Original Article

jfms Journal of Feline Medicine and Surgery

Comparison of analgesic efficacy of tramadol, morphine and methadone in cats undergoing ovariohysterectomy

Journal of Feline Medicine and Surgery
1–9

DOI: 10.1177/1098612X231224662
journals.sagepub.com/home/jfm

This paper was handled and processed by the American Editorial Office (AAFP) for publication in *JFMS*

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Abstract

Objectives The aim of this study was to compare the analgesic efficacy and the effect on physiological variables and behavior of the use of tramadol, methadone and morphine as preoperative analgesia in healthy cats undergoing elective ovariohysterectomy.

Methods Cats undergoing ovariohysterectomy were randomly assigned to receive one of the following premedication treatments intramuscularly: methadone (0.2 mg/kg; n = 10); morphine (0.2 mg/kg; n = 10); or tramadol (3 mg/kg; n = 10). Induction of anesthesia was done with propofol, and maintenance of anesthesia was done with isoflurane. Intraoperative heart rate, arterial blood pressure, respiratory rate, end-tidal isoflurane concentration and frequency of rescue analgesia (fentanyl 2.5 µg/kg) were compared between groups. Postoperative analgesia was assessed using the UNESP-Botucatu Multidimensional Composite Pain Scale, and perioperative serum glucose, cortisol concentrations and postoperative rescue analgesia were evaluated.

Results Intraoperative rescue analgesia was required in 76.5% of cats at some time during surgery, and 27% of cats required postoperative rescue analgesia up to 6 h after extubation. There were no significant differences between groups with respect to intraoperative and postoperative rescue analgesia, pain scale scores and end-tidal isoflurane concentrations. In the immediate postoperative period, after extubation, most of the patients presented with hypothermia; however, 1–6 h postoperatively, hyperthermia was observed in most of the patients, and was most common in the tramadol group.

Conclusions and clinical relevance Under the conditions of this study, methadone, morphine and tramadol produced satisfactory postoperative analgesia in most of the cats undergoing ovariohysterectomy, and the effects lasted up to 6 h postoperatively. Intraoperative analgesia was not sufficient in most cases. Significant cardiovascular or respiratory effects contraindicating the use of these drugs were not found. Postanesthetic hyperthermia occurred with all opioids studied and was more frequent in the tramadol group.

Keywords: Methadone; morphine; tramadol; analgesia; ovariohysterectomy

Accepted: 17 December 2023

Introduction

Domesticated cats usually do not receive adequate perioperative analgesia,[1] due to the difficulty in recognizing pain in this species, as their pain-associated behavior can be confused with fear or stress.[2]

Opioids are drugs commonly used for pain management in small animal practice.[3] Examples are morphine, methadone and tramadol. Morphine acts as a full agonist of the mu (µ) opioid receptor, and it is the

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opioid agonist against which all the other opioids are compared.[4,5] However, its efficacy in cats has been questioned because cats have a deficiency in the enzyme UDP-glucuronosyltransferase,[6] which reduces the production of morphine-6-glucuronide, an active metabolite that produces analgesia in some species. The postoperative analgesic efficacy of morphine has been reported to be inferior when compared with buprenorphine in cats that underwent different types of surgeries.[5] Methadone acts as an agonist of the μ-opioid receptor and as an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor.[7] Methadone has proven to be an effective analgesic for surgical procedures such as feline ovariohysterectomy and orchiectomy.[8,9] Tramadol has an analgesic effect as a μ-opioid receptor agonist, mainly through the actions of *O*-desmethyltramadol, its active metabolite. It also generates analgesia by inhibiting the reuptake of serotonin and noradrenaline.[10] Tramadol has been effective as an analgesic in cats undergoing ovariohysterectomy.[11] However, in a study by Brondani et al,[12] it was stated that 5/10 female cats undergoing ovariohysterectomy required postoperative rescue analgesia after receiving tramadol.

Opioids in cats can produce bradycardia, respiratory depression, nausea, vomiting, constipation, urinary retention, excitement[13] and postanesthetic hyperthermia as side effects.[14]

There are few studies comparing the intra- and postoperative analgesic effectiveness of opioids in cats, and none of them have compared methadone, morphine and tramadol. Therefore, the aim of this study was to compare both the intra- and postoperative analgesic efficacy of these opioids in healthy female cats undergoing ovariohysterectomy.

