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Research Article

The Effects of Intrathecal Administration of Bupivacaine or Ropivacaine Following Administration of Propofol in Dogs Undergoing Ovariohysterectomy [1]

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Abstract

The aim of this study was to compare intrathecal (IT) administration of bupivacaine and ropivacaine after propofol was given to dogs undergoing ovariohysterectomy operation. After propofol was administered to 16 dogs, IT anesthesia was performed with either 20 mg of bupivacaine (bupivacaine group, BG, n=8) or 30 mg ropivacaine (ropivacaine group, RG, n=8) in the lumbosacral space in this randomized, prospective, clinical trial. Noninvasively systolic, diastolic and mean arterial blood pressure, heart rate, respiratory rate and rectal temperatures were recorded after propofol and up to 150 min after IT injections. Onset, duration and the extent of sensory block were determined by using the needle prick during the ovariohysterectomy operation. The duration of IT anesthesia (BG: 89.5±7.6 min; RG: 64.75±6.8 min) was significantly different between the groups (P<0.05). The values in each group were within the reference range although there were differences in terms of arterial blood pressure (systolic, diastolic and mean), heart rate, respiratory rate and rectal temperatures. In conclusion, this study showed that IT bupivacaine and ropivacaine following administration of propofol can provide safe and effective anesthesia in dogs undergoing ovariohysterectomy operations.

Keywords: *Propofol, Intrathecal anesthesia, Bupivacaine, Ropivacaine, Dog*

Ovariohisterektomi Yapılan Köpeklerde Propofol Uygulamasını Takiben Bupivacaine ya da Ropivacainin İntratekal Uygulamasının Etkileri

Özet

Bu çalışmanın amacı ovariohisterektomi operasyonu yapılan köpeklere propofol verildikten sonra bupivacaine ve ropivacaine'in intratekal (IT) uygulamasının karşılaştırılması idi. Randomize ve prospektif olan bu klinik araştırmada 16 köpeğe propofol verildikten sonra IT anestezi lumbosakral boşluğa verilen ya 20 mg bupivacaine (Bupivacaine Grubu, BG, n=8) ya da 30 mg ropivacaine (Ropivacaine grubu, RG, n=8) ile sağlandı. Propofol uygulamasından sonra ve IT enjeksiyondan sonraki 150. dakikaya kadar noninvaziv olarak sistolik, diastolik ve ortalama arteriyel kan basınçları ile nabız, solunum sayısı ve rektal ısı kayıt edildi. Ovariohisterektomi operasyonu sırasında sensorik blokajın başlangıcı, süresi ve derinliği iğne pikürü ile yeterli derinlikte anestezi olup olmadığı değerlendirildi. Anestezi süresi (BG: 89.5±7.6 dk; RG: 64.75±6.8 dk) bakımından gruplar arasında istatistiki olarak önemli derecede bir farklı bulundu (P<0.05). Arteriyel kan basınçları (sistolik, diastolik ve ortalama) ile nabız, solunum sayısı ve rektal ısı açısından bazı farklılıklar olmasına rağmen her bir gruptaki değerler referans aralıkta idi. Sonuç olarak, bu çalışma ovariohisterektomi operasyonu yapılan köpeklerde propofol uygulamasını takiben IT bupivacaine ve ropivacainin güvenli ve etkili bir anestezi sağlayabildiğini gösterdi.

Anahtar sözcükler: *Propofol, İntratekal anestezi, Bupivacain, Ropivacain, Köpek*

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INTRODUCTION

Intrathecal (IT) or subarachnoid anesthesia providing sympathetic, sensory and motor nerve blockage with injection of local anesthetics into the subarachnoid space has become quite popular in recent years [1-3]. IT anesthesia is a simple and more economic approach to anesthesia as it can be administered without the equipment and devices required for inhalation anesthesia, but the experience during administration can be viewed as a disadvantage [1,3]. IT anesthesia is preferred to general anesthesia for hind limb surgery, flank surgery, ovariohysterectomy, cesarean section and tail surgery in many animal species [1-5].

