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RESEARCH ARTICLE

The Comparison of Clinical, Histopathological and some Hemodynamic Effects of Spinal Anesthesia Applied in Dogs Through Bupivacaine HCl and Ropivacaine HCl in Two Different Concentrations [1] [2]

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Summary

The aim of this study was to evaluate the side effects of local and systemic clinical, histopathological and hemodynamics by use of isobaric and hyperbaric bupivacaine in different concentrations during spinal anesthesia which has been a common use within the past few years. The study material consisted of 23 healthy stray dogs with dissimilar sex, age and body weight as well as bupivacaine hydrochloride containing Marcaine® %0.5 (Astra Zenaca, Turkey) and Marcaine® Spinal Heavy %0.5 (Astra Zenaca, Turkey), and ropivacaine hydrochloride containing Naropin® 7.5mg/ml (Astra Zenaca, Germany) so as to create the state of spinal anesthesia. A total of 5 different groups were formed where each study group consisted of 5 dogs and the control group consisted of 3 dogs. The groups were as follows: Aa (Marcaine), Ab (Marcaine® Spinal Heavy), Ba (Naropin®), Bb (Naropin® + Dekstroz) and C (Dekstroz). During the anesthesia; blood pressure, pulse and respiratory rates were measured in all groups. Besides, needle punctures were applied from time to time. The animals were euthanized following a one-week long hospitalization. Then, the parts of the spinal cords on which injections were applied were taken off and investigated histopathologically. In this study no significant were observed with regard to the use of ropivacaine HCl and bupivacaine HCl and their clinical, hemodynamic and histopathologic side effects; on the other hand, bupivacaine HCl was found to be considerably superior to ropivacaine HCl regarding the anesthesia duration and depth.

Keywords: *Spinal anesthesia, Bupivacaine HCl, Ropivacaine HCl, Dog*

Köpeklerde İki Farklı Konsantrasyondaki Bupivacaine HCl ve Ropivacaine HCl ile Oluşturulan Spinal Anestezinin Klinik, Bazı Hemodinamik ve Histopatolojik Etkilerinin Karşılaştırılması

Özet

Bu çalışmada spinal anestezide son yıllarda sıklıkla kullanılan izobarik ve hiperbarik bupivacaine HCl ile ropivacaine HCl'nin köpeklerdeki lokal ve sistemik bazı yan etkilerinin klinik, bazı hemodinamik ve histopatolojik olarak değerlendirilmesi amaçlanmıştır. Çalışmanın materyalini farklı cinsiyet, yaş ve vücut ağırlığına sahip sağlıklı 23 adet sokak köpeği ve spinal anestezi oluşturmak amacıyla bupivacaine hidroklorür içeren Marcaine® %0.5 (Astra Zenaca, Türkiye) ve Marcaine® Spinal Heavy %0.5 (Astra Zenaca, Türkiye) ile ropivacaine hidroklorid içeren Naropin® 7.5mg/ml (Astra Zenaca Almanya) oluşturdu. Her bir çalışma grubunda 5, kontrol grubunda ise 3 köpek yer alacak şekilde Aa (Marcaine), Ab (Marcaine® Spinal Heavy), Ba (Naropin®), Bb (Naropin® + Dekstroz) ve C (Dekstroz) olmak üzere 5 ayrı grup oluşturuldu. Tüm gruplarda anestezi süresince arteriyal kan basıncı, nabız ve solunum değerlerine bakılırken zaman zaman iğne pükürleri uygulandı. Hayvanlara birer haftalık hospitalizasyonu izleyerek ötenazi uygulandıktan sonra enjeksiyon uygulanan bölgeyi içeren spinal kord bölümü çıkarılarak histopatolojik olarak incelendi. Bu çalışmada yan etkiler bakımından ropivacaine HCl ile bupivacaine HCl arasında klinik, histopatolojik ve bazı hemodinamik parametrelerin değerlendirilme sonuçlarına göre kullanılan anesteziklerin herhangi bir yan etkisiyle karşılaşılmadı. Anestezi süresi ve derinliği bakımdan ise bupivacaine HCl'nin, ropivacaine HCl'ye göre oldukça üstün bir anestezi sağladığı ortaya konmuştur.

