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Evaluation of intraperitoneal administration of morphine on post-operative pain management after ovariohysterectomy in dogs

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Abstract

The present prospective randomized experimental study was designed to assess pain control with intraperitoneal morphine following ovariohysterectomy in dogs. A group of 12 mixed breed female dogs, aged 1–2 years, weighing 19.95 ± 0.95 kg were included. Forty minutes after sedation with 0.05 mg/kg intramuscular acepromazine 1%, anaesthesia was induced with propofol (4 mg/kg). The dogs were connected to the inhalation anaesthesia circuit using isoflurane. Ovariohysterectomy was performed, and before the closure of linea alba, the animals received intraperitoneal morphine (0.5 mg/kg) (in group M) and saline (0.2 ml/kg) (in group S). No significant difference was detected in total protein and glucose levels between the groups, while the cortisol level in group M was significantly lower than group S 1, 3 and 6 h after surgery. Furthermore, the comparison of the rectal temperature, heart rates and respiratory rates showed no major differences. Additionally, no significant alterations were detected between the groups considering the changes in the pain scores with simple descriptive score, Glasgow, University of Melbourne pain scale, sedation status and Sammarco methods. Finally, three cases in group S and two cases in group M were given an intramuscular analgesic rescue dose of morphine. Although a significant decline was observed in cortisol levels following intraperitoneal morphine administration, there were no beneficial changes in the efficiency of post-operative analgesia in status and clinical signs compared to the control group. Further studies are required to investigate intraperitoneal morphine effectiveness in post-operative pain management.

KEYWORDS
dog, intraperitoneal, morphine, ovariohysterectomy

1 | INTRODUCTION

Ovariohysterectomy is a common procedure for spaying female dogs (Okkens et al., 1997). The benefits of this surgery include population control, prevention of reproductive system diseases and the reduction of unpleasant behaviours related to sex hormones (Pereira et al., 2018). This surgery is classified as a major surgery (Hardie et al., 1997), which is associated with mild to moderate post-operative pain (Campagnol et al., 2012; Hardie et al., 1997). Pain is an unpleasant experiential sensation associated with actual or potential tissue damage

(Mathews et al., 2018). Post-operative pain, which is acute and pathological pain, cause many negative effects such as food intake degression, protein catabolism rise, diminished respiratory function, uneven heartbeat, central sensitivity rise to painful stimuli and chronic pain (Flecknell & Waterman-Pearson, 2000). To control pain, sedatives with local analgesic effects, local anaesthetics and opioid analgesics are used (Braga & Fantoni, 2005; Campagnol et al., 2012; Carpenter et al., 2004; Chilkoti et al., 2019; Lambertini et al., 2018; Morgaz et al., 2013). In recent years, the use of drugs for analgesia has been increasing (Campagnol et al., 2012). Effective and better pain management is achieved when multiple analgesics are used to target multiple pain pathways (Hellyer et al., 2007; Reuben & Buvanendran, 2007). To control the pain of abdominal surgeries in medicine and veterinary medicine, the intraperitoneal method is used. In this procedure, a local anaesthetic or analgesic is splashed on the viscera before closing the abdomen (Campagnol et al., 2012; Carpenter et al., 2004; Chilkoti et al., 2019; Golubović et al., 2009; Guerrero et al., 2016; Lambertini et al., 2018; Ng et al., 2002).

Opioids are widely used in analgesic techniques to control post-operative pain (Nolan & Reid, 1993). Morphine is one of the main derivatives of opioid analgesics. It binds more to mu receptors and reduces nerve activity by increasing the potassium transport out of the cell or by reducing the flow of calcium into the nerve cell (Pasternak, 2005). Morphine causes pain relief, relaxation and drowsiness through the central nervous system. Other effects of morphine include nausea and vomiting, weakening of the respiratory centre and cough reflex, and narrowing and dilation of the eye pupil (Grimm et al., 2015). The half-life of morphine is short, about an hour, so repeated administration or regular injection is necessary for moderate to severe pain management. The drug is metabolized by the liver and excreted in the urine (Grimm et al., 2015).

