Efficacy of Oral Transmucosal Administrations of Phenylbutazone for Postoperative Analgesia in Dogs Undergoing Ovariohysterectomy

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ABSTRACT

The aim of the present study was to evaluate the efficacy and analgesic duration of a single dose of Phenylbutazone (PBZ) administered by the oral transmucosal (OTM) or via the intravenous (IV) route immediately before induction of anesthesia in dogs undergoing elective ovohysterectomy (OVH). Twenty-seven sexually intact female dogs referred for OVH procedure from a local shelter at regular intervals over 3 months, were included in the study. The dogs were administered PBZ and the placebo on the basis of their respective treatment group (20 mg/kg, IV; 20 mg/kg via OTM administration; 1.75 ml/kg IV 0.9% NaCl) before administration of xylazine. Throughout the study, vital signs were measured at baseline (T_0, before administration of PBZ) and then at 5 (T_1), 10 (T_2), 15 (T_3), 20 (T_4), 25 (T_5), and 30 (T_6) minutes intraoperatively. Postoperative pain was assessed at 0.5, 1, 2, 3, 8, and 24 hours after operation. Groups OTM and IV had significantly lower Composite Measure Pain Scale (CMPS-SF) scores ($p<0.05$) than the control group at the 0.5, 1, 2, 3, and 8 hours postoperatively. The analgesic (carprofen) was used with all dogs. In conclusion, a single dose of PBZ administered via the OTM route before surgery provided some analgesia but was not enough on its own for the postoperative period. Additionally, PBZ administred via the OTM route did not provide a dissimilar analgesia than the IV route.

Key words: Ovariohysterectomy; Pain; Phenylbutazone; Transmucosal.

INTRODUCTION

Phenylbutazone (PBZ) is a nonsteroidal anti-inflammatory drug, first introduced in 1952 for the treatment of arthritis. PBZ has been shown to be effective in managing pain associated with a variety of companion animal diseases (1-4).

Administration of analgesics via the oral transmucosal (OTM) route provides several potential advantages over parenteral administration (5). First, it eliminates pain associated with parenteral injection, and it is relatively convenient and easy to use, with minimal training required. Second, the OTM route allows the drug to bypass the gastrointestial-hepatic portal first-pass metabolism, which increases the bioavailability over orally administered medications. Third, the oral cavity provides a large mucosal surface area, including the areas of the tongue, cheeks, and soft and hard palate, which can enable drugs to be absorbed rapidly into the systemic circulation (5). Various routes of administration for PBZ is commonly used in animals (1-3), but the OTM route has

not been used extensively in dogs due to lack of information regarding dose and efficacy supporting supporting the use of this route.

The pharmacokinetics studies of PBZ have been performed (1, 2, 6-11) in different animal species but the OTM route has not been tested. The clinical importance of the OTM route of PBZ for the management of postoperative pain in dogs is unknown. Furthermore, there is no available data concerning the therapeutic and adverse effects in dogs. Although previously investigated for pain relief of musculoskeletal problems (3), various administration routes of PBZ has not been compared for postoperative pain relief in animals undergoing elective surgery. As ovohysterectomy (OVH) procedure is one of the most common types of procedures presented to veterinary clinics except on puppies (12), the present study included this type of procedure so that the results may be of use by small animal practitioners. We hypothesized that the PBZ administered via the OTM route would be superior to placebo or IV route in providing perioperative and postoperative analgesia in dogs.

In the clinically normal animal, the body maintains euglycemia primarily via equilibrium between the glucose-lowering hormone insulin and the glucose-elevating hormones glucagon, cortisol, epinephrine, norepinephrine, and growth hormone (diabetogenic hormones or counter-regulatory hormones) (13). In 1959, Hume and Egdahl (14) demonstrated that the endocrine response to surgical trauma, as represented by an acute elevation in the adrenal vein corticosteroid concentration, is initiated by transmission of neural impulses via sensory afferent nerves from the site of injury to the central nervous system. We hypothesized that the glucose levels would support pain scores which were investigated in this study for determining the usefulness of PBZ administered via the OTM route compared to the IV route and a placebo.

