THE EFFECTS OF PRE-EMPTIVE ANALGESIA WITH NSAIDS OR TRAMADOL IN DOGS UNDERGOING TUMOR REMOVAL

Master’s Thesis

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By

Nicole M. Karrasch, DVM

Graduate Program in Comparative and Veterinary Medicine

The Ohio State University

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Committee:

Turi K. Aarnes, DVM, MS, DACVAA, advisor

Phillip Lerche, BVSc, PhD, DACVAA

Cheryl A. London, DVM, PhD, DACVIM (Oncology)
Abstract

Cancer is highly prevalent among dogs; over 45% of dogs over 10 years of age die from or are euthanized due to cancer. Studies in human oncology patients have shown that 30-50% of cancer patients will experience moderate to severe pain. The World Health Organization considers NSAIDs to be the first tier of pain control in cancer patients, as inflammation is a major component of oncologic pain. Tramadol is widely used in human and veterinary medicine for treatment of mild to moderate pain. The pharmacologic activity of tramadol includes weak mu opioid receptor agonism, inhibition of norepinephrine and serotonin (5HT) reuptake. Pharmacokinetic and pharmacodynamic studies of tramadol in dogs have differing results. Studies in human patients have shown that pre-emptive use of tramadol can reduce post-operative analgesia requirements.

The objective of our study was to compare the effect of pre-emptive administration of NSAIDs versus tramadol versus no treatment in postoperative pain scores, analgesic requirements, and quality of life scores in dogs undergoing removal of cutaneous tumors. We hypothesized that pre-emptive administration of tramadol or NSAIDs would result in reduced pain scores and lower rescue analgesia requirement in postoperative oncologic patients, and that NSAIDs would result in a greater reduction in pain scores and lower rescue analgesia requirement compared to tramadol.

Thirty-six client-owned dogs were studied. Dogs were randomly assigned to receive an NSAID (carprofen), tramadol or no treatment starting 48 hours prior to
surgical removal of a cutaneous tumor. Pain was assessed by a blinded observer at the following times: screening, immediately prior to surgery, every hour for the first four hours after extubation, every four hours after extubation for 24 hours, and at suture removal. Quality of life (QOL) forms were completed by the owner at the following time points: screening, two days prior to surgery, and days 1, 7 and 14 after discharge.

There were no differences in three pain scoring methods (Visual Analog Scale (VAS), Glasgow Modified Pain Score, or algometry) among groups. There was no difference in time to rescue analgesia among groups. There were no differences in QOL score among groups. QOL VAS scores were improved in the control group and decreased in the NSAID group versus baseline at day 7, but at no other timepoint.

Pre-emptive treatment with carprofen or tramadol for 48 hours prior to cutaneous tumor removal resulted in no clinically significant changes in pain scores, QOL scores or analgesic requirements.
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Vita

June 2003 .................................................. Northwest High School
2003-2006 .................................................. Undergraduate coursework, The Ohio State University
2010 .............................................................. DVM, The Ohio State University
2010-2011 ...................................................... Rotating Intern, Friendship Hospital for Animals
2011 to present .............................................. Resident, Anesthesiology and Pain Management, The Ohio State University

Publications

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Chapter 1: Review of Literature

1.1 Incidence

In studies performed in people, as few as 14% and as many as 90% of oncology patients reported pain associated with their disease.\(^1\) Severe to excruciating pain is reported by 25-30% of cancer patients.\(^2\) In one study, 50% of oncology patients reported experiencing pain most of the time, and 25% of patients reported experiencing pain all of the time.\(^3\) The World Health Organization (WHO) reports that when attempts are made to manage cancer pain, 90% of pain can be adequately managed.\(^1\) Some variation in pain can be attributed to stage of disease; the prevalence of pain has been reported as being 28% in patients with recently diagnosed cancer, 50% in existing disease and up to 80% in patients with advanced tumors and paraneoplastic processes.\(^4\) The Edmonton staging system has been used in human oncologic patients to predict cancer pain and potential response to treatment. This staging system includes the mechanism of pain, characteristics of pain, previous narcotic exposure, psychological distress, tolerance to opioids and prognosis.\(^5,6\) The mechanisms of pain are: visceral (dull, aching, poorly localized), bone-soft tissue (aching, aggravated by pressure, well localized), neuropathic (nerve and/or nerve root, burning), mixed and idiopathic. Pain is characterized as either
incidental (associated with movement, urination, defecation, etc.) or nonincidental.

Cancer is highly prevalent among dogs; over 45% of dogs over 10 years of age die from or are euthanized due to cancer. In non-oncologic outpatient veterinary patients, the incidence of pain in dogs has been reported at 20% and, of those, 17% had pain of more than one month’s duration. Superficial somatic pain was displayed in 38%, deep somatic pain in 51% and visceral pain in 11%. Primary hyperalgesia was present in 82% of dogs, and secondary hyperalgesia in 17%. To date, no studies have described the incidence of cancer pain in veterinary patients.

1.2 Pain pathway

1.2.1 Transduction

Sensory nerve fibers have specialized terminal endings that transduce (transform) stimuli into action potentials, which are transmitted, modulated, projected and then perceived as sensations. These sensations, in somatic tissue, may include touch (pressure, vibration), proprioception, temperature or pain. In visceral tissue, stretch, inflammation and ischemia are noxious stimuli. Nerves are grouped by nerve fiber type, varying in structure, speed of transmission and receptor type. Pain is transmitted by Aδ and C fibers; Aβ fibers typically transmit sensory information that is non-noxious. Disease states such as chronic or pathologic pain, inflammation and neoplasia can alter the type of stimulus transmitted by any nociceptor.

Aβ fibers contain low threshold receptors and transmit non-noxious stimuli rapidly (30-70 m/s) under normal conditions. In pathologic pain, Aβ fibers may
participate in transmission of pain, specifically mechanical allodynia (pain caused by mechanical stimuli which would not otherwise be painful).\textsuperscript{11,15}
Figure 1 The pain pathway

Organization of cutaneous, primary afferent (PAF) input to the dorsal horn of the spinal cord. Abbreviations are as indicated in the general list. This schema does not quantitatively differentiate between various laminae as concerns PAF input. For example, the density of Aδ nerves innervating lamina I is considerably greater than that projecting to lamina II, a principal target of C fiber input. Unmyelinated nerves from muscle, viscera and joints appear to preferentially innervate laminae I and IV/ V/IV rather than II. Cell types (NS (nociceptive specific), WDR (wide dynamic range) or NON-N (non-nociceptive)) are also qualitatively rather than quantitatively indicated in terms of the major class encountered in various laminae. Lamina VI, which functionally complements lamina V, is clearly identifiable only at the level of the cervical and thoracic cord. Lamina X corresponds to the grey matter surrounding the central canal.15

Aδ fibers contain both high and low threshold receptors. The former comprise 25% of the receptors and only respond to intense mechanical stimulation (painful stimuli). The latter comprise 75% of the receptors and respond to low intensity or nonpainful stimuli.10 Myelinated Aδ fibers transmit stimuli rapidly (2.5-30 m/s), thus generating “first” or “fast” pain.16 Fast pain is often described as pricking or sharp in people. The cell bodies of all primary afferent neurons are located in the dorsal root ganglia of the spinal nerves (body) or trigeminal ganglia (head).11,17
Aδ fibers synapse in laminae I, II and IV of the dorsal horn of the spinal cord.\textsuperscript{15,18}

C fibers are unmyelinated and transmit stimuli more slowly than Aδ fibers (<2.5 m/s).\textsuperscript{11,13} Thus, they transmit “second” or “slow” pain. This pain is often characterized as burning or aching in people.\textsuperscript{12,18} C fiber nociceptors are high threshold, or only respond to noxious mechanothermal stimulation.\textsuperscript{12} Both Aδ and C fibers have silent nociceptors that may become activated by inflammation and tissue damage.\textsuperscript{15}

