

Acute Pain Management in Cats: Assurance of Feline Welfare Fulfillment Within Clinical Environment

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Abstract

Assessing, acknowledging, and managing pain in feline patients are often challenging. Failure to recognize and protect the cats from harmful effects of nociception, therefore, often ensue. Feline patients that are afflicted with illness and tissue trauma that may arise from trauma or surgery have acute pain that needs to be addressed. Acute pain can present with varying degree of intensity, a parameter of sensory-discriminatory aspect, and unpleasantness, a perceived feeling that is integral to affective aspect. Notwithstanding its usefulness to protect the tissue from further damage, acute pain is detrimental to the feline's welfare, comprising physical and mental wellness if not managed properly. Uncontrolled pain has also been associated with increased morbidity, prolonged hospitalization period due to delayed recovery, increased health-care cost, and decreased quality of life. This review article is made with the aim to elucidate how acute pain in cats is recognized, prevented, and treated, both pharmacologically and non-pharmacologically.

Keywords: Acute pain, nociception, feline welfare, trauma

Background

Pain in cats is often overlooked. The inability of animals in general to communicate their pain is natural, but it does not nullify the likelihood that they do indeed experience pain. Studies have found that consequences like increased morbidity, impaired quality of life, hampered recovery and subsequent increase in hospitalization period and health-care cost entail refractory pain (Gan, 2017). The lack of pain assessment, recognition, and management has been reported, especially among older and male practitioners, and those who practice in smaller clinical settings,

with multifactorial causes such as limited access to various analgesics, concern over opioid's adverse effect, inadequate curriculum material about pain management taught in veterinary schools and differing subjective perception of pain between the sexes (Dohoo & Dohoo, 1996; Hugonnard et al., 2004; Joubert, 2001). Furthermore, validated pain assessment tools were not widely used within the clinical setting (Coleman & Slingsby, 2007). When pain is unrecognized, less analgesic is used, leading to inadequate pain management (Simon et al., 2017).

According to the International Society of Feline Medicine, the employment of pain scales that are not approved for use in cats was a hurdle that recently has gotten a breakthrough (Steagall et al., 2022). Admittedly, there are species-related pain-related alterations that become major limitations, especially when using dog-validated pain assessment tools to assess pain in cats. These differences can also be seen within the species, based on the pain threshold, temperament, and different cause of pain each individual can have (Reid et al., 2018; Steagall et al., 2022). There are now three validated feline-specific pain assessment tools that can be employed, although the use of whichever will need training for the veterinary staff (the clinicians and nurses) (Belli et al., 2021; Evangelista et al., 2019; Reid et al., 2017). The use of these validated pain scales has also led to an advancement in research and clinical studies, leading to discovery of feline-specific analgesics that significantly improve the margin of safety of the administered drugs (Steagall et al., 2022). This review article will try to elucidate the mechanism behind pain perception, use of these advent feline-specific pain assessment tools, and the art of feline acute pain management, both pharmacologically and non-pharmacologically.

Acute Pain: Why and How It Happens

Acute pain arises from any insults that results in tissue injury and subsequent inflammation.

Acute Inflammation is a physiological response to tissue injury and death to facilitate tissue

recovery. For instance, inflammation gives rise to prostaglandin, a vasoactive, pyrogenic, and neuroactive eicosanoid that facilitates not only the amplification of inflammation, but also inflammation resolution, perception of pain to protect the affected area from further damage through use withdrawal (eg., animals with painful limbs instinctively will not perambulate as much to protect the diseased limbs), and prevention in the proliferation of potentially pathogenic microorganisms through increase in body or the affected area's temperature (Ackermann, 2017). This is termed as "protective pain". Despite its beneficial purposes, uncontrolled acute pain does more harm than good, because it is associated with perpetual tissue deterioration and exacerbation of the preexisting tissue damage. Furthermore, pain that exceeds the threshold of the individual will result in, but not limited to, reduced quality of life (eg., decreased sleep quality, emotional instability due to the perceived "ceaseless perceived pain"), stress that leads to immunosuppression, hypertension, and behavioral changes that can affect the human-animal bond (Muir, 2015). Hence, acute pain should be managed, not necessarily to eliminate the "protective" role of it, but to control the pain so that it does not exceed pain threshold needed for protection. Furthermore, uncontrolled pain can result in pain that is unnecessary and results in increased pain perception that goes beyond its adaptive, protective, and recuperative purpose, often referred to as maladaptive pain (Costigan et al., 2009).

