The Challenge of Evaluating Pain and a Pre-incisional Local Anesthetic Block

Background: Our objective was to test the effectiveness of a local anesthetic line block administered before surgery in reducing postoperative pain scores in dogs undergoing ovariohysterectomy (OVHX). Methods: This study is a prospective, randomized, blinded, clinical trial involving 59 healthy female dogs. An algometric pressure-measuring device was used to determine nociceptive threshold, and compared to three subjective pain scales. Group L/B received a line block of lidocaine (4 mg/kg) and bupivacaine (1 mg/kg) subcutaneously in the area of the incision site and saline subcutaneously as premedication; group L/BM (positive control) received a similar block and morphine (0.5 mg/kg) subcutaneously for premedication; and group SS (negative control) received a saline line block and saline premedication. Criteria for rescue analgesia were defined before the study. Dogs were assessed prior to surgery, at extubation (time 0) and at 2, 4, 6, 8 and 24 hours post-recovery. The data were analyzed with one-way ANOVA, and a Split Plot Repeated Measures ANOVA with one grouping factor and one repeat factor (time). $P < 0.05$ was considered statistically significant. Results: Approximately 33% of dogs required rescue analgesia at some point during the study, with no significant difference between groups. There was no significant difference between treatment groups with any assessment method. Conclusions: As there were no statistically significant differences between positive and negative controls, the outcome of this technique cannot be proven.

Carolyn M. McKune[a]†*, Peter J Pascoe[a], B Duncan X Lascelles[b], Phillip H Kass[c]

[a]Department of Surgical and Radiological Sciences and

[c]Department of Population Health and Reproduction, School of Veterinary Medicine, University of California, Davis, CA, USA

[b]Comparative Pain Research Laboratory, Department of Clinical Sciences & Center for Comparative Medicine and Translational Research, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA

†Current address: Gainesville FL USA

*Corresponding author. Tel.: +1 352 225 3636

Corresponding author's email address: mckune@mythosvet.com

Email addresses of all authors: mckune@mythosvet.com, pjpascoe@ucdavis.edu, dxlascel@ncsu.edu, and phkass@ucdavis.edu

13 Key words: Dog, lidocaine, bupivacaine, local anesthestic, pain assessment

14 Introduction

15 As any verbal responder who has experienced pain may attest to, pain decreases quality of life
16 (1). Therefore, pain management in painful patients is crucial for improving quality of life. Pain
17 management of a non-verbal responder is uniquely challenging for those in the scientific
18 community because it complicates the ability to effectively diagnose and treat the disease. Pain
19 assessment in non-verbal species has been investigated along 3 principle lines: a) objective
20 measures of physiologic responses to experimental pain, b) subjective or semi-objective
21 assessment of behavior postoperatively, and c) quantitative measures of postoperative behavior
22 and physiology. While studies using objective physiological data (i.e. variables such as heart
23 rate, respiratory rate and blood pressure) are easy to perform and analyze statistically, there is
24 considerable debate as to whether these measures are reliable indicators of pain (2, 3). Most
25 peer-reviewed research studies in veterinary medicine have used subjective or semi-objective
26 assessments of postoperative pain or sensitivity of an anatomical site to assess outcomes. In
27 clinical veterinary practice, the use of a formalized pain scale is still unsettlingly rare (4).
28 Algometers (used to quantitate pressure required to cause pain, or what is termed the “nociceptive
29 threshold”) have been used to provide a more objective measurement of incisional sensitivity.
30 The “threshold” reading is objective, but the factor determining the threshold (behavioral
31 response) is subjective. Various mechanical threshold devices have validated of to assess
32 somatosensory processing changes (5).
33 Multimodal analgesia is the combination of analgesic drugs with different methods of action,
34 with the goal of reducing or preventing nociceptive stimulation at multiple receptors and
35 pathways. In humans, multimodal analgesia has been shown to decrease post-operative morbidity
36 and mortality, improving quality of life and patient satisfaction, and decreasing the associated
37 costs to hospitals and insurance companies (6). In addition to the general agreement of a clinical

benefit to this approach (7), there are also an increasing number of research studies in non-verbal species supporting multimodal analgesia (8-10). Thankfully, it appears that while it is uncommon for most veterinarians to use a pain scale, the practice of multimodal analgesia is common (4). One simple way to include multimodal analgesia is the incorporation of a local anesthetic to desensitize a specific region, in combination with systemic analgesic administration.

This study was designed to assess the effect of pre-incisional administration of a combination of local anesthetics on post-operative pain, measured by subjective and objective pain scores after canine OVHX. We hypothesized that pre-incisional infiltration of the incision area with local anesthetic agents (group L/B) would result in similar post-surgical pain levels compared to animals receiving local anesthetic and an opioid (group L/BM), and decreased post-surgical pain compared to animals not receiving any pre-operative analgesics (group SS). Group L/BM (animals receiving opioid plus local anesthetic) was our positive control (or "pain-free" group) and group SS (receiving no pre-operative analgesic) was our negative control, or group for which we were anticipating to see evidence of pain. Criteria for rescue analgesia were defined prior to the study's commencement and strictly adhered to. The premise for drawing such conclusions was based on the assumption there is a significant difference between an animal receiving appropriate analgesia and an animal that does not.

Methods

This study examined 59 healthy intact female dogs admitted to a local animal shelter (Sacramento Society for Prevention of Cruelty to Animals [SPCA], Sacramento, CA, USA), ranging in age from six months to eight years old (1.85 ± 1.81 years, mean ± standard deviation) with weights ranging from 3.4–35.5 kg (17.2 ± 8.2 kg). A physical examination was performed, and temperature, heart rate, and respiratory rate were recorded prior to sedation for anesthesia and surgery. Each dog had a packed cell volume (PCV), total protein (TP), and blood urea nitrogen (Azostick, Bayer Corporation, Elkhart, IN, USA) checked prior to surgery. No dogs with

abnormal physiologic parameters, abnormal blood tests, evidence of a previous OVHX, or requiring extension of the incision beyond the blocked area were used in this study. All protocols were approved by the University of California, Davis, Institutional Animal Care and Use Committee, as well as by administrative study reviewers at the Sacramento Society for Prevention of Cruelty to Animals (SSPCA).

