A Randomized, Blinded, Controlled, Clinical Trial Investigating the Mitigation Effect of Acupuncture Points PC-6, ST-36 and LI-4 on Morphine Induced Nausea and Vomiting in Healthy Dogs

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ABSTRACT

The use of antiemetic agents preoperatively can help reduce the discomfort and postoperative complications experienced by canine surgery patients. The goal of this randomized blinded controlled clinical trial was to determine if dry needle stimulation at acupoints PC-6, ST-36 and LI-4 could reduce the incidence of nausea and vomiting in healthy dogs receiving an acepromazine and morphine injection prior to elective surgical procedures. Twenty-nine clinically healthy dogs were randomly divided into two groups. Ten minutes prior to receiving an acepromazine maleate and morphine sulphate injection, the Test Group received dry needle acupuncture stimulation at LI-4, PC-6 and ST-36 and the Control Group received sham acupuncture at LU-5, BL-36 and BL-40. The outcomes measured included the presence or absence of lip-licking, nausea or vomiting occurring within 10 minutes after receiving acepromazine/morphine premedication. Twelve out of 15 (80%) subjects in the Control Group exhibited vomiting after receiving acepromazine/morphine injection, whereas only 3 out of 14 (21.4%) subjects in the Test Group exhibited vomiting (p = 0.0028). To a lesser degree, and not achieving statistical significance under the sample size of this study, a 15% trend toward nausea reduction (11/14 test versus 14/15 control) was exhibited in the Test Group. The study concluded there was a statistically significant anti-emetic effect of presurgical acupuncture treatment at PC-6, ST-36 and LI-4. These findings support the use of these acupoints by clinicians to reduce vomiting induced by acepromazine/morphine injection in healthy dogs undergoing an elective surgical procedure.

Key words: traditional Chinese veterinary medicine, acupuncture, nausea, vomiting, PC-6, ST-36, LI-4

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ABBREVIATIONS

BL	Bladder
LI	Large Intestine
LU	Lung
Mg/kg	Milligram per kilogram
PC	Pericardium
ST	Stomach
TCM	Traditional Chinese medicine
TCVM	Traditional Chinese veterinary medicine

Opioids are commonly used in veterinary medicine to provide consistent and effective pain relief for animals.[1] The administration of opioids, however, has been associated with adverse effects in dogs, including nausea and vomiting.[1-2] Morphine, a full μ-agonist opioid, is a potent emetogenic agent. It is commonly administered to dogs in conjunction with acepromazine, a phenothiazine derivative tranquilizer to provide peri-operative analgesia and sedation.[1-3] The reported incidence of emesis after intramuscular injection of morphine, dosed at 0.5 mg/kg body weight, ranges between 50% and 75%.[1-2,4] Acepromazine has antiemetic effects via dopamine D2 receptor antagonism, yet it can only reduce, not eliminate the incidence of morphine-induced emesis when administered simultaneously with morphine.[2,5] Nausea and vomiting experienced during the peri-operative period can lead to discomfort in veterinary patients and also contribute to post-surgical complications, such as aspiration pneumonia, gastroesophageal reflux and esophagitis.[2-3,5] For most surgical procedures preoperative emesis may cause mild discomfort in patients, but in certain circumstances where patients are

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suffering from esophageal dysfunction, upper gastrointestinal obstructions, gastric volvulus, esophageal herniation, or severe gastric ulcerations; peri-operative vomiting could contribute to severe complications including aspiration pneumonia.[6-8] This is particularly important for patients who are undergoing certain surgical procedures such as the correction of laryngeal paralysis, where there is increased risk of aspiration involved, and also for patients where an increase in intracranial, intraocular and intra-abdominal pressure are to be avoided.[5,7-9]