In dogs, subarachnoid puncture at the lumbosacral junction is possible and intrathecal or spinal injections may be made with the patient lying in either sternal or lateral recumbency [6,7]. After the spinal needle enters into lumbosacral space by 90°, it should be moved towards the cranial by 45°. In this approach, cerebrospinal fluid (CSF) flow may not always be possible due to the cauda equina in dogs. If it cannot be sure that it has been entered, it should be abandoned. In this case, alternatively it can be entered in the L6-L7 range [8]. To perform the spinal puncture, the two tuberosities of the iliac bone and of the spinal process of the last lumbar vertebra are identified. The lumbosacral space is located immediately below. By sliding the finger in the cephalic direction, the next inter-vertebra space is L6-L7; this is the site where the puncture is performed using a disposable 20-25 G spinal needle which is inserted through median access at approximately 45°. After crossing the arachnoids membrane, the needle mandrel is removed to obtain free CSF leakage- proof of correct needle placement [1,3,6-9].

Propofol, a weak analgesic, has been preferred before anesthesia to ensure quick recovery and minimal side effects, patient comfort, safety and immobility. Although it may cause dose-dependent respiratory depression, advantages are the fact that it is an antiemetic, anti-convulsant and amnestic agent [10-15].

Bupivacaine and ropivacaine are both amide-type local anesthetics and effective, long-lasting, local anesthetics that are quite frequently used in IT anesthesia. Bupivacaine provides advantages over ropivacaine in terms of depth of anesthesia and duration of anesthesia, but it can cause ventricular arrhythmia and cardiotoxicity [2,3,16-18].

Animals are usually sedated before intrathecal anesthesia. However, during the spinal puncture, reactions that cause disgust may be seen. In addition, these reactions negatively affect the quality of anesthesia and it can even result in unwanted accidents. So, propofol may be an alternative to avoid these. The purpose of this study was to compare of the effects of intrathecal administration of bupivacaine and ropivacaine following propofol administration in dogs undergoing ovariohysterectomy.

MATERIAL and METHODS

The study was approved by the Kafkas University Animal Experiments Local Ethics Committee (KAÜ-HADYEK: 2015/052). Consent was also obtained from the animal owners, who were informed about the study.

This study was conducted on 16 dogs brought to the Kafkas University, School of Veterinary Medicine, Department of Obstetrics and Gynecology for a routine ovariohysterectomy operation.

The dogs made general health examination were divided into two groups with one receiving bupivacaine (BG, n=8) and the other ropivacaine (RG, n=8). Before IT anesthesia, 6 mg/kg propofol (Propofol® 1%, 20 mL enj., Fresenious Kabi-Germany) was administered intravenously as a single dose to each dog. Five minutes later, dogs were placed in the prone position. IT anesthesia was performed under aseptic conditions with either 20 mg [1] (4 mL as total dose) bupivacaine (Marcaine®, 5 mg/mL Astra Zenaca) or 30 mg [1] (4 mL as total dose) ropivacaine (Naropin® 7.5 mg/mL, Astra Zenaca) injected into the L7-S1 or L6-L7 as previously described [1,3,5,7,8]. If the spinal puncture was suspicious or unsuccessful, it was not insisted and abandoned.

All dogs were laid in the supine position on the operating table with a slope of approximately 30° to prevent cranial progress of the local anesthetic. An ovariohysterectomy was routinely performed by entering the laparatomy incision, which began approximately 1 cm caudal to the belly button and extended for 5 cm to the posterior along the center line. During the ovariohysterectomy, regular checks were performed to determine whether or not the ovaries, uterus, and *ligamentum latum uteri* were sensitive to touch or dissection.

Each animal was monitored (Veterinary Monitor® MMED6000DP S6-V, Germany) by recording heart rate (HR), noninvasively systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP), mean arterial blood pressure (MBP), electrocardiogram (ECG), respiratory rate (RR), and rectal temperature (RT) initially, at propofol administration, and during anesthesia at 5, 15, 30, 60, 90, 120, 150 min. Also, biochemical measurements were performed on venous blood at 0, 15, 30, 60, and 120 min with a colorimetric assay to determine levels of serum glucose, aspartate aminotransferase (AST), alanine amino-transferase (ALT), blood urea nitrogen (BUN), and creatine.

For ECG measurements, extremity leads were used. QT measurements were corrected for the heartbeat to calculate corrected QT (QTc) intervals. The formula $QTcF = QT/(RR)^{1/3}$ developed by Fridericia [19] was used for evaluation of the measurements.

