TITLE: Quantitative sensory testing with Electronic von Frey Anesthesiometer and von Frey filaments in nonpainful cats: a pilot study

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Quantitative sensory testing with Electronic von Frey Anaesthesiometer and von Frey filaments in non-painful cats: a pilot study

Abstract

Objective Measurement of sensory thresholds could represent a complementary tool to behavioural pain scores in cats. The aim of this study was to investigate the feasibility of quantitative sensory testing (QST) with the Electronic von Frey Anaesthesiometer (EVF) and the von Frey filaments (VFF) in healthy cats, and to assess the limits of agreement (LOA) between the two devices.

Study design Prospective clinical study.

Animals A total of 15 client-owned healthy cats.

Methods Two investigators (A and B) carried out the measurements independently. The EVF and the VFF were applied on the upper lip and at the level of the medial aspect of the stifle. A 1-hour interval was allowed between the sets of measurements taken by investigators A and B; each investigator repeated the entire session of measurements after 24 hours. The LOA between the EVF and the VFF were analysed with the intra-class correlation coefficient (ICC), and with the Bland Altman method.

Results Quantitative sensory testing with both the EVF and the VFF was feasible in healthy cats; however, the willingness of the cats to cooperate was negatively affected by the repetition of the measurements on the second day. The presence of the cat owners seemed to facilitate the trial. There was a fair agreement between the EVF and the VFF (ICC = 0.49; CI: 0.13 – 0.70).

Conclusions and clinical relevance Our findings indicate that both EVF and VFF may be used for QST in cats. Further trials will be needed to verify the usefulness of QST with EVF and VFF in feline patients suffering from actual chronic pain.

Keywords Cat, Electronic von Frey, Pain, Quantitative sensory testing, von Frey Filaments

Introduction

Detecting and managing pain is an important duty for owners and veterinary professionals. Whilst acute postoperative pain can be easily anticipated and has, in most species, some recognizable features, chronic pain is subtle in nature and its recognition may be extraordinarily challenging, especially in cats. Chronic conditions that are common in cats (Klinck et al. 2012; Winer et al. 2016; and carry the potential for the development of chronic pain and central sensitization are feline chronic stomato-gingivitis (FCGS) and osteoarthritis (OA).

Quantitative sensory testing (QST) allows evaluation of the somatosensory function based on measurement of the mechanical sensory thresholds. Both the von Frey filaments (VFF) and the Electronic von Frey Anaesthesiometer (EVF) may be used for this purpose. The VFF are a set of 20 plastic monofilaments of progressively increasing thickness, which apply a force ranging from 0.008 to 300 grams on the body surface. The EVF represents the electronic version of the VFF and is composed of a control unit and a probe equipped with a rigid tip, capable of applying and measuring a force varying from 0 to 1000 grams. The force at which the target behavioural response is evoked – usually withdrawal or escape in non-verbal patients- is defined as threshold pressure. These devices are commonly used in human medicine to detect and quantify allodynia and hyperalgesia, as well as in laboratory rodents for sensory threshold testing (Lambert et al. 2009; Tena et al. 2010; Moore et al. 2013; Addison and Clements 2017). Recently, one study investigated the use of both VFF and EVF to quantify chronic pain associated to feline OA (Addison and Clements 2017).

The aims of the present study were:

- To investigate the feasibility of QST performed with the EVF and the VFF, applied at the stifle joint and at the upper lip of healthy cats, with the assumption that these

anatomical sites might be used in future trials to measure pain associated to OA and FCSG, respectively; and

- To assess the limits of agreement (LOA) between EVF and VFF.

It was hypothesised that QST with both the EVF and the VFF is feasible in cats, and that the LOA between the two devices would be high.

Materials and Methods

A total of 15 client-owned cats were enrolled in this trial. Exclusion criteria were the presence of any disease that may cause pain, as well as any analgesic treatment that could influence the response to the QST. This study was conducted under approval of the Clinical Research Ethical Review Board of the Royal Veterinary College (license number: URN 2016 1647-3) and signed informed owner consent.