Anesthesia

Dogs were allocated into one of three groups using a computer generated randomized block design. All three groups were sedated with acepromazine (Acepromazine maleate, Vedro, St. Joseph, MO, USA) (0.03 mg/kg, subcutaneously [SC]) administered prior to catheter placement. An 18-22-gauge (depending on the animal's weight) over the needle IV catheter was placed in a cephalic vein for drug and fluid administration. Anesthesia was induced with propofol (Diprivan, AstraZeneca LP, Wilmington, DE, USA) to effect (4.2 ± 1.5 mg/kg, IV) and maintained with isoflurane (Isoflurane, Abbot Laboratories, North Chicago, IL, USA) in oxygen to effect. Lactated Ringer's solution was administered at 10 mL/kg/hour until recovery. Heart rate, respiratory rate, and systolic blood pressure were monitored throughout the procedure.

Dogs in group L/B received a line block prior to surgery in the incision area, consisting of 4 mg/kg lidocaine (Lidocaine, Hospira Inc., Lake Forest, IL, USA) and 1.0 mg/kg bupivacaine (Bupivacaine, Hospira Inc., Lake Forest, IL, USA). These dogs also received 0.05 mg/kg of saline SC at the same time as acepromazine administration. Dogs in the positive control group L/BM received a line block prior to surgery, using 4.0 mg/kg lidocaine and 1.0 mg/kg bupivacaine. These dogs also received 0.5 mg/kg of morphine (Morphine sulfate, Baxter Health Care Corporation, Deerfield, IL, USA) SC at the same time as acepromazine administration. Dogs in the negative control group SS received 0.275 mL/kg of normal saline prior to surgery in the incisional area. These dogs also received 0.05 mg/kg of saline SC at the same time as acepromazine administration. The line block or saline (depending on the group) was administered

after induction of anesthesia and initial surgical preparation of the field, approximately five minutes prior to surgical incision.

Line block procedure

Appendix 1 shows the line block in schematic form. Local anesthetic or saline (depending on the group) was infused with a 2.5 inch, 22-gauge spinal needle in three separate lines to form an inverted double "L" administration site. One third of the volume of drug or saline was administered at each site, as volume allowed. The level of the first line (Appendix 1, "1") was roughly halfway between the umbilicus and the first set of nipples below the umbilicus; placement was guided by consultation with the surgeon prior to incision to ensure coverage of the area to be incised (Appendix 1, "A"). The width of this first line ran mediolaterally for approximately 1.25 cm on either side of midline. The second line (Appendix 1, "2") began at the leftmost lateral point of the first line, and ran craniocaudally for the length of the spinal needle on the left side of midline. The third line (Appendix 1, "3") paralleled the second on the right side of the umbilicus. In Appendix 1, "B" denotes the pubis. These blocks were administered in the subcutaneous and fascial planes. Aspiration prior to administration of the block was performed to ensure the drugs were not given intravenously.

Surgical procedure

The hair was clipped from the xiphoid process to the pubis and three cm laterally to the nipple on both sides of the abdomen. The skin was scrubbed with chlorhexedine and rinsed with water 3 times. The line block was applied after initial preparation; additional preparation followed until the area was aseptically prepared. An incision was made extending below the umbilicus to one-third the distance from the umbilicus to the pubis. An OVHX was performed in a standard fashion (11) by one of three experienced surgeons. The skin was closed in a routine manner.

Assessment

Four pain scoring assessments were used; initial values for each were recorded prior to the sedation of the animal for anesthesia and surgery (time negative one). Assessments were then made at zero (time of extubation), two, four, six, eight, and twenty-four hours postoperatively by one veterinarian (CMM) who was blinded to which treatment group each animal was in. Caretakers made additional assessments during the day when animals were handled, to ensure any animal that needed additional analgesia would receive it.

The first pain scoring assessment was a visual analogue scale (VAS) score. This assessment was made of the animal prior to any manipulation or handling. A mark on a ten centimeter (cm) line corresponded to the assessor's visual assessment of the animal's pain, ranging from zero ("not painful") to ten cm ("the most pain an animal could possibly be in"), measured in mm using a standard ruler at each scoring assessment, and recorded after each measurement was taken.

The next two pain scoring assessments were done sequentially. One of these pain scales was based on a previously validated scoring system, the Glasgow Composite Pain Scale (GCPS, http://www.gla.ac.uk/faculties/vet/smallanimalhospital/ourservices/painmanagementandacupuncture, subheading: Short form pain questionnaire). The primary variables included vocalization (quiet, crying, groaning, screaming), attention to painful area (ignoring, looking, licking, rubbing, or chewing), mobility (normal, lame, slow or reluctant, stiff, or refusal to move), response to touch (none, looking around, flinch, growl, snap, or cry), demeanor (happy and content, bouncy, quiet, non-responsive or indifferent to surroundings, nervous or anxious or fearful, or depressed or non-responsive to stimulation), and posture (comfortable, unsettled, restless, hunched or tense, or rigid). The other assessment was made using the University of Melbourne Pain Scale (UMPS) (12). The primary variables included physiologic data (dilated pupils, percentage increase in HR, percentage increase in respiratory rate, rectal temperature, salivation), response to palpation (no change, guards/reacts when touched, guards/reacts before touched), activity (at rest [sleeping or semiconscious, awake], eating, restless [pacing, getting up and down], or rolling/thrashing),

mental status (submissive, overtly friendly, wary, or aggressive), posture (guarding or protecting affected area, recumbency, standing or sitting with head up, standing with head down, moving, or abnormal body posture [prayer/hunched]), and vocalization (none, vocalizing when touched, intermittent vocalization, or continuous vocalization).