Historically, various studies have been conducted to investigate the efficacy of treatments in reducing the incidence of opioid-induced nausea and vomiting.[7,9-12] These involved the use of acepromazine and anti-emetics such as metoclopramide and maropitant.[7,10-15] These studies however, have reported varying results on their efficacy in preventing morphine-induced vomiting and nausea. One study showed dogs that had received acepromazine injection 15 minutes prior to injection of an opioid had a significantly lower incidence of vomiting (18%) than the control groups.[9] Another similar study claimed the frequency of vomiting recorded was high (≥ 75%) for all the treatment groups with different dosages of acepromazine administered.[12] Hence, it remains debatable whether acepromazine could be used to reduce the incidence of morphine-induced vomiting in the dogs. On metoclopramide, one study reported that giving the treatment subcutaneously at 0.2 mg/kg 30 minutes in advance might help reduce the nausea and emesis induced by morphine/dexmedetomidine injection, yet a similar study claimed that the efficacy of metoclopramide in preventing morphine-induced emesis was not as evident.[4,13] While maropitant is one of the more reliable antiemetic drugs reported to reduce the frequency of morphine-induced emesis by as much as 70%, a commonly reported side effect with the use of maropitant is injection site pain associated with subcutaneous injection.[1,10,15]

From a traditional Chinese medicine (TCM) point of view, nausea and vomiting is caused by rebellious *Qi* in the stomach and acupuncture can be used to restore the normal flow of *Qi*.[16] The acupuncture points PC-6, ST-36 and LI-4 were chosen for this clinical trial due to their well-known uses in treating gastrointestinal disorders. PC-6 (*Nei-guan*) is the Master point for chest and cranial abdomen, which aims to regulate *Qi*, calm Heart and *Shen*, and suppress pain.[16] ST-36 (*Zu-san-li*) is the Master point for abdomen and gastrointestinal tract, and is used to tonify *Qi*, to benefit the Stomach function of descending, as well as to benefit the Spleen function of transformation and transportation.[16] LI-4 (*He-gu*) is the Master point for face and mouth, and is commonly used for its calming and anti-spasmodic action.[16]

Acupuncture point PC-6 is one of the most widely investigated acupuncture points to prevent nausea and vomiting.[17] ST-36 is a commonly used acupuncture point to treat gastrointestinal diseases and is often used in combination with PC-6 for treatment of gastric symptoms such as nausea and vomiting.[17-18] Pooled data from various studies that compared stimulation of PC-6 and use of different antiemetics showed that stimulation of PC-6 was superior to antiemetic medication for controlling nausea, and equivalent in controlling vomiting.[19] Other studies suggested that both acupressure and needle stimulation at PC-6 is effective for reducing the incidence of postoperative nausea and vomiting, with no known side effects, and was also economical compared to the use of medication.[20-21] Another study trial reported that electroacupuncture at ST-36 alone, could alleviate the feeling of nausea and vomiting experienced by patients receiving Granisetron therapy.[22] Additionally, while one study suggested that adjunct electroacupuncture at PC-6 and ST-36 for patients with breast cancer receiving high-dose chemotherapy was effective at controlling emesis, another reported that the proportion of patients with postoperative anesthesia-related nausea or vomiting was significantly lower if they received bilateral needle stimulation at PC-6 and LI-4, compared to the group of patients who received needle stimulation only at PC-6.[23-24]

The objective of this randomized blinded controlled clinical study was to determine the effectiveness of dry needle stimulation of acupoints PC-6, ST-36 and LI-4 to reduce the occurrence of nausea and vomiting in healthy dogs administered an acepromazine and morphine injection prior to undergoing an elective surgical procedure. The hypothesis was that stimulation of these acupuncture points (PC-6, ST-36 and LI-4) would result in less nausea and vomiting in dogs administered presurgical acepromazine/morphine when compared to control dogs and have no adverse side effects.

MATERIALS AND METHODS

The subject population for this randomized blinded clinical trial consisted of canine patients between the ages of 5 months to 10 years, presented for routine elective procedures. The study subjects were recruited from a small animal veterinary practice located in Hong Kong. Inclusion criteria for the study included dogs presented for routine elective procedures such as neutering, dentals or sedation for examination, where no underlying health condition had been identified. Exclusion included dogs with known medical conditions, or dogs on long term medications such as antihistamines, anticonvulsant drugs, antacid and/or corticosteroids.

