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Inter- and intra-observer reliability of quantitative sensory testing performed with the SMall animal ALGOmeter (SMALGO) to evaluate pain associated with feline gingivostomatitis

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Abstract

Objectives To evaluate the inter-observer and the intra-observer reliability of quantitative sensory testing performed with the SMALGO (SMall animal ALGOmeter) in healthy cats and in cats with chronic gingivo-stomatitis (CGS), and to evaluate the SMALGO as a tool to detect and quantify pain in cats with CGS.

Methods Thirty cats of a private shelter were included in this study, and assigned to one of two groups: group C (healthy cats; n = 15) and group CGS (cats with chronic gingivo-stomatitis; n = 15). In all cats the mechanical thresholds were measured with the SMALGO, with the sensor tip applied on the superior lip above the canine root, by two independent investigators (A, experienced, and B, unexperienced), on two different occasions (day 1 and day 2) with a 24 hour-interval. A CGS scale was used in the diseased cats to assess the severity of the condition. For the reliability analysis, the intra-class correlation coefficients (ICC) were calculated. Other statistical tests used were Pearson correlation coefficient and paired T-test.

Results The inter-observer and intra-observer levels of agreement were fair (ICC = 0.50) and good, respectively (ICC = 0.73 for investigator A and ICC = 0.60 for investigator B). However, the thresholds measured in healthy cats (169 ± 59 g) did not differ from those obtained from diseased cats (156 ± 82 g; P = 0.35). There was no correlation between the scores of the CGS scale and the thresholds measured in diseased cats (Pearson correlation coefficient = 0.047; P = 0.87).

Conclusions and relevance Quantitative sensory testing performed with the SMALGO in cats are repeatable and reliable regardless the expertise of the investigator. However, the findings of this study suggest that the mechanical thresholds measured with the SMALGO may not be a valuable indicator of pain in cats with CGS.

Introduction

The feline chronic gingivo-stomatitis (CGS) is a severe inflammatory disease of the oral cavity that can affect cats of every age. It differentiates from gingivitis in the fact that inflammation extends not only to the mucogingival junction, but also to the oral mucosa.[1]

The condition may involve different areas such as gingiva, alveolar mucosa, fauces, pharynx, tongue, palate and labio-buccal and caudal oral mucosa.[2] It is characterised by pain, swollen, ulcerated or bleeding gums, hypersalivation, halitosis, anorexia, dysphagia, weight loss and enlarged submandibular lymph nodes, and it can severely affect the quality of life of the affected cats, as well as their behaviour.[3,4] The prevalence of the disease is high, accounting for the 0.7 - 12% of the cats in the United States.[1] Although the exact ethiology of FCGS is still unknown, it is widely recognised that many factors, namely environmental factors, dental disease, various bacterial and viral infections, immune response and stress, contribute to its development.[3-5]

Cats with CGS are very likely to experience pain. Unfortunately, pain can easily go underdiagnosed in feline patients, and quantifying pain in cats can be extraordinarily challenging even for the most experienced veterinarian.[6,7] The scales currently available to evaluate pain in cats have been developed to assess acute surgical pain, and may not be adequate to evaluate chronic, non-surgical conditions.[8,9] Therefore, there is a need for valid and reliable methods to detect and measure chronic pain in cats.

Quantitative sensory testing (QTS) is a semi-quantitative method to assess dysfunctions of the sensory system, and the use of mechanical thresholds has been described in cats,[10-15] also to evaluate chronic pain.[15] Various pressure algometers have been designed for use in animals within the last two decades, of which two were specific for cats.[11,12]

The SMall animal ALGOmeter (SMALGO, Bioseb, France) is a pressure-based algometer designed for measuring allodynia and hyperalgesia in laboratory rodents.[16] The device has also been also used to evaluate chronic and neuropathic pain in small animals,[17] and to perform QTS in dogs with osteoarthritis.[18] The first reports in small-sized companion animals seem to suggest that the SMALGO may be a useful tool to measure various types of pain in clinical feline patients.[14]

If the measurement of mechanical thresholds with the SMALGO could be proven to be an effective tool for the assessment of CGS-associated pain, this finding may potentially represent a step forward in the recognition and management of feline chronic pain.