The potency of morphine is 10 times that of tramadol (Saberi Afshar et al., 2017), and causes more respiratory depression than tramadol (Mastrocinque & Fantoni, 2003). In the past decade, several clinical studies have been published that show the simultaneous administration of opioids, tramadol or morphine and local anaesthetics, bupivacaine, produce longer and deeper analgesia than separate use of each drug following open or laparoscopic abdominal surgery in humans (Golubović et al., 2009; Karsli et al., 2003; Memis et al., 2005; Ng et al., 2002). In a human study, intraperitoneal injections of morphine and bupivacaine were performed after gallbladder resection to control pain, which ultimately produced appropriate analgesia (Hernandez-Palazon et al., 2003; Schulte-Steinberg et al., 1995). In a similar operation, a combination of bupivacaine and morphine was used to induce analgesia in one group, and bupivacaine and magnesium sulfate were used intraperitoneally in another group, revealing that the use of the combination drug had a better analgesic effect (Sadaqa et al., 2018).

In addition, the effects of intraperitoneal injections of bupivacaine, morphine and dexamethasone in the elective caesarean section under general anaesthesia have been evaluated, and appropriate analgesia has been obtained in humans (Hosseini Valami et al., 2017). In a study evaluating intraperitoneal injection of morphine following abdominal

The study was performed to assess pain control with intraperitoneal morphine following ovariohysterectomy in dogs. There were no beneficial changes in efficiency of post-operative analgesia in status and clinical signs compared to the control group.

surgery in rats, a reduction was reported in abdominal visceral adhesions (Bakhtiary et al., 2014).

Regarding the need to control pain with selected drugs and the impossibility of providing analgesics to the patient due to professional ethics and the addictive aspect of these drugs, the intraperitoneal administration of opioids seems beneficial. The authors did not find a published study investigating the analgesic properties of intraperitoneal route of morphine. Therefore, the current study aimed to assess the efficacy of intraperitoneal morphine to manage ovariohysterectomy pain in dogs.

2 | MATERIALS AND METHODS

The project was approved by the Local Committee of the Institutional Animal Care of Shahid Chamran University of Ahvaz, Iran.

2.1 | Animals

The study was done on 12 clinically healthy female dogs of mixed-breed aged 1—2 years old and weighted 19.95 ± 0.95 kg. The dogs were caged separately and nourished with a commercial diet and had free access to water. The dogs were randomly assigned into two groups with six animals in each: Group S (saline) (control) and Group M (morphine) (treatment). Food was not provided for 12 h and water for 2 h before the surgery.

2.2 | Procedure

First, the dogs were sedated using 0.05 mg/kg intramuscular acepromazine (Neurotranq, Acepromazine maleate 10 mg/ml, Alfasan, Woerden-Holland) (Grimm et al., 2015). An angiocatheter (No. 20) was introduced into both the cephalic veins and the ventral abdomen was clipped. Forty minutes after sedation, anaesthesia was induced with 4 mg/kg propofol (Propofol-Lipuro, B. BRAUN, Germany) titration to effect (Grimm et al., 2015). After endotracheal intubation, the dogs were attached to a vaporiser in circuit inhalation anaesthesia machine loaded with isoflurane (FORANE®, ABBOTT, UK) vaporized in oxygen. Isoflurane was administered at 1.5% and 1.5 L oxygen. Anaesthesia was stopped when the incision was sutured. To monitor the dogs, vital parameters (heart rate, respiratory rate, rectal temperature) were assessed at 5 min intervals, but data were not documented. Furthermore, intravenous ketoprofen (2 mg/kg, Ketomax, Royandarou,

Iran) (Lemke & Dawson, 2000), and cefazolin (22 mg/kg, Cefazol, Afa Chemi Co, Iran) were immediately administered before the operation. Note that 10 ml/kg/h Ringer's solution was also administrated through IV during the operation. Then, ovariohysterectomy was done by the same team. Before closing the midline incision, morphine (0.5 mg/kg, Morphine Sulfate 10 mg/ml, Darou Pakhsh, Iran) with the total volume of 0.2 ml/kg was splashed on the abdominal viscera in group M, whereas saline (0.2 ml/kg) was used in group S. After surgery, cefazolin (22 mg/kg) was given intramuscularly every 12 h for 3 days.