The final assessment method used a digital von Frey apparatus (IITC 2390 Series Electronic Von Frey Anesthesiometer, Woodland Hills, CA, USA) (13). The tip of the von Frey apparatus was placed one cm adjacent to the center of the incision. It was pressed with a slow, continuous pressure until a response was noted, with a maximal force of 1000 g. A response was considered an acknowledgement that the stimulus was noxious; this included behaviors such as withdrawing from the stimulus, a cry, active head turn to the stimulus, attempt to bite, etc. This measurement was repeated three times at five-minute intervals, and each value was recorded as force in grams. The average value of these three readings was used in the data analysis. At each time point, algometer measurements were also taken from the lateral thoracic wall in the same manner. These measurements, as well as pre-sedation measurements, acted as controls for analysis.

Rescue analgesia protocol

All animals were assessed by the observing veterinarian (CMM), and rescue analgesia (0.5 mg/kg morphine IM) was judiciously given to any animal that achieved a maximum score in any one category of the GCPS, any animal with a pain score of 8 or greater on the GCPS or who did not improve over time as compared to pre-sedation GCPS score, any animal developing aggression, or a combination of these previous factors. Animal handlers at the SPCA also had the opportunity to declare an animal as in pain, based on their observation, and these animals also received rescue analgesia. Administration of rescue analgesia and the reason for administration was recorded, and these animals were included in assessments; see “Blinding, exclusion criteria and statistical analysis”. Any animal receiving rescue analgesia was reassessed 30 minutes later to ensure efficacy of the rescue analgesia administration.

Blinding, exclusion criteria, and statistical analysis

The evaluator (CMM) was blinded to which dog was in which group (i.e. L/B, L/BM or SS) as well as whether a placebo or a study drug was contained in a particular group. The statistician who performed the data analysis remained blinded to which study drug was contained in each group until the analyses were completed.

Initial power calculations were performed, with significance set at 0.05 and power set at 0.8. These calculations indicated we would need approximately 19 dogs in each group to find significant differences in our study populations, assuming a difference of 2.6 on the Glasgow Composite Pain Scale as being significant (14).

The groups were analyzed for equivalence of factors including age, weight, preoperative temperature, heart rate, respiratory rate, BUN, PCV/TS, propofol dose [mg/kg], and time negative one algometric values, by means of one-way ANOVA. Normality of the errors was assessed by visual inspection of a histogram of the errors and a normal probability plot. Errors were considered normal if the histogram was unimodal and approximately symmetrical (15) and the normal probability plot was an upwardly sloping, approximately straight line. Homogeneity of variance was tested by means of a studentized residual vs. means plot. The response variable of treatment groups was analyzed by means of a split plot repeated measures ANOVA with one grouping factor and one repeat factor (time). Those dogs receiving rescue analgesia were analyzed in a similar fashion in two separate analyses: within their collective treatment group and as a separate subgroup. $P < 0.05$ was considered statistically significant.

Results

Twenty dogs of the fifty-nine dogs initially enrolled required rescue analgesia (seven, three and ten dogs in groups L/B, L/BM, and SS, respectively, with no significant differences in the proportion requiring rescue analgesia between groups). Of all the predetermined rescue analgesia criteria, the only criteria triggering administration of rescue analgesia were animals that achieved

a maximum score in any one category (mobility: refusal to move) of the GCPS and animals developing aggression. The majority of the dogs requiring rescue analgesia required it at time 0 (extubation; 18 of 20 dogs), for refusal to move. All fifty-nine dogs were included in the initial analysis. VAS, GCPS, and UMPS analyses showed no significant difference in pain scores between treatment groups, and a significant effect of time on the pain score in both the dogs that did not receive rescue analgesia and the subgroup that received rescue analgesia (data not shown). Algometric values were compared to one of two controls. Whether the value obtained at the wound was compared to the thoracic measurement obtained at the same time or compared to the pre-incisional control reading (i.e. measurement at abdomen / control measure), there was no significant difference in values obtained between treatment groups, and there was a significant effect of time both for dogs who did not receive rescue analgesia and the subgroup that did receive rescue analgesia (data not shown).

VAS, GCPS, and UMPS analyses showed no significant difference in pain scores between treatment groups, and there was a significant effect of time in both the dogs who did not receive rescue analgesia and the subgroup that received rescue analgesia (see figures 1, 2, and 3). With either algometric control variable, there was no significant difference in values obtained between treatment groups, and a significant effect of time both for the dogs who did not receive rescue analgesia and the subgroup that did receive rescue analgesia (see figures 4 and 5).

Discussion

We chose three different groups to test the efficacy of our line block to improve postoperative pain scores and algometric values. One group of animals (L/BM) was selected to receive morphine premedication to serve as the positive control group (i.e. the group anticipated to have the best analgesia). The group of animals that did not receive analgesia (SS) served as the negative control (i.e. the group anticipated as painful). The treatment group of interest, L/B, was evaluated in comparison to these positive and negative controls. The most profound result of our

study was the lack of statistically significant differences between our positive and negative control at any given time point; that is, there was no statistically significant difference between an animal who received no pre-emptive analgesia and an animal receiving a full mu opioid to provide analgesia, using any of the assessment methods. It is fair to call this result shocking for the authors, not only from the perspective of rendering the effects of our treatment mere speculation, but also in the humbling warning this possess for all investigators researching pain in non-verbal species. We would like to discuss a number of potential reasons for the results obtained, in hopes to guide future efforts to research and manage pain.

Study design is critical to successfully identifying targeted outcome. One potential reason no statistically significant difference between pain scores for any treatment group was evident could result from the limited number of dogs included in the study, and thus limited power of our study. A retrospective power analysis was performed using the experimental standard deviations and a power of 0.8, which indicated that we would need eight dogs in each group to achieve significant differences when the level of significance is 0.05. Since each group had at least eight dogs, it suggests that inadequate power was not the problem. However, because we cannot account for Type II error, our statistical analysis is not conclusive. Additionally, we designed this study specifically to maximize the potential for successful pain identification, and thus we included one group that did not receive any preemptive analgesic medication (negative control). This decision was not made lightly, and the criteria were very strict for the use of rescue analgesia because of this. Even in light of this group that was intentionally in, albeit aggressively managed for, pain, there was still no statistically significant difference between this negative control and our positive control group.

