Efficacy of intravenous phenylbutazone for pain management in dogs undergoing ovariohysterectomy

Ovariyohisterektomi uygulanan köpeklerde intravenöz fenilbutazonun ağrı yönetimindeki etkinliği

ABSTRACT

The aim of the present study was to evaluate the efficacy and analgesic duration of single dose of phenylbutazone (PBZ) administered the intravenous (IV) route immediately before induction of anesthesia in dogs undergoing elective ovariohysterectomy (OVH). Eighteen sexually intact female dogs (weighing between 4.5 and 28 kg, and 1 to 8 yrs. of age) referred for OVH procedure from a local shelter at regular intervals over 4 months were included in the study. The dogs were administered PBZ on the basis of their respective treatment group (20 mg/kg, IV administration) immediately before anesthetic induction. For the IV treatment, PBZ was administered over a period of one minute. Time of completion of PBZ administration was designed as time 0. In control group, 0.9% NaCl was administered IV as over a period of one minute. Throughout the study, pre and postoperative pain was assessed at baseline (before induction of anesthesia) and then at 0.5, 1, 2, 3, 8, and 24 hrs after the surgery. Group IV had significantly lower CMPS-SF scores than the control group at the 0.5, 1, 2, 3, and 8 hour postoperative periods. In conclusion, a single dose of PBZ administered via the IV route before surgery may be particularly beneficial for achieving reasonable perioperative analgesia, but not in postoperative period.

Keywords: Ovariohysterectomy, pain, phenylbutazone, intravenous

ÖZET

Bu çalışmanın amacı planlı overiyohisterektomi yapılan köpeklerde post operatif ağrı yönetiminde damar içi tek doz verilen fenilbutazonun etkinliğini ve ağrı kesici etki süresini değerlendirmektir. Çalışmaya, yerel hayvan barınaklarından kliniğimize 4 ay boyunca ovariyohisterektomi amacıyla getirilen 18 erişkin dişi köpek (ağırlıkları 4,5 ve 28 kg; yaşları 1-8 arasında) dâhil edildi. Köpeklere çalışma gruplarında 20 mg/kg dozda damar içi fenilbutazon hemen operasyon öncesinde verildi. Damar içi uygulama için fenilbutazone 1 dk. süresince verildi. İlaç uygulamasının bittiği an T0 olarak belirlendi. Kontrol grubunda ise 1 dk. süresince % 0,9 NaCl damar içi verildi. Çalışma süresince operasyon öncesi ve sonrası ağrı; başlarken (anestezi uygulaması öncesinde), sonrasında 0,5, 1, 2, 3, 8, ve 24. saatlerde değerlendirildi. Glaskov ağrı değerlendirme formu skorları, damar içi grupta operasyon sonrası 0,5, 1, 2, 3 ve 8. saatlerde kontrol grubundan istatistiksel olarak düşük değerlerdeydi. Sonuç olarak, operasyon öncesinde damar içi verilen tek doz fenilbutazon intraoperatif kabul edilebilir analjezi sağlayabilir ama operasyon sonrasında ağrının kontrolünde yetersizdir.

Anahtar Kelimeler: Ovariyohisterektomi, ağrı, fenilbutazone, intravenöz

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INTRODUCTION

Phenylbutazone is a potent non-steroidal anti-inflammatory drug, first introduced in 1952 for the treatment of arthritis. Phenylbutazone has been shown to be effective in managing pain associated with a variety of companion animal diseases (Williamson et al., 1978; Mbugua et al., 1989; Zech et al., 1993; Mills et al., 1995). The various routes of administration for PBZ are commonly used in animals (Mbugua et al., 1989; Zech et al., 1993; Mills et al., 1995).