Two investigators (investigators A and B) carried out the measurements in a quiet room of the hospital. Fifteen minutes of acclimatization, during which the cats were left undisturbed to explore the environment, were allowed before commencing the measurements. Cat owners were encouraged to attend the clinical trial, if they wished.

The cats were assessed with both the VFF (von Frey Filaments; Bioseb, France) and the EVF (von Frey Anaesthesiometer Type 2390; IICT Life Science, CA, USA) while in a standing or sitting position or sternal recumbency, either on a consult table or on the floor depending on where physical restraint could be kept to a minimum. Both devices were applied at two anatomical sites: the superior lip, at the level of the right canine tooth, and at the medial aspect of the right stifle joint.

The investigators tested the two sites independently, always starting with the VFF. The order by which the two sites were tested, as well as which investigator performed the measurements first, was decided based on simple randomization (flipping of a coin). A time

interval of one hour was allowed between subsequent sets of measurements. Each investigator tested both sites once a day. The entire sessions were then repeated after 24 hours, on day 2.

The measurements with the VFF were carried out as follows: filaments of progressively increasing thickness, starting with 0.008 g, were applied consecutively to each anatomical site, perpendicular to the skin surface, until either the filament bended or a behavioral response was evoked. If the cat reacted to a specific filament with limb/head withdrawal, head turning, watching the site of application, vocalization, hissing, or attempts to bite/scratch, then the same filament was re-applied twice to verify that the behavioural response was consistent. In order to avoid temporal summation, a minimal time interval of 30 seconds was allowed between subsequent applications (Nie et al. 2005). The size of the filament that evoked a consistent behavioral response was recorded as threshold.

The measurements with the EVF were carried out as follows: the 1000 g probe was equipped with the rigid tip. The latter was then perpendicularly applied to the skin surface of the two sites of interest. The force of application was progressively increased until a behavioral response could be evoked as for the VFF. As for the VFF, three subsequent measurements were taken, with 30 second-interval between each. The mean of the obtained values was recorded as threshold.

Statistical analysis

Normality of data was assessed with the D'Agostino, Skewness and Kurtosis tests.

The Spearman correlation coefficient (SCC) was used to analyse the degree of correlation between the measurements obtained with the two devices. According to the guidelines provided by the manufacturer of the statistic software used, for both analyses a result of 0 -0.19 was interpreted as very weak correlation, 0.20-0.39 as weak correlation, 0.40-0.59 as moderate

correlation, 0.60-0.79 as strong correlation; and 0.80-1.0 as very strong correlation (Systat website, 2018). Additionally, the LA between the EVF and the VFF were analysed with the intra-class correlation coefficient (ICC) and with the Bland-Altman analysis, used to define the 95% confidence intervals (CI; upper and lower bounds). The inter-device limits of agreement were scored as follows: ICC < 0.40 = poor; ICC between 0.40 and 0.59 = fair; ICC between 0.60 and 0,74 = good; and ICC between 0.75 and 1= excellent (Cicchetti 1994). For the Bland-Altman method, the number of standard deviations was set at 1.96, with 95% confidential interval (Bland and Altman 1986).

Commercially available software were used (IBM SPSS Statistics 24, IBM Corporation, NY, USA; and SigmaPlot 14 and SigmaStat 4, SYSTAT Software Inc, CA, USA).

Results

A total of 15 mixed breed neutered cats, three females (20%) and 12 males (80%), aged 5.8 ± 4.7 years, were enrolled in the study. Only 4 out of the 15 cats were assessed in the presence of their owner.

All the cats tolerated to complete one set of measurements. However, 11 cats became less cooperative on day 2 and required a break longer than 30 seconds between subsequent applications of the algometers. These cats were allowed to rest unrestrained for about 5 minutes. The remaining 4 cats were the ones whose owners were present throughout the whole experimental session.