It may be that the dogs in this study were experiencing little discomfort, making it difficult to distinguish between the treatment groups. While this may seem unreasonable at face value in regards to an intra-abdominal procedure, pain scores on the only validated scoring

system (GCPS) were very low, never achieving a score of greater than five out of a maximal value of 24 at any one time point. A study evaluating intervention levels using the GCPS suggested "consideration of a clinical decision –point for analgesia gave an intervention score of six of 24", indicating that the GCPSs obtained in the present study were below this threshold (16). With such low pain scores, it is difficult to establish differences between the treatment groups. The low pain scores may have been due to the highly experienced veterinarians who were performing the OVHX and created minimal tissue trauma during surgery (and thus minimal pain associated with the surgery). There is considerable debate about this subject. At least one study suggests experience level of the surgeon was not correlated with a change in postoperative pain score (17). However, recent basic science evidence underscores the importance of deep tissue trauma to the experience of pain (18). Basic science work also supports this on a receptor level; surgical tissue injuries enhanced the membrane translocation of receptors important in post-operative hypersensitivity (19). Surgery performed by experienced surgeons, as was the case in this study, may reduce post-operative pain to levels below our ability to detect.

Another reason for low pain scores on various scales may be due to inherent insensitivity of the measurement techniques, preventing us from seeing a statistically significant difference between positive and negative controls. Surprisingly little work has been performed to produce validated assessment systems for acute pain, with the Glasgow Composite Pain Scale standing out as the most validated scale in this regard (14). However, this scoring system was validated using a variety of surgical procedures, including orthopedic procedures. Additionally, the GCPS has not undergone criterion validation testing. It is possible that a dog undergoing OVHX by an experienced veterinarian may have signs of pain more subtle than this assessment instrument can detect. The von Frey was sensitive to changes in threshold testing with dogs given 1mg/kg morphine (13), and appears reliable in clinically normal dogs (5). However, data gathered by one of the authors (BDXL) found no difference in von Frey thresholds when it was used to assess

wounds being infused with saline or with local anesthetic (20). This suggests that the von Frey may not be the appropriate instrument when assessing sensitivity of clinical wounds. Could testing site make a difference? Perhaps, as previous reports suggest that the canine carpal pad may be the most satisfactory site for testing (13, 21). Because this location was considered unusual for testing sensitivity of an abdominal wound, it was not used for either the control or the test site, which may contribute to the difficulty of using this instrument for assessment. This topic needs further research to understand why the results appear counterintuitive, and to understand appropriate means to assess wound sensitivity.

It may be the assessor (CMM) lacked experience in accurately assessing pain. There is no doubt that expertise of the assessor in regards to pain assessment plays a major role, as evidenced by a single experienced anesthesiologist finding a statistically significant improvement after an incisional block with bupivacaine in dogs undergoing a celiotomy (22). As involved as veterinarians are in the care of animals on a daily basis, it is still possible to misclassify an animal as not in pain for many reasons — including temperament, breed, type of surgery, and surgeon experience. In a study comparing staff observations versus a self-report of pain in young children, staff observations of pain were woefully inadequate (23). However, in some cases such as for animals, there is little alternative to an observer for pain assessment. The negative aspects of such a misclassification are obvious. The inclusion of multiple pain assessment tools with very defined criteria was intended to counter potential inexperience, but cannot negate the possibility altogether. Although the number of animals in the three groups that received rescue analgesia failed to reach statistical significance, the difference between the L/BM group and the SS group (10% vs. 45% treated) is clinically important and suggests that the clinical judgment of when to administer rescue analgesia includes factors that are not captured in the scoring systems that were used.

The effect of time present in this study suggests that we do see changes in pain scale scores and von Frey readings over the course of a 24-hour period. Using subjective pain scores, all values returned to baseline or near baseline by 24 hours, suggesting that we could no longer detect pain effectively at that point. When assessing algometric scores, there was an initial decrease from baseline after extubation, and while values tended to move back towards baseline between 8 and 24 hours, the values never returned to baseline. Together, this suggests wound sensitivity may still be present at a time when it does not seem possible to detect pain using other subjective assessments. An alternative explanation is that the dogs had become behaviorally sensitized to the testing device. Ideally, testing of dogs that were not operated on would have been performed to evaluate the effect of time on threshold readings. Data (24) suggests there is a learned response that decreases thresholds over time in normal dogs, but the data was generated using a more blunt device than the von Frey used in the present study.

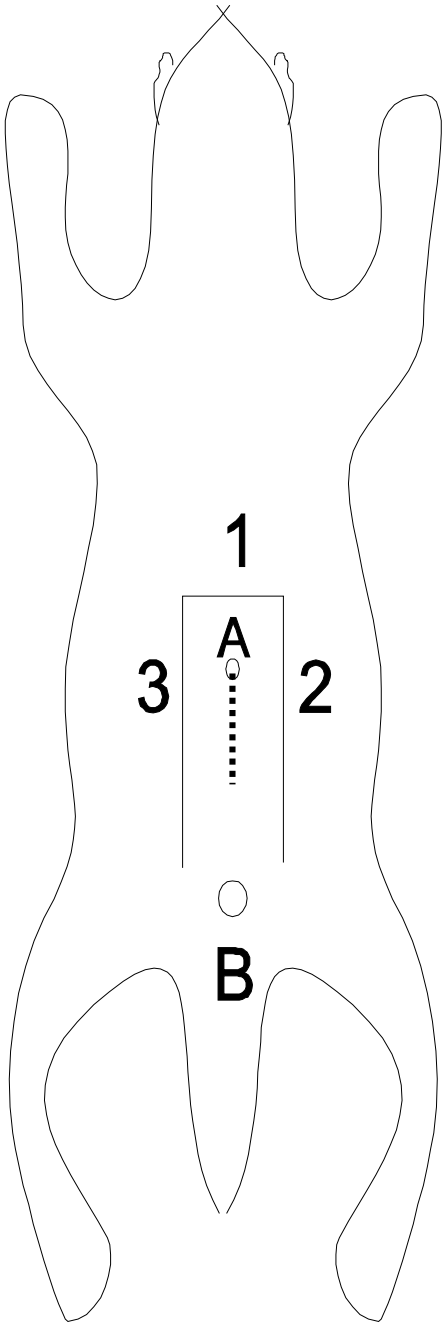
Conclusions

We believe we cannot make firm conclusions about whether or not a line block is effective due to the lack of statistically significant difference between our positive and negative controls. Indeed, the ability to assess pain in non-verbal species even with multiple assessment tools is called into question with the results of this study, necessitating a humble and compassionate approach to pain management in all non-verbal species. No adverse events were documented in this study to suggest that a local anesthetic infiltrative block is harmful to a patient, as opposed to another study examining incisional line block (25). Fitzpatrick et al. (2010) may have seen greater complications because they choose to infiltrate the site of the incision, where as we infiltrated the tissue surrounding the incision. The block took a short time (<2 minutes) to perform. Other studies have found that incisional blocks provide effective analgesia (22, 26).

