



## SHORT COMMUNICATION

### Analgesic Efficacy of Pre-Operative Tramadol in Combination with Acepromazine in Cats Undergoing Ovariohysterectomy

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#### ABSTRACT

In a randomized blind trial, cats undergoing ovariohysterectomy were premedicated subcutaneously with 4 mg/kg tramadol and 0.1 mg/kg acepromazine (Group AT4); 2 mg/kg tramadol and 0.1 mg/kg acepromazine (Group AT2); or 0.1 mg/kg acepromazine (Group ACE). Composite pain scores (CPS), and mechanical thresholds at metatarsal pad (MTp) and surgical site (MTs) were determined at -0.5, 0.5, 2.5, 3.5, 4.5, 6.5, 8.5, 10.5, 12.5, 12 and 48 hours after pre-medication. Post-operatively, CPS was the highest in ACE and all cats required rescue analgesia. None of the cats in AT4 or AT2 needed rescue analgesia. Group AT4 has lower CPS and higher MTp compared to AT2. Decrement of MTs tended to be the least in AT4. This study shows that tramadol at 4 mg/kg provided more profound and longer duration of analgesic effect than 2 mg/kg, when combined with acepromazine for premedication in cats.

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#### INTRODUCTION

Ovariohysterectomy (OHE) is considered to cause moderate to severe pain in cats (Polson *et al.*, 2012). Therefore, choosing an appropriate analgesic is required to reduce the discomfort and suffering in the post-operative period. Tramadol hydrochloride is a synthetic, atypical opioid that acts both as an opioid agonist, and a spinal inhibitor of reuptake of noradrenalin and serotonin (Robertson, 2005). It has recently been approved in Europe for use in dogs, but yet to be authorized for use in cats (Cagnardi *et al.*, 2011).

A dosage of 1-2 mg/kg, intravenously (i.v.), has been suggested for cats (Robertson, 2005). However, in one clinical trial, 50% of cats that was pre-medicated with 2 mg/kg tramadol subcutaneously (s.c.) still required rescue analgesia in the post-OHE period (Brondani *et al.*, 2009). Therefore, we increased the dosage of tramadol to 4 mg/kg, s.c. and compared the analgesic effect to 2 mg/kg when combined with acepromazine as pre-medication for OHE in cats.

#### MATERIALS AND METHODS

The study was approved by the ethics committee of Universiti Putra Malaysia (UPM/FPV/PS/3.2.1.551/AUP-R56). Cats (n=15) presented to UPM Veterinary Teaching

Hospital for elective OHE were recruited following owners' consent. They were randomly assigned to one of three treatment groups: Group AT4-pre-medication with 4 mg/kg tramadol and 0.1 mg/kg acepromazine, s.c., Group AT2-pre-medication with 2 mg/kg tramadol and 0.1 mg/kg acepromazine, s.c., and Group ACE-pre-medication with only 0.1 mg/kg acepromazine, s.c. The initial target was to recruit six cats for each treatment groups, but recruitment into Group ACE was stopped at n=3 as all three cats in this group required rescue analgesia.

Cats were familiarized to the ward, the observer and pain assessment procedures 24 hours before surgery. Following the assigned premedication, cats were induced with 12.5 mg/kg sodium thiopental i.v. and maintained on 2% isoflurane in 100% oxygen. Ovariohysterectomy was performed through ventral midline incision by the same surgeon for all cats. Physiological parameters were determined before skin incision, during skin incision, first ovarian pedicle clamping, second ovarian pedicle clamping, uterine body clamping, linea alba suturing and skin suturing.

Composite pain scores (CPS) and mechanical thresholds at the surgical site (MTs) and metatarsal pad (MTp) were determined by the same blinded observer at 0.5 hours (baseline) before, and 0.5 hours after pre-medication. Following surgery, cats were assessed at 2.5, 3.5, 4.5, 6.5, 8.5, 10.5, 12.5, 24, 36 and 48 hours after pre-medication, which corresponded to 1, 2, 3, 5, 7, 9, 11,

22.5, 34.5 and 46.5 hours post-surgery. The CPS system consisted of seven items with maximum score of 21, as described by Al-Gizawiy and Rude' (2004). Mechanical thresholds were determined in triplicates using a custom-made digital pressure-measuring device (Basiri *et al.*, 2012). Throughout the study, if  $CPS \geq 11$ , tramadol at 2 mg/kg, s.c., would be administered as rescue analgesia.

Data from Group ACE after rescue analgesia were excluded from statistical analysis. Parametric data were analyzed using ANOVA for repeated measures and mixed ANOVA where appropriate. Within treatment, difference from baseline was determined using Dunnett's test. Kruskal-Wallis test followed by Mann-Whitney test with Bonferroni correction were used to detect treatment effect on CPS. Within treatment, Friedman test, followed by Wilcoxon Signed Ranks test with Bonferroni correction were applied to detect difference from baseline. Values are expressed as mean $\pm$ SD and median $\pm$ interquartile range. Level of significance was set at 95% ( $P < 0.05$ ) for all tests.