The aim of the present study was to evaluate the efficacy and analgesic duration of a single dose of PBZ administered by OTM or via the IV route immediately before induction of anesthesia in dogs undergoing elective OVH.

MATERIALS AND METHODS

A randomized, blinded study was conducted. Twenty-seven sexually intact female dogs referred for OVH procedure from a local shelter at regular intervals over 3 months, were included in the study. Before final enrolment, the dogs had to fulfil a set of predetermined inclusion criteria (Table 1). The sample size was calculated according to previous researches (15). The sexual cycle was determined by technique of vaginal smear in dogs.

Table 1. Enrolment criteria for dogs to enter the study.

Body weight ≥5 kg
Age ≥1 year
No previous enrolment in this study
Not too aggressive to safely enable postoperative examinatio and/or pain scoring.
No administration of non-steroidal anti-inflammatory drugs epidural analgesia, or local/regional analgesia within 12 h prior to the study
Not pregnant or lactating
No evidence or history of pre-existing heart disease or clinically significant arrhythmia
No clinically significant hypotension
No evidence or a history of liver disease

The dogs were randomly allocated to one of three groups with nine dogs in each group. These subjects were randomly distributed by picking a note with the subject number out of a box. The right or left cephalic vein was cannulated using a 20 or 22 G over the needle catheter for the subsequent blood sampling. Heparinized blood samples (4 ml) were collected through the indwelling cephalic vein catheter before the administration of PBZ (0 hour) and 3, 8, and 24 hours after operation. The dogs were administered PBZ (Phenylbute, Phoenix, St. Joseph, MO, USA) or the placebo 0.9% NaCl (Serum Fizyolojik, Eczacıbaşı, Istanbul, Turkey) on the basis of their recpective treatment group: [20 mg/kg, IV; 20 mg/kg OTM administration (Phenylbute, Phoenix, St. Joseph, MO, USA); 1.75 ml/kg IV 0.9% NaCl (Serum Fizyolojik, Eczacıbaşı, Istanbul, Turkey)] before administration of xylazine (Alfazine, Egevet, Izmir, Turkey). For OTM administration, PBZ was diluted with equivalent volume 0.9% NaCl. The syringe was placed in the cheek pouch of the dog, and PBZ was slowly administered over a period of 1 to 3 minutes to ensure the drug did not drip out of the dog's mouth, or was not swallowed by the dog. For the IV treatment, it was administered over a period of one minute. The time prior to PBZ administration was designed as T_0. In the control group, 0.9% NaCl was administered over a period of one minute. The placebo was not administered to the IV group as our hypothesis related only to PBZ administration via OTM route as superior to the placebo.

Immediately after PBZ administration, the same anesthesic protocol was used for the three groups. Dogs were

premedicated with xylazine (2 mg/kg intramuscular, IM), (Alfazine, Egevet, Izmir, Turkey). Fifteen minutes after premedication, general anaesthesia was induced with ketamine (10 mg/kg IM), (Alfamine, Egevet, Izmir, Turkey). Electrocardiogram, non-invasive blood pressure, respiratory rate, heart rate, pulse oximetry, and rectal temperature were monitored (G9000, Guoteng Co. Ltd., China) continuously throughout the anesthesia.

Dogs were placed in the Trendelenburg position (15° head down) to facilitate cranial displacement of the visceral contents of the abdominal cavity. The surgery was performed via laparotomy, using a ventral midline approach. Age, American Society of Anesthesiologist's physical status, duration of anaesthesia (from injection of xylazine to final suture) and duration of operation (from the first skin incision to the final skin sture) were recorded for each dog. The ovary ligation procedure was carried out at the T_2 time point.