Our profession must work towards developing more sensitive and specific assessments of pain to evaluate the effectiveness of postulated analgesic interventions, while continuing to provide conscientious therapy knowing we have not yet developed these strategies. It stands to reason that if an experienced observer cannot detect a patient with known pain from one that received adequate analgesia using four different techniques, it is relatively easy to miss a painful patient that cannot self-advocate. If one is inducing something that is likely painful, aggressive pain management is warranted as a moral and ethical obligation.

317 Appendix 1: Site for line block/infiltration of local anesthetic or saline. Please see text for

318 description of labels.



1. Niv D, Kreitler S. Pain and quality of life. Pain Pract. 2001;1(2):150-61.
2. Cambridge AJ, Tobias KM, Newberry RC, Sarkar DK. Subjective and objective measurements of postoperative pain in cats. J Am Vet Med Assoc. 2000;217(5):685-90.
3. Conzemius MG, Brockman DJ, King LG, Perkowski SZ. Analgesia in dogs after intercostal thoracotomy: a clinical trial comparing intravenous buprenorphine and interpleural bupivacaine. Vet Surg. 1994;23(4):291-8.
4. Weber GH, Morton JM, Keates H. Postoperative pain and perioperative analgesic administration in dogs: practices, attitudes and beliefs of Queensland veterinarians. Aust Vet J. 2012;90(5):186-93.
5. Briley JD, Williams MD, Freire M, Griffith EH, Lascelles BD. Feasibility and repeatability of cold and mechanical quantitative sensory testing in normal dogs. Vet J. 2013. Oct 28. pii: S1090-0233(13)00539-X. doi: 10.1016/j.tvjl.2013.10.025. [Epub ahead of print]
6. Skinner HB. Multimodal acute pain management. Am J Orthop (Belle Mead NJ). 2004;33(5 Suppl):5-9.
7. Lascelles BD, Main DC. Surgical trauma and chronically painful conditions--within our comfort level but beyond theirs? J Am Vet Med Assoc. 2002;221(2):215-22.
8. Lascelles BD, Gaynor JS, Smith ES, Roe SC, Marcellin-Little D, Davidson G, et al. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med. 2008;22(1):53-9.
9. Slingsby LS, Murrell JC, Taylor PM. Combination of dexmedetomidine with buprenorphine enhances the antinociceptive effect to a thermal stimulus in the cat compared with either agent alone. Vet Anaesth Analg. 2010;37(2):162-70.
10. Martins TL, Kahvegian MA, Noel-Morgan J, Leon-Román MA, Otsuki DA, Fantoni DT. Comparison of the effects of tramadol, codeine, and ketoprofen alone or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol, and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy. Am J Vet Res. 2010;71(9):1019-26.
11. Fossum TW. Small Animal Surgery. 3rd Edition ed: Mosby; 2007. 1632 p.
12. Firth A, Haldane S. Development of a scale to evaluate postoperative pain in dogs. J Am Vet Med Assoc. 1999;214(5):651-9.
13. KuKanich B, Lascelles BD, Papich MG. Assessment of a von Frey device for evaluation of the antinociceptive effects of morphine and its application in pharmacodynamic modeling of morphine in dogs. Am J Vet Res. 2005;66(9):1616-22.
14. Morton CM, Reid J, Scott EM, Holton LL, Nolan AM. Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. Am J Vet Res. 2005;66(12):2154-66.
15. Petrie A, Watson P. Statistics for Veterinary and Animal Science. Second ed. Oxford, UK: Blackwell Sciences; 2006.
16. Reid J, Nolan A, Hughes J, Lascelles B, Pawson P, Scott E. Development of the short-form Glasgow Composite Measure Pain Scale (GCMP-SF) and derivation of an analgesic intervention score. Animal Welfare. 2007(16(s)):97-104.
17. Wagner AE, Worland GA, Glawe JC, Hellyer PW. Multicenter, randomized controlled trial of pain-related behaviors following routine neutering in dogs. J Am Vet Med Assoc. 2008;233(1):109-15.
18. Xu J, Brennan TJ. Guarding pain and spontaneous activity of nociceptors after skin versus skin plus deep tissue incision. Anesthesiology. 2010;112(1):153-64.

19. Wang Y, Wu J, Guo R, Zhao Y, Wang Y, Zhang M, et al. Surgical incision induces phosphorylation of AMPA receptor GluR1 subunits at Serine-831 sites and GluR1 trafficking in spinal cord dorsal horn via a protein kinase Cgamma-dependent mechanism. Neuroscience. 2013;240:361-70.
20. Hardie EM, Lascelles BD, Meuten T, Davidson GS, Papich MG, Hansen BD. Evaluation of intermittent infusion of bupivacaine into surgical wounds of dogs postoperatively. Vet J. 2011;190(2):287-9.
21. KuKanich B, Lascelles BD, Papich MG. Use of a von Frey device for evaluation of pharmacokinetics and pharmacodynamics of morphine after intravenous administration as an infusion or multiple doses in dogs. Am J Vet Res. 2005;66(11):1968-74.
22. Savvas I, Papazoglou LG, Kazakos G, Anagnostou T, Tsioli V, Raptopoulos D. Incisional block with bupivacaine for analgesia after celiotomy in dogs. J Am Anim Hosp Assoc. 2008;44(2):60-6.
23. Shavit I, Kofman M, Leder M, Hod T, Kozer E. Observational pain assessment versus self-report in paediatric triage. Emerg Med J. 2008;25(9):552-5.
24. Coleman K, Schmeidt C, Kirkby K, Erickson A, Lascelles B, editors. Confounding Factors in Algometric Assessment of Mechanical Thresholds in Normal Dogs. American College of Veterinary Surgeons Veterinary Symposium, 2011; Chicago, Il.
25. Fitzpatrick CL, Weir HL, Monnet E. Effects of infiltration of the incision site with bupivacaine on postoperative pain and incisional healing in dogs undergoing ovariohysterectomy. J Am Vet Med Assoc. 2010;237(4):395-401.
26. Carpenter RE, Wilson DV, Evans AT. Evaluation of intraperitoneal and incisional lidocaine or bupivacaine for analgesia following ovariohysterectomy in the dog. Vet Anaesth Analg. 2004;31(1):46-52.