Painful stimuli were created using a 23-gauge needle to assess superficial and deep pain ventral to the caudal abdomen, tail, perineum, and hind limbs. The needle prick

was evaluated on a scale of 0 to 3 as reported by some study [1,3,5]: 0 = no analgesia and normal strong reaction to stimulus, 1 = mild analgesia and depressed reaction to stimulus, 2 = moderate analgesia and no response to superficial needle-prick stimulation of the skin, and 3 = complete analgesia and no response to insertion of the needle deep into muscle tissue. The needle prick procedure was continued until the end of the anesthesia even if the operation ended early. In addition, it was checked for anesthesia by compressing the paw and tail end with a forceps during the anesthesia.

Before the ovariohysterectomy operation, a 22-G polyurethane catheter was aseptically placed into the ramus dorsalis of vena saphena and an electrolyte solution (saline 0.9 per cent) was administered intravenously at 10 ml/kg/hour for the duration of IT anesthesia.

Routine daily nursing procedures such as postoperative antibiotics (20 mg/kg, iv cefazolin sodium, Sefazol®, Mustafa Nevzat, for five days postoperatively) and analgesia (Carprofen, 4 mg/kg, im, Rimadyl, Pfizer, Turkey, for three days postoperatively) were provided for the dogs undergoing ovariohysterectomy.

Statistical evaluation of the data was performed with a normality test (Anderson-Darling) using the Minitab-16 packet program, followed by the Kruskal-Wallis test for non-parametric data and the ANOVA method (One-way Analysis of Variance-Tukey's pairwise comparisons), with $P<0.05$ accepted as significant.

RESULTS

All study findings were categorized as clinical, hemodynamic *(Table 1)* and biochemical *(Table 2)*.

There was no statistically significant difference between the groups in terms of body weight (BG: 21.5±6.9 kg RG: 25.13±5.0 kg), age (BG: 2.5±1.4 years, RG: 3.2±2.3 years) and ovariohysterectomy operation time (BG: 42.38±5.0 min, RG: 42.50±3.9 min). But, duration of IT anesthesia (BG: 89.5±7.6 min; RG: 64.75±6.8 min) was significantly different between the groups ($P<0.05$). Before recovery from IT anesthesia in all dogs, there was signs of waking up such as head and eye movements because it was more short-term effects of propofol. However, regardless of these symptoms, the duration of IT anesthesia was measured. Also, the effort for reach to the sternal position was not observed until the end of the IT anesthesia.

In both groups, the duration of IT anesthesia was sufficient for the ovariohysterectomy operation and adequate analgesia and muscle relaxation for this operation was achieved. Also, there was no need for additional local anesthetic doses in both groups.

No negative situations were encountered in the intraoperative period; in particular there was no response to any touch and pull of the *ligamentum latum uteri*.

All values for both groups were within the reference range despite some differences in hemodynamic values *(Table 1)*. After the administration of propofol, SBP, DBP, MBP and HR decreased, but this decrease was within the normal range. However, this decrease continued with IT anesthesia, but the decline was less in RG. Following propofol administration, apnea also occurred in all dogs and RR returned to baseline values within a short time. RT was similar in both groups, exhibiting a mild decline. No statistically significant differences were found between groups in ECG measurements.

Table 1. *Mean±sd for heart rate (HR), systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP), mean arterial blood pressure (MBP), respiratory rate (RR), and rectal temperature (RT) with IT bupivacaine (BG) or ropivacaine (RG) following propofol administration in dogs*