To determine the dose and efficacy for IV administration of analgesics in dogs, pharmacokinetic studies (Williamson et al., 1978; Mbugua et al., 1989; Zech et al., 1993; Mills et al., 1995) were performed to evaluate the bioavailability, dosage, and dosing interval for administration via the IV route. The clinical importance of the IV route of PBZ for the management of preoperative and postoperative pain in dogs is unknown. Furthermore, there is no available data about the therapeutic and adverse effects in dogs. Although previously investigated for pain relief of musculoskeletal problems (Mbugua et al., 1989), IV route administration of PBZ have not been evaluated for perioperative and postoperative pain relief in animals undergoing elective surgery. As OVH procedure is the most common type of clinical case referred to veterinary clinics, the present study includes this type of procedure so that the results may be of use to small animal practitioners. We hypothesized that the PBZ administered via the IV route would be acceptable effective in providing preoperative and postoperative analgesia in dogs.

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

MATERIALS AND METHODS

The study protocol was approved by the local ethics committee (approval number: 2014-12). A randomized, double-blinded study was conducted. Eighteen sexually intact female dogs were referred for OVH procedure from a local shelter at regular intervals over 4 months, were included in the study. Before final enrolment the dogs had to fulfill a set of predetermined inclusion and exclusion criteria (Table 1). All dogs were discharged 24 hours after surgery. Heparinized blood samples (4 ml) were collected through the indwelling cephalic vein catheter.

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 examination and/or pain scoring.
No administration of non-steroidal anti-inflammatory drugs epidural analgesia, or local/regional analgesia within 12 hours 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 two groups with nine dogs in each group. The dogs were administered PBZ on the basis of their respective treatment group (20 mg/kg, IV administration) before

administration of xylazine. For the IV treatment, PBZ was administered over a period of one minute. Time of completion of PBZ administration was designed as time 0. In control group, 0.9% NaCl was administered as over a period of one minute.

Immediately after PBZ administration, the same anesthetic protocol was used for three groups. Dogs were premedicated with xylazine (2 mg/kg IM). Fifteen minutes after premedication, general anesthesia was induced with ketamine (10 mg/kg IM). The right or left cephalic vein was cannulated using a 20 or 22 G over the needle catheter for the subsequent blood sampling. Electrocardiogram, non-invasive blood pressure, respiratory rate, heart rate, pulse oximetry, and rectal temperature were monitored (Guoteng Co Ltd, China) continuously throughout the anesthesia. A software application was used for data collection starting before the first incision and then every 5 min until the end of the OVH procedure.

Dogs were placed in the Trendelenburg position (15° head down) to facilitate cranial displacement of the visceral contents of the abdominal cavity. Age, American Society of Anesthesiologist's physical status, duration of anesthesia (from injection of xylazine to final suture) and duration of operation (from the first skin incision to the final skin suture) were recorded for each dog. Ovary ligation procedure was in T2 time point.

Throughout the study, pre and postoperative pain was assessed at baseline (before induction of anesthesia) and then at 0.5, 1, 2, 3, 8, and 24 hrs. after operation. The same researcher, who was unaware of each dog's group assignment, evaluated pain behaviors in all dogs using the short form of the Glasgow composite measures pain scale (CMPS-SF) (Reid et al., 2007). A total pain score ranging from 0 to 24 was calculated for each time point. After measuring postoperative pain behaviors at each time point, the researcher submitted the score sheet to the test leader who then calculated the scores. To control the severity of postoperative pain, if a dog was scored CMPS-SF > 6, IV carprofen (4.4 mg/kg) was to be given as a rescue analgesic. With the exception of subjects receiving penicillin + streptomycin (0.1 ml/kg, IM), all drugs were received as a single dose.

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 SPSS software program (Version 12.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Shapiro-Wilks-W test, which one of normality tests, was used to determine whether the data were distributed normally before the variance analysis. ANOVA test was used to assess the differences between the groups. When the interaction was statistically significant ($p<0.05$), Tukey's test was used for binary comparisons between groups and homogeneous groups were formed.