The primary objectives of this study were therefore the following:

- To evaluate the inter-observer and intra-observer reliability of QST performed with SMALGO in healthy cats and in cats with CGS;
- To determine whether the SMALGO would be a useful tool to differentiate, on the basis of the mechanical sensory thresholds, between healthy cats and cats with CGS.

A secondary objective of this study was to determine whether there was any association between the mechanical thresholds measured with the SMALGO and the scores of a CGS scale, developed by the authors based on previous publications,[19,20] to evaluate the severity of the clinical condition in cats.

We hypothesized that the SMALGO would provide reliable and repeatable measurements of the sensory thresholds, regardless the level of expertise of the investigator, and that the thresholds measured in cats with CGS would be lower than those obtained from healthy cats.

Materials and methods

Ethical approval

The study was conducted with permission of the Clinical Research Ethical Review Board of the Royal Veterinary College (license number: URN 2017 1709-3). A written informed consent was obtained by the owner of the cat shelter prior to commencing the trial.

Animals and determination of sample size

Thirty rescued cats of a private cat shelter (Associazione di Promozione Sociale Amici di Poldo, Udine, Italy) were enrolled in this study.

Based on medical history and physical examination, performed by the veterinarian in charge for routine medical procedures in the shelter, the cats were assigned to one of two groups: group CGS (cats with chronic gingivo-stomatitis) and group C (control: healthy cats). Each group was composed of 15 subjects. Exclusion criteria were presence of other systemic disease or condition other than CGS potentially associated with pain, recent admission to the shelter that would have resulted in limited medical history, administration of analgesics or other medication that could potentially have influenced the assessments, and fractious behaviour. All the cats included in the study were comfortable with the human presence and were used to be handled.

The sample size was based on a calculation performed with a program available on line (https://www.stat.ubc.ca), with the following setting of variables: mean mechanical thresholds of cats of group CGS = 100 g; mean mechanical thresholds of cats of group C = 150 g (50% more of diseased cats); SD = 50 g; α value = 0.05; power = 0.80. This resulted in a minimal number of cats to be included in the trial equal to 13, similarly as reported in previous studies that evaluated the use of QST in dogs with osteoarthritis, in which the sample size was calculated based on pilot data.[18]

Diagnosis of chronic gingivo-stomatitis

Beside the physical examination and a detailed revision of the medical history, a scale developed by the authors was used to discriminate between healthy and diseased cats, to confirm group assignment and to quantify the severity of the clinical condition (CGS scale; Table 1). This scale was derived from two previously published scoring systems, adjusted to match the specific research setting and melded together: the "Feline Chronic Gingivo-Stomatitis Veterinary Surgeon's Questionnaire" and the scale developed by Lommer to evaluate the degree of buccal inflammation in cats with chronic stomatitis.[19,20] Some descriptors of both scales that were considered by the investigators unfeasible in the non-sedated cats, for example the stomatitis index that is part of the original scale from Lommer, were excluded. The total score of the CGS scale used in the current study ranged from 0 to 24. One of the investigators (HM) completed the scale with the help of the shelter volunteers, who fed and handled the cats routinely.

Measurements

The measurements were carried out in an area of the shelter the cats were familiar with, and were they normally spent most of their time, free to roam. An acclimatisation period of 15 minutes was allowed before the beginning of the trial so that the cats could get used to the presence of the investigators. Additionally, one of the volunteers of the shelter with whom the cats were very familiar was present during each measurement, in order to try to minimize the stress related to handling.

During the acclimatisation, the SMALGO was prepared and checked for accuracy as follows: the sensitive probe was equipped with the 3 mm tip and the unit selected (g). Thereafter,

the control unit was zeroed and the key "max" pressed, to enable the algometer to store the maximum force value recorded during the measurement.

During the measurements, the cats were allowed to choose the most comfortable position for them (either sitting or standing), and were minimally restrained in order to minimise the stress. The sensor tip of the SMALGO was applied on the right superior lip, at a level right above the canine root, of each cat, with a steady increasing force until a positive behavioural response was elicited; at that point, the sensor tip was removed and the last force measured was recorded as threshold. In this study vocalization, head withdrawal/turning, hissing or growling, attempt to escape and/or aggression/attempt to bite were defined as positive behavioural responses. In each cat, the measurements were carried out by two investigators with different level of expertise in pain assessment: a resident in Veterinary Anaesthesia and Analgesia (investigator A: HM) and a medicine student with no previous experience in pain evaluation in animals (investigator B: SP).