Materials and methods

Animals

This study was conducted in 2017, using 30 client-owned, healthy, female cats undergoing elective ovariohysterectomy at the University of Chile Veterinary Hospital (10 cats were randomly assigned to one of three groups). The age range of the included cats was 6 months to 7 years. They were considered healthy based on physical examinations and normal blood tests, including complete blood cell counts, clotting times, glycemia, creatinine, albumin, alanine transaminase and gamma-glutamyl transferase. Cats that were pregnant, aggressive or had previously experienced adverse reactions associated with the analgesic drugs used in the present study were excluded. All owners gave written informed consent. Cats included in the study did not receive any drugs in the 7 days before the study.

The cats were admitted to the hospital the night before surgery to acclimatize to a new environment. They were fasted for 8 h (food) and 4 h (water) before the anesthesia. This was a prospective, randomized, blinded study approved by the Bioethics Committee of the University of Chile, Faculty of Veterinary and Animal Sciences (no. 10-2016).

Anesthetic procedure

Computer-generated randomization (Excel; Microsoft) was used to randomly assign 30 cats to receive one of the following treatments intramuscularly (IM): methadone (MET; n = 10) (0.2 mg/kg; Sanderson); morphine (MOR; n = 10) (0.2 mg/kg; Sanderson); or tramadol (TRA; n = 10) (3 mg/kg; Sanderson). These doses were defined by the literature[15] and adjusted to our clinical practice.

Before treatment administration, a baseline pain assessment was performed using the UNESP-Botucatu Multidimensional Composite Pain Scale (UNESP-Botucatu MCPS).[16] After this assessment, the following physiological variables were measured: heart rate (HR) by chest auscultation; respiratory rate (f_R) by observing chest expansion; and rectal temperature using a digital thermometer. Non-invasive arterial systolic blood pressure (SAP) was measured using a Doppler flow detector (LifeDop 150 Series; Cooper Surgical) with an appropriately sized cuff width (approximately 40% of the circumference of the pelvic limb). These variables corresponded to time 0 (T0). After this assessment, the treatment was administered.

After premedication, a time frame of 20 mins was given, and sedation was scored based on the scale by Biermann et al[17] (see Appendix A in the supplementary material). After this, 30 mins after premedication, an intravenous (IV) catheter (22 G × 1 inch) was placed in the cephalic vein and fluid therapy was administered using lactated Ringer's solution at 10 ml/kg/h. Induction of anesthesia was achieved by the administration of IV propofol (2 mg/kg/min) (Fresenius Kabi) until ventro medial rotation of the eyes, loss of the palpebral reflex and loss of jaw tone were observed. Before intubation, 2% lidocaine (0.1 ml) (Sanderson) was instilled on the arytenoids. Each cat's trachea was orally intubated using a cuffed endotracheal tube. Anesthesia was then maintained using isoflurane in oxygen at a flow rate of 400 ml/kg/min via a non-rebreathing circuit (Mapleson F type configuration, non coaxial). The end-tidal isoflurane (FE 'Iso) concentrations were adjusted based on cardiovascular and respiratory parameters, assessment of conventional anesthetic depth and lack of response to surgery. All cats were allowed to breathe spontaneously. Cats were positioned in dorsal recumbency over a circulating warm air blanket (Bair Hugger; 3M).

Intraoperative monitoring took place every 5 mins after induction of anesthesia and was performed by an anesthesiologist unaware of group assignment, using a multiparameter monitor (B40 patient monitor; General Electric) to obtain cardiac rhythm (lead II), pulse oximetry (pulse rate, oxygen saturation [SpO_2]) and f_R. The SAP was measured using the Doppler method (LifeDop150

Series) over the right pelvic limb. FE 'Iso and end-tidal CO_2 (PE 'CO_2) were measured using a side-stream gas analyzer (Vamos plus; Dräger), sampling at 200 ml/min.

All cats underwent routine midline ovariohysterectomy and were operated on by the same surgeon.

Intraoperative analgesic assessment

To assess differences in intraoperative analgesia between groups, a comparison of the frequency of analgesic rescues and the fentanyl dosage during the duration of the procedure was carried out. To assess both the need for rescue analgesia and the side effects, selected physiological variables were evaluated at five time points: T1 (post-intubation); T2 (skin incision); T3 (ligation of the right ovarian pedicle); T4 (ligation of the left ovarian pedicle); and T5 (ligation of the cervix).