Pain is initiated by peripheral stimuli with sufficient intensity that are detected by nociceptors. These stimuli are often referred to as noxious stimuli, and those that fall in this category have the likelihood to cause harm to the body tissue. Nociceptors have some differences in their axons: A δ and C fiber axons. A δ fiber is lightly myelinated and has small diameter, transforming mechanical and thermal stimuli into electrical signals and conducting them more slowly, and giving rise to sharp, rapid pain that is responsible for withdrawal reflex to acute pain. C fibers are entirely unmyelinated and have even smaller diameters than A δ . They respond to chemical,

thermal, and mechanical stimuli, and conduct more slowly than the A δ (Fields et al., 1998). These electrical signals then get transmitted to the central nervous system through dorsal horn ganglia. This signal is then processed, resulting in increased alertness and altered behavioral strategies that are used to avoid further contact with the harmful stimuli (Latremoliere & Woolf, 2009). Sometimes, noxious stimulus with such intensity that overwhelms the pain threshold can result in dysfunction of the components of either peripheral or central nervous system, or both. Though not necessarily a pathologic state, which instead could become integral parts of protective pain, allodynia (*ie.*, pain that results from normally unpainful stimuli) and hyperalgesia (*ie.*, increased pain sensitivity) can arise. Increased neuronal membrane's excitability and synaptic transmission, or reduced neuronal inhibition, can be the causes of such states. This phenomenon is termed as functional plasticity. When the nociceptive afferent neurons are deluged with increased noxious inputs, functional plasticity of the afferent nociceptive neurons occurs, altering the receptive field threshold, and even the spatiotemporal property of nociception. During this plastic state, sensitized peripheral nociceptors become more excitable, so more electrical signals are conveyed towards the central nervous system, evoking a heightened state of pain in affected and the surrounding areas (*ie.*, primary and secondary hyperalgesia, respectively), even with stimulus that are not commonly painful (*ie.*, allodynia) (Tsagareli, 2019).

Assessing Acute Pain in Cats

Effective pain management is only possible if valid, dependable and sensitive pain assessment tool is readily accessible to be utilized. A pain assessment tool is considered reliable and sensitive if it has scientific proofs of consistent results reproducibility in distinction of painful animals from healthy state, valid if it is proved to be able to assess the targeted parameters. These features are essential because pain assessment tool is going to be needed for constant reassessments

to evaluate whether the interventional analgesic given is adequate to relieve the pain of the affected individual. The assessment result will not give valid and accurate result if it could not discriminate between painful and non-painful individuals, and between different pain intensities (Calvo et al., 2014; Steagall & Monteiro, 2019).

Pain is multidimensional. In human medicine, Melzack and Casey (1968) described pain with three dimensions: sensory-discriminative, affective-motivational, and cognitive-evaluative. Sensory-discriminative aspect of pain is assessed through thorough physical examination to determine pain location and intensity, obtainment of complete medical history to determine the duration of the pain. This domain is usually assessed concurrently with the second aspect, affective-motivational. This domain explains the demeanor and behavioral changes that arise from the extent the pain can be perceived as unpleasant to the affected cat. Straightforward changes in the demeanor such as mental dullness or aggression, or more subtle changes like different head position and whiskers tension, can be picked up from the initial assessment, with the help of pain assessment tool and hands-on physical examination. The third domain, cognitive-evaluative, is virtually implausible to evaluate because it involves cognitive alterations due to experienced pain (Merola & Mills, 2016a; Steagall & Monteiro, 2019).