C fiber types can be grouped by the type of receptor or neurotransmitter expressed. Purinergic receptors are activated by adenosine triphosphate (ATP) released from damaged cells, and also transduce chemical stimuli. Other C fiber types express the peptides substance P and calcitonin gene related peptide, as well as the tyrosine kinase A receptor, which responds to nerve growth factor.\textsuperscript{11,13} Both types of fibers express the villanoid receptor VR\textsubscript{1}, which responds to protons (H\textsuperscript{+}, K\textsuperscript{+}) and noxious heat stimuli. The members of the degenerin-epithelial sodium channel family transduce mechanical stimuli.\textsuperscript{13}

Both Aδ and C fibers express toxin tetrodotoxin resistant sodium ion channels as well as voltage gated calcium channels both of which contribute to the excitability of the nociceptor.\textsuperscript{11}

1.2.2. Transmission

Action potentials generated by nociceptors are conducted to the dorsal horn of the spinal cord by peripheral nerves. C fibers transmit stimuli from a smaller field than Aδ fibers.\textsuperscript{12,13} Some neurochemicals are vital to transmission of the pain signal: bombesin,
calcitonin gene-related peptide, cholecystokinin, corticotropin-releasing factor, dynorphin, endorphin, encephalin, galanin, somatostatin, substance P and vasoactive intestinal peptide.\textsuperscript{12}

1.2.3 Modulation

The nerve fibers of primary afferent neurons enter the dorsal horn of the spinal cord via the dorsal root. The stimulus signal is modified by neurotransmitters, spinal cord receptors and supraspinal input. The gray matter of the dorsal horn of the spinal cord is stratified according to nerve fiber type. The superficial laminae I and II relay information from A\(\delta\) and C fibers. Laminae III through VI relay input from A\(\beta\) fibers.\textsuperscript{19} (Figure 1)

After stimulation by A\(\delta\) and C fibers, the dorsal horn releases the neurotransmitter glutamate; glutamate binds to \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate (KAI) and N-methyl-D-aspartate (NMDA) receptors. Activation of the AMPA receptor in particular produces a fast excitatory potential, generating a tactile sensation. Glycine and GABA, two inhibitory substances, are generated by this fast potential. Activation of NMDA receptors results in longer potentiation of the stimulus. Metabotropic glutamate receptors (mGluR), when activated, increase intracellular calcium via second messengers, and can alter gene expression.\textsuperscript{11,12,19} Endogenous opioids such as enkephalin, endorphin and dynorphin reduce the expression of glutamate and substance P, and thus inhibit signal transmission.\textsuperscript{12,20} In addition, GABA, serotonin and norepinephrine inhibit excitation. ATP, substance P, and prostanoids are excitatory neurotransmitters. Inhibitory interneurons further modulate the signal. Serotonin,
norepinephrine and acetylcholine facilitate inhibition, whereas ATP decreases inhibition.\textsuperscript{21}

\textbf{1.2.4 Projection}

Several lateral tracts project the stimulus from the dorsal horn to the brain. The spinocervicothalamic tract transmits superficial pain originating from lamina I as well as wide dynamic range neurons throughout laminae IV, V, VI and VII, and terminates in the thalamus. Wide dynamic range neurons transmit input from both high and low threshold receptors. The spinoreticular tract transmits deep and visceral pain and terminates on the reticular formation and diencephalon. The trigeminal system of the head projects the stimulus from the trigeminal ganglion to the pontine sensory nucleus and spinal nucleus of cranial nerve V.\textsuperscript{12,17}

\textbf{1.2.5 Perception}

The reticular activating system of the brainstem integrates sensory experiences via projections to the thalamus and limbic system. The periaqueductal grey matter (PAG) relays information to the thalamus and hypothalamus. The thalamus then relays information to the cerebral cortex. The PAG also inhibits or facilitates modulation of further input.\textsuperscript{12,22}


1.2.6 Response to pain

The response to pain occurs via segmental and suprasegmental reflexes, endocrine responses, metabolic response, changes in water and electrolytes, changes in ventilation and diencephalic and cortical responses. Segmental and suprasegmental reflexes include increased sympathetic tone; vasoconstriction; increased systemic vascular resistance and preload; increased stroke volume, heart rate and cardiac output; increased arterial blood pressure and myocardial work; increased metabolic rate and oxygen consumption; decreased gastrointestinal and urinary tone; and increased skeletal muscle tone. Endocrine responses include increased adrenocorticotropic hormone, cortisol, antidiuretic hormone, and growth hormone; increased adenosine monophosphate, catecholamines, renin and angiotensin II; increased aldosterone, glucagon and interleukin I; and decreased insulin and testosterone. Metabolic responses include hyperglycemia, glycogenolysis and gluconeogenesis, increased muscle protein metabolism, and increased lipolysis. Water and sodium are retained, and potassium is excreted at an increased rate. Central hyperventilation or segmental hypoventilation may occur secondary to splinting (restricted breathing) and bronchospasm. Anxiety and fear are increased. Blood viscosity and clotting times may vary. These factors may contribute towards development of SIRS (systemic inflammatory response syndrome) and MODS (multiple organ dysfunction syndrome). Prolonged recovery from injury and slower return to normal behaviors have been noted in response to pain.
1.2.7 Peripheral sensitization

Peripheral sensitization is a state of exaggerated response to a noxious or innocuous stimulus at the site of injury resulting in hyperalgesia or allodynia, respectively. At the level of transduction, mediators from either damaged tissues and/or chemical mediators can induce this. Cyclooxygenase 2 (COX-2), proteases, nitric oxide synthase, protons and ATP are released from disrupted tissue. Prostaglandins, serotonin, histamine, bradykinin and cytokines are released by inflammatory cells.\textsuperscript{12,13}

In mouse models of bone pain, sensitization of tissue by substance P and the transcription factor c-Fos have been demonstrated.\textsuperscript{24} In addition, tumors may secrete prostaglandins, tumor necrosis factor-alpha, endothelin, and other inflammatory mediators.\textsuperscript{25} A tumor may also create localized tissue acidosis, leading to further peripheral sensitization.

1.2.8 Central sensitization

If pathologic pain is present in the absence of nociceptor changes in the area of primary hyperalgesia then central sensitization is said to be present. In this state, normally innocuous stimulation of Aβ fibers may result in pain. NMDA receptors become available for stimulation by glutamate via removal of magnesium. Glutamate activates mGluR, NMDA and AMPA/KAI receptors.\textsuperscript{12,26} Brain derived naturietic factor activates TrkB. Substance P activates neurokinin 1 (NK1). TrkB and NK1 activate signaling cascades, which result in an increase in intracellular calcium, inositol triphosphate and protein kinase C. Increased action of these kinases increases gene
expression and induces plasticity in the neuron. In addition, the receptive field of the fiber will increase.\textsuperscript{11}

1.3 Pathologic and cancer pain

Pathologic pain is the experience of pain that is greater than expected for the degree of tissue damage. Pathologic pain may be acute or chronic in nature.\textsuperscript{15,27} Some argue that acute pathologic pain may serve a protective purpose.\textsuperscript{15} However, chronic pathologic pain is considered to be a maladaptive response, and may be present in the absence of tissue damage. Chronic pain can be further classified as malignant (associated with neoplasia and/or its treatment) or non-malignant (non-malignant neuropathic, musculoskeletal, inflammatory).\textsuperscript{27} Treatments for cancer in human patients (radiation, chemotherapy) are often reported to cause pain.\textsuperscript{27} In contrast, cancer treatment in veterinary patients is often focused on quality of life rather than complete eradication of disease; thus pain related to treatment is likely less common than in human medicine.

