Original Article

Use of mechanical thresholds in a model of feline clinical acute pain, and their correlation with the Glasgow Feline Composite Measure Pain Scale scores.

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Abstract

Objectives

To evaluate the use of mechanical thresholds (MT), measured with the SMALGO, to measure pain, and to determine whether there was a correlation between MT and Glasgow Feline Composite Measure Pain Scale (CMPS–Feline) scores in cats undergoing spay surgery.

Methods

Client-owned cats undergoing flank ovariectomy were recruited. Pre- and postoperative pain scores were obtained using the CMPS-Feline scale in each cat by two independent investigators (A and B). MT were measured with the SMALGO, in the surgical area, pre- and postoperatively, only by investigator A. Each cat served as its own control for comparison of pre- and postoperative variables. Reliability statistics were used to assess the level of inter-observer agreement (A versus B) with respect to pre- and postoperative CMPS-Feline scores, while Spearman's Correlation statistics were used to analyse the relationship between MT and CMPS-Feline scores.

Results

Twenty-nine cats completed the study. Preoperative MT (340 [108–691] g) were significantly higher than postoperatively (233 [19–549] g; $P = 0.001$). Whereas for CMPS-Feline scores, there were no significant differences between preoperative (2 [0–7] for investigator A and 3.2 ± 2.3 for investigator B) and postoperative (2 [0–10] for investigator A and 3 [0–8] for investigator B) for either investigator. Reliability statistics revealed that the level of inter-observer agreement with respect to CMPS-Feline was fair for the preoperative assessments, but poor for the postoperative evaluations. There was no correlation between MT and CMPS-Feline scores.

Conclusions and relevance

Although they did not correlate with pain scores, MT increased postoperatively. Assuming that, despite analgesia, susceptibility of the surgical area to mechanical stimulation would increase after surgery, this finding suggests that MT might be useful to assess feline surgical pain. The poor level of inter-observer agreement with respect to postoperative CMPS-Feline scores highlights the potential limitations of this scale.

Introduction

Pain assessment is notoriously challenging in cats. Underestimation of feline pain is perceived as a relevant clinical problem as it is likely to result in insufficient provision of analgesia, and therefore suboptimal patient care.[1]

As a result, various methods aimed at evaluating and measuring pain have been developed for cats and investigated over time. With regards to acute pain scoring systems, scales such as the Glasgow Feline Composite Measure Pain Scale (CMPS-Feline), the UNESP-Botucatu multi-dimensional composite pain scale (UNESP-Botucatu MCPS), and the Colorado State University Feline Acute Pain Scale (CSU-FAPS) have been developed and validated.[2-7] Whilst they are commonly used and are seemingly simple to perform, there is an inherent degree of subjectivity when using them. One of their limitations is that they rely on behavioural indicators, namely posture, facial expressions, and reaction to stroking/palpation that can be affected by fear and anxiety, especially when the cats are assessed in an unfamiliar environment such as the veterinary hospital. In recent years, the use of the CMPS-Feline scale has increased in small animal practice in the UK, and nowadays it is commonly regarded as a useful and reliable tool to detect and address inadequate postoperative analgesia.

Quantitative sensory testing techniques have been investigated in cats as a complementary tool for pain assessment, attempting to reduce the level of intra- and inter-assessor variability and therefore provide a higher degree of objectivity.[8-11] Sensory mechanical thresholds (MT) are obtained by applying and measuring either a force or a pressure on a targeted area of the body of the animal until a specific, predefined behavioural response is observed. Various mechanical algometers have been used in feline experimental and clinical models.[8-12]

Among these, the SMall Animal ALGOmeter (SMALGO; Bioseb, France) was originally developed for use in laboratory rodents. In both healthy cats and cats with chronic pain, the SMALGO has been shown to give repeatable results from users with different background and degree of expertise in pain

assessment, although, in cats with chronic gingivostomatitis, the MT measured with this device did not correlate with the severity of the disease.[8] To the best of the authors' knowledge, the SMALGO has yet to be investigated in a model of feline acute pain.