RESULTS

The dogs were between 4.5 and 28 kg, and 1 to 8 years of age. Subjects from the two groups were similar in age (2.63 ± 0.2 years in group IV and 2.63 ± 0.6 years in the control group) and body weight (group IV, 15.63 ± 1.8 kg and control group, 15.88 ± 2.6 kg) and there was no difference in age and body weight between the groups. The

duration of surgery was 21-40 min. All dogs were classified as having ASA physical status I. During the study, the stages of the estrous cycle in dogs were determined as follows: 13 dogs were in anoestrus, 5 dogs were in dioestrus.

There were no significant differences between the experimental groups taking intraoperative monitoring values (mean ± SD). All of these values were within the respective reference ranges for anesthetized dogs (Pacheco et al., 2018) (Table 2). Mean (± SD) diastolic and mean blood pressure (BP) values increased 20% in the control group following the ligation procedure (Table 2, T2 time point). No data increase was observed in the IV group following the ligation procedure. All of the dogs recovered from the anesthesia normally and without complications.

Table 2. 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	94.86±1.99	88.71±2.92	89.86±2.28	90.71±1.60	91.86±1.92	91.00±2.25	91.50±1.08
Intravenous	93.00±1.83	87.75±2.48	90.12±1.57	91.00±1.65	91.75±1.53	91.57±1.34	92.00±0.96
Respiratory Rate							
Control	11.86±1.01	13.40±1.85	14.50±0.93	12.71±0.61	12.86±1.81	12.17±1.19	12.71±0.81
Intravenous	11.25±0.78	13.05±1.03	13.58±0.79	12.50±0.50	12.63±1.57	12.57±1.00	12.25±0.75
Heart Rate							
Control	80.00±12.05	88.88±10.50	98.57±14.52	87.00±7.27	80.43±9.27	78.71±6.39	78.00±13.32
Intravenous	80.13±10.78	91.38±9.75	95.50±12.63	85.29±8.00	78.38±8.22	74.50±5.89	68.75±10.64
BP(systolic)							
Control	130.33±9.98	150.13±9.09	168.88±10.33	158.25±9.84	147.25±8.25	141.45±8.68	134.63±9.06
Intravenous	135.25±6.58	148.38±7.93	152.63±9.10	143.25±8.66	133.55±8.23	126.00±6.35	123.43±8.54
BP (mean)							
Control	110.13±6.44	135.54±8.98	144.25±10.80	134.63±10.06	126.38±8.38	123.43±7.98	118.54±9.78
Intravenous	111.55±6.96	122.66±8.20	129.13±6.58	125.25±5.35	117.75±6.48	107.88±5.66	112.23±6.86
BP (diastolic)							
Control	99.00±7.88	120.25±7.54	125.52±7.78	118.87±7.32	110.50±5.90	106.00±5.81	102.50±9.55
Intravenous	99.88±6.56	116.38±6.20	103.75±7.87	107.65±7.93	101.60±5.86	105.88±5.62	107.98±8.72

BP: Blood pressure.

In the preoperative period, all animals had a CMPS-SF score of 0. Group 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). The highest and lowest CMPS-SF values were determined at 0.5 h (8.88 ± 0.44) and 24 h after surgery (6.50 ± 0.65) in group IV. Likewise, the highest and lowest CMPS-SF values were determined at 0.5 hr (11.71 ± 0.18) and 24 hr after surgery (7.29 ± 0.48) in the control group. The CMPS-SF scores were >6 in all dogs at different periods in the groups. The rescue 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 hrs. in all groups. Glucose levels differed significantly

at 3 and 8 hours for group IV when measured against the control group (P<0.05). Glucose concentration decreased quicker in group IV 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.

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±0.18 ^{aA}	10.57±0.37 ^{aA}	10.29±0.47 ^{aA}	9.57±0.43 ^{bA}	9.29±0.36 ^{bA}	7.29±0.48 ^{bA}
Intravenous	8.88±0.44 ^{aB}	8.75±0.45 ^{aB}	7.63±0.94 ^{aB}	7.00±0.89 ^{aB}	7.13±0.67 ^{aB}	6.50±0.65 ^{bA}

^{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 IV and control group

Groups	Before operation (0 h)	After operation		
		3h	8h	24h
Control	67.14 ± 6.53 ^{aA}	211.86 ± 19.14 ^{bA}	180.57 ± 20.03 ^{bA}	89.14 ± 14.61 ^{aA}
Intravenous	68.75 ± 4.49 ^{A}	89.88 ± 8.93 ^{B}	85.13 ± 8.11 ^{B}	79.13 ± 9.10 ^{A}

^{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).

