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ORIGINAL RESEARCH

The impact of a stress-reducing protocol on the quality of pre-anaesthesia in cats

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Abstract

Introduction: Transport to the clinic is a major source of stress for cats. The process involves being put into a carrier, driven in a car and handled. Cats are therefore removed from the safe-haven of their territory and experience many stressful stimuli and interactions.
Methods: In the present study, 31 cats were transported to the clinic following a low-stress transport protocol and compared with a control group of 36 cats whose owners did not follow the protocol. This protocol involved preparing a cat carrier basket with F3 pheromone and keeping it covered and stable during the car journey from the home to the clinic. Pre-anaesthesia information was recorded for cardiac rate, respiratory rate, tolerance to handling, time for sedation to be achieved and dose of propofol required for induction and endotracheal intubation.
Results: The group exposed to the low-stress transport protocol took less time to reach sedation and needed a lower dose of propofol for induction than the control group.
Conclusion: These results suggest that, in cats, pre-anaesthetic and induction requirements are influenced by lower-stress transport and handling.

KEYWORDS
anaesthesia, cats, pheromone treatment, stress, transport

INTRODUCTION

In human medicine, it is known that high baseline anxiety causes an increase in intraoperative anaesthetic requirements.[1,2] This has also been observed in studies where pre-operative surgery anxiety was reduced by managing the environment. In a study involving over 200 women, their anxiety was reduced when they were exposed to music for 5 minutes before surgery.[3] In a meta-analysis of the effect of the calming effects of audio-visual exposure, this form of intervention was found to reduce anxiety prior to dental procedures with local anaesthesia in children and helped with patient compliance.[4]

Although veterinarians recognise that transport is a major source of stress for cats, and many have now developed cat friendly handling and transport guidelines,[5] there is relatively little evidence on the impact of transport stress in cats. Cats' territory is their safe-haven, but when taken to the veterinary clinic they are removed from it and placed into a carrier, and then carried or transported in a vehicle to the clinic with the whole process involving a great deal of unfamiliarity, confinement and handling. The influence of pre-operative stress on anaesthesia procedures in cats, and in particular on sedation and induction requirements, has not yet been studied.

Working with healthy cats, Quimby and others[6] found differences in stress parameters before and after transport and showed that cardiac rate, respiratory rate and blood pressure were higher at the veterinary hospital than at home. There is also evidence that anxiolytic drugs can reduce stress in cats if administered before the visit to the clinic. Porters et al[7] used oral trans-mucosal buprenorphine and/or alpha-2 agonists and found that the anxiolytic and anti-nociceptive effects were similar to those of intramuscular administration of the same agents, suggesting that administration at home, prior to the veterinary visit, could be useful for reducing stress and pain responses. Stevens et al[8] found that after a single dose of trazodone, anxiety levels during transport and at the clinic were improved, both from the owner's and the veterinarian's perspective. Additionally, van Haaften[9] showed that cats given gabapentin had lower stress scores compared with placebo. However, the administration of pills to cats is generally not easy, especially when the patient is anxious or reactive.

There is also some evidence that transport stress in cats can be reduced by modifying the environment for the journey to the clinic, for example, using synthetic feline facial pheromone.[10] Desensitising and counter-conditioning to the carrier and transport procedure could be considered the gold standard for cat friendly handling.[11,12] However, it is very demanding for owners to perform and difficult for them to understand and accept, particularly given that they may only take their cats to the veterinarian once or twice each year.

The objective of the present study was to determine the effects of a low-stress, cat-friendly transport protocol on pre-anaesthetic parameters (time to achieve sedation and induction requirements) as well as physiological parameters (heart rate, respiratory rate, plasma cortisol) and tolerance to handling, in cats that were undergoing elective surgery (neutering). The hypothesis was that if pre-operative stress was reduced by improving the transport procedure and clinic environment then pre-anaesthetic parameters would be reduced and physiological parameters would be improved.