Ovariectomy is one of the most common surgical procedures performed routinely in cats in the UK.[13] Since most cats are presumably non-painful before spay surgery is performed, ovariectomy may be regarded as a suitable model of acute pain in otherwise healthy cats. Reliable and objective assessment of acute pain would result in prompt and targeted administration of rescue analgesics in cats undergoing spay surgery. It is the authors' belief that this could improve quality of care and welfare for a large number of cats worldwide.

The primary objective of this study was to evaluate the use of the SMALGO as a method to quantify pain in cats undergoing routine spay, and to determine whether MT would change after surgery. The secondary objective was to assess for correlation between MT measured with the SMALGO and the scores obtained with the CMPS-Feline, both preoperatively and postoperatively.

It was hypothesised that MT would decrease after surgery while the CMPS-Feline scores would increase, and that there would be an inverse correlation between the two variables both preoperatively and postoperatively.

Materials and Methods

Ethical Approval

The study was conducted with permission from the Clinical Research Ethical Review Board (CRERB) of the Royal Veterinary College (license number: URN 2019 1909–3; approval date: September 25, 2019). Written informed consent was obtained from the owner of each cat before enrolment in this study.

Study design

The study was designed as a prospective clinical trial. Client-owned female cats presenting to a primary care practice (Medivet 24 Hour Hendon, London, UK) for routine flank ovariectomy were recruited for the study. Exclusion criteria were cats younger than six months or older than three years, previous diagnosis of neurological conditions that may alter the physiology of pain transmission and perception, aggressive behaviour or poor tolerance to handling, and any analgesic treatment that may increase the MT and/or alter behavioural pain scores.

The study variables were pre- and postoperative CMPS-Feline scores and pre- and postoperative MT. All data were collected by two experienced and trained registered veterinary nurses (Investigator A and Investigator B). After admission to the hospital, each cat was moved to a kennel and allowed an acclimatisation period of at least 15 minutes, so they could get used to the new environment and the presence of the investigators before the beginning of the assessments. Investigators A and B both used, independently and blinded to each other's score, the CMPS-Feline to derive a baseline preoperative score which was then recorded. Each investigator's assessment of the cat and the score they derived was blinded from the other. Thereafter investigator A, who had been previously trained by the authors (DN and CA), measured the MT with the SMALGO (SMALGO, Bioseb, France) in each cat. MT were measured as follows: the sensitive probe of the SMALGO was equipped with the 3 mm tip and the unit "g" (grams) selected. Thereafter, the control unit was zeroed and the key "max" pressed, to enable storage and recording of the maximum force value applied during the probe application. With the cats in standing position, the SMALGO probe was then applied perpendicular to the skin of the left flank, 1 cm caudal to the middle of the surgical incision (Figure 1), with a steadily increasing force, until either a behavioural response was observed, or the maximal force was reached. Vocalisation, head turning towards the stimulation site, back muscle contraction, hissing, and attempting to bite, scratch, or escape were considered positive behavioural responses. The maximal cut-off force was set at 400 g based on previous studies.[9] The force measured was recorded as MT.

After the preoperative assessments, cats were premedicated with intramuscular medetomidine (Sedator, Dechra, UK; 0.01 mg/kg) and buprenorphine (0.03 mg/kg, Vetergesic; Ceva Animal Health, UK) before placement of an intravenous catheter. Anaesthesia was then induced with intravenous propofol (PropoFlo, Zoetis, UK), titrated to effect, before maintenance of anaesthesia with inhalational isoflurane (IsoFlo, Zoetis, UK) in 100% oxygen, delivered via an Ayre's T-piece non-rebreathing breathing system connected to an appropriate size endotracheal tube. Ovariectomy was then performed by a board-certified veterinary surgeon via a left sided flank approach. Intravenous meloxicam (0.2 mg/kg, Metacam; Boehringer Ingelheim Animal Health UK) was given post-operatively to each cat, at the end of the anaesthetic after endotracheal extubation.