Anahtar sözcükler: *Spinal anestezi, Bupivacaine HCl, Ropivacaine HCl, Köpek*

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INTRODUCTION

Through the application of spinal anesthesia, a type of regional anesthesia, local anesthetic agents are injected into the cerebrospinal fluid (CSF) in subarachnoid space. Thus, spinal and motor nerves are affected, which leads to a temporary loss in motor functions [1-8].

Ease of application, nonexistence of anesthetic gas pollution, low pulmonary embolism risk, no harm to the liver functions even in repeated applications, no clogging in the respiratory tract, no risk of aspiring the contents of stomach as coughing reflex is present, the provision of postoperative analgesia, mobilization of patients in a shorter period of time, and being much less costly than general anesthesia are considered as the advantages of spinal anesthesia [3,8-13]; on the other hand, its disadvantages are the following: Its application requires time and expertise; there is application error related post interventional risk of neurological sequels; local anesthetic toxicity; technique related complications; and vets' lack of adequate knowledge [2,7,8,13].

It has been stated that complications such as hypotension, bradycardia, vomiting, cardiac failure, meningitis and meningismus, paralysis, urinary retention and the cauda equina syndrome can be seldom manifested following the application of spinal anesthesia [3-7,11,14-17].

It has been proven that there is a relation between the effectiveness period of local anesthetics and their capacity of binding with proteins; between effectiveness and solubility in oil; and the quality of anesthesia and drug concentration [1,7,14,18]. Ropivacaine HCl, with its protein binding capacity of 90-94%, is similar to bupivacaine HCl; whereas, its solubility rate in oil is almost half of that of bupivacaine HCl and its potency is 60% of that of bupivacaine HCl [19]. With its cardiac depression effects known for a long time, bupivacaine HCl [2,15,19-21] has been preferred widely in spinal and/or epidural anesthesia applications [22-24].

The objective of this study was the clinical, histopathological and hemodynamic assessment of local and systemic side effects manifested in dogs as a result of the application of isobaric and hyperbaric concentrations of bupivacaine HCl and ropivacaine HCl, which are anesthetic drugs that have frequently been used in the recent years in spinal anesthesia practices.

MATERIAL and METHODS

This study was conducted on 23 healthy stray dogs with dissimilar sex, age and body weight in accordance with the decree (dated May 22, 2006, no 08) of Kafkas University, Faculty of Veterinary, Ethics Commission of Experimental Animals. Bupivacaine HCl containing Marcaine® %0.5 (Astra Zeneca) and Marcaine® Spinal Heavy %0.5 (Astra Zeneca, Turkey) and ropivacaine HCl containing Naropin® 7.5 mg/ml (Astra Zeneca, Germany) were used so as to create the state of spinal anesthesia.

The animals used in the study were kept in quarantine for a week, subjected to clinical examinations and distributed to 5 different groups (Aa, Ab, Ba, Bb and C) where each study group contained 5 dogs and the control group contained 3 dogs.

Arterial blood pressure, pulse and respiration rates of the dogs were measured and recorded in the beginning, after the sedation, at the beginning of the anesthesia, at the 15th, 30th and 60th minutes of the anesthesia and at the end of the first week *(Table 1)*. Body temperature of the dogs was also measured at the specified times.

All dogs were laid in the lateral supin position on the operation table with a slope of approximately 30°. Following the shaving and disinfection of the lumbosacral region, local infiltration anesthesia of the region between the skin and the spinal space was done with lidocaine. After entering into the spinal space with a 18 G, 31/2 spinal needle, injection was applied at a very slow pace.

In group Aa, 4 ml (0.5%) isobaric bupivacaine HCl (Marcaine®) (20 mg/total) was administered; in group Ab, 4 ml (0.5%) hyperbaric bupivacaine HCl (Marcaine® Spinal Heavy) (20 mg/total) was administered. On the other hand, in group Ba, 3.75 ml (0.5%) isobaric ropivacaine HCl (Naropin®) (30 mg/total) was administered; in group Bb, 3.75 ml (0.5%) isobaric ropivacaine HCl was administered with 1.25 ml (20%) dextrose (30 mg/total); in the control group C, which consisted of 3 dogs, a total of 4 ml (20%) dextrose was used.