MATERIALS AND METHODS

This was a case control study that compared two groups of patients who came to the clinic for elective surgery (sterilisation). Owners were offered the choice to follow a low-stress transport; those who followed the instructions completely were included in the protocol intervention group, and those who did not follow it were used as a control. The proposed transport protocol was explained to all owners who came to a pre-operative (sterilisation) appointment, first verbally by one of the team members and then in writing. There was no compensation for participation in the study, other than that the pheromone product was provided free of charge.

The study was carried out at the 'Centro Veterinario Integral La Cañada', a general practitioner veterinary clinic located in a residential area of Valencia in Spain, between December 2015 and March 2018. The team included three veterinarians and two assistants. All staff at the clinic routinely apply cat-friendly, low-stress protocols following the International Society of Feline Medicine (ISFM) Guidelines.[5]

The study and protocols were considered and approved by the ethics and animal experimentation committee of the Cardenal Herrera-CEU University.

In order to avoid additional sources of stress, and to ensure that, as much as possible, the main cause of stress was transport, the inclusion criteria for the study were young, healthy animals without any previous pain or pathology (ASA class 1) undergoing elective surgery (neutering), who had come to the clinic no more than three times in their lives and only for routine work such as vaccinations. A healthy animal typically visits this clinic up to 3 times for vaccinations and check-ups, prior to elective surgery. More than three visits would imply that there were prior pathologies, and thus these individuals were excluded from the study. Females at oestrus or pregnant also were excluded from the study. Animals that had undergone training to tolerate transport or were administered anxiolytic medication to facilitate transport, were excluded.

All owners lived locally, and transport duration from their homes to the clinic was a maximum of 10 minutes by car.

The ISFM guidelines were followed to develop a cat-friendly handling and transport protocol based on cat wellbeing. As a standard routine, all owners whose cats undergo surgery at the clinic are shown and encouraged to follow the protocol for ethical and animal welfare reasons. Additionally, all owners whose cats were to be neutered at the clinic during the duration of the study were given free synthetic feline facial pheromone spray (Feliway; Ceva Santé Animale, France) and requested to use it as instructed for transport.

The five requirements of the handling and transport protocol used included:

1. Carriers had to be brand new or thoroughly cleaned with enzymatic agents (commonly used to remove grease stains).
2. Carriers had to be sprayed with synthetic feline facial pheromone (Feliway Classic spray; Ceva Santé Animale, France) once in each of the four corners, at least 30 minutes before placing the cat inside.
3. Cars had to be sprayed with synthetic feline facial pheromone three times, and at least 30 minutes before introducing the carrier with the cat inside.
4. The carrier had to be placed in the most stable place in the car, which is on the floor behind the front passenger seat, and strapped in position.
5. Upon arrival at the clinic, the veterinary nurse asked about compliance with the protocol and then took the carrier with the cat still inside directly to the specific cat consultation room.

The protocol was intended to be as simple as possible, in order to maximise compliance and to test an intervention that could easily be applied in everyday clinical situations.

Upon arrival at the clinic, the veterinary nurse asked owners whether they had used the Feliway classic spray according to the protocol instructions (both in the carrier, after cleaning with enzymatic agents, and in the car). If they had, the owners were then asked about the conditions of transport in the car. If the owners had followed both the pheromone and transport instructions, the case was included in the protocol intervention group. If the owners had not applied Feliway according to the protocol, the case was included in the control group. If the owners had followed the pheromone instructions but not the travel instructions, the cat was excluded from the study for incomplete protocol compliance.

The room that was used for the consultations was dedicated to cat cases; it had never been used for dogs or other species. A synthetic feline facial pheromone diffuser (Feliway Classic; Ceva Santé Animale, France) was permanently installed in this room, and the room was cleaned with enzymatic agents after stressed cats had been in it (if the previous cat was calm, the surfaces were cleaned with standard bactericide). Thus, with appointments being previously arranged, cats also avoided spending any time in the waiting room.