After informed consent by owners, patients were randomly assigned to two groups by the toss of a coin, which resulted in 14 subjects in the Test Group and 15 in the Control Group. Subjects in the Test Group received bilateral dry needle acupuncture treatment at LI-4, PC-6 and ST-36 and those in the Control Group received bilateral sham dry needle acupuncture at LU-5, BL-36 and BL-40 (Table 1). For both groups, identical acupuncture needles[a] were used measuring 0.20 mm in diameter and 13 mm in length (dogs < 10 kg body weight) or 0.20 mm in diameter and 25 mm in length (dogs ≥ 10 kg body weight). Depending on the location of acupoints and the

size of the dog, the needles were inserted to depths of 3 to 10 mm. The acupuncture treatments for both groups were given by the same veterinarian who was certified in veterinary acupuncture. Subjects from both groups received acupuncture treatment at 10 minutes prior to receiving acepromazine maleate[b] (2 mg/ml at 0.04 mg/kg) and morphine sulfate[c] (15 mg/ml at 0.3 mg/kg) mixed in the same syringe and given subcutaneously as a single injection over the nape of their neck. The acupuncture needles remained in place for a further 10 minutes post-injection.

The outcome data collected from each of the study subjects were the presence or absence of lip-licking behavior, nausea, and vomiting occurring within the 10 minutes after receiving acepromazine/morphine premedication. For ease of comparison, the outcome data measured in this study was defined as follows: lip-licking was identified as abnormal when it was accompanied with depression or restlessness coupled with hypersalivation; nausea was defined as the demonstration of exaggerated swallowing and retching where no actual vomitus was produced; and vomiting was identified as the forceful expulsion of gastric contents. When any of these behaviors were observed, the time (from receiving the medication, in minutes) was duly recorded. All of the outcome data were observed and collected by a veterinary technician who was blinded to the subject's treatment group allocation. In order to test the hypotheses comparing the incidence of lip-licking/nausea/vomiting recorded in the two groups, the Fisher's Exact test was applied. For group comparisons on the observed event time, non-parametric Wilcoxon Rank Sum tests[d] were applied. All statistical tests were two-sided, and a null hypothesis (H_0) was rejected if the *p*-value was less than 0.05. The subject number that the study was able to recruit could offer a 79% power for the Fisher's Exact test to reject the null hypothesis with a 0.05 significance level, when expecting a 20% (Test) vs. 75% (Control) difference of incidence. All graphical presentation and statistical analysis were performed using commercial statistical software.[d]

RESULTS

A total of 29 canine patients met inclusion criteria for this randomized controlled study. Signalment of the study dogs included various breeds, aged between 5 months and 10 years of age and of either sex. There was no statistically significant difference in either age ($p = 0.2$), weight ($p = 0.175$), proportion of sex ($p = 1$), nor breed ($p = 1$) between the two groups (Table 2).

Twelve out of 15 subjects (80%) in the Control Group had vomited, whereas only 3 out of 14 subjects (21.4%) in the Test Group vomited (Figure 1). The incidence difference between the two groups was statistically significant ($p = 0.0028$) based on the Fisher's Exact test. Among those subjects that exhibited vomiting behavior, the mean±SD time to vomiting behavior in the Control Group was 6.0±1.5 minutes (median = 6.3), which was greater than the Test Group with a mean±SD of 5.7±3.1 (median = 5.0). The difference of time-to-vomiting between the two groups was not significant ($p = 0.811$) based on the Wilcoxon Rank Sum test.

Fourteen out of 15 (93%) of subjects in the Control Group had nausea behavior, whereas 11 of 14 (78.6%) subjects in the Test Group exhibited nausea after receiving an acepromazine/morphine injection. Even though there was a 15% reduction of nausea in the Test Group, it did not attain statistical significance ($p = 0.33$) under the sample size of this study (Figure 2). Among the subjects exhibiting nausea behavior, the mean time to nausea behavior in the Control Group was 5.3±1.5 minutes (median = 5.3), which was later than that in the Test Group with 4.7±1.3 (median = 5.0). Statistically, the difference of time-to-nausea between the groups was not significant ($p = 0.374$) based on the Wilcoxon Rank Sum test.

Table 1: Acupuncture points used to treat opioid induced nausea in the Test Group and location of sham acupuncture points used in the Control Group.[25]

Acupuncture Point	Anatomical Location
PC-6 *Nei-guan*	Medial 2 *cun* above the carpal fold, between the tendons of the superficial flexor muscles and flexor carpi radialis muscles; lateral across from TH-5
ST-36 *Zu-san-li*	3 *cun* distal to ST-35, lateral at the height of the distal end of the tibial tuberosity, in a depression roughly in the center of the cranial tibialis muscle
LI-4 *He-gu*	Between the first and second metacarpal bones, at the level of the middle of the second phalanx of the first toe in the front paw
LU-5 *Chi-ze*	Medial in the elbow fold, between the brachial muscle and the biceps tendon
BL-36 *Cheng-fu*	In the muscle channel between the biceps femoris and semitendinosus muscle, directly ventral to the tuberosity of the ischium
BL-40 *Wei-zhong*	In the middle of the popliteal fold, at the center of the transverse crevice in the popliteal fossa, between the biceps femoris and semitendinosus muscles

Table 2: Summary statistics (mean ± SD) for study dog signalment.