Needle punctures were applied in the groups without doing any operational intervention in order to determine the duration and the quality of anesthesia. Then, animals' responses were categorized and recorded as 0, 1, 2 or 3 in accordance with the intensity of their responses.

Each animal was euthanized following a one week long hospitalization. The region on which injection was applied was dissected and removed together with the spinal cord. The removed parts were fixed in formal (10%) and subjected to decalcification in formic acid (10%) for 20 days. The tissues were carried through alcohol and xylol, and embedded into paraffin. Then, they were sectioned with microtomes into 4-6 µm wide pieces. Preparations dyed with haematoxylin and eosin were analyzed under light microscope.

The statistical assessment of the data obtained in this study was conducted in SPSS (SPSS Inc, Chigago, IL, USA) 12.0 by using ANOVA method. Inputs were given as mean ± standart error. The data with a P value less than 0.05 were accepted as statistically significant.

RESULTS

At minute zero, a difference was noted with regard to the respiratory rates between Aa and Bb (P<0.05), Ab and Bb (P<0.05), Ba and Bb (P<0.05), and Bb and C (P<0.05). No difference was noted between the remaining combinations (P<0.05).

A statistical difference was noted with regard to the diastolic values between Aa and Ab (P< 0.05), Ab and Ba (P<0.01), and Ba and C (P<0.05).

A marked difference was found at the 15th minute of the spinal anesthesia with regard to diastolic values between Aa and Ab (P<0.01), Ab and Ba (P<0.01), and Ba and Bb (P<0.05); whereas the differences between Aa and Ba, and Aa and Bb were not considered significant.

A difference was noted at the 30th min with regard to diastolic between Aa and Ba (P<0.05), whereas no statistically significant difference was found among the groups with regard to the other parameters. It was observed that this difference between these groups kept diminishing but remained existent until the end of the first hour (P<0.01). At the end of the first week, no statistically significant difference was found among the groups with regard to any of the parameters *(Table 1)*.

The time periods elapsed between the administration of the spinal injections and the entrance into the state of anesthesia were as follows: Aa 3.3 minutes, Ab 5.6 min, Ba 4 min and Bb 3.6 min. The anesthesia durations were: 196.4 min for Aa, 156.4 min for Ab, 100 min for Ba and 72.4 min for Bb.

The difference among the groups regarding the findings related to the intensity of animals' reactions to the needle punctures were not found to be statistically significant.

After the euthanasia, before the spinal cord was removed by dissection, the conditions of subdermal tissues in the injection region were assessed. In two cases (Aa1, Aa2), hematoma was found to be spread under the skin covering the injection region.

No significant difference was noted among the groups in the histopathological analyses. In only one case (Bb1), satellitosis was observed in posterior root, white matter and posterior gray horn *(Fig. 1)*. Besides, in this case, degenerative changes (congestion in veins and Waller degeneration) were also detected. Moreover, in two cases (Aa4, Ba4), intraspinal hemorrhage was detected.

Table 1. *Distribution of the parameters that were measured for each group with respect to time*
Tablo 1. *Gruplararasında ölçüm yapılan parametrelerin zamana göre dağılımı*