After reaching a surgical plane of anesthesia, the isoflurane vaporizer setting was increased by 0.5% in animals presenting a rise of over 20% in at least two of their physiological variables (HR, f_R or SAP) relative to T1. If the variables remained high for more than 5 mins, fentanyl IV (2.5 µg/kg; Sanderson) was administered as rescue analgesia. If the same variables rose again, another dose of fentanyl (2.5 µg/kg) was given.

Postoperative analgesic assessment

A postoperative pain assessment was performed using the UNESP-Botucatu MCPS[16] by the same unaware observer at T0 and at 1, 2, 4 and 6 h after extubation (Post 1–6). The need for rescue analgesia and the pain scores were compared between groups. The Botucatu pain scale scoring system is in the range of 0–30 points. In this study, rescue analgesia was administered with a score >7,[16] and it consisted of the same treatment drug, dose and route as the premedication. Pain score data after rescue analgesia were excluded from analysis.

Measuring glycemia and serum cortisol concentrations was used as a complementary method for surgical stress assessment. Basal values were considered as Glu-Pre and Cor-Pre for glycemia and cortisol, respectively. These were determined after basal pain scores and physiological variables had been evaluated. New blood samples were drawn for analysis 3 h after extubation, corresponding to Cor-Post and Glu-Post. Hyperglycemia was considered at values >120 mg/dl.

Each patient received a subcutaneous dose of meloxicam (0.2 mg/kg; Boeringer Ingelheim) after the last pain score evaluation.

Laboratory tests

Blood samples were drawn from the medial saphenous vein (2 ml). Glycemia was measured in whole blood using a glucometer (UltraMini; OneTouch). To measure serum cortisol concentrations, the blood sample was centrifuged for 10 mins at 3000 *g* and serum was frozen at −20°C for subsequent measurement of basal serum cortisol using the ELISA method (Feline Cortisol ELISA Test Kit; Endocrine Technologies, Inc).

Adverse effects

Physiological variables were assessed to establish each drug's impact on the cardiovascular and respiratory systems. Adverse effects were recorded as a frequency of occurrence, starting from the premedication. Cardiovascular and respiratory adverse effects were evaluated at T1. A SAP <90 mmHg was considered hypotensive, HR <120 beats/min was considered bradycardia and PE 'CO_2 >45 mmHg (5.99 kPa) was considered hypercapnia.[18]

Temperature was evaluated at the end of surgery and at every postoperative evaluation time. When patients developed hypothermia (<36.7°C),[19] they were kept with an external heat source (Bair Hugger) until their temperature was normalized. Hyperthermia was defined as a temperature >39.2°C.[20] Miscellaneous side effects recorded were nausea, vomiting, euphoria (evidenced by purring, rolling and kneading using the forepaws), dysphoria (evidenced by restlessness, agitation and vocalizations) and postanesthetic hyperthermia.

Statistical analysis

D'Agostino–Pearson's test was used to assess normal distribution of the data. A power analysis conducted using published data suggested that 10 cats would be sufficient to determine significant differences in intraoperative and postoperative analgesic rescue[21] with a power >0.8 and the alpha level set at 0.05. The intra- and postoperative rescue analgesia frequency between groups was compared using a χ^2 test. An ANOVA was used to compare normally distributed data, such as the propofol doses, and post hoc analyses were conducted using Tukey's test. A Kruskal–Wallis test was used to compare non-normally distributed data, including pain scores, physiological variables, isoflurane requirements, and serum cortisol and glycemia concentrations, between groups. The Dunn test was used for post-hoc analyses. Wilcoxon's test was used to compare glycemia and serum cortisol concentrations within groups. GraphPad Prism version 8 software was used for the analyses. The differences were regarded as significant with values of P <0.05. The results are expressed either as the median (interquartile range [IQR]) or as the mean ± standard deviation (SD), depending on the distribution.

