg/min (0.12mg/kg/hr) to 0.01mg/kg/min (0.6mg/kg/hr)	Higher infusion rates are during surgery and tapered in the recovery period		
Gabapentin	Dogs: starting dose 10mg/kg by mouth (PO) every 8 to 12 hours Cats: starting dose 5mg/kg PO every 12 hours	Dose can be altered according to the response. Treatment may be required for several weeks – gradual withdrawal recommended. Main side effect of this drug is sedation		
Medetomidine	● Dogs: 0.001mg/kg to 0.005mg/kg IV or IM followed by constant rate infusion (CRI) 0.001mg/kg/hr to 0.005mg/kg/hr IV ● Cats: 0.001mg/kg to 0.005mg/kg IV or IM followed by a CRI 0.001mg/kg/hr to 0.005mg/kg/hr IV	In conscious or anaesthetised dogs, where sedative and cardiopulmonary effects can be tolerated, low doses of medetomidine can be administered, either as a bolus or CRI		

Table 5. Adjunctive analgesic drugs in dogs and cats.

Several drugs are available that do not fall into the major traditional classes of analgesic that can be included in pain management protocols. Doses are indicated in **Table 5**.

Ketamine

Ketamine is an N-methyl-D-aspartate receptor antagonist that has been increasingly used as part of multimodal analgesia to manage moderate to severe pain in the perioperative period for major surgery. Ketamine is particularly indicated when neuropathic or chronic pain is present.

Studies that evaluate the perioperative analgesic effects of ketamine are limited. Dogs undergoing forelimb amputation receiving a ketamine bolus, followed by CRI at rates similar to those aforementioned, resulted in a significantly lower pain score with respect to a control group, 12 and 18 hours after surgery, although opioid requirements were not significantly different between the groups (Wagner et al, 2002).

Gabapentin

Initially developed as an anti-seizure drug, gabapentin has been used as part of multimodal treatment in humans with neurogenic pain, and perioperatively in laboratory animals with induced nerve damage.



Figure 2. Wound soaker catheter for continuous or intermittent administration of a local anaesthetic (such as bupivacaine) into the wound during the postoperative period.

Very few studies have been published assessing its analgesic action in small animals. When given postoperatively in dogs with intervertebral disc surgery, or dogs undergoing forelimb amputation (Wagner et al, 2010; Aghighi et al, 2012), no significant benefit was found from the use of gabapentin at a dose of 10mg/kg every day; however, additional studies with different doses, frequencies and other painful conditions are warranted.

In the long-term treatment for chronic pain in head trauma and musculoskeletal disease in cats unresponsive to traditional analgesic therapy (Lorenz et al, 2013), supporting gabapentin at an average dose of 6.5mg/kg every 12 hours indicated satisfactory pain control.

Alpha-2 agonists

Although alpha-2 agonists are not considered first-line analgesics, however, they are successfully used as adjunctive analgesics in a variety of clinical settings, supplementing analgesia and producing a synergistic analgesic effect when administered with opioids while reducing stress response. The major factor that limits their use in pain management protocols is their significant haemodynamic side effects, which can be reviewed elsewhere (Sinclair, 2003; Murrell and

Hellebrekers, 2005).

Recent attention in veterinary medicine has focused on the administration of CRI alpha-2 agonists during the intraoperative and postoperative periods to supplement anaesthesia and analgesia, although little evidence exists evaluating the effectiveness of these infusions in veterinary patients.

Other than systemic administration, alpha-2 agonists may be administered by novel routes. In dogs, incorporating a low dose of medetomidine combined with opioids or local anaesthetics into an epidural protocol produces synergistic analgesic effects (Pacharinsak et al, 2003). In conjunction to local anaesthetics, medetomidine prolonged sensory and motor blockade after radial nerve block in dogs (Lamont and Lemke, 2008) and may prove to be an effective adjunct to local blocks.

Local anaesthetics

Local anaesthetics are the main drugs used for locoregional anaesthesia and analgesia (Lemke and Dawson, 2000; **Figures 2 and 3**). Evidence shows local anaesthetics not only have antinociceptive, but also immune-modulating antimicrobial and tissue-healing, effects (Johnson et al, 2008; Cassuto et al, 2006).