Parameter	Group		Time						
			Beginning	Sedation	0th min	15th min	30th min	60th min	1st week
Respiration Rate	A	Aa	17.2± 2.8	13.6±2.2	14.4±5.2	9.6±2.1	11.6±3.9	13.8±5.1	17.4±1.4
		Ab	21± 3.7	15.2±4.2	11.8±3.3	10.6±4.4	10.8±4.1	12.8±4.9	21±3.8
	B	Ba	18.8± 2.8	15.8±5.3	11.6±3.6	8.6±3.3	9±3	13±2.2	18±4.6
		Bb	19.2± 1.1	15.2±1.2	11.8±0.4	10±1.4	11.6±1.7	15.2±2.3	18.4±2.6
	C		21.3± 3.2	15.7±2.5	11.3±1.2	-	-	-	21.6±3.5
Pulse Rate	A	Aa	99.2± 4.5	88.4±8.6	46.4±8.8	38.4±8.3	31.2±5.9	37.2±7.6	99±4.9
		Ab	94.6±12.9	81.6±14.9	47±4.4	40.4±5.5	36.8±6.8	52.6±7.1	95.6±10.01
	B	Ba	89.4±17.5	71.6±12.5	44.8±2.7	36.2±1.8	33.6±1.7	63.4±11.2	91±16.03
		Bb	80±7.9	62.8±5.6	47.2±3	36.8±3.8	36.4±4.9	65.2±5.2	78.4±8.05
	C		101±16.5	76.7±10.3	71.3±7.6	-	-	-	105±13.23
Systolic Value	A	Aa	172.8±21.9	169.2±20.5	161±23.9	155.6±20.5	146.8±19.3	145.4±19.4	165.4±28.8
		Ab	163±24.3	155.4±21.3	146.2±23.2	132.6±24.6	130.4±25.4	146.0±22.1	163±22.4
	B	Ba	148.2±39.5	136.8±38.3	124.2±36.9	118±37.8	115.6±37.4	130.8±35.9	149±35.1
		Bb	170±41.4	155.8±36.9	147.6±35.9	138±32.9	139.6±28.3	156.4±39.5	171.6±44.6
	C		145.7±36.1	129±33.1	121.7±31.6	-	-	-	149±34.3
Diastolic Value	A	Aa	118.6±29.5	115.4±24	107.8±23.8	106.6±27.8	94.4±18.5	90.2±12.4	117±29.7
		Ab	98.6±13.5	92.2±13	88.4±12.2	83±10.6	88.2±8.4	101±27.3	99±13.08
	B	Ba	98.2±32.3	94.2±32.5	90.8±33.5	89±33.9	88.4±35.1	93±32.7	99.2±30.8
		Bb	98.8±28.1	87.2±24.8	81.4±22.7	75.4±18.9	76.4±18.3	92.7±26.9	98.2±30.07
	C		81±16.5	75±15.7	73±15.6	-	-	-	1.3±15.8

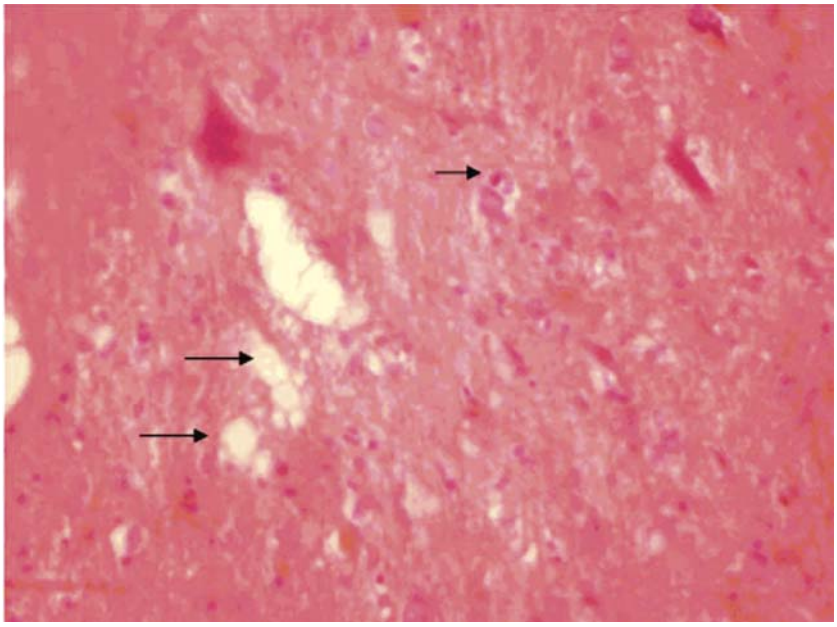

Fig1. Satellitosis (the short arrow) and vacuolar degeneration *(long arrows)* in the case Bb1, HEx40