Results

Characterization of the population

Of the 30 healthy female cats included in the study, 29 were domestic shorthairs and one was Persian. The median weights in the MET, MOR and TRA groups were 2.95 kg (IQR 2.2–3.7), 2.65 kg (IQR 2.5–3) and 2.9 kg (IQR 2.3–4.6), respectively. The median ages in the MET, MOR and TRA groups were 6 months (IQR 6–30), 6.5 months

Table 1 Number of analgesic rescues per group at different intraoperative time points

		Time					
	Group	T1	T2	T3	T4	T5	Total
Number of intraoperative analgesic rescues	MET*	0	0	5	6	2	13
	MOR	0	0	3	3	0	6
	TRA†	0	1	1	8	0	10
	Total	0	1	9	17	2	29

*Three cats needed two rescues (one at T3 and T5, and the other two at T3 and T4); one patient needed three rescues (at T3, T4 and T5)
†One cat needed two rescues (at T2 and T4)
MET = methadone; MOR = morphine; T0 = baseline; T1 = post-induction; T2 = skin incision; T3 = ligation of the first ovarian pedicle; T4 = ligation of the second ovarian pedicle; T5 = ligation of the cervix; TRA = tramadol

(IQR 6–40) and 8.5 months (IQR 6–36), respectively. There were no significant differences among groups regarding body weight ($P = 0.2319$) or age ($P = 0.5812$).

Sedation and anesthesia

Twenty minutes after premedication, profound sedation was observed in one cat from the MET group (score 3), whereas mild sedation occurred in two (score 1) and five (score 1) cats in the MOR and TRA groups, respectively. The median sedation scores were 0 (IQR 0–3), 0 (IQR 0–1) and 1 (IQR 0–1) in the MET, MOR and TRA groups, respectively.

The mean propofol doses were 7.4 ± 2.2 mg/kg, 9.0 ± 2.3 mg/kg and 7.7 ± 3.0 mg/kg in MET, MOR and TRA groups, respectively. The mean anesthetic time in the MET, MOR and TRA groups was 41.89 ± 6.23 mins, 36.63 ± 3.38 mins and 39.67 ± 5.61 mins, respectively. There were no significant differences among groups in propofol dose ($P = 0.3531$) or anesthetic time ($P = 0.1445$).

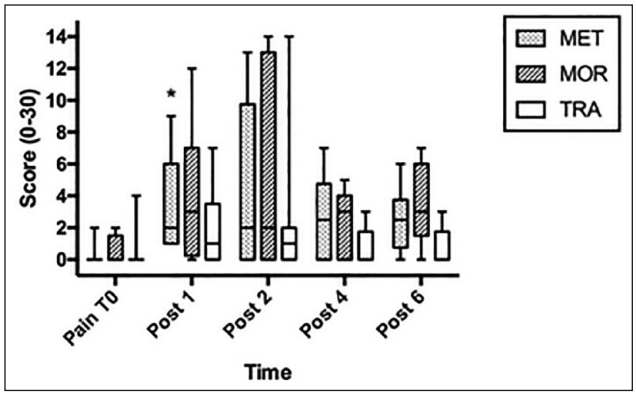

Figure 1 Pain scale scores during the study. MET group (n = 10): cats received methadone; MOR group (n = 10): cats received morphine; TRA group (n = 10): cats received tramadol.[16] Data are expressed as the average group score of pain (0–30). *Statistically significant difference in the MET group between Pain T0 and Post 1 ($P < 0.05$)

Intraoperative analgesia

Of the 30 patients, 23 required rescue analgesia. No differences were found in the frequency of intraoperative rescue analgesia between groups. Table 1 shows the number of rescues per group. The greatest number of rescues occurred at time T4. Five cats needed more than one intraoperative rescue, four of which belonged to the MET group and one to the TRA group. When the total fentanyl dose used for rescue analgesia was compared, no significant differences between groups were found. The median doses were 3.1 µg/kg (IQR 2.5–5) in the MET group, 2.5 µg/kg (IQR 2.18–2.5) in the MOR group and 2.5 µg/kg (IQR 2.5–2.5) in the TRA group. Isoflurane requirements were analyzed by comparing FE 'Iso (MET 1.44 ± 0.26%; MOR 1.43 ± 0.18%; TRA 1.40 ± 0.19%). No significant differences between the groups were found.

Postoperative analgesia

For postoperative analgesia, 26/30 cats were assessed. Four cats (one from the MET group, two from the MOR group and one from the TRA group) were discarded from postoperative evaluation due to aggressive behavior. When comparing pain scores between groups, no significant differences were found (Figure 1). When analyzing results within groups, MET had a higher pain score in Post 1 compared with T0 (0 [IQR 0–0] vs 2 [IQR 0.25–7]; $P = 0.017$) (Figure 1).

Rescue analgesia was required for 7/26 cats up to Post 6 and these cats were discarded from further analysis. The first rescues occurred in Post 1 in the MET and MOR groups, while the largest number of rescues occurred in Post 2. Of these seven cats, three belonged to the MET group, three to the MOR group and one to the TRA group. There were no significant differences in the frequency of rescue analgesia between groups.