On the day of the appointment for surgery, and once inside the clinic, the veterinary nurse asked the owners whether they had followed the instructions or not. Cats whose owners had only followed the protocol instructions partially were excluded from the study. Those who had not followed the protocol (n = 36, 14 males and 22 females) were included in group 1 (Control), and those who had followed it (n = 31, 18 males and 13 females) were included in group 2 (Protocol). The study was blinded; information about whether the cats had been transported according to protocol was not made available to the veterinarians until all the clinical data had been collected and the clinical process completed. However, owners were aware of the purpose of the study and were informed of the purpose of the use of the cat-friendly handling protocol and its potential effects on anaesthetic parameters. Owners signed a consent form, which included consent for the use of surplus blood for cortisol analysis, at the same time as the consent form for anaesthesia and surgery.

Once the cat had been assigned to a group, the owner left the clinic. While the cat was still in the specific cat consultation room, one of the two qualified veterinarians performed a general physical examination of the patients and registered their physiological parameters, such as heart rate, respiratory rate and weight.

Prior to general anaesthesia, a jugular blood sample was taken from all cats, for the purpose of routine haematology and biochemistry testing to ensure that the animals were healthy. These procedures were in accordance with the standard pre-anaesthetic protocol the clinic would apply to all patients. Remainder material from the samples was used for plasma cortisol testing. All samples were refrigerated at the clinic until they were sent to the external laboratory, where they were processed within 24-48 hours.

Each cat was administered a lumbar intramuscular injection of a commonly used combination of a benzodiazepine, an opioid and an alpha-2 agonist, with all doses being adjusted to the cat's bodyweight.[13] In this study we chose the following drugs and doses: Medetomidine (0.01 mg/kg), pethidine (5 mg/kg) and midazolam (0.3 mg/kg). This type of sedation was chosen because in most cases (based on the authors' experience), it is enough for the duration of the perioperative period, and it is effective from the anaesthetic standpoint.

Cats were then placed back in their carrier and remained in the same consultation room with the lights dimmed while they were continually observed. At 3 minutes after sedative administration, the cats were checked to see whether an appropriate level of sedation, (Quality of sedation level 3, as described later) had been achieved. If not, they were thereafter checked at 2-minute intervals until 15 minutes. If, after 15 minutes, sedation had not been achieved, the patient received supplemental drug administration. We considered sedation to be appropriate when the patient was in a lateral or sternal position and did not resist manipulation for intravenous catheter placement.

Prior to surgery, the foreleg and surgical site were shaved and cleaned three times using surgical alcohol and povidone-iodine.

Once the intravenous catheter had been placed, the animal was taken to the operating room, and the propofol dose needed to induce anaesthesia was calculated. Boluses of propofol (0.5 mg/kg) were administered until endotracheal intubation was possible. If the anaesthetist considered the degree of consciousness of the patient required a higher dose, induction was initiated with 1 mg/kg propofol bolus.

A scheme of the complete procedure is shown in Figure 1:

The following information was collected during the protocol and anaesthetic induction:

Character of the animal: Refers to the general response of the cat to human contact, based on previous experience of the animal. We used a custom-made scale scoring from 0 to 3.

- 0 = Affectionate cat, seeks contact, can be touched and lifted off the ground.
- 1 = Friendly cat, allows contact, tries to evade being caught, is not aggressive.
- 2 = Distant cat, afraid of humans, inhibited but not aggressive.
- 3 = Irascible cat, intensely fearful, aggressive.

Handling before sedation: Refers to the ease of handling during the general physical examination. We used a custom-made scale scoring from 0 to 3.

- 0 = Impossible to handle and carry out a general examination, double towel technique for restraint is required for intramuscular injection.
- 1 = General examination possible but double towel technique is required for intramuscular injection.
- 2 = General examination possible and low-level restraint required for intramuscular injection (two people were needed to complete the exam and/or the intramuscular injection).
- 3 = General examination and intramuscular injection performed with no restraint required (one person was able to carry out both procedures without assistance).

Cardiac rate and respiratory rate: Refers to cardiac and respiratory rates measured before and after intramuscular sedation.