Several sensations are described in people experiencing pathologic pain: dysesthesia, hyperalgesia, paresthesia and allodynia. Dysesthesia is described as a tingling sensation.\textsuperscript{23} Hyperalgesia can be primary (in the area of tissue damage or initial injury) or secondary (outside of the area of tissue damage/initial injury). As discussed previously, primary and secondary hyperalgesia are mediated by peripheral and central sensitization, respectively. Paresthesia is an abnormal but not unpleasant sensation, which may be spontaneous or evoked.\textsuperscript{15} Allodynia is the experience of pain evoked by a stimulus that should not normally cause pain.
Pathologic pain is often described as nociceptive or neuropathic. Nociceptive pain is the result of ongoing stimulation of primary afferent neurons and abnormal modulation of the pain stimuli. Neuropathic pain cannot be explained by continued stimulation, and is a result of aberrant processing.\textsuperscript{28}

In addition to causing changes in tissue acidity, receptor population, modulation and compression of nerves as previously discussed, cancer pain causes several hallmark pain syndromes in people.\textsuperscript{28} These syndromes are associated with base of skull metastases, vertebral syndromes, diffuse bone pain and pain due to neoplastic involvement of viscera. A syndrome of sinus pain and the experience of head fullness or stuffiness are described by human patients with base of skull metastases. This pain is dependent upon the location of metastasis with some patients reporting pain upon head flexion. Patients with fractures or subluxation of vertebrae report diffuse or referred neck and shoulder pain, a hallmark of the vertebral syndromes. Diffuse bone pain is reported even in the absence of radiographic abnormalities in some people with multiple bony metastases. Visceral pain is less well described and more variable; pain may result from obstruction of hollow viscera or involvement of neural plexuses. These syndromes have not been described in veterinary oncologic patients.

In addition to these pain syndromes, changes in modulation of pain occur. In mouse models of cancer pain reorganization of spinal cord segments has been documented.\textsuperscript{25} Upregulation of dynorphin, a pro-hyperalgesic substance, has also been documented.
1.4 Treatment of Cancer Pain

1.4.1 World Health Organization recommendations

The World Health Organization (WHO) recommends nine steps in evaluation of cancer pain.²⁹

1) **Believe the patient’s report of pain.** In the case of veterinary patients, self-reporting is not possible. However, communication with owners is important in identifying and treating pain.⁴

2) **Initiate discussions about pain.** Specific questions about pain should be asked. In addition, observations by caregivers, vocalizations, facial expressions, changes in physiologic responses and response to a trial dose of analgesic should be considered.

3) **Evaluate severity of pain.** Severity may be assessed by limitation of activity, sleep or degree of relief obtained with medication or pain relieving procedures.

4) **Take a detailed history of the pain.** Location, distribution, quality, timing and factors that enhance or reduce pain should be described.

5) **Evaluate the psychological state of the patient.** Anxiety, depression and functional capacity should be evaluated. Depression is reported in 25% of human cancer patients.

6) **Perform a careful physical examination.** A full physical exam may enhance diagnosis of the cause of pain.

7) **Order and personally review any necessary investigations.** Medical imaging (radiographs, CT, MRI) may enhance diagnosis and treatment of pain.
8) Consider alternative methods of pain control. Palliative radiation and stabilization of pathologic fractures should be considered.

9) Monitor the results of treatment. A team approach between health care workers and caregivers should be implemented.

Five treatment strategies are used that comprise the WHO cancer pain treatment strategy. These strategies were designed in a multi-center field study.\textsuperscript{30}

1) By mouth. Analgesics should be given orally as often as possible.

2) By the clock. Fixed interval dosing should be utilized. Dose may be titrated, but the next dose should be given before pain recurs. Rescue doses should be available for breakthrough pain.

3) By the ladder. First signs of pain should be treated with a non-opioid (NSAID: acetylsalicylic acid or acetaminophen) and adjuvants. If pain persists or increases, an opioid for mild to moderate pain (tramadol, codeine, buprenorphine) may be added. If pain again persists or increases, an opioid for moderate to severe pain (pure mu agonist) may be added.

4) For the individual. Doses should be titrated for effective pain control and minimization of side effects.

5) Attention to detail. The patient’s regimen should be clearly written for the patient and caregivers. Regular administration of pain relief drugs should be emphasized.
1.4.2 Pharmacology

1.4.2.1. Nonsteroidal Antiinflammatory Drugs (NSAIDs)

The NSAID drug class inhibits two isoforms of cyclooxygenase (COX), an enzyme whose isoforms are essential in the formation of inflammatory mediators in the arachidonic acid pathway.\textsuperscript{31}

Figure 2 Arachadonic acid pathway

The arachidonic acid pathway\textsuperscript{31} is responsible for the development of both pro-inflammatory and homeostatic mediators. Steroids inhibit the entire pathway, while NSAIDs inhibit cyclooxygenases to varying degrees.
The COX-1 isoform is constitutive and contributes to the maintenance of the gastric mucosa, hemostasis and renal function.\textsuperscript{32} The COX-2 isoform is inducible and constitutive in some tissues (the reproductive tract and eye, for example). It is upregulated by synoviocytes, fibroblasts, monocytes and macrophages in proinflammatory states. A recent study demonstrated that there is some overlap in COX-1 and COX-2 activity.\textsuperscript{33} COX-1 and COX-2 isoforms both participate in spinal cord modulation of both neuropathic and inflammatory pain. The COX-2 isoform also contributes to maintenance of renal blood flow and reproductive function.\textsuperscript{33,34} A COX-3 isoform has been identified and is associated with pyrexia.\textsuperscript{1} The selectivity of NSAIDs is often described by the ratio of IC\textsubscript{50} (concentration of drug required to inhibit the enzyme activity by 50\%) COX-1:COX-2, which is often referred to as the selectivity of the drug. Aspirin (IC\textsubscript{50} COX-1:COX-2 0.4\textsuperscript{35}), phenylbutazone, ketoprofen, ketorolac and flunixin meglumine inhibit both COX-1 and COX-2 enzymes. Meloxicam, carprofen (IC\textsubscript{50} COX-1:COX-2 1.8, 5, 9, 16.8), etodolac, vedeprofen and tolfenamic acid are COX-2 selective with weak COX-1 inhibition. Deracoib and firocoxib are highly COX-2 selective. Acetaminophen is COX-3 selective with weak COX-1 and COX-2 activity.\textsuperscript{17}

NSAIDs exhibit both peripheral and central effects.\textsuperscript{36,38} The peripheral effects are antinociceptive and helpful in inflammatory conditions. These effects occur via prevention of prostaglandin synthesis and inhibition of nuclear factor κβ (NF-κβ).\textsuperscript{40,41} The central effects occur at spinal and supraspinal levels.\textsuperscript{36}

The side effects of NSAIDs are generally manifested as gastrointestinal tract ulceration (after \textit{per os} administration), renal damage, hepatopathy and inhibition of
platelet function.

Gastrointestinal effects result from direct irritation of the gastric mucosa and inhibition of PGE$_2$, which contributes to gastric mucosal blood flow, mucus production, bicarbonate secretion and turnover of epithelial cells.$^{40}$ Carprofen has been shown to induce fewer gastrointestinal effects compared to etodolac, flunixin meglumine, ketoprofen and meloxicam in dogs.$^{41}$ Dogs with mast cell tumors (MCTs) may experience gastric hyperacidity secondary to hyperhistaminemia, thus making them more susceptible to the side effects of NSAIDs.$^{42}$

In the kidney, prostaglandins regulate vascular tone, sodium excretion and reabsorption, chloride transport and renin.$^9,38$ Renal blood flow is decreased in hypovolemic patients receiving COX-2 inhibitors.$^{43}$ Therefore, NSAIDs are used with caution or avoided in patients with renal disease, hypovolemia and hypotension.