Postoperative assessments were performed when the cats had fully recovered from general anaesthesia, shortly before they were discharged from the hospital. Postoperative assessments were performed in the same manner as preoperative: CMPS-Feline by investigators A and B, independently, and MT measured by investigator A. Intervention level for re-evaluation of the postoperative analgesic plan by a veterinary surgeon was set at score of 5/20 or higher, as assessed by both investigators, of the CMPS-Feline scale.[2] Cats with a score of 5 or greater received, as rescue analgesia, methadone (Comfortan, Dechra, UK; 0.2mg/kg IV) every 4 hours for 12-18 hours based of pain score and were discharged the day after surgery.

Statistical methods

The sample size was calculated separately for the two different aims of the study. In order to detect a difference between preoperative and postoperative MT with either a paired T-test or the non-parametric Wilcoxon Signed Rank test, the expected difference in means (preoperative – postoperative values) was set as 100 g, with expected standard deviation of 100 g, desired power of 0.9 and alpha as 0.05. This calculation indicated 23 as the minimum number of subjects to be included in the study. A second calculation was performed with the purpose of investigating the relationship between the variables MT and CMPS-Feline score. Variables were set as follows: α value: 0.05; power: 0.8; ß value: 0.2; type of test: two-sided test;

standard normal deviate for α (Zα): 1.960; standard normal deviate for ß (Zß): 0.842; expected correlation coefficient r: -0.5.[14] This resulted in a minimum number of subjects equal to 29. Data distribution was analysed with both the Kolmogorov-Smirnov and the Shapiro-Wilk tests. The non-parametric Wilcoxon Signed Rank test was used for paired comparison of preoperative and postoperative MT.

Reliability statistics were used to analyse the level of inter-observer agreement between investigators A and B, which was scored as follows: Intraclass Correlation Coefficient (ICC) <0.40 = poor agreement; ICC between 0.40 and 0.59 = fair agreement; ICC between 0.60 and 0.74 = good agreement; and ICC between 0.75 and 1 = excellent agreement.[15]

Spearman's Rank Order Correlation statistics were used to determine the relationship between MT, following logarithmic (base-10) transformation, and demographic variables (age, body weight and BCS), and between MT, following logarithmic (base-10) transformation, and CMPS-Feline scores.

Commercially available statistical software (SigmaStat 3.5, Systat Software, CA, USA and IBM SPSS Statistics 26), as well as a validated on-line calculator from the Clinical & Translational Science Institute of the University of California (https://sample-size.net/correlation-sample-size/) were used.[16] *P*-values <0.05 were considered statistically significant.

Results

Data are presented as either means and standard deviations, or medians and ranges [min-max], depending on data distribution.

Data were collected between November 2019 and June 2020. Twenty-nine cats were included in the study; they were 10 [6–26] months old, weighed 3.1 ± 0.5 kg, and had a Body Condition Score (BCS) of 4 [3–5]/9. Surgery and anaesthesia were unremarkable for all cats. Three cats had a postoperative CMPS-Feline of 5 or higher assigned by both investigators. These cats remained hospitalised and were given rescue analgesia as per the study design protocol.

Preoperative MT (340 [108–691] g) were significantly higher than postoperative MT (233 [19–549] g; P = 0.001; Figure 2), whereas there were no statistically significant differences between preoperative (2 [0–7] for investigator A and 3.2 ± 2.3 for investigator B) and postoperative (2 [0–10] for investigator A and 3 [0–8] for investigator B) CMPS-Feline scores, for either investigator (P = 0.94 and P = 0.90 for investigators A and B, respectively; Figure 3). Cats assigned a preoperative CMPS-Feline score greater than 5 were assessed by a veterinary surgeon and deemed to be non-painful.

Reliability statistics revealed that the level of inter-observer agreement between investigators A and B for CMPS-Feline was fair for the preoperative assessments (ICC = 0.545; 95% Confidence Interval: 0.03–0.79), but poor for the postoperative evaluations (ICC = 0.312; Confidence Interval: -0.47–0.68).