## RESULTS

Surgery and anesthesia times were  $21 \pm 6.5$  (AT4:  $22 \pm 6$ , AT2:  $18 \pm 5$ , ACE:  $26 \pm 5$ ) minutes and  $46.5 \pm 3.8$  (AT4:  $45 \pm 4$ , AT2:  $43 \pm 8$ , ACE:  $50 \pm 5$ ) minutes respectively. There was no difference among the three groups in surgery and anesthesia time. Systolic blood pressures tended to increase during the clamping of pedicles and uterine bodies in all groups, with significance detected during clamping of the first ovarian pedicle in AT2 (Table 1). There was neither significant time, nor treatment effect in the pulse rate and respiratory rate during surgery.

Composite pain scores in ACE were significantly higher than scores in both AT2 and AT4 at 2.5 and 3.5 hours post-medication (Fig. 1). All cats in ACE required rescue analgesia at 4 hours post-medication. Thereafter, the CPS reduced and cats did not require more analgesia within the 48 hours observation. None of the cats in AT2 and AT4 required any rescue analgesia throughout the 48 hours observation. Composite pain score in AT2 tended to be higher than AT4 for the first 11 hours, with significant difference detected at 4.5 and 6.5 hours post-medication.

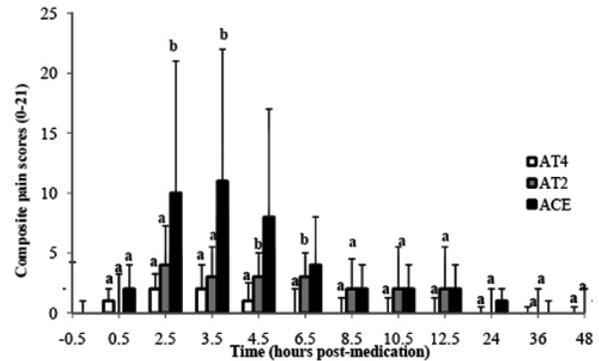
Mechanical thresholds at the metatarsal pad in ACE remained low and not different from baseline at 0.5, 2.5 and 3.5 hours post-medication (Fig. 2). In both AT2 and AT4, metatarsal thresholds increased steadily following pre-medication. Significant increase from baseline was demonstrated at 4.5 hours in AT2, compared to 3.5, 4.5 and 6.5 hours in AT4.

Mechanical thresholds at surgical site decreased significantly from baseline following OHE in all groups (Fig. 3). The decrement was not significantly different amongst the three treatment groups. However, the decrement tended to be less in AT4 compared to AT2. No significant side effect was observed during the 48 hours post-operative monitoring. None of the cats that had received tramadol required further analgesia.

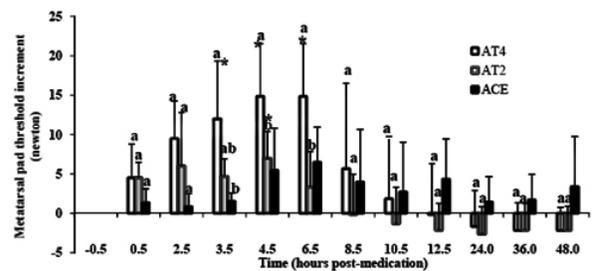
## DISCUSSION

In this study, the addition of tramadol at both 2 mg/kg and 4 mg/kg, s.c. to 0.1 mg/kg acepromazine pre-

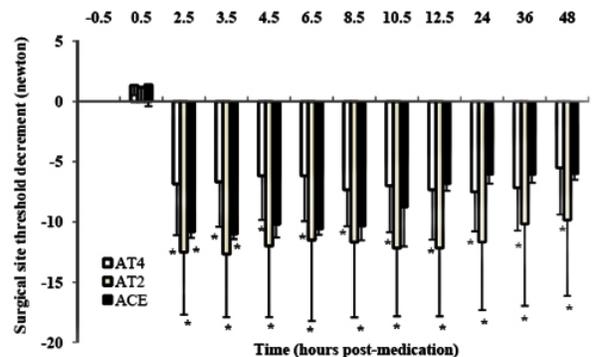
operatively resulted in lower pain scores and eliminated the need for rescue analgesia following OHE in all cats. Tramadol at 4 mg/kg produced more profound and longer antinociception than 2 mg/kg. The addition of tramadol at 2 and 4 mg/kg increased mechanical thresholds at metatarsal pad in a dose-related manner, but did not prevent decrement of thresholds at the surgical site.



**Fig. 1:** Composite pain scores (median $\pm$ interquartile range) of cats following ovariohysterectomy and subcutaneous premedication with 4 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT4); 2 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT2); and 0.1 mg/kg acepromazine (n=3, Group ACE). At each time point, groups with similar alphabet are not different ( $P > 0.05$ ).