An increase in glycemia was observed between Glu-Pre and Glu-Post in the MET group (69.5 mg/dl [IQR 64–72) vs 102.5 mg/dl [88.25–115]; $P = 0.03$) and the TRA group (73 mg/dl [IQR 70.25–100] vs 105 mg/dl [IQR 92.25–118.5]; $P = 0.01$). No differences in postoperative values were observed in the MOR group when compared

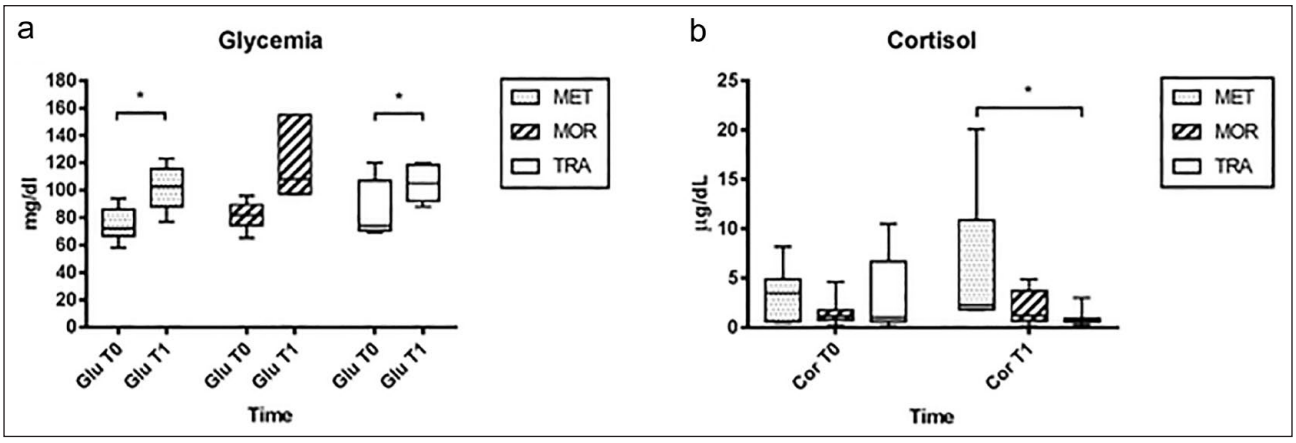

Figure 2 (a) Glycemia levels (mg/dl) evaluated at different time points in the different groups. (b) Cortisol levels (µg/dl) evaluated at different time points in the different groups. MET group (T0: n = 10; T1: n = 9): cats received methadone; MOR group (T0: n = 10; T1: n = 8): cats received morphine; TRA group (T0: n = 10; T1: n = 9): cats received tramadol. Data are expressed as median for each group. *Significant differences were observed between time points in panel (a) and between the MET and TRA groups in panel (b) ($P < 0.05$)

with preoperative values (Figure 2a). Significant differences between groups were not found.

No significant difference was found in serum cortisol concentrations within each group (Figure 2b). When comparing cortisol concentrations between groups, no differences were found in Cor-Pre. However, in Cor-Post, the MET group had higher values than the TRA group (2.28 µg/dl [IQR 1.84–10.86] vs 0.72 µg/dl [IQR 0.58–0.95]; $P = 0.01$) (Figure 2b).

Adverse effects

When HR was evaluated, a decrease at T1 was observed in all groups in comparison to T0 ($P < 0.05$) (Table 2). HR comparisons between groups showed a lower HR at T1 in the MOR group (115 beats/min[1] [IQR 101–145]) compared to the MET group (143 beats/min[1] [IQR 136–161]) ($P = 0.02$). Bradycardia was observed in 50% of the patients in the MOR group at T1, while in the MET and TRA groups, only one cat in each group presented with