Hepatic effects of NSAIDs are either dose-dependent (intrinsic) or dose-independent (idiosyncratic). Intrinsic toxicity is most commonly associated with overdose, while idiosyncratic hepatotoxicity has been reported with every NSAID, with Labrador Retrievers receiving carprofen being overrepresented.$^{38,44}$ However, it is important to note that Labrador Retrievers are a popular breed that commonly experiences osteoarthritis and orthopedic injury; the results of this report may be skewed by this fact.

The effects of NSAIDs on platelet function may be mediated by inhibition of thromboxane A$_2$ (TXA$_2$). Studies evaluating platelet function and bleeding times after administration of NSAIDs have had differing and inconclusive results.$^{45-48}$ NSAIDs are
used with caution in patients with bleeding disorders or potential platelet dysfunction.

Carprofen is available in injectable, chewable and tablet formations and is approved in the United States for use in dogs for treatment of postoperative pain and treatment of osteoarthritis.49 Total drug exposure is the same after a single dose as at steady state.50

1.4.2.2 Tramadol

Tramadol is a multimodal analgesic. Sixty percent of its activity is attributed to inhibiting uptake of norepinephrine and serotonin, with the remaining 40% due to weak mu receptor agonism.9,51 Tramadol is used in the treatment of mild to moderate acute pain and neuropathic pain.9,17 Tramadol and the COX-3 inhibitor metamizole are efficacious in controlling cancer pain and improving QOL used with or without concurrent NSAID administration in dogs.52 The M1, M2 and M5 metabolites are considered to be active, with M1 being the most potent metabolite. After one week of tramadol administration in people, the incidence of strong/unbearable cancer pain was reduced from 98% to 48%.53

The oral bioavailability of tramadol in dogs has been reported as 65 ± 38%, with a half-life of 1.71 ± 0.12 hours. In the same study, the M1 metabolite had a half-life of 2.18 ± 0.55 hours.54 In a more recent study, the M1 metabolite was detected at very low levels, and there was no antinociceptive effect.55 The activity of tramadol may vary widely.

Use of tramadol with monoamine oxidase inhibitors (MAOIs) may lead to serotonin syndrome and is contraindicated. Concurrent administration of ondansetron has
been shown to decrease the efficacy of tramadol.\textsuperscript{56}

1.4.2.3 Steroids

Glucocorticoids inhibit the conversion of phospholipase to arachidonic acid. Thus, they inhibit both the COX and lipoxygenase (LOX) branches of the pathway and exhibit less specific and more potent anti-inflammatory activity than NSAIDs. However, the propensity for increased side effects and suppression of wound healing make steroids less desirable for management of pain.\textsuperscript{17}

1.4.2.4 Opioids

Opioid agonists act at pre- and post-synaptic sites that are present in both the peripheral and central nervous system.\textsuperscript{51} Opioid receptors are classified as mu, kappa or delta. Agonism of mu receptors results in most potent analgesia and they are thus the target of most therapy.\textsuperscript{51} Agonism of any opioid receptor results in inhibition of adenylyl cyclase via $G_i$ proteins.\textsuperscript{9,51} Within the nociceptive pathway opioids decrease transduction, transmission, modulation, projection and perception.

Acute pain is often managed by administration of a pure mu agonist. Morphine, oxymorphone, hydromorphone, meperidine, fentanyl, sufentanil, alfentanil, remifentanil and methadone can be administered intravenously, either as boluses or as constant rate infusions (CRIs). Methadone and morphine are available in oral formulations with decreased bioavailability.\textsuperscript{51,57} Buprenorphine is a partial mu agonist with high affinity for the mu receptor that results in longer duration of effect but decreased analgesic effects
compared to full mu agonism.\textsuperscript{17} Buprenorphine is often administered transmucosally (in cats) and, like fentanyl, is available as a transdermal patch. Previous designs of fentanyl patches have had varied efficacy in veterinary patients; however, a new patch approved for use in dogs may prove to be more useful.\textsuperscript{58} Opioids are also efficacious when administered neuraxially, epidurally and intrathecally.\textsuperscript{17} Side effects of opioids include sedation, dysphoria, emesis, bradycardia, respiratory depression, panting, hyperthermia (in cats) and histamine release (morphine and meperidine).\textsuperscript{9}

Codeine is a weak opioid agonist which may be effective for mild pain when administered orally, although it has poor bioavailability.\textsuperscript{9,17,56}

1.4.2.5 Local anesthetics

Local anesthetics (lidocaine, ropivacaine, bupivacaine) block voltage-gated sodium channels, interrupting transduction and transmission of nociception. Local anesthetics can be delivered intravenously, transdermally, epidurally, intrathecally, intra-articularly or neuraxially. Duration of effect is related to the drug selected, dose and mode of administration.\textsuperscript{9}

1.4.2.6 Alpha-2 Adrenoceptor Agonists

Alpha-2 adrenoceptor agonists (xylazine, detomidine, dexmedetomidine) are useful anesthetic adjuvants. Their analgesic effect is via inhibition of norepinephrine reuptake. These drugs can be administered intravenously, intramuscularly or epidurally. Side effects of alpha-2 adrenoceptor agonists include sedation, bradycardia,
bradyarrhythmias, hypertension, hypotension, emesis, respiratory depression, gastric atony and transient hyperglycemia.⁹

1.4.2.7 Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs)

Tricyclic antidepressants (imipramine, amitriptyline, clomipramine) are useful analgesic adjuncts. Analgesia is mediated via serotonin and norepinephrine re-uptake inhibition, anticholinergic and antimuscarinic activity.⁴,⁹ Weak activity at opioid receptors may also play a role in analgesia. Some SSRIs (fluoxetine) inhibit serotonin reuptake only. Use of an SSRI concurrently with an NSAID may impair platelet aggregation.⁹ These drugs may be particularly useful in the treatment of chronic and neuropathic pain.

1.4.2.8 Anticonvulsants

Anticonvulsants (gabapentin, pregabalin, carbamazepine) are especially useful for treating neuropathic pain.⁶⁰ These drugs suppress ectopic discharge via reduction of calcium ion conductance. Gabapentin also has NMDA receptor antagonist activity (see below) and activity at alpha-2 receptors in the dorsal horn.⁶¹ Sedation and cost are potential disadvantages to these drugs. Gabapentin has been shown to be ineffective in providing pre-emptive analgesia in greyhounds undergoing forelimb amputation.⁶²
1.4.2.9 NMDA receptor antagonists

NMDA receptor antagonists (ketamine, amantadine, gabapentin, methadone) are particularly useful in the presence of temporal summation (‘windup’) or in cases of hyperalgesia or allodynia.\(^9\) Antagonizing these receptors prevents prolonged depolarization. In addition to NMDA receptor antagonism, ketamine binds to nicotinic, muscarinic, opioid, AMPA, KAI and GABA receptors. It also inhibits serotonin and dopamine reuptake, and affects sodium and potassium channel function. Ketamine is often used as an anesthetic as well as an adjunctive analgesic. Amantadine is available in an oral formulation and used in refractory osteoarthritic and cancer pain in people.\(^9\) Methadone also has opioid mu receptor agonist activity.

1.4.2.10 Bisphosphonates

Pamidronate is a bisphosphonate that inhibits osteoclast activity. It is administered intravenously once monthly for relief of bone pain.\(^4\)

1.4.2.11 Adjunctive and complementary therapies

Nutraceuticals (omega-3 fatty acids, polysulfated glycosaminoglycans (PSGAGs)) may be efficacious in reducing inflammation via substrate competition with the arachidonic acid pathway.\(^4\) Acupuncture may modulate inflammation and release endorphins and serotonin.\(^9\) Physical rehabilitation therapies such as electronic stimulation, massage, transcutaneous electrical nerve stimulation, heat and cold therapy may also contribute to pain relief.\(^4\) Low level laser therapy is contraindicated in patients
with neoplastic disease, as this therapy may encourage tumor growth and metastasis.