Figure 1

Figure 1.

Visual Analogue Scale (VAS), from 0-10 centimeters, prior to premedication (time -1), extubation (time 0), and 2, 4, 6, 8 and 24 hours post-operatively. Note: L/B received saline premedication and local anesthetic line block, L/BM received morphine premedication and a local anesthetic line block, and SS received a saline premedication and saline line block.

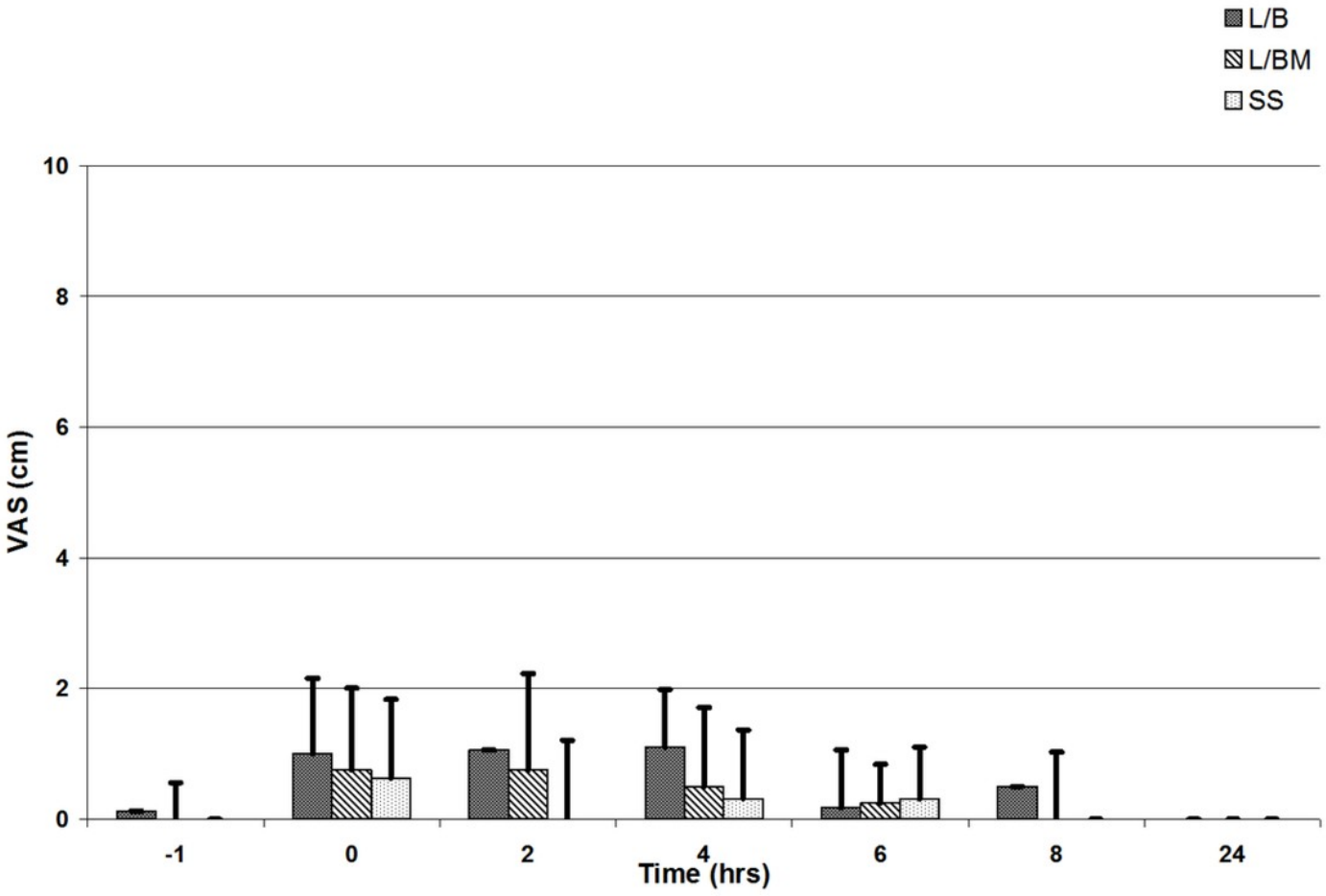


Figure 2

Figure 2

Glasgow composite pain scale (GCPS) scores from 0 to 24 prior to premedication (time -1), at extubation (time 0), and 2, 4, 6, 8 and 24 hours post-operatively. Note: L/B received saline premedication and local anesthetic line block, L/BM received morphine premedication and a local anesthetic line block, and SS received a saline premedication and saline line block.