No statistically significant correlations were detected between preoperative MT and CMPS-Feline scores obtained by either investigator (A: Correlation Coefficient (CC) = 0.038; P = 0.843, and B: CC = -0.08; P = 0.663), between postoperative MT and CMPS-Feline scores obtained by either investigator (A: CC = 0.02; P = 0.920, and B: CC = 0.25; P = 0.188) (Figure 4), or between MT and demographic variables, namely age (CC = -0.05; P = 0.69), body weight (CC = -0.10; P = 0.45), and BCS (CC = -0.23; P = 0.07).

Discussion

The findings of this study were that MT decreased postoperatively, although they did not correlate with the pain scores in cats undergoing routine spay, and that the level of agreement of two experienced nurses with respect to the postoperative CMPS-Feline score was unexpectedly poor.

Our hypothesis that MT would decrease postoperatively was confirmed, which was the primary objective of this study. The changes in MT in the study cats were similar to that of a previous study, in which a novel mechanical algometer was applied to the user's index finger and used to measure MT in male cats undergoing castration.[10] Although adequate analgesia is expected to increase MT, it is reasonable to assume that cats who underwent surgery would have increased sensitivity at touch and pressure applied to the

surgical area, and therefore their postoperative MT would still be lower than preoperative values, even when pain therapy is provided. The decrease in MT after surgery was interpreted as a sign of pain in the study cats, although decreased tolerance to mechanical stimulation, which has been described in cats after repeated testing, cannot be completely excluded. The concern for decreased tolerance after repetition of testing was the reason why, when the study was designed, it was decided that only one of the investigators would measure MT, in order to decrease the number of measurements for each cat. In a previous study, however, the effect of repetition was only seen after more than two testing sessions within time intervals shorter than 45 minutes.[9] This did not apply to the cats of the current study that were evaluated twice with several hours elapsing between measurements.

As MT are expected to correlate with the actual degree of pain, the authors hypothesised that the study cats would show some degree of correlation with the scores of the CMPS-Feline, a recognised and validated scale to assess acute pain in cats. However, this hypothesis was disproved as CMPS-Feline scores were not found to correlate with MT values. This could be due to lack of validity of either MT, or CMPS-Feline scores, or both, as tools for the assessment of feline pain after surgery. The unexpectedly poor level of agreement between the two investigators with respect to postoperative CMPS-Feline scores, however, raises some concerns regarding the repeatability and objectivity of assessments when this scale is used.

One possible explanation for this finding is that there is some degree of inherent subjectivity within the CMPS-Feline scale. Although the investigators involved were both experienced registered veterinary nurses, who are familiar with the use of the CMPS-Feline scale, it is still possible that the subjectivity of the scale lead to results inconsistent with the degree of pain the cats were experiencing. Part of this subjectivity has to do with how literally the wording in the scale is taken by the examiner. To corroborate this theory, one of the study cats was assigned preoperative CMPS-Feline scores of 6 and 0 by investigators A and B, respectively. The cat was vocalising very often but intermittently, a behaviour that investigator A scored by literally compiling the scale; she therefore assigned a score of 1 and 2 to questions 1 and 6 of the

CMPS-Feline. Investigator B, who presumed the cat was not in pain, despite having observed the cat vocalising, chose to answer the same questions based on the time in which the cat was intermittently silent, and assigned therefore a score of 0 to both questions 1 and 6. As a result, the CMPS-Feline scores assigned independently by the two investigators for this same pain-free cat were very different. This may have been the case for other cats with preoperative CMPS-Feline scores greater than six, which should be not possible for presumably non-painful cats. The CMPS-Feline does not allow for differentiation between behaviours indicative of fear or anxiety, and pain. Behaviours such as cowering at the back of the kennel or growling at the examiner, which can be caused by either stress/anxiety or pain, add points to the overall scale, which may reach moderate scores even in a patient who is non-painful but is uncomfortable in the hospital setting. As an attempt to avoid the inclusion of anxious and fearful cats, aggressive behaviour and poor tolerance to handling were listed among the exclusion criteria. Nevertheless, it is possible that some study cats who were deemed non-fearful on admission to the practice developed anxiety later, after separation from their owner, a drawback that could have affected CMPS-Feline scoring. One way in which this could be prevented in future studies would be the utilisation of a habituation periods longer than 15 minutes for the cats to settle into their new environment before assessment. However, this may be uneasy to achieve in busy clinical practices. Therefore, the limitations of the CMPS-Feline when used in fearful and anxious cats likely represent issues commonly seen in clinical practice.