1.4.3 Pain Assessment

Evaluation of cancer pain has been divided into three components: palpation-induced pain, activity parameters and behavioral parameters. Historical questions about a veterinary patient’s behavior may include questions about the animal’s appetite, grooming, and urinary and bowel elimination. Activity assessment may include willingness to go outside, go on walks, eagerness to jump, and assessment of gait. Behaviors in response to palpation that may indicate pain are vocalization, guarding, escape behavior or an attempt to bite.

Physiologic factors have been found to be unreliable indicators of pain. When comparing heart rate, respiratory rate and pupil dilation to pain scores, no correlation was found between pain score and any physiologic variable. Thus, these parameters cannot be used as the sole means of assessing pain. Several models of pain assessment systems have therefore been developed.

1.4.3.1 Subjective and semi-objective pain assessment tools

Pain scales may be classified as: simple descriptive, visual analog, numerical rating or composite scales. Simple descriptive scales may include descriptors such as “none, mild, moderate or severe pain”. Visual analog scales (Appendix A) include a 100mm line upon which the observer places a mark indicating the level of pain that they perceive the animal to be experiencing. Numerical rating scales assign a numerical score
to describe the level of pain that the observer perceives. These three categories of scales are simple and easy to use, but assess only the intensity of pain and may be subject to bias. These scales or combinations of these scales have been used in studies involving ovariohysterectomy, castration, orthopedic surgery, auricular surgery, thoracotomy and soft tissue surgeries. Significant inter-observer variation was noted when using these types of scales.

Two numerically-scored composite scales have been used in veterinary medicine. The University of Melbourne Pain Scale (UMPS) assesses physiologic data, response to palpation, activity, mental status, posture and vocalization. This scale also demonstrated high inter-observer variation.

The Glasgow Modified Pain Score (Appendix A) was designed to incorporate behavior, postural and palpation related changes in dogs following surgery. The scale successfully differentiated between dogs who had undergone orthopedic versus soft tissue surgery.

1.4.3.2 Objective pain assessment

Objective measurements of pain may include algometry, Von Frey filament threshold, force plate analysis and thermal threshold analysis. Algometry has been used successfully to assess the efficacy of methadone administration in cats. Von Frey filament testing has been used in multiple species to test withdrawal threshold. Force plate analysis has been used to detect gait abnormalities, but has not been correlated with pain scores. Thermal threshold analysis has been utilized in research subjects, but
reports of efficacy are widely variable.\\textsuperscript{72}

1.4.4 *Quality of Life Assessment*

“With a cancer diagnosis, a client’s initial hopes may center around curing the cancer and the pet living longer and then move toward spending special time with loved ones, finding meaning, and then seeking a peaceful death.”\\textsuperscript{1} To this end, assessing and prioritizing quality of life (QOL) is a common goal of both owners of oncology patients and their veterinarians.

Quality of life has been described as being close to psychological well being, happiness, life satisfaction and contentment.\\textsuperscript{73} Because these areas cannot be assessed in nonverbal patients, caregivers’ perception of the patient’s stress, pain, fear and overall wellbeing are substituted. A QOL survey has been validated in veterinary oncologic patients.\\textsuperscript{74} Areas evaluated are: happiness, mental status, pain, appetite, hygiene, water intake, mobility, general health versus initial diagnosis, general health versus last visit and a VAS of QOL. This form was used in the present study (Appendix B).

1.5 Specific aims and hypotheses

The objective of our study was to compare the effect of pre-emptive administration of NSAIDs versus tramadol versus no treatment in postoperative pain scores, analgesic requirements, and quality of life scores in dogs undergoing removal of cutaneous tumors. We hypothesized that pre-emptive administration of tramadol and NSAIDs would result in reduced pain scores and lower rescue analgesia requirement in
postoperative oncologic patients, and that NSAIDs would result in a greater reduction in pain scores and lower rescue analgesia requirement compared to tramadol.
2.1 Materials and Methods

2.1.1 Animals

Thirty-seven client-owned dogs were recruited for the study. All dogs had been previously diagnosed with neoplastic cutaneous masses greater than 1 cm in diameter. A complete blood count (CBC) and chemistry profile were obtained, and a physical examination was performed in all dogs to assess organ function. Dogs with cardiac, renal or hepatic disease were excluded from the study. Dogs receiving non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or ondansetron within 7 days, or selective serotonin reuptake inhibitors (SSRIs) within 30 days, prior to enrollment were excluded. Dogs with pre-existing pain necessitating the use of chronic preoperative analgesics were also excluded. This study was approved by the Clinical Research Advisory Committee; owner consent was obtained. Owners completed a quality of life (QOL) survey at the time of enrollment. A pain assessment was also performed at enrollment. Dogs were randomly assigned to one of three groups: NSAID (N), tramadol (T) or no treatment (C). Group N received carprofen (Zoetis, Florham Park, NJ) 2.2 mg/kg orally every 12 hours for 48 hours prior to surgery. Group T received tramadol (Teva, Sellersville, PA) 3 mg/kg orally every 8 hours prior to surgery. Group C received no analgesics prior to surgery.
All owners completed a QOL survey two days prior to surgery. The QOL survey asked owners to evaluate their dog’s status in each of 9 categories on a numerical scale (1-5). The categories were: happiness, mental status, pain, appetite, hygiene, hydration, mobility, general health and general health versus initial diagnosis of cancer. A visual analog scale of current QOL was also included (Appendix B).

Pain scores were performed on all dogs on the day of surgery.

Table 1 Experimental design

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial consultation</td>
<td>Pain evaluation (MGM, VAS, algometry), QOL survey, enrollment in study</td>
</tr>
<tr>
<td>Two days prior to surgery</td>
<td>QOL survey, Start treatment (groups N, T)</td>
</tr>
<tr>
<td>Morning of surgery</td>
<td>Pain evaluation</td>
</tr>
<tr>
<td>Post operative</td>
<td>Pain evaluation 1, 2, 3, 4, 8, 12, 16, 20 and 24 hrs after surgery and every 24hrs until discharge</td>
</tr>
<tr>
<td>Days 1 &amp; 7</td>
<td>QOL survey</td>
</tr>
<tr>
<td>Suture removal - 10-14 d post sx</td>
<td>Pain evaluation, QOL survey</td>
</tr>
</tbody>
</table>

2.1.2 Anesthetic protocol

All dogs were premedicated with midazolam (0.2 mg/kg, Novaplus, Irving, TX) and hydromorphone (0.1 mg/kg, West-ward, Eatontown, NJ) intramuscularly (IM). Intravenous (IV) catheters (Surflo Terumo Medical Corporation, Somerset, NJ) were placed in a peripheral vein in all dogs. Anesthesia was induced with propofol (2 ± 2
mg/kg, Abbott, Abbott Park, IL) IV. Patients were connected to standard small animal anesthetic breathing circuits. Anesthesia was maintained with isoflurane in oxygen. Anesthetic vaporizer setting and oxygen flow rate were adjusted based on assessment of anesthetic depth as evaluated by jaw tone, eye position, palpebral reflex, heart rate (HR), respiratory rate (RR) and blood pressure. Patients were ventilated if end-tidal CO$_2$ was greater than 60 mm Hg, if SpO$_2$ was less than 90%, or if RR was lower than 4 breaths per minute. Blood pressure was monitored via Doppler method. The Doppler crystal was placed over the superficial palmar branch of the radial artery. A cuff with a width 30-40% of the circumference of the limb was placed above the carpus. The cuff was inflated with a sphygmomanometer until the audible Doppler signal was no longer present. The sphygmomanometer was deflated until the return of the audible Doppler signal. The sphygmomanometer pressure at this point was recorded as the systolic arterial pressure (SAP). Heart rate was obtained by direct count of pulse. Bradycardia was treated with glycopyrrolate (5 µg/kg IV) if the HR remained lower than 55 beats per minute for longer than five consecutive minutes. Heart rhythm was monitored via a three lead configuration in lead II. A Cardell MAX-12 Duo HD multiparameter monitor (Midmark, Versailles, OH) was used to monitor all patients. Additional intra-operative analgesia was administered if the patient exhibited signs of a light plane of anesthesia (movement, marked increase (>20% change) in HR, RR, or SAP) that could not be controlled by increasing the isoflurane concentration. Additional intra-operative analgesia was provided via fentanyl infusion (2 µg/kg bolus followed by a constant rate infusion (CRI) of 5-10 µg/kg/hr). If sedation was required in recovery to treat emergence delirium or
dysphoria, acepromazine (0.02 mg/kg) was administered IV.