For each cat, the investigator who started the measurements was chosen randomly by flipping a coin. Each investigator obtained three threshold values from every cat included in the study; a minimal interval of 30 seconds was allowed between subsequent measurements carried out by the same investigator, in order to avoid temporal summation.[21] The means of the three measured values were used for statistical analysis. One hour-break was allowed before the second investigator could commence the measurements in the same cat. The entire trial was repeated after 24 hours, with an inverted order of the investigators compared to the previous day.

Statistical analysis

158 Data were analysed with commercially available software (IBM SPSS Statistics 24, IBM
159 Corporation, NY, USA; and SigmaPlot 10 and SigmaStat 3.5, SYSTAT Software Inc, CA, USA).
160 P values < 0.05 were considered statistically significant.

161 Data distribution was analysed with the Shapiro-Wilk test. Paired t-test was used to assess
162 normality of the data.

163 The intra-observer and the inter-observer reliability were assessed by calculating the intra-
164 class correlation coefficient (ICC), with a two-way mixed Cronbach's Alpha model and 95%
165 confidence intervals (CI; upper and lower bounds); the type of agreement selected was absolute
166 agreement. The level of agreement (both inter- and intra- observer) was scored as follows: ICC <
167 0.40= poor; ICC between 0.40 and 0.59= fair; ICC between 0.60 and 0.74= good; and ICC between
168 0.75 and 1= excellent.[22]

169 A paired-T test was used to compare the thresholds measured in the two groups of cats
170 (healthy versus diseased). The Pearson Correlation Coefficient was calculated to identify any
171 correlation between the mechanical sensory thresholds measured with the SMALGO and the
172 scores of the CGS scale.

173

174 **Results**

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

177 Thirty cats, of which 14 were spayed females and 16 neutered males, completed the trial.
178 Their estimated age ranged from 1 to 18 years old and their body weight was 4 [3-5] kg. Of the 15
179 cats with CGS, 6 were FELV and FIV positive.

The mechanical sensory thresholds were normally distributed when each set of measurements was analysed separately; however, data distribution was not normal when all the values were pulled together. The score of the CGS obtained from the diseased cats was 7 [3-12].

The inter-observer reliability was fair (ICC = 0.50), whereas the intra-observer reliability was good for both investigators A (HM; ICC = 0.73) and B (SP; ICC = 0.60). The details of reliability analysis are presented in Table 2. Data pertaining to sensory thresholds measured by the two investigators on day 1 and day 2 are shown in Figure 1.

There was no statistically significant difference between the thresholds measured in the cats with chronic gingivo-stomatitis (156 ± 82 g) and those measured in healthy cats (169 ± 59 g; P = 0.35; Figure 2). There was no statistically significant correlation between the scores of the CGS scale and the mechanical thresholds measured with the SMALGO in the group of cats with CGS (Pearson Correlation coefficient: 0.047; P = 0.87).

Discussion

The main finding of this study is that the SMALGO is a reliable tool to measure mechanical thresholds in cats, regardless the expertise of the investigator and the repetition of the measurements. However, as demonstrated by a lack of difference in thresholds between healthy and diseased cats, the quantitative sensory testing performed with the SMALGO failed to detect and quantify pain in cats with chronic gingivo-stomatitis.

There may be various reasons for this outcome. The number of animals used in this study may be too small, the application site of the sensor tip may not be the most appropriate to detect chronic pain associated to gingivo-stomatitis, the mechanical thresholds may not increase in cats

with gingivo-stomatitis or, alternatively, the SMALGO may not be sensitive enough to differentiate between buccal pain and normal sensory response.

The sample size was determined based on the assumption that healthy cats would reasonably have thresholds of about 100 g, and that in cats with gingivo-stomatitis this value may increase by approximately 50%. The data obtained from the study cats suggest that such difference in thresholds may be much smaller than expected, as indicated by the very similar threshold values recorded in the two groups of cats. This suggests that a larger sample size may be needed to differentiate between healthy cats and cats with gingivo-stomatitis by means of quantitative sensory testing.

Regarding the application site for the sensor probe, this could also carry the risk for bias. A previous study that investigated the use of algometers other than the SMALGO in healthy cats concluded that the sensor probe applied at the mouth carries the potential for results misinterpretation, as a result of discomfort of the cats, when the device is applied near the head and can therefore be directly seen, or when the whiskers are mechanically stimulated.[13] Applying the sensor probe directly over the buccal mucosa, on the other hand, was found by the investigators unfeasible in untrained cats.

