Title:

The efficacy of vapocoolant spray for reducing intravenous catheter pain in emergency patients

Structured Summary:

Objective:

This study aimed to determine if dogs and cats presenting as an emergency had improved tolerance of intravenous catheterisation following the application of vapocoolant spray when compared to a saline control.

Method:

A randomised controlled trial of client-owned dogs and cats presenting as an emergency and requiring intravenous catheterisation was performed. Patient signalment and mentation score were recorded. All animals were restrained and had their fur clipped over the catheterisation site. They were then randomly allocated to either have a swab saturated with vapocoolant spray (treatment group) or a swab saturated with saline (control group) applied to the clipped area prior to intravenous catheterisation. The procedure was video recorded from the point of restraint until placement of the catheter. A single blinded observer reviewed the recordings and assigned reaction scores (0-3) at 4 time points (initial restraint, limb handling, swab application and skin puncture). A Mann-Whitney U Test was used to compare the scores between the groups.

Results:

Between October 2020 and January 2021, a total of 100 patients (79 dogs, and 21 cats) were enrolled, with 50 in the control group and 50 in the treatment group. No significant difference in species, age, breed, sex or mentation score was detected between the two groups. There was no significant difference in reaction scores between the groups at any time point with the

exception of a significantly increased swab application reaction score in the canine treatment group compared to the saline group ($P<0.001$).

Clinical Significance:

The application of vapocoolant spay via a swab prior to catheterisation does not significantly reduce the reaction of dogs to intravenous catheterisation in an emergency setting, with the present study likely underpowered to determine its effect in cats.

Word Count: 279

Introduction:

The pain and stress associated with venipuncture and catheter placement has long been accepted as an unavoidable consequence of therapies routinely used in veterinary care (Chebroux, Leece and Brearley, 2015). The degree of pain associated with intravenous catheterisation is believed to be minimal (Chebroux, Leece and Brearley, 2015), but any degree of pain ~~this painful stimulus~~ can result in aversive responses by patients, and can potentially make intravenous catheterisation (IC) more difficult.

Vapocoolant sprays (VS) are a class of cryoanaesthetics widely used in human emergency departments which contain a volatile liquid (commonly ethyl chloride) that evaporates once applied to the skin lowering the surface temperature (Lomax *et al.*, 2017, 2018). This cooling effect reduces nerve conduction in a linear fashion until 10^{O}C, at which point neural transmission and receptor sensitivity, including nociception is effectively blocked (Denny-Brown *et al.*, 1945; Paintal, 1965; Kunesch *et al.*, 1987; Millis, 2004). The results of randomised controlled trials involving emergency and non-emergency populations, and meta-analyses in people have demonstrated that the application of VS effectively reduces the discomfort of IC placement in adults and children (Mace, 2016; Barbour, O'Keefe and Mace, 2018; Zhu *et al.*, 2018). The benefits of VS in children may however been limited due to the cold sensation often being perceived as painful (Shah, Taddio and Rieder, 2009; Hogan *et al.*, 2014), although its application in children has also been demonstrated to improve the success of first intravenous catheterisation attempts (Farion *et al.*, 2008).

Despite VS being available to the veterinary market for several years, there is limited research in the veterinary literature examining the analgesic effects of VS. A small number of large animal studies have demonstrated its efficacy in reducing pain associated with a variety

of minor procedures, including intra-articular injections, ear notching and ear tagging (Fjordbakk and Henning, 2011; Lomax *et al.*, 2017, 2018; Van Der Saag *et al.*, 2019). Unfortunately due to variation in skin characteristics between species and target location for anaesthesia the results of these studies cannot be readily extrapolated to dogs and cats (Fjordbakk and Henning, 2011; Lomax *et al.*, 2017, 2018).

The primary aim of this study was to determine if the application of VS (Ethycalm, Invicta Animal Health Ltd) prior to IC resulted in reduced reaction to the procedure in dogs and cats presenting to an emergency department. Our secondary aim was to determine if the use of VS would result in improved IC placement success. We hypothesised that the use of VS would significantly reduce patient reaction and improve IC success when compared to a saline control.