Variables	Groups	Time (min)								
		0 (initially)	Propofol+1	IT +5	15	30	60	90	120	150
SBP (mm Hg)	BG	132.5±11.3^{a}	124.5±8.4^{ab}	118.1±8^{b}	115.2±8.6^{b}	123.8±6^{ab}	125±8.8^{ab}	126.5±9.3^{ab}	124±9.2^{ab}	130±9.2^{ab}
	RG	133.3±6^{a}	123.1±6.7^{b}	113.1±6.9^{c}	109.7±7.9^{c}	116.5±6.2^{bc}	126.5±3.3^{ab}	130.2±3.8^{ab}	132.5±5.1^{ab}	132.5±6.2^{ab}
DBP (mm Hg)	BG	96.5±6.8^{a}	92.2±6.3^{ab}	87.2±8.7^{b}	86.5±4.8^{b}	88.7±4.8^{ab}	92.2±4.33^{ab}	94±5.8^{ab}	95.1±6.6^{ab}	95.8±6.7^{a}
	RG	95.2±5.4^{a}	91±5.3^{ab}	86.2±3.9^{bc}	84.5±5.5^{bc}	83.2±3.2^{c}	87.1±3.5^{bc}	89.5±5.2^{abc}	94±5.9^{ab}	95.2±4.5^{ab}
MBP (mm Hg)	BG	113±3.8^{a}	107.8±3.4^{ac}	102±3.8^{b}	101.3±3.8^{b}	104.3±4.9^{bc}	108.5±5.4^{ac}	111.2±5.2^{ac}	111.7±3.9^{ac}	113.2±3.5^{ac}
	RG	111.5±2.9^{a}	106.3±3.8^{a}	99±3.5^{b}	94.6±2.9^{b}	94±3.5^{b}	100.7±5.5^{b}	108.5±5.9^{a}	110.7±3.5^{a}	111.7±3.2^{a}
HR (bpm)	BG	85.3±2^{a}	81.5±1.4^{b}	78.5±1.4^{c}	78±1.5^{c}	76.7±2.6^{c}	78.1±2.2^{c}	82±1.8^{b}	83.5±2.7^{ab}	85±2.6^{a}
	RG	85.6±2.5^{a}	81.2±2.1^{b}	78±1.8^{c}	77.8±1.1^{c}	78.8±2.2^{c}	81.3±1.4^{bc}	83.2±1.4^{ab}	84.2±1.9^{ab}	85.1±1.5^{a}
RR (bpm)	BG	26.5±3.3^{a}	17.8±1.8^{b}	16.8±2.2^{b}	16.6±1.9^{b}	18.6±1.9^{b}	21.2±1.9^{bc}	24.1±2.9^{ac}	25.2±3.1^{a}	26.7±3.9^{a}
	RG	27.7±3.2^{a}	16.8±3.9^{b}	17.7±2.8^{b}	17.2±3^{b}	19.6±2.3^{bc}	22.5±2^{c}	25.3±2.9^{abc}	26.5±3^{a}	27.2±3.9^{a}
RT (°C)	BG	38.5±0.1^{a}	38.4±0.1^{ab}	38±0.1^{b}	37.9±0.1^{b}	37.9±0^{b}	38.2±0.5^{b}	38.2±0.5^{ab}	38.2±0.1^{ab}	38.4±0.2^{ab}
	RG	38.6±0.1^{a}	38.2±0.2^{b}	38±0.1^{b}	37.9±0.1^{b}	37.9±0^{b}	38.2±0.1^{b}	38.4±0^{a}	38.5±0^{a}	38.5±0.1^{a}

a-c: *Differences between average values are shown by different letters on the same line ($P<0.05$)*

Table 2. *Mean ± sd for biochemical parameters according to anesthesia intervals*

Variables	Groups	Time (min)				
		0 (Initially)	15	30	60	120
Glucose (mg/dL)	BG	71.2±5.6 [a]	76.3±5.2 [a]	77.6±3.8 [ac]	79.8±4.8[bc]	84.8±4.0 [c]
	RG	68.6±3.6 [a]	69.9±8.7 [a]	64.1±77.6 [a]	77.6±11.5 [a]	79.3±14.2 [a]
AST (IU)	BG	49.0±4.3 [a]	42.1±2.5 [b]	40.0±2.7 [b]	34.8±1.5 [c]	35.1±1.5 [c]
	RG	49.3±2.6 [a]	43.4±2.4 [b]	37.0±2.6 [c]	33.8±2.6 [c]	37.3±4.4 [c]
ALT (IU)	BG	64.7±9.6 [a]	44.6±4.8 [b]	38.8±6.9 [b]	28.8±3.3 [c]	25.6±2.8 [c]
	RG	58.6±9.8 [a]	43.2±4.7 [b]	36.1±3.3 [b]	28.0±3.0 [c]	34.6±5.8 [bc]
BUN (mg/dL)	BG	6.9±2.0 [a]	9.8±3.7 [a]	9.8±3.7 [a]	17.18±4.5 [b]	20.0±5.0 [b]
	RG	7.1±2.5 [a]	8.7±1.7 [a]	11.8±1.7 [a]	17.2±4.7 [b]	19.6±4.1 [b]
Creatine (mg/dL)	BG	0.64±0.1 [a]	0.76±0.1 [ab]	0.85±0.1 [b]	0.91±0.1 [bc]	1.07±0.1 [c]
	RG	0.71±0.1 [a]	0.71±0.0 [a]	0.78±0.0 [ab]	0.85±0.0 [b]	0.88±0.1 [b]

a-c: *Differences between average values are shown by different letters on the same line (P<0.05)*

In addition, recovery from depressed hemodynamic parameters lasted longer in BG but was more short-lived in RG.