Surgery duration; time between starting incision up to closing it and recovery duration; and time between inhalation anaesthesia stoppage and sternal recumbency were recorded. The pain was graded, and vital parameters (respiratory rate, heart rate, and rectal temperature) were documented at 30 min, 1, 3, 6, 12 and 24 h after extubation. To assess the patients' sedation status, a score range of 0 (without sedation) to 3 (deep sedation) was used (Lambertini et al., 2018). Also, Sammarco method (Groppetti et al., 2011; Sammarco et al., 1996), descriptive pain assessment methods, simple descriptive score (SDS), the University of Melbourne pain scale (Saberi Afshar et al., 2017) and short-form Glasgow Composite Measure Pain Scale (CMPS-SF) were applied (Reid et al., 2017). The CMPS-SF score $\geq$6 out of 24 or 5 out of 20 (Lambertini et al., 2018), led to rescued with 0.5 mg/kg morphine intramuscularly (Campagnol et al., 2012).

Furthermore, the serum levels of cortisol (ELISA method, Monobind, Germany), glucose and total protein (Colorimetric assay kits, Parsazmoon, Iran) were assessed. Blood was sampled before sedation, before intraperitoneal splash and 1, 3 and 6 h after extubation. The sera were refrigerated at −70°C.

2.3 | Statistical analysis

IBM SPSS Version 23 (SPSS Inc.; IL, USA) was used for data analysis. Independent samples t-test and Mann–Whitney U test were used to compare the physiologic values and sedation scores between treatments, respectively. Repeated measure analysis of variance and Wilcoxon signed-rank test were used to analyze the physiologic data and sedation scores within each treatment, respectively. The statistical power on the basis of cortisol means on the third and fourth sampling times with the sample size six were estimated at 0.996 and 1.000, respectively. Also, the statistical power on the basis of pain means on the first and second and third scoring times with the sample size 6 were estimated at 0.994, 0.991 and 0.989, respectively. Data were showed as mean $\pm$ standard error. The point of significance was assumed as $p < 0.05$.

3 | RESULTS

The animal's weight, the surgery time and the recovery duration did not show any significant differences between treatments (Table 1). No statistically significant differences were observed in the comparison of heart rates between the study groups and during the evaluation

TABLE 1 Weight, surgery duration and recovery duration resulted as mean $\pm$ SE in dogs before and after ip administration of 0.5 mg kg^{-1} morphine (M) (0.2 ml kg^{-1} diluted) or administration of 0.2 ml kg^{-1} saline (S) undergoing ovariohysterectomy ($n = 6$)

Groups / Parameter	Weight (kg)	Surgery duration (min)	Recovery duration (min)
S	21.03 ± 1.62	41.66 ± 1.66	34.16 ± 3.27
M	18.66 ± 0.56	42.50 ± 2.14	42.50 ± 5.73

process in group M. In group S, 6 ($p = 0.039$) and 24 ($p = 0.041$) h after surgery, a significant decrease was observed in heart rate compared to the baseline time (Table 2). Comparing the respiratory rate, no significant difference was observed between treatments. In group M, there were fluctuations in the number of breaths, but these changes were not considered significant. While in group S, 30 min ($p = 0.022$), 1 h ($p = 0.019$) and 6 h ($p = 0.029$) after surgery, the respiratory rate decreased significantly (Table 2). The rectal temperature did not change statistically between the study groups and also the study times in each of the groups (Table 2).