Methods and Materials:

This blinded randomised controlled trial prospectively enrolled cats and dogs presenting as a referral or first opinion emergency to a university teaching hospital. Ethical approval was granted by the university teaching hospital's ethics and welfare committee (URN 2020 1998-3) and written client consent was obtained prior to enrollment.

All animals requiring an intravenous catheter as part of their hospital treatment were included in the study if owner consent was obtained. Recruited patients had age, sex status, and breed recorded as well as a previously described mentation score (Hayes et al, 2010) which was assessed by attending clinician immediately prior to catheter placement (Appendix 1).

At the time of enrollment into the study the patients were randomised to either receive vapocoolant spray (treatment group – TG) or a saline control (control group - CG), using an internet-based randomisation tool (Sealed Envelope, Sealed Envelope Ltd, UK).

The process of IC was video recorded from the point of initial patient restraint until placement of the catheter. Intravenous catheter placement site was either cephalic, or lateral or medial saphenous vein (determined by the person placing the catheter). Placement protocol was standardised with the fur over the vein being clipped and then aseptically prepared using a chlorhexidine gluconate solution (Chloraprep, BD). The TG had the prepared area wiped four times with a swab that had been soaked with VS for a duration of four seconds. The CG had a saline soaked swab applied as an alternative, to mimic the four wipes of the TG.

All recordings were sound edited to remove any indication of potential treatment and were subsequently reviewed by a single blinded observer (LC). The observer assigned reaction scores (0-3) at 4 time points; initial restraint, touch of the limb by the person placing the catheter, application of treatment or control swab and when the skin was punctured by the catheter using previously described scoring systems (Table 1 and 2) (Flecknell, Liles and Williamson, 1990; Gibbon *et al.*, 2003; Wagner *et al.*, 2006; van Oostrom and Knowles, 2018; Crisi *et al.*, 2020).

Whether an adverse reaction was noted at the site where the skin was swabbed, whom had attempted to place the catheter (student, nurse, or veterinarian), whether the intravenous catheterisation attempt was successful, and if the patient later required sedation for future IC attempts were all recorded.

Sample size calculation

Data comparing the efficacy of VS compared to placebo in reducing pain associated with calf ear tagging was used to calculate the sample size (Lomax *et al.*, 2017). Based on calculations using a commercial statistical program (Epi Info™, CDC, USA) 50 animals per group were required to detect a four-fold decrease in odds ratio of response to catheterisation in the TG compared to the CG, with 90% power and a 5% type I error rate.

Statistical Analysis:

All statistical comparisons were performed using SPSS (IBM Corp., Armonk, USA). Data was tested for normality using a Shapiro-Wilk test. Normally distributed data was presented as mean+/-SD and non-normally distributed data expressed as median (IQR and range). An unpaired t-test was used to compare normally distributed continuous data, the Mann-Whitney U test was used to compare non-normally distributed ordinal data, with p-values adjusted using a Bonferroni correction, and a Chi-Squared test was used to assess categorical data. Significance was determined as a P value <0.05.

Results:

A total of 107 animals were recruited between October 2020 and January 2021 with 7 excluded for failure to comply with the video or standardised catheterisation protocol correctly (Figure 1). Of the 100 animals, a total of 79 dogs and 21 cats were enrolled with a mean age 6.4 years (SD ± 5.1 years) and a median mentation score of 0 (IQR: 1, Range: 0-3).

50 patients were randomised to the TG (38 dogs and 12 cats) and 50 to the CG (41 dogs and 9 cats) with no statistical difference in species, sex status, breed, age or mentation detected between the two groups.

When considering who placed the IC (students 69, Nurses 18, Veterinarian 13) no difference between the two groups was detected.

Reaction Scores

When comparing reaction scores between dogs in the two groups, no significant difference was detected when assessing patient response to restraint, limb handling, or skin puncture (Figure 2), but those patients in the TG demonstrated an increased score during swab application compared to the CG ($P<0.001$) (Figure 3).

The reaction scores in the two cat groups were not significantly different at any measurement point (Figures 4 and 5).

No adverse skin reactions were reported in either group, whilst only two patients (one from each group) required sedation prior to future intravenous catheter attempts.