Short duration local anaesthetic (LA) – low potency	Intermediate duration LA – intermediate potency	Long duration LA – high potency	
Procaine 0.5% to 1% Slow onset of action Duration: 60 to 90 minutes Maximum recommended dose: 12mg/kg in dogs and 6mg/kg in cats Relative potency: 1	Lidocaine 1% to 2% Fast onset (1 to 4 minutes) Duration: 120 to 240 minutes Maximum recommended dose: 6mg/kg in dogs and 2mg/kg in cats Relative potency: 2 Mepivacaine 1.5% Rapid onset Duration: 90 to 150 minutes Maximum recommended dose: 4mg/kg in dogs and 2mg/kg in cats Relative potency: 2	Bupivacaine 0.25% to 0.75% Intermediate onset (10 to 20 minutes) Duration: 18 to 0 360 minutes Maximum recommended dose: 2mg/kg in dogs and 1.5mg/kg in cats Relative potency: 8 Ropivacaine 0.75% Intermediate onset Duration: 180 to 300 minutes Maximum recommended dose: 2mg/kg in dogs and 1mg/kg in cats Relative potency: 4	

Table 6. Potency and duration of most commonly used local anaesthetics.

The most commonly used local anaesthetics, potency and duration are listed in **Table 6**, and the most important and common locoregional delivery techniques are found in **Table 7**.

Lidocaine can be used IV as a bolus or as a CRI in dogs to provide prokinetic, antiarrhythmic, inhalant-anaesthetic sparing, anti-inflammatory effects and systemic analgesia. It can be combined with methadone (or morphine)

and/or ketamine in a CRI for postoperative analgesia (Figure 4).

A pilot study on the analgesic effects of IV lidocaine in dogs undergoing intraocular surgery (Smith et al, 2004) demonstrated a bolus of 1mg/kg, followed by a CRI of 0.02mg/kg/min produced comparable postoperative analgesia to morphine 0.15mg/kg IV bolus followed by a CRI of

0.1mg/kg/hr. However, other studies on the use of lidocaine infusions in cats (Thomasy et al, 2005; Pypendop et al, 2006) suggest caution should be taken until more data is available. These studies failed to show any beneficial antinociceptive effects in cats with moderate plasma levels of lidocaine. This drug also presents greater toxic effects in cats compared to dogs.

Non-pharmacological pain management post-surgery

The use of non-pharmacological therapy, alongside a good pharmacological treatment as part of a multimodal approach to pain, is becoming more popular and evidence is emerging to support their use.

Cold therapy

Cryotherapy, or cold therapy, is the least expensive, easiest and most effective nonpharmacological method to decrease acute inflammatory pain (such as that induced by surgery, trauma or exercise).

Postoperative orthopaedic, neurological and soft tissue (when appropriate) patients can receive immediate cold therapy on their incisions and surgery sites. Cold therapy immediately after cranial cruciate ligament surgery can significantly decrease pain, swelling and increase the joint's range of motion. When combined with compression, it has proved to be more effective (Drygas et al, 2011).

Commercial canvas packs or resealable plastic bags of ice wrapped in a towel can be used for 10 to 20 minutes every 6 to 8 hours. A dampened towel allows for a more rapid transfer of heat and quicker cooling of treated tissues (Dragone et al, 2014), as shown in **Figure 5**. Owners can be instructed to continue cold therapy at home until any swelling and oedema diminishes – usually for three to four days post-surgery, depending on the procedure.



Figure 3. Rostral maxillary (infraorbital) blocks affect bone, teeth and intraoral soft tissue from the maxillary third premolar rostral.



Figure 4. Methadone, ketamine and lidocaine constant rate infusion for pain management during the postoperative period.



Figure 5. Cold compress as part of the non-pharmacological postoperative pain management in a soft tissue case (large mass removal from the left-hand side of the face).

Other approaches

Further methods of non-pharmacological management include the use of physiotherapy, when appropriate, good nursing care or recovering the patient in a comfortable and warm environment.