It is also possible that the SMALGO, whilst this study proved its reliability, repeatability and simplicity to use even for investigators with no previous experience in pain assessment, is not a sensitive enough instrument to detect a difference in thresholds between cats with normal and diseased buccal mucosa.

One interesting finding of this study is that the mechanical sensory thresholds not only were useless to discriminate between healthy and diseased cats, but also failed to serve as a measure of the severity of the disease, as demonstrated by their lack of correlation with the score of the CGS

scale. The CGS scale was used by the authors to quantify the severity of the gingivo-stomatitis. With the attempt to obtain a more comprehensive evaluation of the clinical condition, two different published scoring systems were melded together to obtain one single scale, used in the current study to quantify the severity of the CGS in the diseased cats.[19,20] The modified version implied the exclusion of a number of questions regarding certain details, such as specific location of the lesions within the oropharynx, which would have been impossible to answer without sedating the cats. The scale used in the current study, however, is not validated and might not be a sensitive instrument to quantify the severity of feline CGS.

One considerable limitation of this study is that cats with different stages and degree of CGS were recruited. This implies that the population was poorly standardised with respect to the severity of the clinical condition and, presumably, to the degree of pain and discomfort perceived by the cats varied between subjects. To complicate this picture, pain assessment in cats has always been considered extraordinarily challenging,[6] and feline gingivo-stomatitis is a chronic condition subject to re-acutisation episodes, whose associated pain is likely to be complex, with both chronic and acute components.[3,4]

Quantitative sensory testing in non-verbal patients has an important intrinsic limitation. Although the idea to quantify and measure pain is fascinating, this semi-quantitative method still relies on a subjective evaluation of the investigator, who is in charge to classify the behavioural responses to mechanical stimulation as either “positive” or “negative”. The cat may, indeed, turn its head because distracted by the surrounding environment or as an attempt to escape a painful stimulus. As a result, the force values recorded as threshold may be affected by procedural variabilities as well as by the level of attention of the cats.

Conclusions

Quantitative sensory testing performed with the SMALGO failed to detect any differences in mechanical thresholds between healthy cats and cats with chronic gingivo-stomatitis. Although the SMALGO provided reliable and repeatable measurements regardless the level of expertise of the investigator, its use cannot be recommended to evaluate pain associated to feline CGS.

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Conflict of interest The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Figure legends

Figure 1 Mechanical sensory thresholds (g) measured with the SMall Animal ALGOmeter by two independent investigators (investigator A and investigator B) in 30 cats of a shelter. Each investigator repeated the measurement twice, with 24 hour-interval between the two measuring sessions. The boxes represent the second and third quartiles, with the vertical line inside indicating the median value. The lower (25%) and upper (75%) quartiles are shown as horizontal lines either side of each box. The dots represent the outliers.