Of the 100 recorded intravenous catheter attempts 69 were performed by students (TG 30, CG 39), 18 by nurses (TG 10, CG 8), and 13 by veterinarians (TG 10, CG 3) with no significant difference in reaction scores between groups of catheter placers ~~the groups~~ ($p=0.076$).

Intravenous Catheter Success:

Intravenous catheterisation success was reported in 57% (57/100) animals of which 58% (29/50) placements were successful in the TG and 56% (28/50) were successful in the CG, this was not significantly different.

When divided by species, similarly no significant difference in catheterisation success rate was demonstrated between the two groups for dogs (TG 61% (23/38), CG 59% (24/41)) and cats ((TG 50% (6/12), CG 44% (4/9)). There was no significant difference in intravenous catheter success when considering who attempted to place it (student, nurse or veterinarian).

Discussion:

The results of this study failed to demonstrate that the application of VS using the described technique caused a significant reduction in reaction scores to IC in a population of dogs and cats presenting to an emergency department. These results differ to similar studies in humans and large animals where the application of VS prior to catheterisation and minor procedures was demonstrated to significantly reduce distress and discomfort (Fjordbakk and Henning, 2011; Mace, 2016; Lomax *et al.*, 2017, 2018; Barbour, O'Keefe and Mace, 2018; Zhu *et al.*, 2018).

Application techniques vary considerably between these studies, however all typically rely on direct application of the product to the skin surface for a variety of times ranging from 5 seconds (children) to 15 seconds (horses) in order to achieve optimal cryoanaesthesia (Robinson *et al.*, 2007; Fjordbakk and Henning, 2011; Zhu *et al.*, 2018). Optimal application techniques in large animal studies have generally been established by preliminary experimental validation studies, in which small sample size groups are subjected to a variety of application techniques, and are either assessed by their proposed response scoring system

(Fjordbakk and Henning, 2011), or through the use of in dwelling temperature probes in live and dead tissues (Lomax *et al.*, 2017, 2018). To the authors' knowledge, there are no published reports of a validated technique for the application of VS in companion animals. The technique chosen in this study was based on the recommendation of the manufacturer (R Watkins 2020, personal communication, 10th July), with the application of the VS to a swab used as a means of reducing any adverse response to the noise and force generated by the pressurised spray, which is a reported complication in human studies, particularly amongst children (Hogan *et al.*, 2014).

In the three previously reported veterinary studies, control groups received aerosolised water spray (Fjordbakk and Henning, 2011; Lomax *et al.*, 2017, 2018). In these studies no assessment of the response to the treatment or control spray were reported, with assessments made only on the basis of response to the procedural stimulus, and as such it is unclear if these species demonstrate an aversion to pressured sprays (Fjordbakk and Henning, 2011; Lomax *et al.*, 2017, 2018).

The present study demonstrated a significantly greater adverse response to VS application to the skin via a swab when compared with the saline control when assessing the entire population. This difference when divided by species was however only evident in the canine patients, with feline patients demonstrating adverse responses to the swab application regardless of whether it was soaked with VS or saline. The VS swab is notably cold when compared to the saline control and this coldness is a suggested cause of discomfort in children, even when the vapocoolant spray is applied to a cotton ball(Shah, Taddio and Rieder, 2009).

When assessing VS efficacy in veterinary species, the effect of mentation has previously not been assessed given that the application has only been described in populations of healthy animals (Fjordbakk and Henning, 2011; Lomax *et al.*, 2017, 2018; Van Der Saag *et al.*, 2019). Mentation scoring in this study was based on the ordinal scale described by Hayes and colleagues (Hayes *et al.*, 2010). By recording the mentation scores, it enabled assessment for variation in patient presentation and ensured that results weren't significantly influenced by mentation status, In the human literature patient mentation is often considered in the inclusion criteria with patients required to be mentally competent to understand the consent form, with patients excluded if considered critically ill or unstable (Mace, 2016; Barbour, O'Keefe and Mace, 2018). In the present study patients with higher mentation scores (2 and 3) were not excluded, and only accounted for 12% (6/50) and 10% (5/50) of the total patients in the TG and CG respectively.