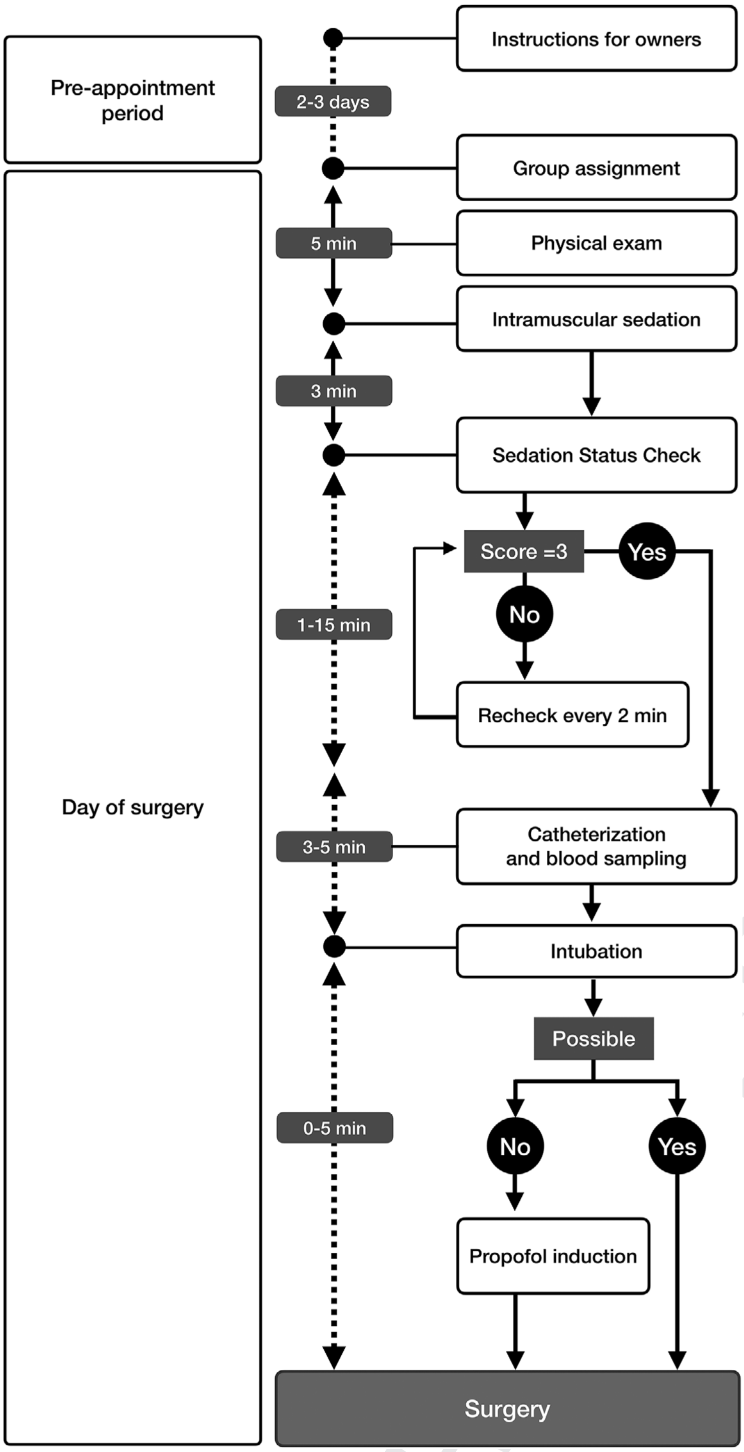

FIGURE 1 Flow chart showing the complete process of measurement collection, from patient recruitment until anaesthetic induction, on the day of surgery

Quality of sedation: Refers to the level of sedation obtained 15 minutes after intramuscular sedation administered. Score range used 0–3:

- 0 = Animal awake, able to walk, needs supplemental sedation.
- 1 = Animal in sternal recumbence but uncooperative, assistance needed to place the catheter.
- 2 = Animal in sternal/lateral recumbence, cooperative, no assistance needed to complete work.
- 3 = Animal in lateral recumbence, deep sedation, no assistance needed to complete work.

Sedation time: Refers to the elapsed time between intramuscular injection and the onset of sedation (when the quality of sedation score was 3), or a maximum of 15 minutes, which is the theoretical onset of the three drugs used for sedation.