Throughout the study, vital signs were measured at baseline (T_0, before administration of PBZ) and then at 5 (T_1), 10 (T_2), 15 (T_3), 20 (T_4), 25 (T_5), and 30 (T_6) minutes intraoperatively. Postoperative pain was assessed at 0.5, 1, 2, 3, 8, and 24 hours post surgery. The same researcher, who was blinded to each dog's group assignment, evaluated pain behaviors in all dogs using the short form of the Glosgow composite measures pain scale (CMPS-SF) (16). No dog were sedated for evaluating pain at any time point. The researcher calculated the scores to decide whether the animal needed rescue analgesia. After measuring postoperative pain behaviors at each time point, the evaluator passed the data to the resarch leader, who was not blinded, and the research leader analyzed all the data at the end of the study. To control the severity of postoperative pain, if a dog was scored CMPS-SF > 6, IV carprofen (4 mg/kg) (Rimadyl, Zoetis, Parsippany, NJ, USA) was to be given as a rescue analgesic. Penicillin (10000 IU/kg) + streptomycin (20 mg/kg, IM) (Penstrep, Provet, Istanbul, Turkey) were postoperatively administered as a single dose. All dogs were discharged 24 hour after surgery.

Blood samples tested for plasma glucose were centrifuged at 1500 g for 10 minutes at room temperature. The plasma was removed and the blood samples were stored at -80°C in Eppendorf tubes. At the end of the study they were analyzed for glucose concentration by a commercial laboratory using a BA-88A Semi-Auto Chemistry Analyzer (Mindray, China). The enzymatic response technique was used by the analyzer to measure glucose.

Statistical analysis

ANOVA and Tukey's multiple range tests were used to assess the differences between the groups. The SPSS software program (Version 12.0, SPSS Inc., Chicago, IL., USA) was used for statistical analysis. For intergroup comparison, the distribution of the data was first evaluated for normality using the Shapiro-Wilk test. For intergroup comparison, the data of the rescue requirement was evaluated by Pearson's χ^2 test. A probability value of equal to or less than 0.05 was considered to indicate statistical significant differences.

The study protocol was approved by the local ethics committee (approval number: 2014-12).

RESULTS

The dogs were between 5 and 30 kg, and 1 to 7 years of age. Subjects from the three groups were similar in age (3.0 ± 1.2 years in group OTM; 2.63 ± 0.6 years in group IV; and 2.63 ± 1.8 years in the control group) and body weight (group OTM, 15.38 ± 6.3 kg; group IV, 15.63 ± 5.4 kg, and control group, 15.88 ± 7.80 kg) and there was no statistical difference in age and body weight betwen the groups ($p=0.645$). The duration of surgery was 20-42 minutes. There was no statistical difference in duration of surgery betwen the groups ($p>0.360$). During the study, the stages of the sexual cycle in dogs, which is the determined by vaginal smear, were determined as follows: 17 dogs were in anoestrus, 5 dog were in dioestrus, and 2 dog were in metoestrus. In addition, one dog was pregnant, one dog was pseudo-pregnant, and one dog was propubertas. All dogs included in the study were examined before, during and after the OHE operation by gynecologist as author in the manuscript.

As the gestation period of the dog was less than 21 days, her pregnancy could not be determined in the ultrasonographic examination. During the operation, this animal was found to be pregnant. In the pseudo-pregnant dog, however there was a history of vaginal bleeding, abdominal and mammary gland growth, and that she was not pregnant as determined by ultrasound before the surgery. This dog was clinically confirmed to be pseudo-pregnant. The other dog was considered prepubertal in the clinical examination due

Table 2a. Distribution of intraoperative vital functions in dogs (Mean ± SD).