A significant decrease was detected in the serum cortisol levels in group M compared to group S, 1 ($p = 0.001$), 3 ($p = 0.00$) and 6 ($p = 0.005$) h after surgery (Table 3). In group S, there was no significant alteration in the serum cortisol levels over time compared to the baseline. However, in group M, the serum cortisol levels declined significantly 3 ($p = 0.013$) and 6 ($p = 0.041$) h after surgery compared to the baseline (Table 3). No significant difference was distinguished between treatments concerning the serum glucose levels when comparing all studied times. In group S, a significant increase was showed in the glucose levels at all times compared to the baseline (5 min before peritoneal administration [$p = 0.002$], 1 h [$p = 0.001$], 3 h [$p = 0.014$] and 6 h [$p = 0.005$] after surgery) (Table 3). In group M, an increase was observed in the serum glucose levels at all times compared to the baseline, which was statistically significant 5 min before the peritoneal administration ($p = 0.010$) and 1 ($p = 0.016$) and 6 h ($p = 0.047$) after surgery compared to the baseline (Table 3). Intergroup comparisons did not show any significant difference in total protein during the study period. Decreasing changes in this parameter in group S were considered significant at all evaluation times compared to the baseline (5 min before peritoneal administration [$p = 0.008$], 1 h [$p = 0.002$], 3 h [$p = 0.001$] and 6 h [$p = 0.002$] after surgery) (Table 3). In group M, a significant decrease was observed in the protein levels in all evaluation times compared to the baseline time (5 min before peritoneal administration [$p = 0.007$], 1 h [$p = 0.002$], 3 h [$p = 0.000$] and 6 h [$p = 0.001$] after surgery (Table 3).

Regarding the pain assessment data obtained via simple descriptive SDS method and also University of Melbourne pain scale and Glasgow methods, no major differences were detected between the two treatments and also within each group during the study period. Moreover, there was no major difference between treatments in pain evaluation data using the simple descriptive Sammarco method. However, in group M, the increasing trend of pain scaling was significant 6 ($p = 0.041$), 12 ($p = 0.042$) and 24 h ($p = 0.039$) after surgery

TABLE 2 Vital signs results as mean ± SE in dogs before and after IP administration of 0.5 mg kg^{-1} Morphine (M) (0.2 ml kg^{-1} diluted) or administration of 0.2 ml kg^{-1} Saline (S) undergoing ovariohysterectomy (n = 6)

Parameters	Group/ Times	Before surgery 30 min (*) a	After surgery 30 min (†) b	1 hour c	3 hours d	6 hours e	12 hours f	24 hours g
Hear rate (rate/min)	S	114.83 ± 13.76 eg	125.50 ± 3.26 cdefg	109.33 ± 6.92 beg	88.83 ± 10.64 b	82.66 ± 8.55 abc	91.00 ± 11.13 b	74.33 ± 4.88 abc
	M	112.50 ± 3.99	129.00 ± 7.89 deg	108.00 ± 8.24	96.00 ± 9.22 b	93.66 ± 8.22 b	102.00 ± 7.39	97.66 ± 9.31 b
Respiratory rate (breath/ min)	S	27.20 ± 1.35 bcd	16.83 ± 1.79 afg	18.00 ± 1.86 af	19.83 ± 2.37 af	23.33 ± 3.95	24.00 ± 2.12 bcd	24.00 ± 2.28 bc
	M	24.00 ± 1.82	21.33 ± 1.97	24.66 ± 2.45	27.33 ± 5.10	21.33 ± 1.68	29.00 ± 5.72	25.66 ± 2.49
Rectal Temp- erature (°C)	S	38.90 ± 0.09	37.28 ± 0.31	37.31 ± 0.16	37.76 ± 0.16	38.08 ± 0.12	38.40 ± 0.14	38.36 ± 0.31
	M	38.68 ± 0.13	37.00 ± 0.23	36.85 ± 0.26	37.06 ± 0.38	37.58 ± 0.28	38.00 ± 0.23	38.43 ± 0.18

*Indicates a significant difference between groups (p < 0.05).
Different letters in each row indicate a significant difference with the time before surgery in each group (p < 0.05).
(p < 0.05).

TABLE 3 Blood serum parameters as mean ± SE in dogs before and after IP administration of 0.5 mg kg^{-1} morphine (M) (0.2 ml kg^{-1} diluted) or administration of 0.2 ml kg^{-1} saline (S) undergoing ovariohysterectomy (n = 6)