Conclusions

Delivery techniques	Indications	Drugs	Comments
Topical anaesthesia	To aid intubation	Lidocaine 20mg/ml oromucosal spray	For use in cats
	To help with IV catheter placement	Lidocaine and prilocaine cream	A short 15 to 20 minute wait is normally sufficient
Line and infiltrative blocks	Mass excisions, minor lacerations, surgical incision site	Lidocaine or a combination of lidocaine and bupivacaine	Local anaesthetic can be injected SC at the expecte incision site or infiltrated postoperatively Avoid IV or intra-arterial injection
	Intratesticular block	Lidocaine or a combination of lidocaine and bupivacaine	Indicated for orchiectomy
Splash blocks	Direct application to the body wall before closing the skin on surgical incision site Intraperitoneal, intrapleural	Lidocaine 2% or bupivacaine 0.5% topically	Do not flush the area after applying local anaesthetic
Wound soaker catheter (localised continuous or intermittent local anaesthetic delivery)	After large tumour resection or limb amputation	Lidocaine or mepivacaine for continuous administration (dogs) Bupivacaine for intermittent administration 4 to 6 hours	Keep in place one to three days. If longer, strict aseptic technique is required Potential complications: intravascular or intraneural anaesthetic, infection and seroma formation
IV regional block	Distal limb surgery, digit amputation	Lidocaine or mepivacaine	Potential complications – if tourniquet fails, it can result in possible systemic toxicosis. Ischaemic damac if tourniquet is left >90 minutes NEVER use bupivacaine
Epidural (neuroaxial anaesthesia)	Pelvic limb and posterior abdomen	Local anaesthetic (such as lidocaine 2%) +/- opioid¹ (such as morphine) Opioid (such as morphine) +/- alpha-2 agonist² (such as medetomidine)	Doses of epidural drugs should be calculated by using ideal lean weight of the patient Preservative-free morphine formulations have not been associated with neurotoxicity and are safe to us epidurally and intrathecally
Peripheral nerve blocks	Intraoperative anaesthesia, analgesia and muscle relaxation for orthopaedic and soft-tissue surgery of, for example, the thoracic and pelvic limb, oral surgery or retrobulbar blocks	Lidocaine Bupivacaine	Depending on local anaesthetic and length of the surgery can provide postoperative analgesia Extra equipment: peripheral nerve stimulator +/- ultrasound machine if possible

Table 7. Local anaesthetics delivery techniques (locoregional anaesthesia; see Table 5 for indicative doses).

An appropriate postoperative analgesia regime should prevent upregulation of pain pathways and the development of central and peripheral sensitisation (pre-emptive analgesia), and should be combined with regular pain assessments.

Although opioids and NSAIDs remain the cornerstone for postoperative pain management, the use of adjuncts should always be considered for patients undergoing very painful procedures or where traditional analgesic drugs are insufficient to provide adequate analgesia. Adjunctive drugs can be administered via separate infusion devices to allow adjustment of doses independently.

Non-pharmacological management of postoperative pain (such as physiotherapy and cold therapy) should be applied, when appropriate.

Acknowledgement

The author would like to thank Alessandra Mathis, DVM, CertVA, DipECVAA, MRCVS, for reviewing this article.

References

- Aghighi SA, Tipold A, Piechotta M, Lewczuk P and Kastner SB (2012). Assessment of the
 effects of adjunctive gabapentin on postoperative pain after intervertebral disc surgery in
 dogs, Vet Anaesth Analg 39(6): 636-646.
- Boström IM, Nyman GC, Lord PE, Häggström J, Jones BE and Bohlin HP (2002). Effects of carprofen on renal function and results of serum biochemical and hematologic analyses in anesthetized dogs that had low blood pressure during anesthesia, Am J Vet Res 63(5): 712-721.