Cortisol levels: Refers to plasma cortisol levels. Analysed at the laboratory Sagunto 99, Valencia, with chemiluminescence technique.

Induction dose: Refers to total propofol dose administered (dosed at 0.5 mg/kg per bolus).

In order to collect values for the cardiac and respiratory rate variables, the cats had to be handled for proper auscultation. Four patients in group 1 (control) and seven patients in group 2 (Protocol) were purring so loudly that accurate readings could not be taken. In some cases, respiratory rate could be taken ’hands off’ but in a few cases (10 from group 1 and eight from group 2), the patient was panting or moving a lot, and an accurate measurement could not be taken. Although there are a number of different approaches to replacing missing data, most cannot be used if the cause for the missing values is non-random. Imputing missing values in such circumstances is likely to introduce systematic bias in the dataset. Given that in the present study, the missing data were mostly related to stress and handling, it was decided that the best way to avoid biasing the data was to substitute missing values with the mean for the group. In addition, data were only missing from secondary outcome measures, and not the primary measures of sedation quality, time to sedation and propofol dose.

The distribution of all data was tested using the D’Agostino and Pearson normality test, and then a suitable parametric or non-parametric test was selected for each contrast. Chi-square test was used to compare the proportion of males and females between the groups. Bonferroni correction was applied where multiple comparisons were made between groups. Statistical analysis was performed using GraphPad Prism version 8 and SPSS version 25 software for Mac.

RESULTS

A total of 67 patients were included (32 males and 35 females) with ages ranging from 5 to 36 months. Both crossbreed and pure breed cats were included.

There were no complications as a result of anaesthetic administration in any of the patients. All surgery procedures were successful, and all patients recovered from anaesthesia as expected. There was no significant difference between the groups with respect to sex, age, character of the cat, handling before sedation, quality of sedation, plasma cortisol, weight or any of the heart rate or respiratory parameters.

There was a significant difference between the two groups with respect to time to sedation (Mann-Whitney U = 220.5, $p < 0.0001$) and propofol induction dose (Mann-Whitney U = 353, $p = 0.004$).

Sedation was achieved in all cats from 3 to 15 minutes after drug administration; median sedation times for group 1 (control) and group 2 (protocol) were 6 and 3 minutes, respectively (Figure 2).

Fourteen of 36 patients from group 1 (Control) and 24 of 31 from group 2 (Protocol) did not require administration of any propofol for induction. Median induction doses for group 1 (control) and group 2 (protocol) were 0.9 mg/kg and 0.0 mg/kg, respectively (Figure 3).

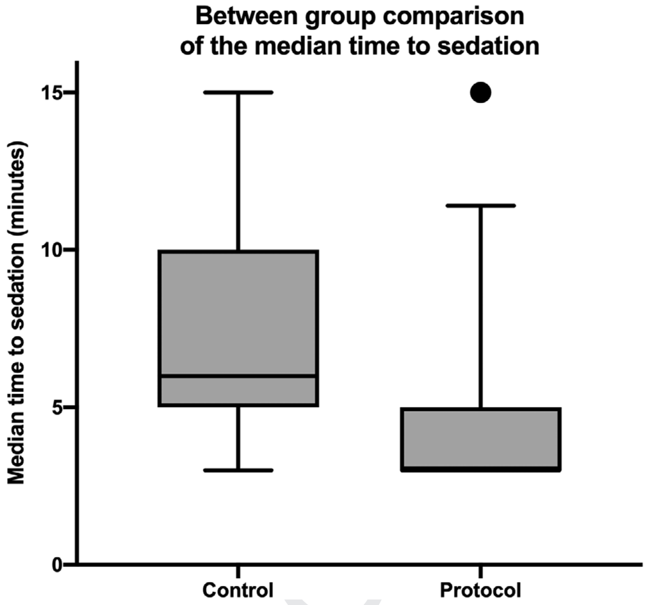

FIGURE 2 Box plot showing the difference in median time to sedation (in minutes) between the protocol group (which followed the complete low-stress transport protocol) and the control group (which did not follow the transport protocol). Boxes show the interquartile range, with a line marking the median. Whiskers show the range of the 95% confidence interval and dots indicate outliers