**Fig. 2:** Changes in metatarsal pad mechanical thresholds (mean $\pm$ SD) of cats following ovariohysterectomy and subcutaneous premedication with 4 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT4); 2 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT2); and 0.1 mg/kg acepromazine (n=3, Group ACE). At each time point, groups with similar alphabet are not different. \* denotes significant difference from baseline ( $P < 0.05$ ).



**Fig. 3:** Changes in surgery site mechanical thresholds (mean $\pm$ SD) of cats following ovariohysterectomy and subcutaneous premedication with 4 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT4); 2 mg/kg tramadol and 0.1 mg/kg acepromazine (n=6, Group AT2); and 0.1 mg/kg acepromazine (n=3, Group ACE). \* denotes significant difference from baseline ( $P < 0.05$ ).

**Table 1:** Changes in physiological parameters of cats during ovariohysterectomy

Parameter	Group	T1	T2	T3	T4	T5	T6	T7
S.B.P.	AT4	76±15	76±7	98±21	110±31	104±37	86±24	97±35
	AT2	76±15	83±18	110±23*	106±31	94±23	85±15	98±11
	ACE	66±23	69±23	102±28	123±19	95±40	82±26	84±43
Pulse Rate	AT4	137±31	146±27	164±23	165±25	159±40	137±24	129±19
	AT2	132±18	137±19	149±19	157±33	141±21	124±17	142±17
	ACE	139±25	137±3	147±26	132±21	146±18	142±24	137±13
Respiratory Rate	AT4	12±5	12±1	16±6	16±6	16±7	12±7	13±7
	AT2	12±5	15±6	16±6	15±6	15±7	14±5	14±6
	ACE	14±3	16±2	18±4	18±8	18±7	19±5	17±7

Group AT4: 4 mg/kg tramadol and 0.1 mg/kg acepromazine, Group AT2: 2 mg/kg tramadol and 0.1 mg/kg acepromazine, Group ACE: 0.1 mg/kg acepromazine, T1: Before skin incision, T2: During skin incision, T3: First ovarian pedicle clamping, T4: Second ovarian pedicle clamping, T5: Uterine body clamping, T6: Linea alba suturing and T7: During skin suturing. S.B.P.: Systolic Blood Pressure. Values are indicated in mean±SD. \* denotes significant difference from baseline ( $P<0.05$ ).

The dose-dependent increment of metatarsal mechanical thresholds in our study concurred with the findings by Pypendop *et al.* (2009) where, higher doses of tramadol resulted in earlier detection and longer duration of increased thermal thresholds. In our study, tramadol at 4 mg/kg did not prevent primary hyperalgesia at the surgical site, but the decrement of thresholds tended to be less compared to 2 mg/kg tramadol. Composite pain scores also tended to be lower for the first 11 hours following the higher dose of tramadol. Thus, if there were limited resources to monitor cats for needs of additional analgesic in the immediate post-OHE periods, pre-medication with 4 mg/kg tramadol would be recommended.

The fact that all cats in Group ACE, while neither AT4 nor AT2 required rescue analgesia clearly demonstrated the need to incorporate an analgesic in the anesthetic protocol of cats undergoing OHE. Following rescue analgesia with 2 mg/kg tramadol s.c. in Group ACE, pain score reduced while mechanical thresholds tended to increase. None of these cats required further analgesia until the end of the 48 hours post-operative observation. This shows that tramadol at 2 mg/kg is useful to treat pain after OHE.

In the study by Brondani *et al.* (2009), 50% of the cats that received 2 mg/kg tramadol required rescue analgesia, while none of the cats in AT2 in our study required rescue analgesia. The difference may be due to the lower threshold set in Brondani's study, i.e. 33% of the maximum CPS, compared to 50% used in our study. If similar threshold was used in our study, two of the six cats in AT2 would have required rescue analgesia. This further supports the need for dosing tramadol higher than 2 mg/kg, s.c.

The tendency of blood pressures to increase during clamping of pedicles and uterine bodies in all groups suggests that stimulation of the sympathetic system during noxious stimulation were not obtunded by acepromazine, tramadol or level of anesthetic used in this study. Significantly higher blood pressure in Group ACE

compared to AT4 and AT2 was not detected, likely due to the low number of animals in this group.

Euphoria, sedation, excessive salivation and facial itching after administration of tramadol had been reported in cats (Pypendop *et al.*, 2009). In our study, we did not observe any adverse effects, except for euphoria and mydriasis. All cats in AT4 were relaxed, friendly, playful, and had mydriasis. These effects subsided by 6.5-8.5 hours post-injection. In AT2, only one cat showed signs of euphoria. Mydriasis was observed in 2 cats, which subsided by 5.5 hours post-injection.

In conclusion, subcutaneous injection of tramadol in combination with acepromazine at the dosages of 2 and 4 mg/kg have been shown to produce analgesic effect. Tramadol at 4 mg/kg provided more profound and longer duration of analgesic effect than 2 mg/kg.

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