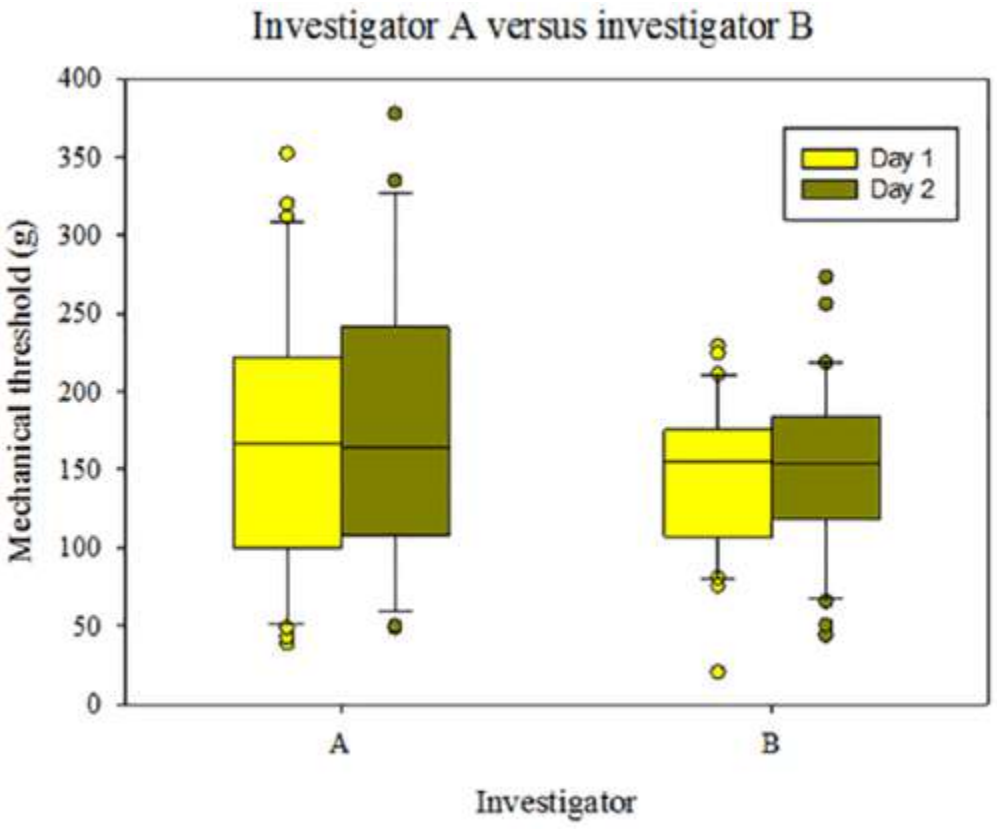
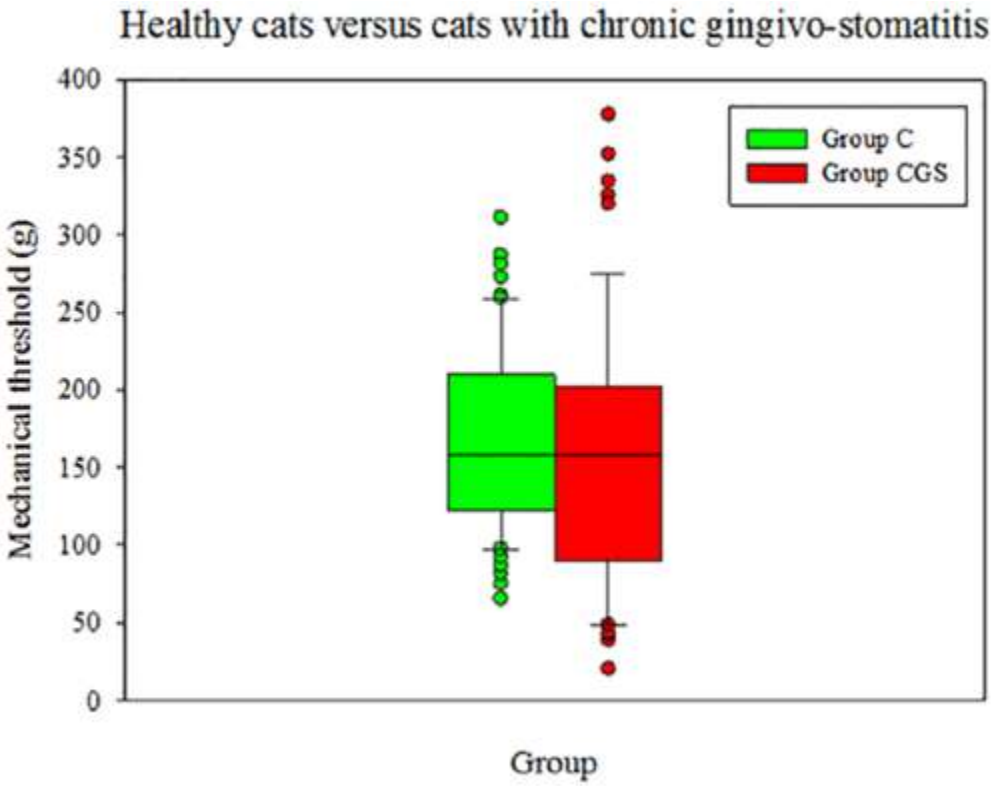


Figure 2 Mechanical sensory thresholds (g) measured with the SMall Animal ALGOmeter in 30 cats of a shelter, of which 15 had Chronic gingivo-stomatitis (group CGS) and the remaining 15 were healthy (group C; control). The boxes represent the second and third quartiles, with the vertical line inside indicating the median value. The lower (25%) and upper (75%) quartiles are shown as horizontal lines either side of each box. The dots represent the outliers.



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