Figure 1. A cat with painful abdomen due to urinary obstruction. This cat was depressed, hyporexic, and expressing “grimace” (Self documentation)

There are common pitfalls that can make pain evaluation ambivalent, especially when relying solely on behavioral or physiological changes. First, detection of these changes can be subjective, as many studies have pointed out (Dohoo & Dohoo, 1996; Hugonnard et al., 2004; Joubert, 2001; Williams et al., 2005). This is exacerbated by the lack of use of validated pain assessment tool (Coleman & Slingsby, 2007). Variations in pain behaviors between individuals have complex affecting factors that can arise from the environment, the individual's disposition, and anesthetic influence (in post-operative patients). The latter is especially true in post-operative patients, where veterinarians would frequently discharge the animals following elective surgical procedure (eg., orchiectomy) without analgesics, because there is a bias of dysmorphia following anesthesia recovery (Buisman et al., 2016; Williams et al., 2005). Painful cats can be characterized by the

change in their demeanor, either becoming more dull or aggressive. However, other conditions may cause this change, or overshadow coexisting pain perception, such as patients presenting with shock and central nervous system disorders. Cats, being closely related to other big cats, may conceal painful behaviors due to their predatory instinct (Berteselli et al., 2014). Individuals with high fear, anxiety, and stress level may have alterations in their physiological and mental variables, especially when they are evaluated in settings that are unfamiliar, so that metrology evaluation scores higher when the cats are assessed at home than at clinical settings. Anorexia is also a sign of acute pain. However, not eating can also mean they are already in satiated condition (Steagall et al., 2022). Although acute pain assessment by the judgment of either behavioral or physiological alterations is insufficient (Merola & Mills, 2016b, 2016a), display of multiple behavioral signs can be a tip-off information that encourages further pain assessment and recognition.



Figure 2. Same cat in figure 1, after rescue analgesia was given. Although some of its facial components still indicated pain, the cat was appetent, of which behavior is usually absent in cat with uncontrolled pain (Self documentation)

Due to the subjectivity of pain evaluation, pain assessment metrology is used to help making a more sound, unbiased clinical judgment. Three validated feline-specific pain assessment are now available (Belli et al., 2021; Evangelista et al., 2019; Reid et al., 2017). As mentioned before, pain is multidimensional. Therefore, a good, validated pain assessment should be composite, that it comprises of sensory and other aspects that reliably detect for the feeling of unpleasantness due to pain. These three pain assessment tools have their respective discerned parameters, and cut-off value of which interventional analgesic is indicated once reached or even surpassed. Nonetheless, none of these tools have a sensitivity or specificity of near 100%, making these, to some extent, are still possible to overlook pain in cats. Whatever metrology is used, sufficient training is necessary to reduce bias and judgment differences among the veterinary staff.

Universidade Estadual Paulista (UNESP)-Botucatu (UFEPS) multidimensional pain assessment scale – The initial study of the use of this pain scale was conducted in cats with postoperative pain, following ovariohysterectomy. However, many studies have used this pain scale. It discerns pain expression (miscellaneous behaviors, vocalization, reaction to palpation of surgical wound), psychomotor change (level of activity, posture, attitude), and physiological variables (appetite, blood pressure) (Steagall & Monteiro, 2019). This scale is also the first validated multilanguage feline-specific assessment tool. UNESP-Botucatu scale, however, has limited practicability due to its extensive subscales and assessed variables, including blood pressure monitoring. This issue has been addressed by the creation of a shorter version (UFEPS-Short Form [SF]), evaluating the cat's posture, level of activity, attitude, and reaction to palpation on painful area. A study conducted by Belli et al (2021) indicated good validity, although the current study lacked a more randomized, blinded evaluation. It has strong criterion correlations between the UFEPS and UFEPS-SF. A moderate sensitivity with known increase in psychomotor change score in cats previously induced with ketamine (Buisman et al., 2016). Both UFEPS and UFEPS-SF is slightly

higher in specificity than sensitivity. Inter-rater reliability remains as a limitation for this pain scale. Original study performed by Brondani et al (2013) and most recent study where veterinary anesthesia and analgesia specialists were enrolled to assess (Luna et al., 2022) indicated higher inter-rater reliability (CI 0.93-0.97 for the former study, and CI 0.84), whereas other studies reported lower, moderate inter-rater reliability (CI 0.79-0.82) (Belli et al., 2021), with considerably high variability in one study (Benito et al., 2017). These findings corroborate the need for extensive staff training, should this valid, reliable pain scale be used in- clinic. It is recommended to access the site (www.animalpain.com.br) for online training using provided videos and other information. The cut-off value of UFEPS-SF and UFEPS are $\geq 4/12$ and $\geq 7/24$, respectively.