- Brondani JT, Loureiro Luna SP, Beier SL, Minto BW and Padovani CR (2009). Analgesic efficacy of perioperative use of vedaprofen, tramadol or their combination in cats undergoing ovariohysterectomy, *J Feline Med Surg* 11(6): 420-429.
- Brondani JT, Mama KR, Luna SP, Wright BD, Niyom S, Ambrosio J, Vogel PR and Padovani CR (2013). Validation of the English version of the Unesp-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats, *BMC Vet Res* 9: 143.
- Calvo G, Holden E, Reid J, Scott EM, Firth A, Robertson S and Nolan AM (2014).
 Development of a behaviour-based measurement tool with defined intervention level for assessing acute pain in cats, *J Small Anim Pract* 55(12): 622-629.
- Cassuto J, Sinclair R and Bonderovic M (2006). Anti-inflammatory properties of local anesthetics and their present and potential clinical implications, *Acta Anaesthesiol Scand* 50(3): 265-282.
- Campagnol D, Teixeira Neto FJ, Giordano T, Ferreira TH and Monteiro ER (2007). Effects
 of epidural administration of dexmedetomidine on the minimum alveolar concentration of
 isoflurane in dogs, Am J Vet Res 68(12): 1,308-1,318.
- Crandell DE, Mathews KA and Dyson DH (2004). Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation, Am J Vet Res 65(10): 1,384-1,390.
- Dragone L, Heinrichs K, Levine D, Millis D and Tucker T (2014). Superficial thermal modalities. In Millis D and Levine D (eds), Canine Rehabilitation and Physical Therapy (2nd edn), Saunders, Philadelphia: 312-327.
- Drygas KA, McClure SR, Goring RL, Pozzi A, Robertson SA and Wang C (2011). Effect of cold compression therapy on postoperative pain, swelling, range of motion, and lameness after tibial plateau levelling osteotomy in dogs, J Am Vet Med Assoc 238(10): 1,284-1,291.
- Fox SM, Mellor DJ, Stafford KJ, Lowoko, CR and Hodge H (2000). The effect of ovariohysterectomy plus different combinations of halothane anaesthesia and butorphanol analgesia behaviour in the bitch, Res Vet Sci 68(3): 265-274.
- Giordano T, Steagall PV, Ferreira TH, Minto BW, de Sá Lorena SE, Brondani J and Luna SP (2010). Postoperative analgesic effects of intravenous, intramuscular, subcutaneous or oral transmucosal buprenorphine administered to cats undergoing ovariohysterectomy, *Vet Anaesth Analg* 37(4): 357-366.
- Goodman L, Torres B, Punke J, Reynolds L, Speas A, Ellis A and Budsberg S (2009).
 Effects of firocoxib and tepoxalin on healigin a canine gastric mucosal injury model, *J Vet Intern Med* 23(1): 56-62.
- Gowan RA, Baral RM, Lingard AE, Catt MJ, Stansen W, Johnston L and Malik R (2012). A
 retrospective analysis of the effects of meloxicam on the longevity of aged cats with and
 without overt chronic kidney disease, *J Feline Med Surg* 14(12): 876-881.
- Hansen B, Hardie EM and Carroll GS (1997). Physiological measurements after ovariohysterectomy in dogs: what's normal?, Appl Anim Behav Sci 51(1-2): 101-109.
- Hofmeister EH and Egger CM (2004). Transdermal fentanyl patches in small animals, J Am Anim Hosp Assoc 40(6): 468-478.

- Hunt J, Knowles T, Lascelles BDX and Murrel J (2015). Prescription of perioperative analgesics by UK small animal veterinary surgeons in 2013, *Vet Rec* **176**(19): 493.
- Johnson SM, Saint John BE and Dine AP (2008). Local anesthetics as antimicrobial agents: a review, *Surg Infect (Larchmt)* **9**(2): 205-213.
- Katz J, Clarke H and Seltzer Z (2011). Preventive analgesia: quo vadimus? Anesth Analg
 113(5): 1,242-1,253.
- Kukanich B (2010). Pharmacokinetics of acetaminophen, codeine, and the codeine metabolites morphine and codeine-6-glucuronide in healthy greyhound dogs, *J Vet Pharmacol Ther* 33(1): 15-21.
- Lamont LA and Lemke KA (2008). The effects of medetomidine on radial nerve blockade with mepivacaine in dogs, *Vet Anaesth Analg* **35**(1): 62-68.
- Lemke KA and Dawson SD (2000). Local and regional anesthesia, *Vet Clin North Am Small Anim Pract* **30**(4): 839-857.
- Lorenz ND, Comerford EJ and Iff I (2013). Long-term use of gabapentin for musculoskeletal disease and trauma in three cats, *J Feline Med Surg* **15**(6): 507-512.
- Mathews KA (2010). Non-steroidal anti-inflamatory analgesics. In Ettinger SJ and Feldman EC (eds), Textbook of Veterinary Internal Medicine (6th edn), Elsevier Saunders, St Louis: 606-613.
- Monteiro-Steagall BP, Steagall PV and Lascelles BD (2013). Systemic review of nonsteroidal anti-inflamatory drug-induced adverse effects in dogs, J Vet Intern Med 27(5): 1,011-1,019.
- Morton CM, Reid J, Scott EM, Holton LL and Nolan AM (2005). Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs, Am J Vet Res 66(12): 2,154-2,166.
- Murrell JC and Hellebrekers LJ (2005). Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog, Vet Anaesth Analg 32(3): 117-127.
- Pacharinsak C, Greene SA, Keegan RD and Kalivas PW (2003). Postoperative analgesia in dogs receiving epidural morphine plus medetomidine, *J Vet Pharmacol Ther* **26**(1): 71-77.
- Pascoe PJ (2000). Opioid analgesics, Vet Clin North Am Small Anim Pract 30(4): 757-772.
- Pypendop BH, Ilkiw JE and Robertson SA (2006). Effects of intravenous administration of lidocaine on the thermal threshold in cats, Am J Vet Res 67(1): 16-20.
- Robertson SA, Taylor PM, Lascelles BD and Dixon MJ (2003). Changes in thermal threshold response in eight cats after administration of buprenorphine, butorphanol and morphine, Vet Rec 153(15): 462-465.
- Robertson SA, Lascelles BD, Taylor PM and Sear JW (2005). PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration, J Vet Pharmacol Ther 28(5): 453-460.
- Skarda RT and Tranquilli WJ (2007a). Local anesthetics. In Tranquilli WJ, Thurmon JC and Grimm KA (eds), Lumb and Jones' Veterinary Anesthesia and Analgesia (4th edn), Blackwell Publishing, Ames: 395-418.
- Skarda RT and Tranquilli WJ (2007b). Local and regional anesthetic techniques: dogs. In