Intravenous catheterisation success was not significantly improved by the application of VS in all categories of placers (student, nurse and veterinarian). This has similarly been reflected in previous human studies, where VS was found to not improve intravenous catheter success (Zhu *et al.*, 2018). When assessing the available veterinary literature our findings reflect those of a similar study involving the use an alternative topical anaesthetic (EMLA™ Cream, AstraZeneca), did not significant improve intravenous catheter success across a number of placer skill levels (van Oostrom and Knowles, 2018).

No adverse skin reactions were reported secondary to the application of the VS in any of the patients in the current study. Although the VS was applied indirectly in our study, similar results have been found in human and veterinary studies when the VS was applied directly to the skin (Zhu *et al.*, 2018; Fjordbakk and Henning, 2011) . Significant tissue injury

secondary to cryoanaesthesia has been reported to occur when tissue temperatures are reduced to below -20 ^{O}C (Evans, Lloyd and Green, 1981) ~~and~~ but it is very unlikely that the techniques used in our study and the aforementioned studies reached low enough temperatures to cause tissue injury.

There were a number of limitations with this present study. The scoring systems used in the study were adapted from previous studies assessing the effect of topical anaesthesia on the reaction patients to IC and venipuncture. The scoring systems used to assess reaction to limb touch, swab application and skin puncture have been previously used in canine and feline studies (Flecknell, Liles and Williamson, 1990; Gibbon *et al.*, 2003; van Oostrom and Knowles, 2018). However, the scoring system to assess patient response to restraint has only previously been used in cats, as such it was modified for use in canine patients (Wagner *et al.*, 2006; Crisi *et al.*, 2020). None of these scoring systems have been validated for use in the observed assessment of pain and distress in response to restraint or IC. V~~There is currently no validated scoring system for the observed assessment of pain and distress in response to restraint or IC. The scoring systems used were adapted from previous studies assessing IC and venipuncture. The previous reported restraint reaction scoring system from Crisi et al (Crisi *et al.*, 2020) and Wagner et al (Wagner *et al.*, 2006) was used specifically for the restraint scoring (Table 1). This scoring system was previously used in feline only studies and as such, was modified canine patients. The scoring system used for the remaining three reaction scores (Table 2) has been widely used studies involving canine and feline patients (Flecknell, Liles and Williamson, 1990; Gibbon *et al.*, 2003; van Oostrom and Knowles, 2018).~~

~~Traditional~~ alidated scoring systems for veterinary pain are used for the assessment of sustained discomfort, and routinely rely on distance examination, with assessment made on the basis of body posture and/or facial expression (Evangelista *et al.*, 2019). As such they we~~a~~re not deemed appropriate to assess behavioural response to restraint or IC, and future studies should aim to validate the~~se~~ scoring systems used in this study.~~.~~

The scoring system used in this study was ~~an~~ ordinal ~~scoring system~~ which inherently limits assessment to predefined options, as such it is possible that this scoring system was not sensitive enough to demonstrate subtle changes in patient reaction. By contrast in Fjordbakk and Hennings' (2011) study and in many of the human studies, visual analogues scales where patients or observers are asked to rank their experience on a line from 0 to 100 were utilised (Bijur, Silver and Gallagher, 2001; Hartstein and Barry, 2008; Çelik *et al.*, 2011). These continuous scales are likely to be more sensitive at detecting subtle differences in reactions than pre-formed ordinal scales and therefore their use should be considered alongside or in place of the ordinal scales in future studies.

This study included a heterogenous population of animals as well as intravenous catheter placers. The patient population examined included both first opinion and referral patients many of which had received prior treatment. It is unclear if patients' reactions were significantly affected by any pre-hospital treatment such as analgesia, or previous ~~intravenous catheterisation~~IC experiences. The inherently heterogenous population of intravenous catheter placers resulted in a variety of skill levels performing the task, and as such could have also influenced our results, particularly the success of ~~intravenous catheterisation~~IC.

Probably the most important limitation was that this study relied on a mixed population of dogs and cats. It is possible that inherent differences in skin and behaviour could have meant that the two species should not have been combined in one study, meaning that the sample size calculation was not valid. Given the smaller number of cats in the study, it is possible that the number enrolled was insufficient to detect a difference in response to catheterisation. A further single species study may be of benefit.