Table 2 Physiological variables recorded at different time points

		Time					
	Group	T0	T1	T2	T3	T4	T5
HR (beats/min)	MET	196 (186–212)	143 (136–161)a*	134 (123–157)	194 (181–199)	194 (173–212)	182.5 (161–195)
	MOR	202 (181–216)	115 (101–145)b*	124 (108–172)	180 (151–200)	180 (167–203)	171 (158–187)
	TRA	188 (152–198)	133 (126–147)*	132 (123–144)	190 (182–194)	195 (176–211)	172 (158–186)
f_R (breaths/min)	MET	44 (20–58)	26 (20–38)	28 (23–37)	32 (23–40)	30 (20–35)	28 (16–31)
	MOR	44 (37–63)	20 (16–36)*	28 (20–34)	32 (23–34)	28 (20–32)	28 (22–39)
	TRA	56 (42–60)	24 (15–25)*	18 (15–25)	30 (21–34)	22 (15–30)	14 (12–22)
SAP (mmHg)	MET	130 (119–142)	70 (69–80)a*	75 (68–100)	130 (116–146)	127 (98–140)	120 (108–130)
	MOR	132 (125–150)	67 (50–76)*	80 (67–91)	122 (105–155)	127 (110–138)	112 (103–120)
	TRA	120 (107–152)	61 (55–66)b*	75 (72–93)	155 (137–170)	142 (125–172)	117 (110–128)
PE $'CO_2$ (mmHg)	MET	–	27 (25–30)	30 (27–32)	25 (22–30)	27 (22–31)	26 (23–35)
	MOR	–	30 (25–31)	30 (29–32)	29 (24–32)	28 (24–30)	29 (23–36)
	TRA	–	30 (25–33)	33 (30–34)	31 (26–35)	31 (25–35)	31 (27–37)
PE $'CO_2$ (kPa)	MET	–	3.6 (3.3–3.9)	3.9 (3.6–4.3)	3.3 (2.9–3.9)	3.6 (2.9–4.1)	3.5 (3.0–4.7)
	MOR	–	3.9 (3.3–4.1)	3.9 (3.9–4.3)	3.9 (3.2–4.3)	3.7 (3.2–3.9)	3.9 (3.1–4.8)
	TRA	–	3.9 (3.3–4.4)	4.4 (3.9–4.5)	4.1 (3.5–4.7)	4.1 (3.3–4.7)	4.1 (3.6–4.9)

Data are expressed as median (interquartile range). Significant differences between groups are indicated by letters, with 'a' being a greater value than 'b'

*Statistically significant difference between T0 and T1 within the group ($P < 0.05$)

MET = methadone; MOR = morphine; T0 = baseline; T1 = post-induction; T2 = skin incision; T3 = ligation of the first ovarian pedicle; T4 = ligation of the second ovarian pedicle; T5 = ligation of the cervix; TRA = tramadol

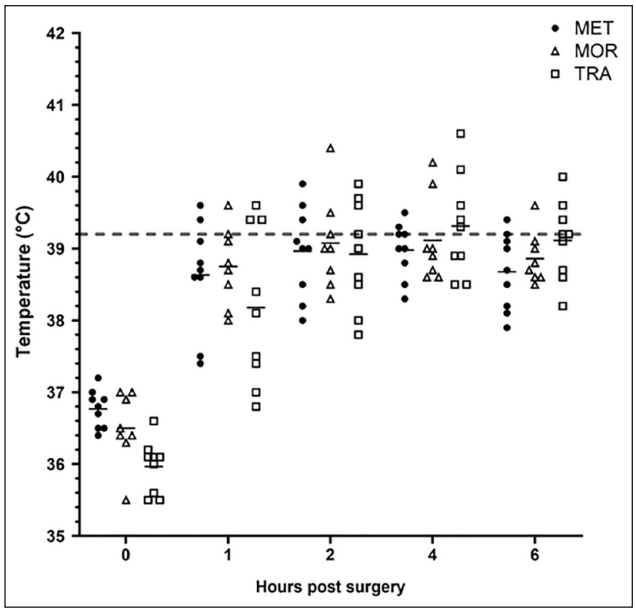

Figure 3 Postoperative rectal temperatures (°C) at 0–6 h postoperatively. MET group (n = 10): cats received methadone; MOR group (n = 10): cats received morphine; TRA group (n = 10): cats received tramadol. Rectal temperature of cats at tracheal extubation (0 h) and 1, 2, 4 and 6 h postoperatively for each treatment group. The data are expressed as individual values of °C. The dotted line is the upper limit of normal body temperature in cats (39.2°C)

bradycardia at T1. SAP was significantly reduced at T1 in all groups in comparison with T0 ($P < 0.05$) (Table 2). Hypotension was evident in 97% of patients at T1, and the TRA group (61 mmHg [IQR 55–66.25) had lower values than the MET group (70 mmHg [IQR 69–80]; $P = 0.04$). f_R was significantly decreased at T1 in both the MOR and TRA groups in comparison to T0 ($P < 0.05$) (Table 2). PE 'CO_2 did not significantly change between or within groups. Regarding behavioral changes, euphoria (one cat) and dysphoria (one cat) were observed 10 mins after premedication in the MET group. Conversely, in the MOR group, one cat presented with dysphoria during anesthetic recovery. None of these behavioral changes were observed in the TRA group. Nausea and vomiting were also observed minutes after the premedication. In the MOR group, one cat presented with nausea and four experienced vomiting, while in the TRA group, one cat showed nausea. In the MET group, none of these side effects occurred.