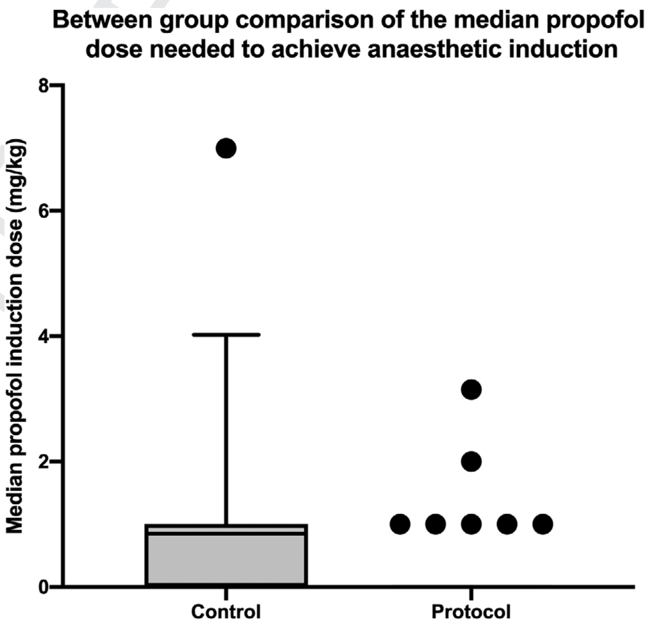

FIGURE 3 Box plot showing the difference in median propofol dose required to achieve anaesthetic induction between the protocol group (which followed the complete low-stress transport protocol) and control group (which did not follow the transport protocol). Boxes show the interquartile range, with a line marking the median. Whiskers show the range of the 95% confidence interval and dots indicate outliers. Median induction for the protocol group was zero

DISCUSSION AND RELEVANCE

The present study aimed to evaluate the influence of the implementation of a simple cat-friendly transport protocol, including low-stress handling and synthetic feline facial pheromone, on pre-anaesthesia sedation and induction of general anaesthesia.

We found that both time to sedation and the anaesthetic induction (propofol) dose administered were significantly lower in cats for which the protocol had been followed. In order to understand these results, consideration must be given to the fact that most physiological stress responses are mediated by numerous neurotransmitters and neuromodulators, including cortisol, glutamate and noradrenaline.[14] It is known that in people the higher the stress level is, the higher the levels of stress mediators such as noradrenaline, cortisol and glutamate are.[15] It would be expected that in cats, acute stress caused by manipulation and transport would have the same effects.

In order to interpret the results obtained, it is worth reviewing the basic mechanisms of acute stress and of the drugs used in the study. The drug combination of an opioid, a benzodiazepine and an alpha-2 agonist is well described in the veterinary literature.[16] In our study we chose medetomidine, pethidine[17] and midazolam because these drugs have complimentary modes of action and an onset of action of approximately 15 minutes. Medetomidine is a centrally acting alpha-2 agonist that decreases noradrenaline release and is thus a dose-dependent hypnotic. Pethidine is an opioid mu-agonist and neural inhibitor that affects the central nervous system and the peripheral nervous system, opening K^+ channels and mainly causing analgesia. Midazolam is a GABA agonist, mainly causing sedation. Stress is expected to be reduced by the transport protocol, which would be expected to lead to a reduction in circulating noradrenaline, which in turn would facilitate the effect of medetomidine as well as a reduced glutamate release facilitating the effect of midazolam. Statistically significant differences were found in 'sedation time' supporting the hypothesis that with the protocol, there were lower noradrenergic and glutaminergic effects at the time patients received the injection for sedation.

Propofol was used to induce anaesthesia. It acts on the $GABA_A$ pentameric receptor, opening Cl-channels, but at a different site than benzodiazepines (such as midazolam), and as a glutamate antagonist on the NMDA receptor.[18] Statistically significant differences were found in propofol 'induction dose' between the two groups, suggesting that lower stress levels allowed for a lower dose of propofol to be administered. Again, a lower level of glutamate facilitates the effect of propofol, allowing for smaller doses to be used in anaesthetic induction.