Parameters / Group	Intraoperative Times						
	T0 (0 min)	T1 (5 min)	T2 (10 min)	T3 (15 min)	T4 (20 min)	T5 (25 min)	T6 (30 min)
				SpO_2			
Control	94.8 ± 5.9	88.7 ± 8.7	89.8 ± 6.8	90.7 ± 4.8	91.8 ± 5.7	91.0 ± 6.7	91.5 ± 3.2
OTM	92.1 ± 6.0	91.0 ± 5.7	90.0 ± 5.7	91.1 ± 4.7	92.0 ± 4.3	90.2 ± 5.0	91.0 ± 9.6
IV	93.0 ± 5.4	88.1 ± 7.4	90.1 ± 4.7	91.0 ± 4.9	91.7 ± 4.5	91.5 ± 4.0	92.0 ± 2.8
				Respiratory Rate			
Control	11.8 ± 3.0	13.4 ± 5.5	14.5 ± 2.7	12.7 ± 1.8	12.8 ± 5.4	12.1 ± 3.5	12.7 ± 2.4
OTM	11.5 ± 2.0	12.9 ± 3.0	13.4 ± 2.2	12.1 ± 1.7	12.7 ± 4.0	12.6 ± 3.2	12.6 ± 1.6
IV	11.2 ± 2.3	13.0 ± 3.0	13.5 ± 2.3	12.5 ± 1.5	12.6 ± 4.7	12.5 ± 3.0	12.2 ± 2.2
				Heart Rate			
Control	80.0 ± 36.1	88.8 ± 31.5	98.5 ± 43.5	87.0 ± 21.8	80.4 ± 27.8	78.7 ± 19.1	78.0 ± 39.9
OTM	80.8 ± 24.0	91.3 ± 29.4	96.3 ± 34.7	86.6 ± 18.2	79.3 ± 20.6	77.1 ± 14.9	75.7 ± 22.4
IV	80.1 ± 32.3	91.3 ± 29.2	95.5 ± 37.8	85.2 ± 24.0	78.3 ± 24.6	74.5 ± 17.6	68.7 ± 31.9

OTM: Oral transmucosal, BP: Blood pressure, IV: Intravenous.

Table 2b. Distribution of intraoperative vital functions in dogs (Mean ± SD).

Parameters / Group	Intraoperative Times						
	T0 (0 min)	T1 (5 min)	T2 (10 min)	T3 (15 min)	T4 (20 min)	T5 (25 min)	T6 (30 min)
				BP (systolic)			
Control	130.3 ± 29.9	150.1 ± 27.2	168.8 ± 30.9	158.2 ± 29.5	147.2 ± 24.7	141.4 ± 26.0	134.6 ± 27.1
OTM	132.2 ± 27.6	143.5 ± 28.6	150.6 ± 22.0	140.3 ± 25.5	132.2 ± 23.9	124.9 ± 28.7	121.7 ± 22.8
IV	135.2 ± 19.7	148.3 ± 23.7	152.6 ± 27.3	143.2 ± 25.9	133.5 ± 24.6	126.0 ± 19.0	123.4 ± 25.6
				BP (mean)			
Control	110.1 ± 19.3	135.5 ± 26.9	144.2 ± 32.4	134.6 ± 30.1	126.3 ± 25.1	123.4 ± 23.9	118.5 ± 29.3
OTM	109.7 ± 27.0	119.9 ± 26.6	127.6 ± 28.9	108.5 ± 22.5	106.5 ± 20.1	105.7 ± 23.3	110.5 ± 25.9
IV	111.5 ± 20.8	122.6 ± 24.6	129.1 ± 10.7	125.2 ± 16.0	117.7 ± 19.4	107.8 ± 16.9	112.2 ± 20.5
				BP (diastolic)			
Control	99.0 ± 23.6	120.2 ± 22.6	125.5 ± 23.3	118.8 ± 21.9	110.5 ± 17.7	106.0 ± 17.4	102.5 ± 28.6
OTM	94.2 ± 27.7	92.2 ± 25.0	96.5 ± 28.5	98.5 ± 26.0	96.7 ± 18.7	98.2 ± 23.1	95.6 ± 14.9
IV	99.8 ± 19.6	116.3 ± 18.6	103.7 ± 23.6	107.6 ± 23.7	101.6 ± 17.5	105.8 ± 16.8	107.9 ± 26.1

OTM: Oral transmucosal, BP: Blood pressure, IV: Intravenous.

to her appearance and young age, and the ovaries during operation were small.