	Test Group (n = 14)	**Control Group** (n = 15)	***p*-value**
Age (year)	4.8 ± 3.0	3.2 ± 3.3	0.2
Weight (kg)	4.5 ± 2.9	8.1 ± 7.4	0.175
Sex	F 42.9% M 57.1%	F 46.7% M 53.3%	1
Breed	7 breeds in total Poodle: 50%	9 breeds in total Poodle: 46.6%	1

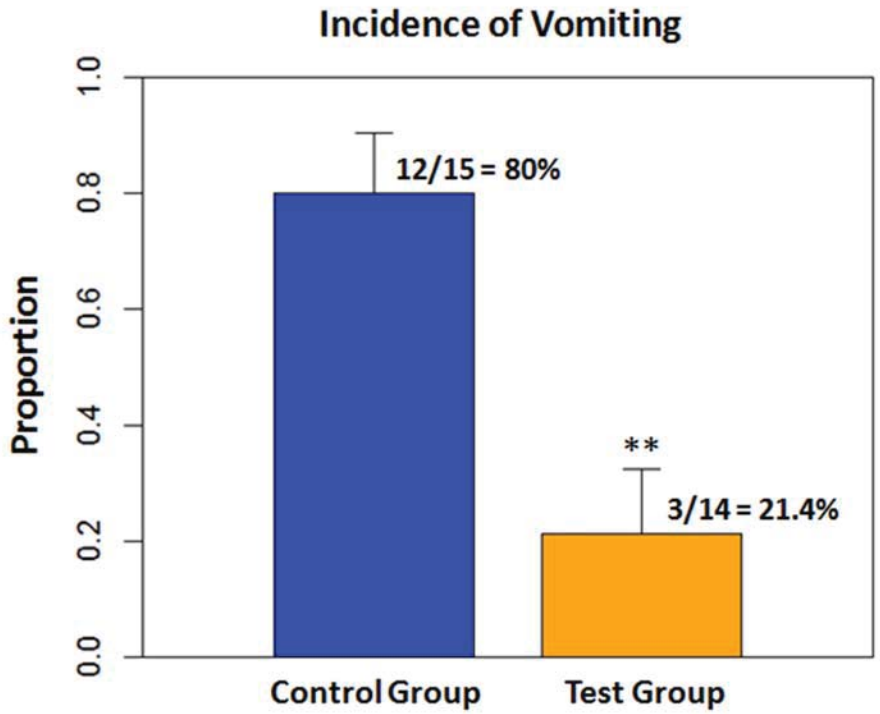

Figure 1: Observed incidence of vomiting in each subject group. ** Value indicated at top of bar differs very significantly (p<0.01).

All subjects in either group had lip-licking behavior after receiving an acepromazine/morphine injection. The time-to-lip-licking recorded in the Control Group was 3.2±1.1 minutes (median = 3.0), which is later than that in the Test Group with 2.9±0.97 (median = 3.0). Statistically, the difference between the groups was not significant (p = 0.387) based on the Wilcoxon Rank Sum test.

DISCUSSION

Statistical analysis of the data collected in this 29 subject randomized controlled blinded clinical trial supports the study hypothesis that dry needle acupuncture at PC-6, ST-36 and LI-4 can reduce the occurrence of vomiting in dogs premedicated with acepromazine and morphine prior to an elective surgical procedure (p<0.05). To a lesser degree, and not achieving statistical significance under the sample size of this study, a 15% trend toward nausea reduction (78.6% test versus 93.3% control) was also exhibited by the Test Group. There were no significant differences between study groups for lip-licking (all study dogs affected) and mean time to nausea or vomiting (p>0.05). There was no evidence that the overall study outcome was affected by

the differences in age, sex proportion, body weight or breeds between the two groups.