Tumor dimensions were recorded at the initial visit and after surgical preparation.

2.1.3 Pain Assessments

2.1.3.1 Visual Analog Scale

The blinded observer approached the patient at rest. A vertical line was placed on a horizontal line 100mm in length in order to indicate the perceived pain of the patient.\(^{76}\)

2.1.3.2 Modified Glasgow Method

The patient was approached in the kennel by a blinded observer. The dog’s vocalization (or lack thereof) and attention to wound were assessed. If the patient was wearing an Elizabethan collar, the collar was then removed. The patient was then led out of the kennel and the patient’s reaction to rising was assessed. Gentle pressure was applied to the wound, and the reaction was noted. Two subjective scores regarding overall attitude and posture were recorded. The score from each category was totaled (Appendix A).

2.1.4 Algometry

The algometer was calibrated by the manufacturer prior to use in the study (FDIX25 Algometer, Wagner Instruments, Greenwich, CT). An algometer with a 1 cm circumference tip was covered with a disposable latex guard to avoid cross-contamination of surgical incisions. The 1 cm circular tip was applied to areas 1 cm from
the center of the mass (prior to surgery) or the incision (following surgery). The algometer was first applied without pressure until the patient accepted the algometer without response. Once the dog accepted the algometer, force was applied until a behavioral response was elicited. Behavioral responses included: turning toward the pressure, vocalization, moving away, or any attempt to bite. No more than 5 kg/cm² was applied to avoid tissue damage.

Figure 3 Algometer
Hand-held algometer unit, with 1 cm diameter round sensor tip at the top of the unit. Peak force applied displayed in kg/cm². (www.wagnerinstruments.com)

2.1.5 Pain assessments and rescue analgesia
All dogs were evaluated via the modified Glasgow method, VAS and algometry immediately after extubation and then: once an hour for four hours, and once every four hours until 24 hours after extubation. Pain threshold was also assessed via algometry at each time point. Analgesia (hydromorphone 0.1 mg/kg IM) was provided if a pain score
greater than or equal to 7 (out of a possible 24) was obtained, or a score of 40mm or more was measured on the VAS.

Sedation was assessed at each pain evaluation. A sedation score ranging from 0 (not sedate) to 3 (nonresponsive) was generated (Appendix C). In addition, a sedation VAS was generated.

Owners completed QOL surveys 1, 7 and 14 days after discharge. If suture removal was performed at the OSU VMC, a pain score was performed at that time.

2.2 Data Analysis

Changes in: QOL score, QOL VAS, pain score, pain VAS, sedation score and sedation VAS were compared across drug groups using linear mixed models. For the pain scores, a smooth trend was fit to data collected over the first 24 hours and changes from baseline at 14 days were compared using a separate one-way ANOVA. Since algometer site scores were censored at 5 kg/cm², we compared the distribution of scores at 24 hours and 14 days across groups using log-rank tests. Time to rescue was also compared across groups using a log-rank test. If an overall difference across groups was found in any of the analyses, the groups were compared using a Bonferroni corrected p-value.
Chapter 3: Results

3.1 Patient demographics

There were no differences among groups in age, gender or weight (Table 2).

Table 2 Patient ages and weights. Age and weight listed as mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Tramadol</th>
<th>NSAID</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.3 ± 2.7</td>
<td>8.4 ± 2.6</td>
<td>8.1 ± 2.1</td>
<td>8.0 ± 2.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0 (0%)</td>
<td>1 (9.1%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>FS</td>
<td>5 (35.7%)</td>
<td>7 (63.6%)</td>
<td>3 (30%)</td>
<td>15 (42.9%)</td>
</tr>
<tr>
<td>MC</td>
<td>9 (64.3%)</td>
<td>3 (27.3%)</td>
<td>7 (70%)</td>
<td>19 (54.3%)</td>
</tr>
<tr>
<td>Weight (kilograms)</td>
<td>34.7 ± 14.9</td>
<td>23.0 ± 9.4</td>
<td>30.4 ± 12.2</td>
<td>29.1 ± 13.1</td>
</tr>
</tbody>
</table>
No breed was overrepresented overall or in any group (Table 3). A wide variety of tumor types was present, and no tumor type was overrepresented overall or in any group (Table 3).

Table 3 Patient breeds and tumor descriptions

<table>
<thead>
<tr>
<th>Group</th>
<th>Breed</th>
<th>Tumor type</th>
</tr>
</thead>
</table>
| NSAID (n=10) | Golden Retriever (n=1)  
Labrador Retriever (n=1)  
Chinese Pug (n=1)  
Beagle (n=1)  
German Shorthaired Pointer (n=1)  
Mixed breed (n=5) | Spindle cell tumor (n=1)  
Lipoma (n=4)  
Mast cell tumor (n=1)  
Soft tissue sarcoma (n=2)  
Benign epithelial mass (n=1) |
| Tramadol (n=12) | Australian Shepherd (n=2)  
Miniature Schnauzer (n=1)  
Cocker Spaniel (n=1)  
Labrador Retriever (n=2)  
Mixed breed (n=6) | Soft tissue sarcoma (n=3)  
Mast cell tumor (n=4)  
Lipoma (n=3)  
Chronic pyogranulomatous dermatitis (n=1)  
Basal cell tumor (n=1) |
| Control (n=14) | Cavalier King Charles Spaniel (n=1)  
Cane Corso (n=1)  
Boxer (n=1)  
Wheaton Terrier (n=1)  
Greyhound (n=1)  
Miniature Schnauzer (n=1)  
Labrador Retriever (n=1)  
English Mastiff (n=1)  
Weimaraner (n=1)  
Presa Canario (n=1)  
Doberman Pinscher (n=1)  
Mixed breed (n=3) | Epithelial mass (n=1)  
Mast cell tumor (n=5)  
Pilomatrixcoma (n=1)  
Lipoma (n=3)  
Soft tissue sarcoma (n=4) |
3.2 Anesthesia and surgery

There was no difference among groups in propofol requirement (Table 4).

No dogs required blood pressure support. One dog in group C required heart rate support with glycopyrrolate. Seven dogs required IPPV, four in group C, one in group T, and two in group N. No intraoperative rescue analgesia was required. Three dogs in group C, five in group T, and four in group N required sedation in recovery. Anesthesia and surgery times were widely dispersed in each group (Table 4).

Table 4 Anesthesia and surgery times. Anesthesia time and surgery time listed as median (range). Propofol requirement listed as mean ± standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Tramadol</th>
<th>NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia Time</td>
<td>85 (67-145)</td>
<td>109.5 (41-180)</td>
<td>98.5 (50-210)</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery Time</td>
<td>40 (25-89)</td>
<td>43 (16-105)</td>
<td>56.5 (15-153)</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol Requirement</td>
<td>4.5 ± 1.5</td>
<td>4.1 ± 1.4</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>(mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3 Pain scores and time to rescue analgesia

3.3.1 Visual analog scale

There were no significant differences in pain VAS at any time point (Figure 4). Scores are reported as change from baseline (screening). VAS scores tended to increase in all groups up to 8 hours post extubation and then decrease over time, but there were no significant differences among groups or differences from baseline.