There were no significant differences in intraoperative monitoring values between the experimental groups (mean ± SD, Table 2). Mean (± SD) heart rate, systolic, diastolic, and mean blood pressure (BP) values increased 20% in the control group following the ligation procedure (Table 2, T_2 time point). These values were not significantly different from baseline ($p>0.05$). No data increase was observed in the OTM group. Only respiratory rate values increased greater than 20% in the IV group following the ligation procedure. All of the dogs recovered from the anesthesia normally and without complications except for hypoxemia.

Groups OTM and IV had significantly lower CMPS-SF scores ($p<0.05$) than the control group at the 0.5, 1, 2, 3, and 8 hours postoperatively (Table 3). There was no difference in CMPS-SF scores between group OTM and group IV in the postoperatively. The highest and lowest CMPS-SF values

Table 3. Mean CMPS-SF scores from each groups of dogs at each time point.

Groups	Postoperative					
	0.5h	1h	2h	3h	8h	24h
Control	11.71±0.54 ^{aA}	10.57±1.11 ^{aA}	10.29±1.41 ^{aA}	9.57±1.29 ^{bA}	9.29±1.08 ^{bA}	7.29±1.44 ^{bA}
OTM	9.44±1.32 ^{aB}	8.89±0.78 ^{aB}	8.22±0.66 ^{aB}	6.89±1.77 ^{bB}	6.78±1.86 ^{bB}	6.44±1.80 ^{bA}
IV	8.88±1.32 ^{aB}	8.75±1.35 ^{aB}	7.63±2.82 ^{aB}	7.00±2.67 ^{aB}	7.13±2.01 ^{aB}	6.50±1.95 ^{bA}

OTM: Oral transmucosal. IV: Intravenous. ^{abc} means with different superscripts within one row differ significantly ($p<0.05$).
^{ABC} Different letters in the column indicate the significant differences ($p<0.05$).

Table 4. Plasma glucose levels (means±SD) taken from dogs treated with phenylbutazone given OTM or IV and control group.

Groups	Before anesthesia (0h)	After operation		
		3h	8h	24h
Control	67.14 ± 19.59 ^{aA}	211.86 ± 57.42 ^{bA}	180.57 ± 40.09 ^{bA}	89.14 ± 33.83 ^{aA}
OTM	70.44 ± 14.22 ^{A}	83.89 ± 22.68 ^{B}	80.33 ± 30.45 ^{B}	76.22 ± 25.17 ^{A}
IV	68.75 ± 13.47 ^{A}	89.88 ± 26.79 ^{B}	85.13 ± 24.33 ^{B}	79.13 ± 27.30 ^{A}

OTM: Oral transmucosal. IV: Intravenous. ^{abc} Means with different superscripts within one row differ significantly ($p<0.05$).
^{ABC} Different letters in the column indicate the significant differences ($P<0.05$).

were determined at 0.5 hour (9.44 ± 1.32) and 24 hour after surgey (6.44 ± 1.80) in group OTM. Likewise, the highest and lowest CMPS-SF values were determined at 0.5 hour (group IV, 8.88 ± 1.32; control group, 11.71 ± 0.54) and 24 hour after surgey (group IV, 6.50 ± 1.95; control group 7.29 ± 1.44) in the other groups. The CMPS-SF scores were >6 in all dogs at different periods in the groups. The analgesic (carprofen) was used with all dogs.

Table 4 demonstrates the mean (± SD) plasma glucose levels at each time point. Glucose concentration spiked at 3 hour in all groups. Glucose levels differed significantly at 3 and 8 hours for groups OTM and IV when measured against the control group ($p<0.05$). Glucose concentration decreased quicker in groups OTM and IV groups than in the control group. Only the values at 3 and 8 hours after the surgery were significantly ($p<0.05$) higher than the baseline value in the control group.

DISCUSSION

Pharmacokinetic parameters for PBZ have been evaluated in several species (6). Dogs were selected in this study for several reasons: i) numerous formulations are available for use in this pet animal species; ii) administration of PBZ by the OTM route had not been approved for postoperative analgesia in dogs.