Postoperative hyperthermia was observed in all three groups. Hyperthermia was observed in 4/9 cats undergoing surgery in the MET group, and one of them showed sustained hyperthermia up to 6 h postoperatively. In the TRA group, 5/9 cats presented hyperthermia at different times postoperatively, and in 3/9 cats, hyperthermia persisted at 6 h postoperatively. In the MOR group, 4/8 cats showed hyperthermia at some time during the postoperative period, persisting in one cat until the end of the study (Figure 3).

Discussion

The aim of this study was to evaluate the intra- and postoperative analgesic efficacy of the opioids methadone, morphine and tramadol. Interestingly, tramadol produced intra- and postoperative analgesia similar to both methadone and morphine in cats undergoing ovariohysterectomy.

Intraoperative analgesia was evaluated using rescue analgesia requirements, as well as requirements of isoflurane during surgery. Regarding intraoperative times, most analgesic rescues occurred at T4. This corresponds to the second ovarian pedicle ligation, which is considered a high-intensity nociceptive stimulus.[22] Analgesic rescue was required by 76.7% of the patients at some time along the assessed time points, with no differences between the three groups, and the administered doses of fentanyl did not differ between groups. In addition, the requirements of isoflurane were similar across the groups and remained close to the minimum alveolar concentration described for cats in previous studies.[23]

One explanation for the high percentage of cats needing intraoperative analgesic rescue may, in part, be due to the use of opioids-only premedication. The addition of another analgesic drug with a different mechanism of action could have decreased analgesic requirements. In one study, 40.9% of female cats undergoing ovariohysterectomy required rescue analgesia when methadone and dexmedetomidine were used,[24] which represents a lower percentage compared with our results. Furthermore, the doses of the drugs used were close to the lowest range.[4]

However, the results obtained in this study in relation to intraoperative rescue analgesia should be taken with caution, since the small group size and low values obtained may be influencing the analysis. Future studies with a larger number of animals are necessary to draw conclusions in this area.

The UNESP-Botucatu MCPS, a scale validated for assessing ovariohysterectomy pain in cats, was used for assessing postoperative pain.[16] Pain assessment methods that integrate observations and interactions with the animal, as the pain scale used in this study does, are considered the most reliable techniques available to detect pain.[25] No differences were observed between the postoperative analgesia provided up to 6 h postoperatively by the three treatments investigated in this study. Appropriate postoperative pain relief was also observed in cats after ovariohysterectomy using methadone and tramadol, which produce effective postoperative analgesia.[8,11] It should be noted that tramadol, an 'atypical' opioid, produced postoperative analgesia without

significant differences from morphine in our study, which may be partly explained by the high concentrations of the active metabolite M1 found in cats, which provides better analgesia than in other species, such as dogs.[10]

Of the 30 cats, four behaved aggressively during manipulation and were therefore discarded from the postoperative analyses. This was due to the fact that the behavior interferes with the interpretation of the different items of the pain scale. Higher scores have been described in shy or aggressive cats and lower scores in friendly cats.[26]

In this study, hyperglycemia was observed in 27% of the cases, with no differences in its pattern between treatments. Pain can cause several changes in the neuroendocrine axis. This may result in an increase in glycemia and serum cortisol concentrations,[27] which can be used as a complementary tool for surgical stress assessment;[28] however, cortisol may not be associated with the level of analgesia, because it is poorly correlated with acute pain in cats.[29] Our results showed that the concentrations of cortisol were greater in the MET group than in the TRA group. These results coincide with those described by other investigators, where methadone has been reported to increase the plasma concentrations of cortisol in dogs without pain, but this has not been reported in cats.[30]

Postanesthetic hyperthermia has been previously described for cats after the administration of opioids.[12,20,31,32] In our study, we found a high incidence of postoperative hyperthermia in all the groups, with a trend to higher values in the TRA group. Cannarozzo et al[33] reported an incidence of hyperthermia of 56% in cats that were administered morphine, similar to our study with an incidence of 50%. Reports on the effect on body temperature of tramadol and methadone in cats are lacking. Opioid-associated hyperthermia is due to alterations in the temperature set point at the hypothalamus, but the ability to thermoregulate remains intact; this effect is usually transitory and self-limiting.[33] Nevertheless, it is important to recognize opioid-induced hyperthermia and to monitor it closely, since this could affect the recognition of true fever in a clinical setting.