Şekil 1. Bb1 nolu olguda satellitozis (kısa ok) ve vakuoler dejenerasyon *(uzun oklar),* HEx40

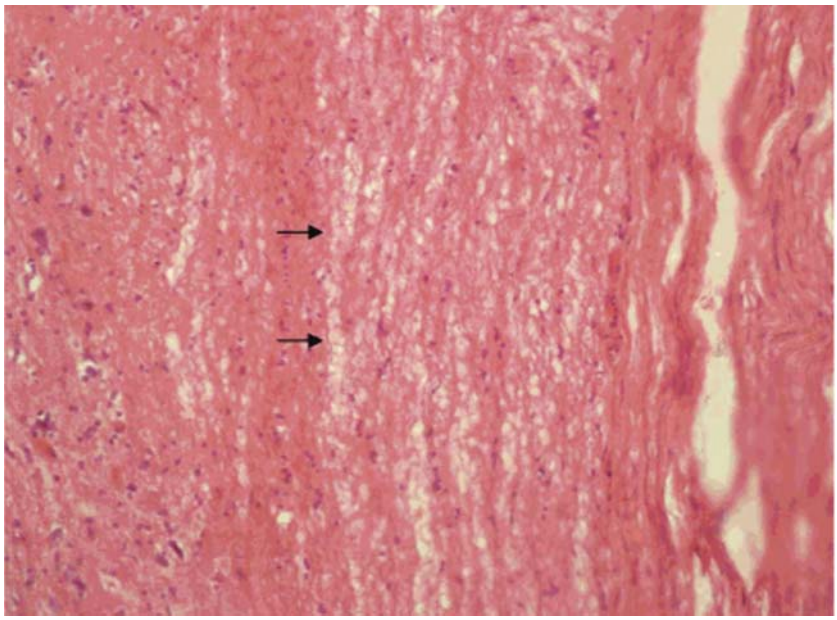

Fig 2. Waller degeneration *(arrows)* characterized by vacuolization in posterior root (case Bb1), HEx20

Şekil 2. Bb1 nolu olguda posterior root'ta vakuolizasyon ile karakterize Waller dejenerasyonu *(oklar),* HEx20

DISCUSSION

While Grene [5], asserted that spinal anesthesia's side effects on the respiratory system were very low. Şahin [24], stated that a hyperbaric solution which was injected via L_{2-3} or L_{3-4} space diffused towards cranium and that the risk of respiratory insufficiency increased. In another study, it was stated that the anesthetic agent could reach the chest and neck area and that it could induce respiratory insufficiency by blocking the transfer in intercostal and phrenic nerves; moreover it was emphasized that in some cases it could proceed to the cranium and stress the respiratory system and vasomotor centers [1]. Although respiration rates were decreased in all the experimental groups the difference between groups was not clinically significant. Although this study makes one think that spinal anesthesia's side effects on the respiratory systems are very low, it should be noted that this might have been due to the inclination of the operation table which prevented the diffusion of the anesthetic agent toward the cranium.

With its high anesthetic power, Bupivacaine HCl's onset of action is slow (3-8 min) and its anesthesia duration is long (2-5 h) [2,5,7,11,20,24]. In this study, in the group Aa where isobaric bupivacaine HCl was used, the onset of anesthesia was 5.6 min on average and the

duration of anesthesia was 196.4 min; in the group Ab where hyperbaric bupivacaine HCl was used, the onset of anesthesia was 3.3 minutes on average and the duration of anesthesia was 156.4 min. The results of other studies [5,11,24], which investigated the onset and the duration of the anesthesia were found to be parallel with the results of this study.

Şahin [24], stated that hyperbaric solutions had a more rapid onset and a shorter duration of anesthesia when compared to the isobaric solutions. In this study, in the group Ab where hyperbaric solution was used, the onset of action was more rapid (Aa: 5.6 min, Ab: 3.3 min) and the duration of anesthesia was shorter (Aa: 196.4 min, Ab: 156.4 min) when compared to the group Aa where isobaric solution was used. The anesthesia durations of the groups Ba, where isobaric ropivacaine HCl was used, and Bb, where a hyperbaric solution was made with the addition of dextrose, (Ba: 100 minutes, Bb: 72.4 min) were parallel to anesthesia duration of the groups where bupivacaine HCl was administered. No significant difference was noted between Ba and Bb with regard to the onset of anesthesia (Ba: 4 mins, Bb: 3.6 min).