Figure 4 Change in VAS from baseline

The x-axis represents time after extubation in hours. The y-axis represents change from baseline VAS in millimeters. The blue group represents the control group, red the tramadol group and green the NSAID group.
3.3.2 Modified Glasgow pain scores

There were no significant differences in Modified Glasgow pain scores at any time point (Figure 5). Scores are reported as change from baseline (screening). Modified Glasgow pain scores tended to rise until 4 hours post extubation and then decline after 8 hours until hours 20, with a slight increase at the 24 hour timepoint.

Figure 5 Change in Modified Glasgow scores from baseline

The x-axis represents time after extubation in hours. The y-axis represents change from the Modified Glasgow score at baseline. The blue group represents the control group, red the tramadol group and green the NSAID group.
3.3.3 Algometry scores

At day 0 (day of surgery) only 1 dog in group T responded to an algometer force applied of up to 1 kg/cm². Six out of 14 dogs in group C, 3 out of 10 dogs in group N, and 6 out of 12 dogs in group T responded to a force between 1 and 5 kg/cm² (Figure 6). The remaining dogs in all groups withstood a maximum of 5 kg/cm². There were no significant differences in algometry scores between groups.

Figure 6 Day 0 Algometer site force applied

The x-axis represents kg/cm² force that achieved a behavioral response. The y-axis represents the proportion of dogs in each group whose algometer score exceeded the given force.
Compared to baseline, at 24 hours post-extubation dogs in all groups tended to be more sensitive to a given force applied by the algometer (Figure 7). Four out of 14 dogs in group C, 2 out of 12 dogs in group T and 2 out of 10 dogs in group N responded to a force <1 kg/cm$^2$. Six out of 14 dogs in group C, 8 out of 10 dogs in group N, and 8 out of 12 dogs in group T responded to a force between 1 and 5 kg/cm$^2$ (Figure 7). The remaining dogs in groups C and T withstood a maximum of 5 kg/cm$^2$. There were no significant differences in algometry scores between groups at this timepoint.

Figure 7 24hr Algometer site force applied

The x-axis represents kg/cm$^2$ force that achieved a behavioral response. The y-axis represents the proportion of dogs in each group whose algometer score exceeded the given force.
Fourteen days after surgery, dogs responded to algometry in a similar manner to baseline (Figure 8). Two dogs in group C responded to a force less than 1 kg/cm². One out of 14 dogs in group C, 4 out of 10 dogs in group N, and 9 out of 12 dogs in group T responded to a force between 1 and 5 kg/cm² (Figure 8). The remaining dogs withstood a maximum of 5 kg/cm². There were no significant differences in algometry scores between groups.

Figure 8 Day 14 Algometer site force applied

The x-axis represents kg/cm² force that achieved a behavioral response. The y-axis represents dogs in each group whose algometer score exceeded the given force.
3.3.4 Rescue analgesia

Three of 10 dogs in group C, 5 of 12 dogs in group T, and 4 of 14 dogs in group N required rescue analgesia (Figure 9). No dog in any group required rescue analgesia until 1 hour post-extubation, and no dogs in group N required rescue analgesia until 3 hours post-extubation (Figure 9). There were no significant differences among groups.

Figure 9 Time to rescue analgesia

The x-axis represents hours after extubation, with zero hour being time of extubation. The y-axis represents the proportion of dogs in each group requiring their first dose of rescue analgesia.
3.4 Sedation score

Sedation VAS and scores peaked at extubation (0 hours), then declined until 12 hours post-extubation, before increasing slightly until 20 hours post-extubation, after which they declined again (Figures 10, 11). There were no differences among groups in sedation VAS or scores.

Figure 10 Change in sedation score

The x-axis represents hours after extubation, with time zero being time of extubation. The y-axis represents change in sedation score from baseline.
3.5 Quality of Life

There was no difference among groups in QOL scores (Table 5). QOL VAS scores were significantly different at day 7 (Table 6). At this timepoint, QOL VAS scores increased by 8.2 (± 3.0) mm (mean ± standard error) in the group C versus baseline, and were decreased by 5.9 (± 3.5) mm in group N compared to baseline.
Table 5 QOL Scores. Values are estimated means ± standard error.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Δ Day 1</th>
<th>Δ Day 7</th>
<th>Δ Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>109 ± 2</td>
<td>-13 ± 3</td>
<td>-4 ± 2</td>
<td>-2 ± 2</td>
</tr>
<tr>
<td>Tramadol</td>
<td>103 ± 2</td>
<td>-22 ± 3</td>
<td>-3 ± 3</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>NSAID</td>
<td>108 ± 2</td>
<td>-15 ± 4</td>
<td>-6 ± 2</td>
<td>-1 ± 2</td>
</tr>
</tbody>
</table>

Table 6 QOL VAS Scores in mm. Values are estimated means ± standard error. * = significant difference (Bonferroni-adjusted p-value < 0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Δ Day 1</th>
<th>Δ Day 7</th>
<th>Δ Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83.6 ± 6.9</td>
<td>-5.30 ± 6.6</td>
<td>8.2 ± 3.0*</td>
<td>9.6 ± 2.3</td>
</tr>
<tr>
<td>Tramadol</td>
<td>78.5 ± 5.8</td>
<td>-24.5 ± 7.3</td>
<td>-1.2 ± 3.2</td>
<td>6.3 ± 2.5</td>
</tr>
<tr>
<td>NSAID</td>
<td>81.8 ± 3.9</td>
<td>-17.2 ± 8.3</td>
<td>-5.9 ± 3.5*</td>
<td>2.8 ± 2.7</td>
</tr>
</tbody>
</table>
Chapter 4: Discussion

Our hypotheses were that pre-emptive administration of tramadol and NSAIDs would result in lower pain scores and reduce rescue analgesia requirements in postoperative oncologic patients, and that NSAIDs would result in a greater reduction in pain scores and rescue analgesia requirement than tramadol. Our data show that: 1) there were no differences at any point in VAS, pain scores or algometry site force among groups as compared to baseline; 2) there were no differences in postoperative rescue analgesia among groups; 3) there were no differences in QOL scores among groups, except in the day 7 QOL VAS; and 4) that QOL VAS, but not scores, were improved at day 7 in control dogs and worse in dogs that received an NSAID. Both hypotheses were disproved.

Our data support the findings of several previous studies. Pre-emptive gabapentin was found to be ineffective at reducing post operative analgesic requirements or pain scores in greyhounds undergoing forelimb amputation.62 Our study also supports findings that pre-emptive analgesia with a mixed local anesthetic/morphine epidural and/or a morphine/lidocaine/ketamine infusion does not affect postoperative pain scores or analgesic requirements after tibial plateau leveling osteotomy (TPLO).76 Pre-emptive
tramadol has been found to be ineffective at reducing pain scores in pediatric tonsillectomies in human medicine.\textsuperscript{77}

Our findings are in contrast to several studies finding reduced pain scores or analgesic requirements with pre-emptive analgesia with NSAIDs or tramadol. In veterinary medicine, carprofen reduced pain scores and analgesic requirements after dogs receiving TPLO surgery.\textsuperscript{78} Pre-emptive analgesia with tramadol has been reported to be effective at reducing pain in women undergoing abdominal hysterectomy.\textsuperscript{79} Tramadol has also been shown to be effective pre-emptively in oromaxillofacial surgery.\textsuperscript{80}