DISCUSSION

Pharmacokinetic parameters for PBZ have been evaluated in several species (Lees et al., 2004). 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 IV route had not been approved for perioperative and postoperative analgesia in dogs.

It is reported that heart rate and blood pressure values are direct physiological indicators of intraoperative sympathetic reaction to nociceptive stimulation (Thurman et al., 1996; Ortega and Cruz, 2011). In lambs, heart rate and blood pressure were demonstrated to be more accurate as signs of pain than cortisol or ACTH plasma measurements (Peers et al., 2002). Systolic, mean and diastolic blood pressure values, and respiratory rate increased 20% in the control group after ovarian ligation procedure. No value increased by that much in the IV groups. The parameters applied here showed that the intensity of pain had determinable physiologic impact on the animals as determined by a researcher. We are not aware of many published articles that evaluate the physiological effects of IV administration of PBZ in dogs but, it was noted that these route were relatively reliable in normal dogs.

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 (Grandemange et al., 2013). Acknowledging

that no scoring system is perfect, the Glasgow CMPS-SF (Reid et al., 2007) was chosen for evaluation of pain in this study. This scoring system has been 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 (Reid et al., 2007). In the current study, the CMPS-SF points were significantly reduced in group IV when compared to the control group throughout the monitoring period, except at 24 hrs. All times were showed values higher than 6 points. Use of only one researcher also restricted the variability in evaluating pain using the CMPS-SF.

Strength analysis was achieved before the beginning of the study based on the notion that a numerical distinction in a pain score of 3 using the CMPS-SF would be clinically suitable when contrasting postoperative analgesics (Hunt et al., 2013). This notion rests on previous studies investigating the CMPS-SF in a clinical setting (Gruet et al., 2013; Hunt et al., 2013) which found that a 95% reliance interval for the difference in median pain value (dogs requiring analgesia-no analgesia) was attained using 3-5 scores. In all dogs (IV and control) CMPS-SF scores were higher than 6 and that all of them required rescue analgesia with carprofen. This means that PBZ was not effective enough to provide dogs with appropriate postoperative analgesia.

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. All of the dogs with CMPS-SF scores above the thresholds given above is perhaps due to the fact that opioids were not applied in any dog. Successful control of pain after surgical procedure requires mixed therapy with opioids and nonsteroidal anti-inflammatory drugs (Gruet et al., 2013; Hunt et al., 2013). Second, the restrictions of non-inferiority research using positive controls are well known (Gruet et al., 2013; Hunt et al., 2013). In this case, use of a placebo would have advanced ethical and recruitment issues in this study as a number of anti-analgesics are recorded for intraoperative use in dogs and substantially used. Although it has been proposed that a placebo group should be contained to confirm the scoring system when controlling pain (Carpenter et al., 1995; Grandemange et al., 2013), there are considerable welfare concerns related to abnegating dogs' postoperative pain relief under clinical status.

Serum glucose concentration was detected as the objective measure for understanding the biochemical stress response to open surgery. Serum glucose concentration is a useful evaluator of surgical stress, although quantifying glucose may not be an absolute means of determining surgical stress. Marcovich et al., (2001) researched the changes of serum glucose and cortisol levels 24 hrs. after different nephrectomy techniques in dogs. Serum glucose levels were significantly lower in IV group when compared to the control group at the 3 and 8 hr time points.

CONCLUSION

It was concluded that administered via the IV route before OVH this is an effective analgesic with minimal intraoperative adverse effects. In conclusion, a single dose of PBZ administered via the IV route before surgery may be particularly beneficial for achieving reasonable perioperative analgesia, but not in postoperative period.

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