The data for VFF applied at the lip showed a two-sided distribution, with the 60 g and 300 g filaments being the sizes mostly recorded as threshold (10% and 44% of the cases, corresponding to 6 and 25 out of 58 measurements, respectively). Regarding the

measurements carried out with the VFF at the stifle, the 300 g filament was recorded as threshold in 87% of the cases (51 out of 58 measurements).

Overall, there was a fair agreement between the EVF and the VFF (ICC = 0.49; CI = 0.13 – 0.70; LOA = -188 +280; Bias = 47). The thresholds obtained for each pair of measurements, as well as the values for SCC, ICC and 95% CI are presented in Table 1.

Discussion

The main finding of this study is that performing QST in cats with both the EVF and the VFF is feasible, and that the sensory thresholds measured at the lip and at the stifle with these two algometers are comparable, indicating a fair inter-device agreement. However, owing to practicability, wider range of numerical outcome, and need for less subsequent applications, the EVF may be regarded superior for QST in cats than its mechanical counterpart.

Our findings suggest that the uncooperative nature of cats may be exacerbated after repeated assessments, a drawback that would affect feasibility after the first set of measurements, and that time intervals longer than 24 hours may be needed between subsequent evaluations. As the assessments progressed, most cats decreased their tolerance to the procedure and returned inconsistent responses to the stimuli, sometimes anticipating the application of the filament/probe with an escape reaction. On the other hand, some cats showed instead some degree of habituation and seemed to get used to the measurements. In these cats, the thresholds recorded on day 2 were higher than on day 1. These different responses may be due to the personality of each individual cat.

Beside the repetition of the measurements and the individual personality of each cat, other factors, such as the environment and the presence of the cat owner during the trial, seemed to determine an effect on the attitude of the cats. The cats physically restrained by their owner during the measurements were perceived as more cooperative and tolerant to the

procedure than those restrained by one of the investigators. Unfortunately, as most cat owners were not willing to assist during the trial, this variable could not be standardized. Nevertheless, it should be considered that the current study was designed with the purpose of future applications for assessing chronic pain in clinical patients, which is more likely to happen in a clinical scenario, without the cat owners being present.

The anatomical sites were chosen in perspective of possible future applications, being the stifle and the lip commonly affected by conditions potentially associated to chronic pain in cats. The choice of the lip as anatomical site for the measurements, however, posed some important limitations. The presence of the whiskers, crucial for feline tactile perception (Williams and Kramer 2010), may increase the sensitivity especially to the VFF, as the smaller filaments may generate a prickling sensation, thus evoking a behavioural response caused by discomfort rather than pain. Some of the cats enrolled in the study, indeed, showed a rubbing gesture when the filaments were applied on the lips. Moreover, measuring thresholds at the lip implies that the cat is able to see the probe, which may itself affect its behavioral response. The medial aspect of the stifle posed some limitations as well, as this area is difficult to reach in standing cats.

In most cats, at the level of the stifle the thickest VFF was recorded as threshold, and this may be interpreted as a pitfall of the measuring instrument. There is, indeed, a large step between the second to last and the last filaments (from 180 g to 300 g), which may jeopardize the ability of the operator to detect small differences in thresholds. In that respect, EVF may represent a better choice than the mechanical filaments in feline patients.

Another important limitation of the present study is the animal model used. Presumably, the presence of chronic pain would decrease the sensory thresholds compared to the study population, composed of healthy cats. This may allow the investigator to better detect small differences in sensitivity between subjects, especially when using the VFF. Still

regarding the study population, a sample size calculation could have been performed by using the means obtained from pilot measurements carried out by both operators before commencing the trial. Since a pre-study trial could not be conducted, the number of cats to be enrolled in the project was decided based on previously published literature. As a result, a too small sample size cannot be excluded.

Conclusion

Quantitative sensory testing are feasible in cats with both the EVF and the VFF, as long as the measurements are not repeated within a short time interval. Further trials are needed to determine the usefulness of QST with EVF and VFF in feline patients suffering from actual chronic pain.

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