In order to draw more solid conclusions regarding the use of validated pain scales and their correlation with MT in a model of acute surgical pain, one possible strategy could be to increase the number of assessors, and possibly include other validated scales, such as UNESP-Botucatu, in the study protocol.[4] Nevertheless, increasing assessor numbers would have been challenging in this study whilst maintaining the intense workflow of a busy practice. Moreover, for the reasons mentioned earlier in this manuscript, increasing the number of MT measurements would not improve reliability.

During this study, the SMALGO was found to be simple to use by the investigator and did not become broken or damaged at any point during its use or storage. These factors are to the SMALGO's benefit in being used in a busy clinical practice setting, where robust nature and intuitive design are key features to ensure integration into pain assessment.

Conclusions

The SMALGO may have potential applications as a tool for assessment of acute postoperative pain in cats. However, the lack of correlation between MT and CMPS-Feline scores in this study, as well as the poor inter-observer agreement with respect to postoperative CMPS-Feline scores, seem to suggest that more prospective studies are needed to improve the methods of pain assessment in cats, and to clarify the role of mechanical testing in measurement of feline acute pain.

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A licence covering the use of the CMPS-Feline for non-commercial purposes (research) was obtained from NewMetrica prior to use for this study.

Conflict of interest

The authors declare no conflict of interest in the design, execution, or publication of this study.

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Ethical approval

The work described in this manuscript involved the use of non-experimental (owned or unowned animals) and procedures that differed from established internationally recognised high standards ('best practice') of

258 veterinary clinical care for the individual patient. The study therefore had prior ethical approval from
259 established (or ad hoc) committee as stated in the manuscript.

260 **Informed consent**

261 Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s)
262 described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s)
263 undertaken (prospective or retrospective).

264 No animals or people are identifiable within this publication, and therefore additional informed consent for
265 publication was not required.

266 **Figure Legends**

267 **Figure 1**

268 Diagram of a cat demonstrating the positioning of the Small Animal Algometer (SMALGO) probe for
269 mechanical threshold (MT) testing in this study. The application site was 1cm caudal to the middle of the
270 surgical incision area, on the left flank.

271 **Figure 2**

272 The box plots represent the mechanical thresholds (MT), measured with the Small Animal Algometer
273 (SMALGO) preoperatively and postoperatively by two independent investigators (A and B), in 29 female
274 cats undergoing spay surgery. The upper and lower quartiles (interquartile range box) represent the data
275 greater (25%) and lesser (25%) than the median, respectively, accounting for 50% of the total data. The
276 whiskers represent the ranges for the bottom 25% and the top 25% of the data values. The dots represent
277 the outliers.

278 **Figure 3**

279 The box plots represent the Glasgow Feline Composite Measure Pain Scale (CMPS-Feline) scores obtained
280 preoperatively and postoperatively, by two independent investigators (A and B), from 29 female cats
281 undergoing spay surgery. The upper and lower quartiles (interquartile range box) represent the data greater

(25%) and lesser (25%) than the median, respectively, accounting for 50% of the total data. The whiskers represent the ranges for the bottom 25% and the top 25% of the data values. The dots represent the outliers.

Figure 4

Scatterplot representing the correlations between the Glasgow Feline Composite Measure Pain Scale (CMPS-Feline) scores and mechanical thresholds (MT) measured with an algometer. Assessments were performed preoperatively (preop) and postoperatively (postop), by two independent investigators (A and B), in 29 female cats undergoing spay surgery.

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