Glasgow composite measure pain scale-Feline (Glasgow CMPS-F) – Glasgow CMPS-F included behavioral parameters like vocalization, level of activity, posture, attention to wound, response to palpation, and reaction in response to the caretaker. The most updated version also included facial expression of pain (shape of muzzle, ear pinna position). The developmental stage of this tool creation included positive control groups with different health problems that result in pain: trauma, surgery, and other medical illnesses (Calvo et al., 2014). Hence, it can be more appropriate to use in clinical settings where diverse pain inciting agents may present. Moreover, as opposed to the validity assessment of UFEPS, Glasgow CMPS-F validation was conducted in clinical environments where it was assessed by observers of different levels of experience, so it can be more applicable in small animal practices where veterinary anesthesia and analgesia specialists are not present. This study also proved a much higher pain discriminatory ability among the observers, resulting in less inter-rater reliability (Reid et al., 2018). Nonetheless, this pain scale needs more studies to prove its reliability. Rescue/interventional analgesia is given when cut-off point of $\geq 5/20$ is reached (Gruen et al., 2022; Steagall & Monteiro, 2019).

Feline Grimace Scale (FGS) – FGS is the most recent validated pain assessment tool which uses

facial components of the cats. Validated grimace scales have been developed for other species, such as mice (Langford et al., 2010), rabbits (Keating et al., 2012), and horses (Dalla Costa et al., 2014). The evaluated facial components, referred to as “action units” that construct a facial expression, comprise of ear position, degree of orbital tightening, muzzle tension, whisker position, and head position. This assessment tool can be less invasive (due to the absence of hands-on approach) and more practical. Indeed, the assessment can be carried out real-time or through a photograph of the cat, unperturbed and unrestrained inside the kennel, as any forms of handling and restraints will affect the facial expression (Holden et al., 2014). FGS has been reported to be valid, reliable, sensitive, and specific. However, note should be taken that brachycephalic breeds may present with either false positive or false negative result (*ie.*, higher and lower score than the cut-off point, respectively), due to their different facial conformities compared to mesocephalic breeds (Evangelista et al., 2019). Cut-off point for FGS is $\geq 4/10$.

Pain Management: A Pre-emptive, Multimodal Approach

From previous paragraphs, the author beseeches the readers that becoming sufficient in pain assessment is just as important as becoming proficient in physiological evaluation. Failure to recognize pain results in *oligoanalgesia*, a state of inadequacy in pain management (Simon et al., 2017). When referring to pain management, the term analgesia is conjured up. However, the term itself means “the absence of pain sensation”, which may become a virtually implausible objective to obtain when managing pain. Pain should be effectively controlled, to the point that it does not interfere with the welfare of the patient. Conversely, when pain is expected, as in surgery, it is now generally accepted that pain prevention is favorable than once tissue damage and subsequent pain are produced (Gruen et al., 2022). Pain management goal should focus on the most pain alleviation and comfort level that can be achieved, while minimizing

the potential adverse drug reactions. Therefore, a multimodal approach is advised to: (1) control pain through multiple drugs with differing mechanism of actions, as pain pathways are often redundant (Zochodne, 2012), and (2) possible dose reduction when multiple analgesics are used. The author is trying to summarize some of pharmacological and non-pharmacological interventions that are proven to provide analgesia in cats. Nevertheless, some surgical procedure, or pathomechanisms, may elicit more pain than the others, and hence could become more challenging to manage.

Pharmacologic Agents

There are a few things to be considered in the administration of analgesics. Steagall et al (2022) proposed the acronym “T.E.L.L.S” to determine the type, dose, frequency, and route of analgesic(s) to be given to the patient: Type of noxious stimuli (eg., visceral, neuropathic, oncologic, somatic, orofacial), Expected duration of the nociception (eg., transient stimuli such as endoscopy vs extended pain perception as in surgery), Location of noxious stimuli (eg., onychectomy procedure can benefit from femoral and sciatic nerve blocks), Location of the patient throughout the medication (out- vs inpatient), and Severity of noxious stimuli.