- Tranquilli WJ, Thurmon JC and Grimm KA (eds), *Lumb and Jones' Veterinary Anesthesia and Analgesia* (4th edn), Blackwell Publishing, Ames: 561-594.
- Skarda RT and Tranquilli WJ (2007c). Local and regional anesthetic techniques: cats. In Tranquilli WJ, Thurmon JC and Grimm KA (eds), *Lumb and Jones' Veterinary Anesthesia* and Analgesia (4th edn), Blackwell Publishing, Ames: 595-604.
- Sinclair MD (2003). A review of the physiological effects of alpha 2-agonists related to the clinical use of medetomidine in small animal practice, Can Vet J 44(11): 885-897.
- Smith LJ, Bentley E, Shih A and Miller PE (2004). Systemic lidocaine infusion as an analgesic for intraocular surgery in dogs: a pilot study, Vet Anaesth Analg 31(1): 53-63.
- Srithunyarat T, Höglund OV, Hagman R, Olsson U, Stridsberg M, Lagerstedt AS and Pettersson A (2016). Catestatin, vasostatin, cortisol, temperature, heart rate, respiratory rate, scores of the short form of the Glasgow composite measure pain scale and visual analogue scale for stress and pain behaviour in dogs before and after ovariohysterectomy, BMC Res Notes 9: 381.
- Steagall PV, Carnicelli P, Taylor PM, Luna SP, Dixon M and Ferreira TH (2006). Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats, J Vet Pharmacol Ther 29(6): 531-537.
- Thomasy SM, Pypendop BH, Ilkiw JE and Stanley SD (2005). Pharmacokinetics of lidocaine and its active metabolite, monoethylglycinexylidide, after intravenous administration of lidocaine to awake and isoflurane-anesthetized cats, Am J Vet Res 66(7): 1,162-1,166.
- Valverde A, Dyson DH and McDonell WN (1989). Epidural morphine reduces halothane MAC in the dog, Can J Anaesth 36(6): 629-632.
- Vesal N, Cribb PH and Frketic M (1996). Postoperative analgesic and cardiopulmonary
 effects in dogs of oxymorphone administered epidurally and intramuscularly, and
 medetomidine administered epidurally: a comparative clinical study, Vet Surg 25(4):
 361-369.
- Wagner AE, Walton JA, Hellyer PW, Gaynor JS and Mama KR (2002). 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(1): 72-75.
- Wagner AE, Mich PM, Uhring SR and Hellyer PW (2010). Clinical evaluation of perioperative administration of gabapentin as an adjunct for postoperative analgesia in dogs undergoing amputation of a forelimb, *J Am Vet Med Assoc* 236(7): 751-756.