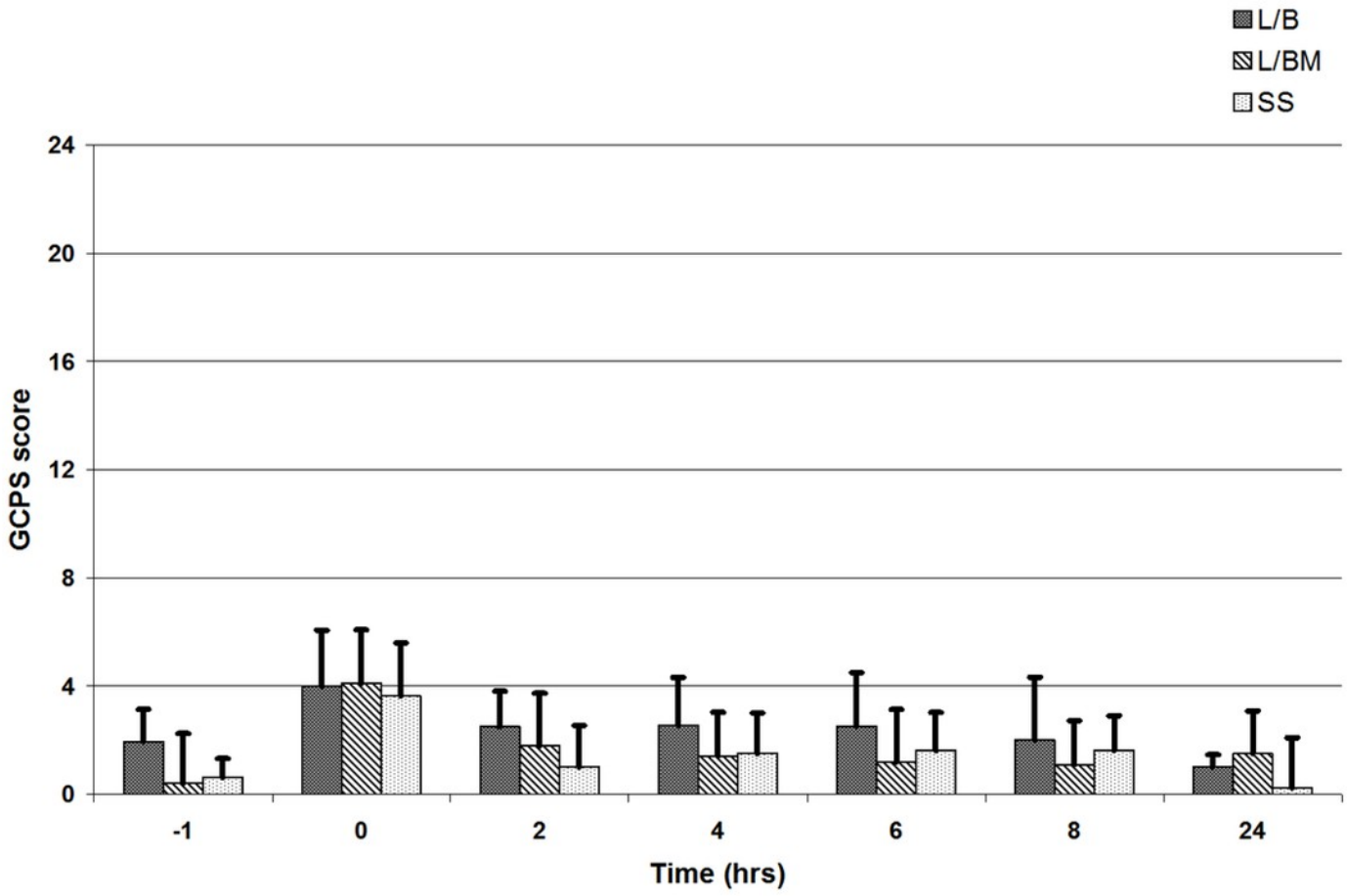


Figure 3

Figure 3

University of Melbourne Pain Scale scores from 0 to 27 prior to premedication (time -1), at extubation (time 0), and 2, 4, 6, 8 and 24 hours post-operatively. Note: L/B received saline premedication and local anesthetic line block, L/BM received morphine premedication and a local anesthetic line block, and SS received a saline premedication and saline line block.