While opioids can provide adequate peri-operative analgesia and sedation, they often lead to side effects including nausea and vomiting, which could affect the comfort level of patients, as well as contributing to possible post-surgical complications.[1-5] In recent years alternative therapies have gained an increasing popularity within routine clinical practice. Acupuncture has been used in China for over 3000 years for the treatment of different diseases. A key concept of TCVM is the flow of *Qi*, vital forces or life energy, within the body.[25] *Qi* is postulated to flow through the body via pathways better known as Meridians or Channels.[25] These Meridians are interconnected and form an exquisite network that ensures the supply of *Qi* within the body to ensure its normal function and to fight off any "evil" energy, or pathogens, from invading the body.[25] The basic rationale of acupuncture is to restore proper physiological balance within the body through the insertion of needles at specific points along the Meridians known as acupuncture points.[25] Among studies determining the efficacy of acupuncture to treat various diseases, the best support for acupuncture comes from studies of its effects on preventing nausea and vomiting.[26-27]

Unfortunately, there are not sufficient studies to verify the efficacy of an acupuncture point or a combination of acupuncture points to alleviate nausea and vomiting. Parfitt reviewed 9 studies on the effect of acupuncture on controlling peri-operative nausea and vomiting, where 5 of the studies reported acupuncture was favored over the control treatments, and 4 studies found no advantage of acupuncture treatment over control treatment.[26-35] There were large variations, however, among the designs of the different studies, and all were conducted on human subjects.[27]

To the best of the authors' knowledge, there are no other published studies that investigated the efficacy of using dry needle stimulation of the acupoints PC-6, ST-36 and LI-4 to control morphine induced nausea and vomiting in dogs. Clinical research studies have been conducted on using conventional medicine to prevent vomiting and salivation associated with acepromazine and morphine premedication. A randomized, blinded, prospective controlled clinical trial (3 groups of 20 dogs) was conducted to evaluate whether the antiemetic (maropitant) injected subcutaneously (1 mg/kg) either 30 minutes prior or simultaneously with intramuscular injection of acepromazine/morphine compared with control dogs receiving saline instead of maropitant would reduce the incidence of salivation, retching and emesis in study dogs. The study reported no significant effect on the incidence of retching/vomiting when maropitant was administered at the same time as morphine/acepromazine,

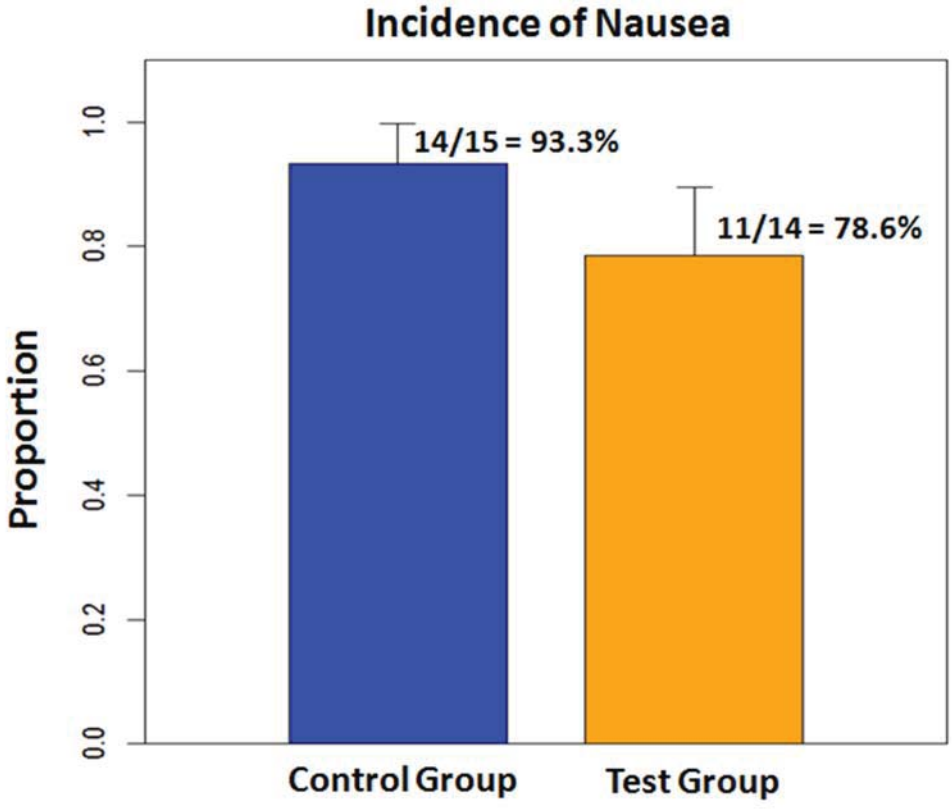

Figure 2: Observed incidence of nausea in each subject group.