Parameters	Group/ Times	Before surgery 30 min (a)	Before IP administration 5 min (b)	After surgery 1 hour (c)	3 hours (d)	6 hours (e)
Cortisol (μg/dl)	S	18.27 ± 1.8	18.51 ± 0.77	19.00 ± 1.38	16.68 ± 1.13	16.70 ± 1.38
	M	15.71 ± 1.23 de	17.71 ± 0.74 cde	11.18 ± 0.59 * bd	7.27 ± 1.02 * abc	5.74 ± 2.53 * ab
Glucose (mg/dl)	S	57.33 ± 7.14 bcde	304.50 ± 47.23 acde	202.16 ± 23.70 abde	124.33 ± 18.57 abc	104.00 ± 7.66 abc
	M	46.50 ± 5.19 abce	239.50 ± 44.42 ae	168.66 ± 31.68 a	144.66 ± 40.87	106.66 ± 23.74 ab
Total protein (g/dl)	S	6.21 ± 0.23 bcde	5.18 ± 0.27 a	5.41 ± 0.24 a	5.08 ± 0.11 a	5.34 ± 0.25 a
	M	5.76 ± 0.14 bcde	5.08 ± 0.28 a	4.95 ± 0.11 a	4.75 ± 0.13 ae	4.86 ± 0.12 ad

* Indicates a significant difference between groups (p < 0.05).
Different letters in each row indicate a significant difference with the time before surgery in each group (p < 0.05).
(p < 0.05).

compared to the baseline (Table 4). The statistical evaluation of relaxation data showed no important alteration between both groups. However, group S, 12 (p = 0.034) and 24 (p = 0.020) h after surgery and group M, 3 (p = 0.046), 6 (p = 0.034), 12 (p = 0.038) and 24 (p = 0.025) h after surgery were statistically more relaxed (Table 4). In some animals and at some points of time in both groups, morphine was administered based on the Glasgow pain assessment index (Table 5).

4 | DISCUSSION

Inadequate pain management is common and can have serious consequences. Effective prevention and relief of acute pain may improve surgical outcomes, prevent side effects and increase the quality of life (Apfelbaum et al., 2003). Local anaesthesia has been used alone or in combination with opioid analgesics to reduce post-operative pain (El-Labban et al., 2011; Khan et al., 2012). Ovariohysterectomy in healthy dogs is a selective surgical procedure associated with moderate post-

operative pain (Caulkett et al., 2003). In this study, the intraperitoneal injection of morphine was examined if it could induce post-operative analgesia or not. In 2006, Boddy and Rhodes (2006) found positive effects for intraperitoneal injection during a study on the intraperitoneal injection of local anaesthesia in abdominal laparoscopic surgery.

Clinicians measure heart rate to assess a patient's pain response because cardiovascular function control systems are closely related to pain perception (Faye et al., 2010). Terkelsen et al. (2005) examined electrocardiography and focused on respiratory rate (RR) intervals; they found that following acute pain, the average RR intervals decreased due to circulating catecholamines and increased heart rate. In the present study, group M did not show any statistically significant difference compared to the baseline during the evaluation process, while group S revealed a significant decrease compared to the baseline 6 and 24 h after surgery. Other parameters such as respiration and anal temperature were also evaluated. In 2017, Jafari et al (2017). demonstrated that acute pain increased the number, flow and volume of respiration. No statistical alteration was showed between

TABLE 4 Sedation and pain scoring results as median (min-max) in dogs after termination of surgery of 0.5 mg kg^{-1} morphine (M) (0.2 ml kg^{-1} diluted) or administration of 0.2 ml kg^{-1} saline (S) undergoing ovariohysterectomy ($n = 6$)

		Before surgery	After surgery				
Parameters	Group/Times	30 min (*)	1 h	3 h	6 h	12 h	24 h
Sedation	S	3 (2–3)	2 (2–3)	2 (2–3)	1.5 (1–3)	1 (1–2) *	1 (1–1) *
	M	2 (2–3)	2 (2–3)	2 (2–2) *	2 (1–2) *	1 (1–2) *	1 (0–1) *
SDS	S	0 (0—3)	0 (0—0)	0 (0—0)	0 (0—1)	0 (0—1)	0 (0—1)
	M	0 (0—1)	0 (0—1)	0 (0—0)	0 (0—0)	0 (0—1)	0 (0—0)
Sammarco	S	5.5 (0—6)	5 (1—7)	5 (0—6)	6 (0—6)	6 (4—8)	6 (5—6)
	M	3 (3—5)	3 (1—5)	5 (1—7)	0 (0—3)*	7 (6—8)*	6 (6—6)*
UMPS	S	3.5 (0–5)	3.5 (0–7)	2.5 (1–5)	4 (0–5)	4.5 (4–6)	4 (3–7)
	M	3 (0–7)	3 (0–5)	3.5 (3–6)	3.5 (2–4)	3 (2–4)	3 (2–3)
CMPS-SF	S	1.5 (1–3)	1 (1–3)	3 (1–5)	3 (1–4)	3 (1–6)	2 (1–6)
	M	1 (1–4)	1 (1–4)	1 (1–6)	3 (1–4)	1.5 (1–6)	2 (1–3)