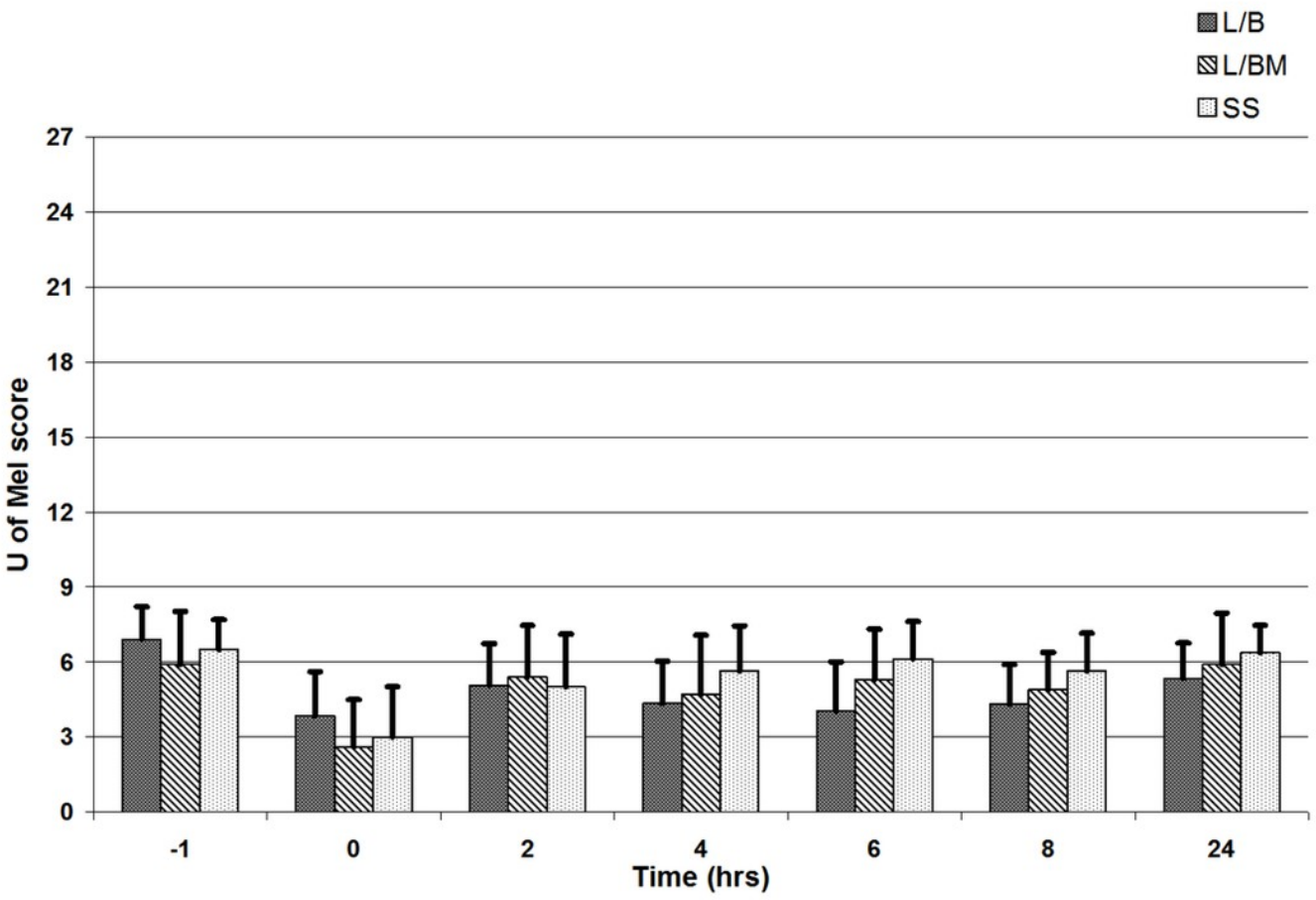


Figure 4

Figure 4

Algometric value, depicted as a ratio compared to the value obtained at the abdomen versus the value obtained at the thorax at the same time points: at premedication (time -1), at extubation (time 0), and at 2, 4, 6, 8 and 24 hours post-operatively. Note: L/B received saline premedication and local anesthetic line block, L/BM received morphine premedication and a local anesthetic line block, and SS received a saline premedication and saline line block.

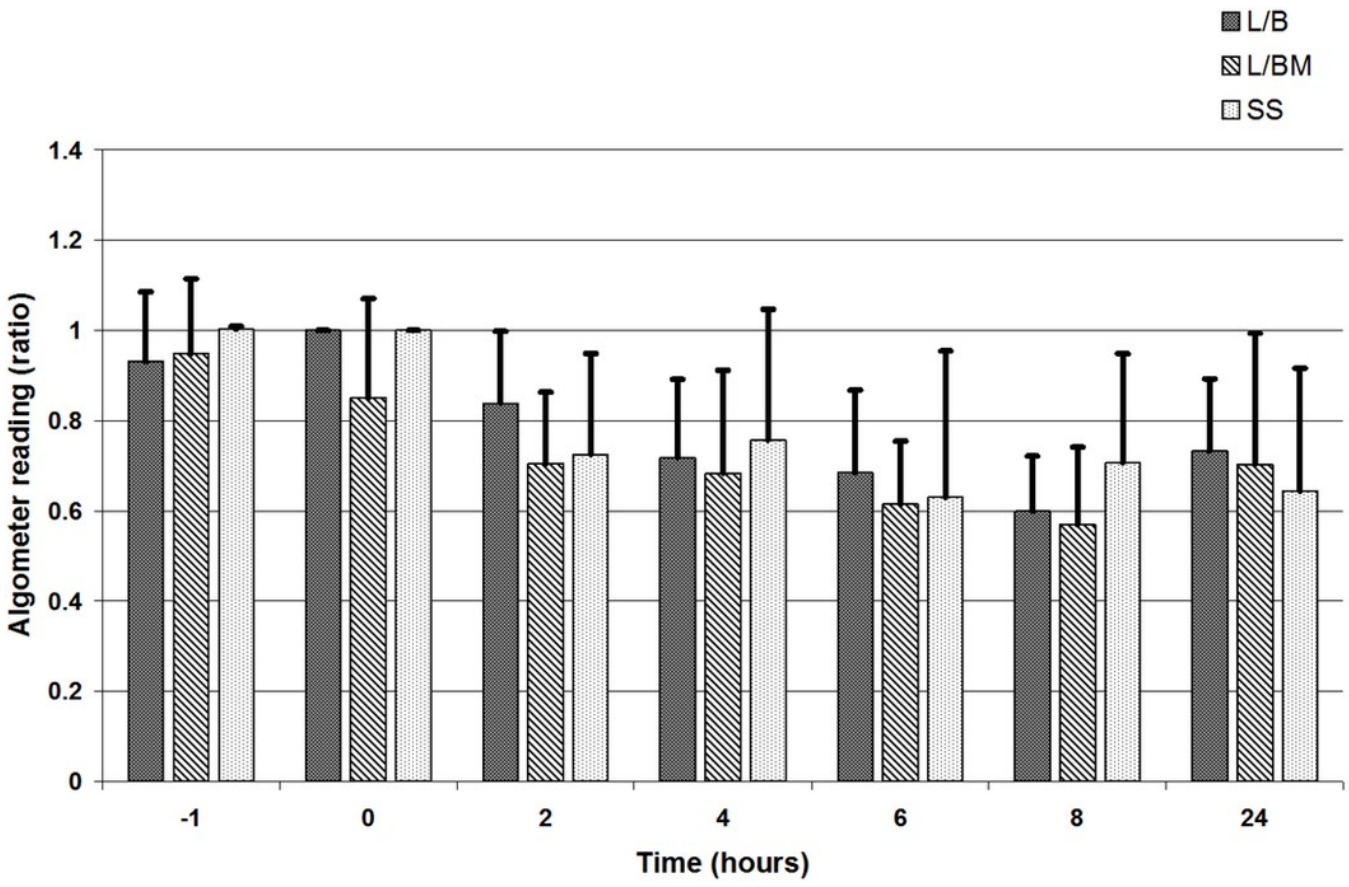


Figure 5

Figure 5

Algometric value, depicted as a ratio comparing the value obtained at each individual time point to values obtained at the abdomen prior to premedication (i.e. time, but not location, is the dependent variable). Time points for comparison to pre-medication values include pre-medication (time -1), extubation (time 0), and 2, 4, 6, 8 and 24 hours post-operatively. Note: L/B received saline premedication and local anesthetic line block, L/BM received morphine premedication and a local anesthetic line block, and SS received a saline premedication and saline line block.