Opioids

Opioids act on opioid receptors, and opioids can be categorized based on the matching receptor: mu, delta, and kappa. Although the functional effects of each receptor are different once activated, they have similar cellular responses after becoming activated. Dissociation of alpha-guanosine triphosphate (αGTP) and beta-gamma complex of the receptor’s plasma membrane

results in decrease in intracellular adenylyl cyclase, hence in turn reducing cyclic adenosine monophosphate levels, dampening signal transduction. Moreover, activation of mu- opioid receptors increases potassium and decreases calcium influx, rendering the neurons hyperpolarized. Since the central nervous system expresses an ample of opioid receptors, less pain is perceived once these receptors are activated (Pathan & Williams, 2012).

Because opioid receptors are expressed in high levels in the nervous system, according to a recent proposal for acute pain management in both cats and dogs, opioids should be the first choice when pain is evident, but the causative factor is not determinable immediately. Once the pain has subsided into a more comfortable level, diagnostic workup should be performed to pinpoint the etiology of pain (Gruen et al., 2022). Opioid selection should be based on veterinary staff's pain assessment of the patient. If moderate to severe pain (eg., cat with pancreatitis, cat who undertakes invasive surgery like ovariohysterectomy and orthopedic procedures) is indicated or predicted, opioid that exerts more activation of mu-opioid receptor is recommended. Single dose of methadone (0.2-0.6 mg/kg IV/IM q6h) or pethidine (5-10 mg/kg SC/IM q1-2h) can be given initially, and reassessment should be done to evaluate the requirement of other rescue analgesia. In the author's experience, methadone is inaccessible in our practice, so pethidine is the only full mu-opioid we can get access to. However, pethidine has short plasma half-life, and repeated injection can add stress and exacerbate pain. If pain is indicated to be prolonged, constant rate infusion (CRI) of fentanyl (0.005 mg/kg bolus, followed by 0.003-0.02 mg/kg/h IV) is recommended. Although there was a concern of the use of morphine due to its need for glucuronidation (Bell, 2009), it has been reported that there is no significant difference in morphine elimination rate between cats and dogs. Instead, cats may have reduced active metabolite bioavailability (Bloomfield et al., 2001). Mild to moderate pain can be managed with buprenorphine (0.02-0.04 mg/kg IV/IM q8h), a partial mu-opioid

receptor agonist. Nonetheless, variabilities in the response to the opioid treatments, irrespective of the receptors they are working on, have been reported, so it is important to always reassess the patient to cater to the patient's need on individual basis (Bloomfield et al., 2001; Johnson et al., 2007).

Although opioid use is recommended in management of acute pain, the author acknowledges that opioid may be inaccessible in many practices. This shortage has become an issue in the effectiveness of a pain management protocol when opioid is not included, as NSAID alone has been proven to be inadequate to control post-ovariohysterectomy pain, even when intraperitoneal bupivacaine is added (Steagall et al., 2018). Involvement of multiple stakeholders like governmental bodies, pharmaceuticals, and drug regulatory bodies may be necessary to resolve this inaccessibility to opioid drugs (Steagall et al., 2022).

Non-steroidal anti-inflammatory drugs (NSAIDs)

As the name suggests, NSAID works best when acute tissue damage and subsequent inflammation are highly determinable. Oftentimes, NSAID can be indicated in conditions such as neoplasia, lymphoplasmacytic gingivostomatitis, idiopathic cystitis, uveitis, and even in other condition where short-term use of NSAID can be opted to make better clinical judgment based on the therapeutic response, owing to its anti-inflammatory, antipyretic, and analgesic properties. In cats, there are only two approved NSAID for use in cats. NSAIDs exerts its anti-inflammatory, antipyretic, and analgesic actions by inhibition of cyclooxygenase (COX), an enzyme that catalyzes the production of prostanoids. There are two isoenzymes: COX-1 and COX-2. Concerns regarding the use of non-selective NSAID raise from its inhibitory effect on COX-1, which is constitutively expressed in nearly all cells in the body to carry out physiological functions,