Abbreviation: UMPS, University of Melbourne pain scale.
The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < 0.05$).
* indicates a significant difference with baseline in each group ($p < 0.05$).
† indicates a significant difference between groups ($p < 0.05$).

TABLE 5 Numbers of dogs received morphine (0.5 mg kg^{-1}, im) in 12 dogs before and after ip administration of 0.5 mg kg^{-1} morphine (M) (0.2 ml kg^{-1} diluted) or administration of 0.2 ml kg^{-1} saline (S) undergoing ovariohysterectomy ($n = 6$)

Groups/ Times	After surgery						
	30 min (*)	1 h	3 h	6 h	12 h	24 h	Total
S	0	0	1	1	2	3	7
M	0	0	0	0	1	1	2

the groups compared to the baseline concerning the respiratory rate, but in group S, a significant decrease was observed 30 min, 1 and 6 h after the surgery. Changes in anal temperature were not significant among the study groups during the study period compared to the baseline.

Severe pain has profound physiological effects on the endocrine system. Severe pain (acute or chronic) initially increases the activity of the hypothalamic–pituitary–adrenal pathway which in turn leads to the elevation of serum hormones such as adrenocorticotropin and cortisol (Tennant, 2013). Therefore, serum cortisol levels can be a good criterion for tracking pain (Tennant, 2012). In some studies, cortisol concentrations have been used to assess the presence of pain in addition to pain assessment scales (Devitt et al., 2005; Kongara et al., 2012). No major difference was showed between the two groups except 1 ($p = 0.001$), 3 ($p = 0.000$) and 6 ($p = 0.005$) h after the surgery. In group S, these changes were not significant at any time compared to the baseline due to the significant increase in the serum cortisol levels. However, in group M, a significant decrease was observed in the serum cortisol level 3 and 6 h after surgery compared to the baseline time.

During their study in 2001, Greisen et al. (2001) examined serum glucose levels during acute pain and concluded that acute pain primarily reduces insulin sensitivity by affecting non-oxidative glucose

metabolism. Increased cortisol levels can also lead to elevated glucose levels (Cradock & Hawthorn, 2002; Greisen et al., 2001). In the present study, cortisol was changed in some time points between treatments (Table 3). In group S, a statistically significant difference was detected at all times (5 min before administration and 3 and 6 h after surgery) related to the baseline. In group M, an increase was detected in the glucose levels at all times compared to the baseline, which was statistically significant only 5 min before the intraperitoneal injection and 1 and 6 h after the surgery compared to the baseline.

Total serum protein is a biochemical test to evaluate plasma proteins, namely albumin and globin. Many disorders are associated with changes in serum protein concentrations (Franceschini et al., 2012). The purpose of measuring protein levels was to assess the possible dehydration status of the body and as a parameter to confirm health. If the animal is dehydrated, the concentration of glucose and cortisol will also increase and will lead to errors in checking the final results. The measurement of the total serum protein did not detect any statistical alteration between the study groups, and the lack of significant change in this parameter shows a relatively stable status. Despite significant differences in the cortisol levels (in favour of morphine), no significant clinical manifestations of pain were observed. Therefore, the intraperitoneal administration of morphine did not provide an advantage over group S. Further research is recommended to explain the possibility and effectiveness of intraperitoneal morphine administration.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

ETHICAL STATEMENT

AUTHOR CONTRIBUTION

Aida Rezaeipour: Investigator, data recording and manuscript prepration; Hadi Naddaf: Thesis and Surgery, Misagh Jalali: Clinical pathology assessments, Soroush Sabiza: Thesis, Surgery and manuscript preparation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.668

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