There was no significant difference for blood plasma cortisol. Cortisol results are usually very difficult to interpret. Daily cortisol level variation and acute cortisol release have not been fully studied in cats; however, the few studies available do not indicate a great variability.[19,20]

There was a lack of significant differences between the groups for parameters that might be expected to be affected by stress, such as 'handling before sedation', cortisol and the heart rate and respiratory parameters. Perhaps this was because the immediate acute stress of being in the clinic and being handled was more influential on these parameters than the period of transport that had gone before. This study that was conducted under the typical conditions that occur within general practice, so despite the efforts made to homogenise the conditions of reception of cases, it is inevitable that the presence of different veterinarians, manipulations and the unusual environment will lead to differences in stress response. As this source of stress is added to that recently caused by transport, it is not easy to isolate it from a behavioural point of view, but we have detected it from a physiological point of view, through the different response to drugs, both in pre-operative sedation and anaesthetic induction.

The transport protocol we used in this study was an easy for owners to apply. Other methods that could have been considered to reduce the stress in patients coming to the clinic include transport habituation and anxiolytic drugs.

Handling and transport desensitising studies have been carried out in the laboratory with cats,[11] where for several weeks they were trained with cat-friendly methods to accept the presence of and contact with their caregivers and to enter and stay inside their carriers. Even though this kind of training would be desirable, the time and effort required from the owners make it unrealistic for the average cat owner in the author's experience.

There is evidence that anxiolytics can reduce stress parameters in cats when they are administered before arrival at the clinic.[8,9] The use of anxiolytics was ruled out in this study for two reasons. They would have to be administered mixed with food (to avoid force and stress to the patient), which is not recommended before general anaesthesia, and because of the difficulty most people have given cats their oral medication.[20]

While all owners were encouraged to apply the cat friendly handling protocol, only some complied, and the reasons for differences in compliance are unknown. However, for ethical reasons arising from our confidence in the effectiveness of the protocol, it would not have been appropriate to assign cats to a trial group. As a result, there was a non-random allocation of the study population, which resulted from biases that could include owner attitude towards cat welfare as well as practical considerations.

There is a clear interest in low-stress handling in modern veterinary practice. Owners are equally concerned and appreciate being able to reduce their pets' stress during visits to the veterinary clinic or hospital. The result of applying low-stress methods is a better experience for both the animal and its caregivers, which leads to a better bond with the clinician and an increase in the owner's loyalty to the clinic. The consequences include satisfaction with the medical treatment that the patient is given and increased benefits for the clinic. The results of this study support the effectiveness of a protocol that could be easily implemented by any clinic. If this protocol was used for all clinic visits for cats, it could make a substantial impact on welfare, especially if combined with anxiolytic medication and desensitisation protocols for those cats that are known to experience particularly high stress at the clinic.

CONCLUSIONS

The results indicate that the cat-friendly transport protocol was an effective way to reduce time to sedation time and anaesthetic induction dose with propofol. If such an approach is able to help improve anaesthetic parameters, it may also have a positive impact on other aspects of the animal's welfare and experience of being in the clinic.

No negative effects were observed in any of the cats selected for the present study as a result of the application of the transport protocol. Rather, it seems to have had a positive effect on the anaesthetic parameters of time to achieve sedation and induction requirements. Further studies are needed to determine whether the addition of training and the use of certain anxiolytic drugs (e.g., orally/by mouth) before transport to the clinic would improve upon the results obtained here.

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AUTHOR CONTRIBUTIONS

Study design: Juan Argüelles and Jaume Fatjó. Recruitment: Juan Argüelles and Mónica Echaniz. Data collection: Juan Argüelles and Mónica Echaniz. Drafting of the paper: Juan Argüelles, Mónica Echaniz, Jonathan Bowen and Jaume Fatjó. Statistical analysis: Jonathan Bowen. Project supervisor: Jaume Fatjó.

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