Phenylbutazone is indicated for the relief of musculoskeletal inflammation and mild to moderate somatic or visceral pain particularly in post-operative pain in dogs, horses, and cattle (17). The apparent analgesic effect is probably related mainly to the compound's anti-inflammatory properties. The pharmacokinetic parameters for PBZ after IV and IM injections have been published (7, 18). The average plasma clearance after IV injection have been found to range from 4.6 (18) to 14.4 mL.kg–1.h–1 (7). The elimination half-life in the study was about 11 (7) and 18 h (18). These values can be of value to to clinician veterinarians for pain management.

The adverse effects of PBZ have been previously documented. In overdose, PBZ is one of the more toxic NSAIDs (19). It is now well known that the NSAID, including phenylbutazone, inhibit or reduce the biosynthesis of prostaglandins that accompanies the pathological process and thus exert their therapeutic effects. Authenticated cases of agranulocytosis associated with the drug have occurred in dog (20). To guard against this possibility, in this study we conducted routine blood counts at weekly intervals for two weeks thereafter.

It is reported that heart rate and blood pressure values are direct physiological indicators of intraoperative sympathetic reaction to nociceptive stimulation (21). In lambs, heart rate and blood pressure have been demonstrated to be more accurate as signs of nociception than cortisol or ACTH plasma

measurements (22). Systolic, mean and diastolic blood pressure values, and respiratory rate increased 20% in the control group after ovarial ligation procedure. No value increased by that much in the OTM group. Nevertheless respiratory rate values increased by morte than 20% in the IV group. The parameters applied here showed that the intensiy of pain had determinable physiologic impact on the animals as determined by a researcher. Therefore, it may be stated that, although it appeared that PBZ may decrease the response to nociceptive input from the ligation of the ovaries, this trend did not achieve statistical significance and may be a random finding. We are not aware of any published articles that evaluate the physiological effects of OTM and IV administration of PBZ in dogs.

Although arterial blood gas analysis is commonly considered the gold standard for assessment of oxygenation, pulse oximetry offers multiple advantages. These include ease of use, cost effectiveness, and pro-vision of continuous or long-term monitoring without the requirement for arterial catheter placement or repeated arterial puncture. However, it is recognized that the performance of pulse oximetry can be affected by many patient-related factors such as movement artifact, ambient light, skin pigment, hypoperfusion, hypotension, hypothermia, severe anemia, and dyshemoglobinemias (23).

Hypoxemia, which occurred in this study, can be dependent on hypothermia caused by anesthesia regime. Furthermore, there may be direct inhibition of the combination of xylazine and ketamine on the respiratory center. If, it was caused by hypothermia, it would become more severe with time, but in this study it improved. This is also supported by the better SpO_2 at T_4 compared to T_3 and T_5, since skin closure, which occurred during this time, may decrease anesthetic depth. This, and not pain, may have affected other physiologic parameters. Therefore, we recommend supplying oxygen to dogs anesthetized using this protocol.

Many pain-scaling systems, such as verbal rating scales, numeric rating scales, simple descriptive scales, and the visual analogue scale, are used to evaluate the degree of pain and stress in the postoperative period (22). Acknowledging that no scoring system is perfect, the Glosgow CMPS-SF (16) was chosen for evaluation of pain in this study. This scoring system has seen to be a dependable clinical device for determining different pain severity as well as modifications in the degree of pain over time in a population of dogs undertaking a range of open surgeries (16). In the current study, the GMPS-SF points were significantly reduced in group OTM and group IV when compared to the control group throughout the monitoring period, except at 24 h. More studies using different dosage PBZ via OTM are necessary before any long term usefulness can be recognized. Luna *et al.* (2015) used 7 cases in a carprofen group and in these cases 3 dogs needed rescue analgesia (24). Dzikiti *et al.* (2006) reported that carprofen provided analgesia equal with morphine in dogs undergoing OVH (25). Guerrero *et al.* (2015) compared metamizole and carprofen. One dog in the metamizole group and 2 dogs in the carprofen group needed rescue analgesia (26). In all dogs (OTM, IV and control) CMPS-SF scores were higher than 6 and all of them required rescue analgesia with carprofen. This possibly indicates that this dosage of PBZ was not high enough to provide dogs with appropriate postoperative analgesia. New studies using different dosage PBZ via OTM are necessary before long term usefulness and safety can be recognized. Otherwise, it is possible that bioavailability of PBZ is low in dogs and this may explain the high pain scores. As specified before, pharmacokinetic parameters for PBZ have not been evaluated before in dogs.