Regarding cardiorespiratory effects, opioids can cause bradycardia by increasing parasympathetic activity in neurons that innervate the heart.[15] In this study, bradycardia was observed at T1 in the three groups, with the HR in the MOR group being significantly lower than in the MET group. Hypotension was found in 97% of cases at T1 relative to T0. However, this could have been caused by the hypotensive effect of propofol,[34] which was used during anesthetic induction at comparable doses to those required in cats without premedication.[35] Fluid therapy was administered using lactated Ringer's solution at 10 ml/kg/h throughout the procedure, a fluid rate that it is no longer recommended for cats during anesthesia, because during the time of this study the fluid therapy protocol in the hospital was not updated according to the last anesthesia and monitoring guidelines of the American Animal Hospital Association.[36] Hypotension was treated by lowering the vaporizer setting or giving an IV fluid bolus (10 ml kg^{-1}) of lactated Ringer's solution. When comparing the propofol doses between groups, no differences were found.

Respiratory depression is associated with the use of opioids through the inhibition of the neurons of the medulla oblongata in response to hypercapnia.[37] The impact on the respiratory system suggested a relevant decrease of the f_R in the MOR and TRA groups at T1 in comparison to T0. However, this decrease was not followed by hypercapnia measured through capnography; nevertheless, arterial blood gases should have been measured to confirm this, and dead space was not calculated.

Behaviorally, sedation was mild in most patients in all groups. Moderate sedation was found in only one patient from the MET group. Sedation is an expected effect in dogs after the administration of opioids, but it is less common in cats.[4] When sedation was observed, it did not last through the postoperative period, which allowed not only for a rapid recovery but also for pain assessments 1 h after extubation. After premedication in the MET group, euphoria was observed in one cat and dysphoria in another. Robertson[25] described euphoria in cats after the use of opioids at therapeutic doses. Bortolami et al[8] also observed euphoria in cats after the administration of methadone in combination with acepromazine. Dysphoria, which has been described for opioids used at therapeutic and supratherapeutic doses in cats,[15] was observed in one cat from the MOR group during recovery. Behavioral changes were not observed in the TRA group. This could have been caused by a weak effect in the μ-opioid receptor,[14] which could be an advantage in comparison to the pure μ-opioid receptor agonists.

In this study, nausea and vomiting were observed in the MOR group. The use of morphine in cats is associated with nausea and vomiting due to the stimulation of the chemoreceptor trigger zone.[14] One cat in the TRA group showed nausea, which is not commonly described with the use of tramadol administered via the IM route. However, Jiwlawat and Durongphongtorn[38] described vomiting in 1/8 cats receiving 2 mg/kg tramadol IM. No patient in the MET group experienced nausea or vomiting, which represents an advantage in comparison with the use of morphine as described in the literature.[14]

A limitation of this study was that it may be underpowered due to the exclusion of cats that received rescue analgesia in the postoperative time. Further studies should consider a larger number of animals to account for this limitation. Another limitation might arise from the dose of each drug used; whether these doses are equally potent has not been described in the literature, and this

could alter the analgesic results obtained with each drug. For these reasons, further investigation is warranted.

Conclusions

Methadone, morphine and tramadol produced adequate postoperative analgesia in 19/26 healthy female cats undergoing ovariohysterectomy, without differences between groups. However, some cats required postoperative rescue analgesia, so this should be considered in clinical practice decision making. Intraoperative analgesia was not sufficient. Significant cardiovascular or respiratory effects contraindicating the use of these drugs were not found.

Hyperthermia was a common side effect; body temperature should be monitored closely during recovery in cats that have been administered opioids. Tramadol administered IM may be a suitable preventive alternative for postoperative pain management in cats, especially given the restrictions on the use of opioids in veterinary medicine in some countries.

Supplementary material The following file is available as supplementary material:
Appendix A: Sedation score table.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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