but when given 30 minutes prior to morphine/acepromazine; the incidence of retching/vomiting was significantly decreased ($p<0.02$). The incidence of salivation and time to first emetic event was similar among all 3 groups.[10] It is interesting to note that the results recorded from the current research study using acupuncture technique is comparable to the findings of the comparative study. It would be interesting if a future study conducted a direct comparison of the conventional drug maropitant to acupuncture.

The study reported herein was not conducted without some limitations such as sample size, sham acupuncture for control group treatment, variability of exact anatomic acupoint location and evaluation of only dry needle acupuncture needle stimulation. Small sample size limits the robustness of a study to evaluate a large number of animals with the clinical signs of interest, as well as limits the number of different therapies that can be compared (i.e. dry needle versus electro-acupuncture). In addition, statistical power to prove differences between groups is more challenging. Although there was a statistically significant reduction in incidence of vomiting in test dogs ($p<0.05$), only a trend towards increased nausea was noted (without statistical significance) most likely related to sample size of this study. This could be more optimally evaluated with a larger number of animals to look at.

The use of sham acupuncture as a placebo in this study is a controversial topic. While, unlike humans, dogs are unlikely to suffer from placebo effect, it has been reported that sham acupuncture may produce similar though less pronounced effects when compared to the clinically indicated effective acupuncture points. Some studies have included a non-treated control group in addition to the sham acupuncture group for comparison.[36-37] While one might argue that the use of sham acupuncture is doubtful as a control group, the current study was still able to demonstrate a statistically significant difference between the use of the proposed acupuncture points and the sham points in preventing morphine-induced vomiting.

It is also worth noting that the exact location of acupuncture points used in research studies may differ slightly, depending on the measuring unit, literature and anatomical landmarks used. For example, in the current study LI-4 is identified as the point between the first and second metacarpal bones, at the level of the middle of the second phalanx of the first toe in the front paw.[25] In another study that investigated the effect of acupuncture on prevention of relapses of recurrent otitis in dogs, LI-4 is listed as simply the angle between the dog's first and second metacarpal bones.[38] Lindley and Cummings described the location of LI-4 as located between the dew claw and the second metacarpal bone, however, alternatively Matern, describes the location of LI-4 as being located between the second and third metacarpal bones approximately at the height of their center.[25,37,39] This is also the reference point used in a number of other veterinary acupuncture literatures.[40-41] This acupoint location inconsistency is likely related to transposition of human acupuncture points onto different animal models.[41-42] While some acupoints along the body can be easily transposed, differences in anatomy between species can make transposition difficult, especially when it comes to the distal extremities.[41-42] Unfortunately, these discrepancies in acupuncture point location may affect results obtained from similar clinical trials conducted by different acupuncturists.

In conclusion, this 29 subject randomized controlled clinical trial demonstrated dry needle acupuncture at PC-6, ST-36 and LI-4 is associated with a statistically significant reduction of the occurrence of vomiting in dogs receiving a subcutaneous injection of acepromazine/morphine prior to an elective veterinary procedure. There were no adverse side effects and this procedure is relatively simple to perform and cost effective. Based on the results of this study, dry needle acupuncture at specific acupoints is recommended for treatment of morphine associated nausea. As a logical extension of this study, future studies with a larger study population are needed to evaluate the current protocol on both healthy dogs as well as subjects with pre-existing medical conditions and include different acupuncture techniques (electro-acupuncture, laser acupuncture) to evaluate optimal relief of morphine associated nausea.

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Declaration of Interest

The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of this paper.

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FOOTNOTES

a. Tai Chi needles, Lhasa Oms, Inc, China
b. Acepromazine maleate, Delvet Pty Ltd, Sven. Hills, NSW, Australia.
c. Morphine sulfate injection, Hameln Pharmaceuticals Ltd., UK
d. R version 3.5.2. The R Foundation for Statistical Computing, Vienna Austria; http://www.R-project.org

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