The significant limitations of the study are debated below. First, the researcher was to apply rescue analgesia at any time during the postoperative period if needed, and all dogs were provided with this therapy. That all of the dogs exhibited GMPS-SF scores above the thresholds given above is perhaps due to the fact that opioids were not applied in any dog. The pain score at base line were not taken. Therefore there is no certainty that all animals had the same base line score. But all subjects were young and healthy. It can be considered that all animals had the same base line scores. Guerrero *et al.* (2015) determined < 1 base line pain scores in their groups (26).

Successful control of pain after surgical procedure requires multi-modal therapy with opioids and nonsteroidal anti-inflammatory drugs (27,28). However, it has been demonstrated that the anesthetic protocol may affect pain scores (29). An opioid drug couldn't be used for rescue analgesia as opioids sales are illegal in country of study. Therefore, carpofen, which minimally effects the mucosa of the stomach, was selected as the rescue analgesia. However, this may mean that some pain scores evaluated the efficacy of carprofen and not only PBZ. Second, the restrictions of non-inferiority research using by positive controls is well known (27, 28). In this case, use of a placebo would have advanced ethical and

recruitment issues in this study as a number of analgesics are recorded for intraoperative use in dogs and substantially used. The intravenous group was also evaluated as this method has been described and noted as efficacious for peri- and postoperative pain (30, 31). Although it has been proposed that a placebo group should be contained to confirm the scoring system when controlling pain (22,32), there are considerable welfare concerns related to abnegating dogs' postoperative pain relief under clinical conditions. Third, the use of 20 mg PBZ/kg in clinical settings is now accessible as commercial brands of PBZ are present only at concentrations of 200 mg/ml. Therefore, we diluted the PBZ with an equal volume of 0.9% NaCl solution in order to avoid local irritation. There were no complication with application of PBZ. Fourth and last, we chose to administer PBZ at the same time point (immediately before the induction). Different Tmax after OTM and IV administration can be expected. When intraoperatively evaluateing analgesia, different values of Tmax can unmask unreliable results. Fourth, α-2 agonists such as xylazine have analgesic properties. Therefore, whether they were reversed or not is important in such studies. No antagonist agent such as yohimbine or atipamezole was administered in the end of the surgery in this study.

Serum glucose concentration was detected as the objective measure for understanding the biochemical stress reponse to open surgery. Serum glucose concentration is a useful evaluator of surgical stress, although quantifiying glucose may not be an absolute means of determing surgical stress. The changes of serum glucose and cortisol levels 24 h after different nephrectomy techniques in dogs (15) have been researched. Serum glucose levels were significantly lower in OTM and IV group when comapred to the control group at the 3 and 8 h time points. Hume and Egdahl (14) showed that denervation of the injured tissue prior to the insult results in a lack of corticosteroid release. Such denervation obviously leads to anesthesia of the injured part. The dependence of both the endocrine response to injury and the perception of pain on similar intact afferent neural pathways has led to the concept that pain may be quantified in a more or less objective fashion by measurement of the magnitude of the neuroendocrine response.

The OTM route did not provide different analgesia compared to the IV route, which had a significantly superior pain score as compared to the control group. In conclusion, a single dose of PBZ administered via the OTM route before surgery provides some analgesia but it is not enough on its own for the postoperative period. Additionally, PBZ administred via the OTM route did not provide a different analgesia with IV route. The results of the study strongly suggest that additional studies using different dosages of PBZ via OTM are necessary before any long term usefulness can be determined.

CONFLICT OF INTEREST STATEMENT

None of the authors of this article has any conflict of interest.

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