Flor \textit{et al} found that tramadol and metamizole with and without an NSAID were effective in reducing pain scores and improving QOL scores in dogs with chronic cancer pain.\textsuperscript{52} This study initially dosed tramadol at 2 mg/kg and increased by 30\% if the dogs were still painful at days 7 and 14, or if pain scores were greater than 40 mm on a 100 mm VAS for 72 hours. The median effective range in the tramadol and metamizole group was 2.3 mg/kg. The dogs studied by Flor \textit{et al} were not undergoing surgical removal of tumors. As such, a slightly higher dose was selected for our study. Tramadol and metamizole, when combined with an NSAID, resulted in even lower pain scores and improved QOL scores. Dogs in this study had already failed NSAID-only analgesic therapy.\textsuperscript{52} Our study may have yielded different results if we had included a group of dogs receiving combination tramadol/NSAID therapy, or if the tramadol dose had been titrated over several weeks prior to surgery to achieve control of any central sensitization that may have been present.
Pre-emptive analgesic treatment with carprofen or tramadol prior to marginal resection of cutaneous tumors may indeed be ineffective. Cutaneous tumors and their removal may not cause enough pain for detection of a benefit. Alternatively, our model may have been ineffective at detecting any benefit. A literature search revealed no information about incidence of pain after removal of cutaneous tumors in dogs. Hypersensitivity following removal of cutaneous melanomas has been reported in people. In addition, the surgical procedure, site of procedure nor the surgeons were consistent. A larger sample size may have illuminated differences based upon procedure, site or surgeon. A previous study evaluating treatment of cancer pain in dogs has not included surgical removal. The analgesia provided by premedication with hydromorphone may have masked any benefit provided by pre-emptive analgesia in our study. In addition, sedation in recovery may have masked pain, although sedation scores and VAS were not different among groups.

The duration of administration of pre-emptive drugs was chosen based upon projected client compliance. Longer administration of either drug may have resulted in a reduction in central or peripheral sensitization, if present, and consequently may have decreased pain scores and analgesic requirements. Owner compliance is a major limiting factor of any clinical trial. Drug administration may not have been at the correct times, or given at the correct doses, or may not have been performed at all.

Detection of differences in pain is a challenge faced in clinical studies assessing efficacy of analgesic drugs in animals. Both subjective (VAS, Glasgow Modified form) and objective (algometry) methods were used in the present study to assess pain.
Subjective methods of pain assessment are dependent upon recognition and interpretation of pain behavior. A VAS measures pain as a one-dimensional experience, and may appear to be more sensitive compared with other scales, an attribute which may be overinterpreted. A VAS is made more sensitive by adding the words “for this procedure” to “worst possible.” Inter-observer variation was high, even when four anesthesiologists scored the same patient. The Glasgow Modified form can differentiate between dogs receiving orthopedic versus soft tissue pain, but may not be able to detect subtle differences in soft tissue pain. Algometry has been used to describe differences in thermal and mechanical thresholds in cats receiving methadone, but has not been used to describe acute surgical pain. Individual variation in experience and expression of pain, when combined with differences in tumor size and location, may make differences difficult to detect.

Other potential limitations of this study include: lack of pharmacokinetic data to confirm adequate drug levels, a lack of standardization of post discharge analgesia, and continued pain scores after rescue analgesia. Tramadol in particular may have highly variable pharmacokinetics. Post discharge analgesia was given at the discretion of the attending clinician. Differences in post discharge analgesia may have affected the post discharge QOL scores and VAS. A standardized post-discharge analgesic protocol may have eliminated these differences. However, this study was aimed at evaluating pre-emptive, not postoperative analgesic protocols. Pain scores recorded after rescue analgesia were reflective of both pre-emptive and rescue analgesics. Elimination of pain scores after rescue analgesia may have detected differences in pain or QOL.
The clinical significance of an increased QOL VAS on day 7 in the control group and a decreased QOL VAS in the NSAID group is debatable. The variation in post-discharge analgesic drug protocols may have contributed to this change. Another consideration is that most medications at discharge are prescribed for 3-7 days. It is possible that this decrease in QOL VAS coincided with a real or perceived change that occurred as the NSAID administration was discontinued.

In conclusion, it is possible that all protocols used in the present study provided similar pain control because all groups had similar, relatively low average pain scores during the 24 hour post-operative period. If a larger sample size had been examined, if dogs with similar tumor size, type or location were compared, or if pre-emptive analgesia was administered for a longer duration of time, we may have found statistical significance in pain, analgesic requirements or QOL. If post-discharge analgesia had been standardized, more concrete conclusions could be drawn regarding changes in QOL VAS at day 7. From our data, we can conclude that pain and QOL were highly variable. These pre-emptive analgesics, combined with pre-operative hydromorphone, frequent observation and rescue analgesia when indicated, resulted in satisfactory analgesia in the 24 hour postoperative time period, with no apparent side effects.
References


51. Stoelting RK, Hillier SC. Opioid agonists and antagonists. In: Pharmacology and


75. Welsh EM, Gettinby G, Nolan AM. Comparison of a visual analogue scale and a numerical rating scale for assessment of lameness, using sheep as a model. *Am J Vet Res*. 54


Appendix A Visual Analog Scale and Modified Glasgow Pain Score

In the section below, please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in kennel
   Is the dog?
   (a) Quiet 0
   (b) Ignoring any wound or painful area 0
   Crying or whimpering 1
   (b) Looking at wound or painful area 1
   Growling 2
   (b) Licking wound or painful area 2
   Screaming 3
   (b) Rubbing wound or painful area 3
   Chewing wound or painful area 4

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?
   (c) Normal 0
   (d) Does it?
   Lame 1
   (d) Do nothing 0
   Slow or reluctant 2
   Look round 1
   Stiff 3
   Flinch 2
   It refuses to move 4
   Growl or guard area 3
   Snap 4
   Cry 5

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.
   (b) Is the dog?

D. Overall
   Is the dog?
   (e) Happy and content or happy and bouncy 0
   (f) Comfortable 0
   Quiet 1
   Unsettled 1
   Indifferent or non-responsive to surroundings 2
   Restless 2
   Nervous or anxious or fearful 3
   Hunched or tense 3
   Depressed or non-responsive to stimulation 4
   Rigid 4

Total Score (a+b+c+d+e+f)=........
Appendix B Quality of Life Form

Cancer Treatment Form

<table>
<thead>
<tr>
<th>Survey Date</th>
<th>Pet Owner</th>
<th>Name of Person Completing Survey</th>
<th>Pet Name</th>
<th>Weight</th>
<th>Species</th>
</tr>
</thead>
</table>

**Instructions:** Please indicate your assessment by circling the number on the scale next to each question, providing your opinion on your pet's current health status.

**Example:**

<table>
<thead>
<tr>
<th>Happiness</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet wants to play</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>My pet responds to my presence</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>My pet enjoys life</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Mental Status**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet has more good days than bad days</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet sleeps more, is awake less</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet seems dull or depressed, not alert</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Pain**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet is in pain</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet pants frequently, even at rest</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet shakes or trembles occasionally</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Appetite**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet eats the usual amount of food</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet acts nauseous or vomits</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet eats treats / snacks</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Hygiene**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet keeps him/herself clean</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet smells like urine or has skin irritation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet's hair is greasy, matted, rough looking</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Water Intake (Hydration)**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet drinks adequately</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet has diarrhea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet is urinating a normal amount</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Mobility**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My pet moves normally</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet lays in one place all day long</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My pet is as active as he/she has been</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**General Health**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health compared to last evaluation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>General health compared to initial diagnosis of cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Current quality of life</td>
<td>Very Poor</td>
<td>Same</td>
</tr>
</tbody>
</table>

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Appendix C Sedation Visual Analog Scale and Score

Sedation score:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No discernible signs of sedation</td>
</tr>
<tr>
<td>1</td>
<td>Signs of sedation but reactive to acoustic stimuli</td>
</tr>
<tr>
<td>2</td>
<td>Signs of sedation, no reaction to acoustic stimuli but reactive to physical examination</td>
</tr>
<tr>
<td>3</td>
<td>Sedated and no reaction to acoustic or physical stimuli</td>
</tr>
</tbody>
</table>