The onset, depth and duration of sensory block in spinal anesthesia obtained with ropivacaine HCl were stated to be similar to those obtained with bupivacaine HCl administration; however, the depth and duration of motor block obtained with ropivacaine HCl were stated as lower when compared to bupivacaine HCl administration. In this study, the duration of anesthesia obtained with isobaric ropivacaine HCl was found to be shorter than that obtained with isobaric bupivacaine HCl (Aa: 196.4 min and Ba: 100 min); and the results obtained with hyperbaric solutions was also similar to the former (Ab: 156.4 min and Bb: 72.4 min). The depth of anesthesia was found as the same in all groups until the 30th min; however, after the 30th min, in the groups Ba and Bb, the groups where ropivacaine HCl was used, the depth of anesthesia was observed to begin to decrease. As of the end of the first h, in the groups Aa and Ab, i.e. bupivacaine HCl administered groups, the desired level of anesthesia depth was observed to be present; whereas, in the groups Ba and Bb, this depth was observed to have decreased.

Bradycardia has long been accepted as a possible typical cardiovascular response to spinal anesthesia [25,26]. In this study, as of the 0th min of the anesthesia, a decrease in pulse rates was assessed as bradycardia in all groups. In ropivacaine HCl administered groups (Ba and Bb), pulse rates approached to normal values after the first h of the anesthesia; however, in bupivacaine HCl administered groups (Aa and Ab) a slight bradycardia was observed to continue.

In various studies, hypotension has been stated to be the cardiovascular complication observed commonly in spinal anesthesia practices. Besides, the reason of hypotension has been reported as reduction in blood pressure and heart rate [2,5,12,15,16]. In this study, on the other hand, in addition to a decrease in pulse rates; systolic and diastolic blood pressures also decreased in all groups. This situation is thought to have stemmed from a decrease in heart rate during spinal anesthesia which brought about a slowdown in blood flow rate. The fact that these decreases in pulse rates were parallel to the duration of anesthesia was evaluated as a support for this thesis.

Horlecker et al.[18], stated the ratio of spinal anesthesia caused neural damages as 38%. Rosen et al.[26], reported that spinal anesthesia related subpial vacuolization, axonal swelling, macrophage infiltration and demyelination were formed in the spinal cord. In all studies conducted by Takenamia et al.[13,27,28], it has been found as a common result that histopathological changes took place in posterior root and that lesions were characterized by macrophage infiltration, and the degradation of the axonal structure and myelin sheath. It has also been stated in the studies that other regions in both roots which contained the peripheral part were not affected. In this study, no difference was noted among the groups at the end of the histopathological analyses; on the other hand, in only one case (Bb1) satellitosis was observed in posterior root, white matter and posterior gray horn. Besides, in this case, degenerative changes (congestion in veins and Waller degeneration) were also detected.

Many studies have reported that spinal hematoma can seldom be observed as a result of spinal anesthesia [7,10,16,17,24]. In this study, hematoma was observed in subdermal tissues of 2 cases (Aa1 and Aa2); and hemorrhage was detected in two cases (Aa4 and Ba4) in spinal cord related histopathological assessments.

As a conclusion, according to the results of this study where clinical, histopathological and hemodynamic assessment of local and systemic side effects of the isobaric and hyperbaric concentrations of bupivacaine HCl and ropivacaine HCl was made, it is not possible to conclude that anyone of these drugs is superior to the other; on the other hand, it was determined that doctors can choose which drug to use considering the estimated duration of the operation. Therefore, in consideration of the results of this study, it can be said that both drugs are qualified to be used for spinal anesthesia purposes in clinical practices. Indications of these drugs can be expanded by trying these drugs on other animal species.

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