All values were within the range of reference values in the groups *(Table 2)* although there were some statistically differences in terms of biochemical values.

DISCUSSION

Propofol is used with many different combinations to immobilize the patient, and maintain safe comfortable anesthesia and easy recovery from anesthesia with minimal side effects by administering before anesthesia despite its weak analgesic effect [10-15]. In our study, the patient was prepared for anesthesia by using propofol before IT anesthesia in ovariohysterectomy operations. An induction that is effective in a short time was achieved in all cases in this study. Therefore, difficulties were not encountered in the transition of the *ligamentum flavum* during subarachnoid or IT punctures. In addition, desensitization at this location does not require local anesthesia. Total immobility was provided for all of the dogs, and this situation was the positive contribution for IT anesthesia during surgery.

A dose-dependent depressive respiratory effect is expected with propofol administration [10-13]. There was apne in our study, but respiration rate after recovering apnea was within the range of normal physiological reference values [20]. Therefore, the lowest possible dose is recommended, and the intravenous injection should not be performed too rapidly.

It has been reported that neurological complications after subarachnoid or IT anesthesia can be caused by local anesthetic toxicity and that this complication varies depending on pH, oil solubility and the protein binding power of the local anesthetic [1,2]. The effective duration of a local anesthetic is determined by its protein binding power. Both bupivacaine and ropivacaine are members of the long-acting, amide class of local anesthetics [1,2,16,18]. It has been reported that the effect of bupivacaine lasts longer than ropivacaine, but bupivacaine may have cardio-pulmonary side effects [1,2,16]. A statistical difference was found between BG and RG with regard to the duration of IT anesthesia (BG: 89.5±7.6 min; RG: 64.75±6.8 min) (P<0.05). Other studies [1,5] have reported similar findings. In addition, recovery from depressed hemodynamic para-meters lasted longer in BG but it was more short-lived in RG. In our study, no complications of IT anesthesia that induced clinical findings or behavioral changees were observed in the dogs. Furthermore, abnormal symptoms in the dogs' general condition, such as inactivity, loss of appetite, moaning after the anesthesia or in the post-operative period were not observed. Moreover, the animal owners did not report any subsequent negative feedback.

Bupivacaine and ropivacaine are metabolized in liver and in kidney (up to 10%) within 24 h of administration [20]. Also, propofol is metabolized in the liver [11]. Even though there was a statistically significant difference (P<0.05) between the initial values and the values observed during anesthesia in biochemical parameters. However, the obtained values were in the range with the reference values [20]. Hence, it can be said that the side effects of drugs used in spinal anesthesia on the liver or kidney are less because they joined slowly in a long time to systemic circulation.

The cranial progression of local anesthetics in cerebro-spinal fluid throughout medullar canal is not a desirable situation during subarachnoid, IT or spinal anesthesia. It can lead to the development of hypotension, migration of local anesthetic towards the cranial area, and respiratory depression due to blockage of the diaphragm and inter-costal muscles, possibly resulting in death. Therefore, the choice of local anesthesia for spinal or IT anesthesia is critical [1-3,6-9].

There are many studies where the advantages of bupivacaine and ropivacaine are demonstrated [1,2,16,17]. However, these local anesthetics may extend to the cranial area. To prevent this from occurring, either the solution should be in hyperbaric concentrations, or the patient may be inclined on the operating table to take advantage of gravity [1-3,5]. In our study, the spread of local anesthetic agents to the cranial area was limited by tilting the operating table to elevate the animal's head. Additionally, hemodynamic values in both groups were within the physiological reference range despite a statistically significant difference compared to baseline values, and no life-threatening changes were observed. Therefore, we believe that tilting the operating table during spinal anesthesia should not be ignored.

Some authors have reported that an increase in heart rate, respiration rate and systolic blood pressure values of 20% or more during the operation are thought to be an indication of intraoperative pain [3,5,15,21]. In our study HR, RR and SBP were almost the same as baseline values. Hence, there was no evidence of intraoperative pain in this sense or any other indication during the operation.

The results of this study comparing IT bupivacaine and ropivacaine after propofol administration for ovario-hysterectomy operations in dogs demonstrate that safe and effective anesthesia can be achieved using IT ropivacaine and bupivacaine, and that it can be a practical and functional option after propofol administration.

Conflict of Interest

None of the authors of this paper have any financial or personal relationship with other individuals or organizations.

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