including maintenance of renal perfusion and electrolyte homeostasis, and gastric mucosal integrity (Fromm, 1987; Kim, 2008). Meloxicam and robenacoxib are the only two approved NSAIDs for use in cats. Studies have indicated generally accepted use safety in cats, even when used for extended period (dose 0.01-0.03 mg/kg q24h per oral), in which cases can benefit the cats by reducing pain level, especially in chronic musculoskeletal pain (Gunew et al., 2008). Meloxicam is also present as a promising analgesic in cats with “stable” chronic kidney disease (i.e., cats with CKD of IRIS stage 1-2, with minimal to no change in bodyweight and plasma creatinine level in 1-2 months), although this study was retrospective, therefore is subject to biases (Monteiro et al., 2019). Robenacoxib is licensed for therapeutic use of up to 6 days. Although pharmacokinetic studies have shown robenacoxib to have elimination half-life of 2 hours in cats, high protein-binding rate may facilitate persistence of robenacoxib within inflamed tissue. It should be underscored that cats have different hepatic metabolism in comparison with dogs, and studies have reported inter-individual differences in the rate of NSAID elimination, therefore different toxicity threshold and response to analgesic property when NSAID is administered, even if approved NSAID is used (Court, 2013; Sparkes et al., 2010).

Adjunctive Analgesics

Although NSAID and opioid can be used concurrently as a multimodal approach, oftentimes pain management requires other pharmacologic agents to provide breakthrough in pain pathway redundancy. It is helpful to remember the T.E.L.L.S. that has been mentioned in previous paragraph. For instance, if neuropathic pain is indicated, use of gabapentin (alpha-2- delta calcium channel disruptor), or addition of ketamine (N-methyl-D-aspartate [NMDA] antagonist) can be considered. Gabapentin exerts its antineuropathic pain through disruption of alpha-2-delta

voltage-gated calcium channel (VGCC), which reduces interactions between its subunits with NMDA receptors. Both VGCC and NMDA receptors are found in the central nervous system, modulating pain sensory signals, and inhibitory effect of gabapentin therefore will result in decreased pain sensation, though gabapentin use alone may not alleviate acute pain (Dolphin, 2013; Park & Luo, 2010; Steagall et al., 2022). Although ketamine is extensively excreted by renal elimination route and may accumulate in the plasma in patients with renal insufficiency, it has been indicated that sub-anesthetic dose of ketamine administered continuously (ie., CRI, 0.01 mg/kg/minute) is safe and can provide neuropathic pain amelioration through downregulation and reduced phosphorylation of NMDA receptors (Steagall et al., 2022).

Other Supportive Pharmacologic Agents

Besides from provision of analgesia, patients with other existing health condition should also be managed properly. For example, nauseous and vomiting cats should be controlled through the administration of antiemetic agent (eg., maropitant 1 mg/kg q24h IV; ondansetron 0.5 mg/kg IV bolus, followed by 0.5 mg/kg/h CRI for 6 hours) and/or gastrointestinal protective agents (decision to use such agents should consult a consensus statement regarding the rationale for gastrointestinal protectants administration [Marks et al., 2018]). Cats with high fear and anxiety level may benefit from gabapentin (50-100 mg per cat). Use of premedication like medetomidine (alpha-2 agonist) provides a degree of muscle relaxation, sedation, and analgesia, though patients with compromised cardiovascular health is contraindicated. Tramadol, a racemic mixture that possesses opioid receptor agonist, serotonin and norepinephrine reuptake inhibitory properties. Its use is deterred due to its unpleasant taste in cats, although it has been shown to be more efficacious in cats than dogs (Steagall et al., 2022).

Non-Pharmacological Interventions

A positive interaction between the caretaker and the cat is the hallmark of non-painful cats. Cats should be approached and handled gently to maximize level of comfort and prevent exacerbation of pain. Cage enrichment is recommended. For instance, provision of a cardboard box for hiding and perching, and layers of sheets for comfortable bedding are encouraged. The ward environment should be kept as quiet as possible to prevent stress in cats (Rodan et al., 2011; Steagall & Monteiro, 2019).

Conclusion

Effective pain control in cats is a serious matter to be reckoned with. Appropriate veterinary staff training for pain recognition and assessment is pivotal in a successful pain management, and all staff, including the veterinarians and paramedics, should be involved. Pain control protocol should always be tailored in a case-by-case manner, and provision of a feline-friendly environment is as important as the administration of pharmacological interventions.

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