The present study demonstrates the application of VS via a swab prior to catheterisation does not significantly reduce the reaction of dogs and cats to intravenous ~~catheterisation,~~ ~~or~~catheterisation or improve first time placement success in the emergency department. It is unclear if the technique used in this study provided sufficient cooling effect to provide the required cryoanaesthesia to influence patient reaction. Future studies should be used to determine optimal VS application technique in dogs and cats, as well as examine its application in other populations and procedures.

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Table 1: Restraint reaction scoring system for assessment of animal compliance during restraint for catheterisation		
Criteria	Observation	Score
Restraint - Struggling	None	0
	Mild (Tense Body)	1
	Moderate (Struggle)	2
	Severe (Escape Restraint)	3
Restraint - Aggression	None	0
	Mild (Hisses/Snarl)	1
	Moderate (Attempt to Scratch)	2
	Severe (Attempt to Bite)	3
Adapted from Crisi et al 2020 and Wagner et al 2006		

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Table 2: Reaction scoring system for assessment of animal response to their limb being handled, swab application and skin puncture during catheterisation	
Observation	Score
No reaction	0
Slight movement of limb, tensing of muscles	1
Limb withdrawal, attempting to move away	2
Marked attempts to escape, aggressive behaviour, vocalisation	3
Adapted from Flecknall *et al* 1990, van Oostrom *et al* 2018, Gibbon *et al 2003*	

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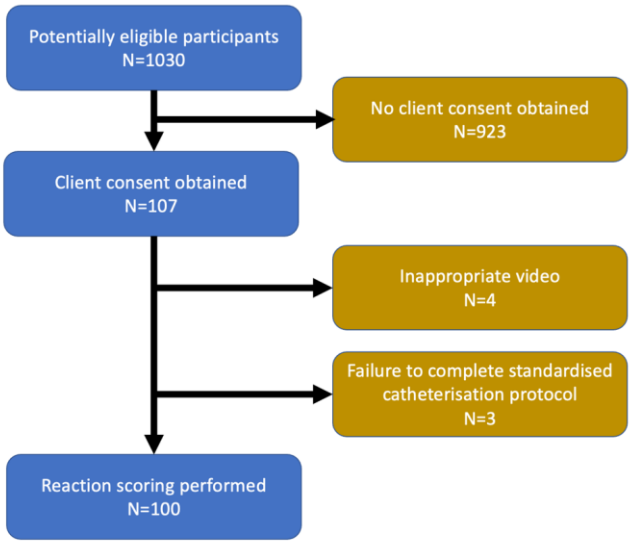

Figure 1: Flow of participants

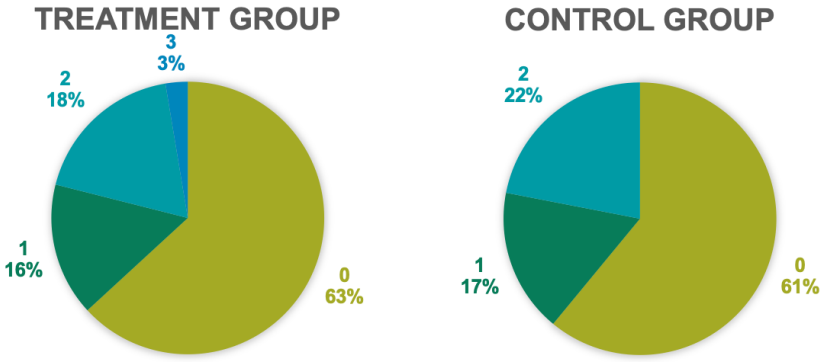

Figure 2: Comparison of the reaction scores of dogs to skin puncture between the treatment group and control group. No significant difference was detected (P 0.896)

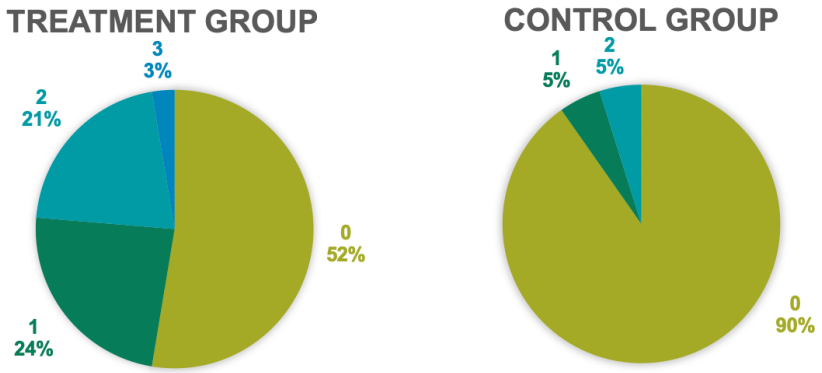

Figure 3: Comparison of the reaction scores of dogs to swab application between the treatment group and control group. Dogs in the treatment group demonstrate a significantly greater reaction to swab application (P<0.001)

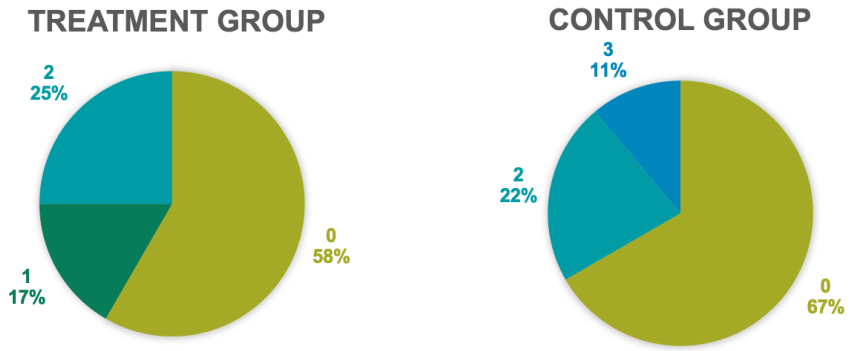

Figure 4: Comparison of the reaction scores of cats to swab application between the treatment group and control group. No significant difference detected (P=1.00)

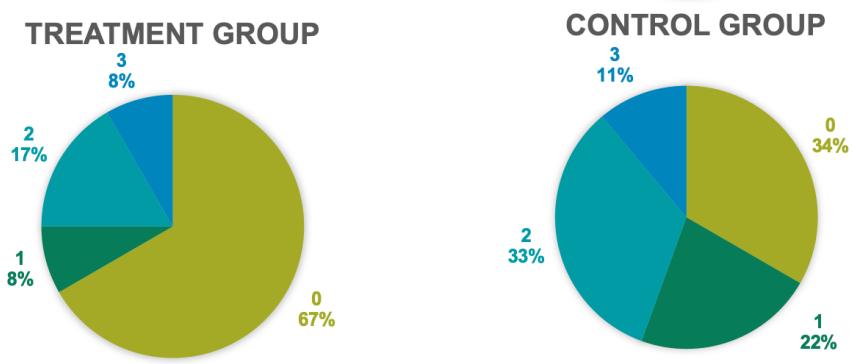

Figure 5: Comparison of the reaction scores of cats to skin puncture between the treatment group and control group. No significant difference detected (P=0.27)

Reference:

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Appendix 1:

ER Vapocoolant (EthyCalm™) Study Recruitment Form

Attach Case Label Here

Date: _____/___/___

Who placed the catheter?:

Student	☐	Nurse	☐	Vet	☐

MENTATION SCORE Assess immediately prior to catheter placement (Circle One):				
0. Normal	1. Able to stand unassisted. Responsive but dull	2. Can stand only when assisted. Responsive but dull	3 Unable to stand. Responsive	4 Unable to Stand. Unresponsive

1. Start recording at the point the patient is restrained for catheterisation
2. The recording should show the limb where IV is being placed, face and the majority of the patient's chest
3. Aseptically prepare the skin
4. If randomised to receive Ethycalm, please spray this on to a clean dry swab for 4 seconds off camera immediately prior to application. If randomised to receive placebo apply 2ml of saline flush solution to a clean dry swab, off camera
5. Wipe the Ethycalm/Saline swab along the catheter insertion site 4 times
6. Single wipe of catheter insertion with an alcohol wipe
7. Place intravenous catheter

Any skin reaction (erythema/swelling/papules) at site prior to catheterisation? Yes / No

Details of skin reaction: _____

First attempt at IV placement successful? Yes / No

Requirement for sedation for IV placement? Yes / No