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RESEARCH ARTICLE

COMPARISON OF SENSORY AND MOTOR PERIPHERAL NERVE BLOCKADES WITH 1.33% LIPOSOMAL BUPIVACAINE, 1% ROPIVACAINE AND 2% LIDOCAINE WITH DEXAMETHASONE

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ABSTRACT

Introduction: Main goal of nerve blockade is to provide analgesia that will outlast duration of pain as long as possible. Deficiency of currently available local aneasthetics is relatively short duration of action. The aim of this study was to compare sensory and motor blockade after perineural application of liposomal bupivacaine, ropivacaine or lidocaine with addition of dexamethasone during peripheral nerve blockade in Wistar rats. ***Materials and methods:*** A rat sciatic nerve block model was used. The study was conducted in accordance with the principles of laboratory animal care and was approved by the Laboratory Animal Care and Use Committee. Thirty adult Wistar rats both sexes were studied. After induction of general anesthesia, and sciatic nerve was exposed unilaterally. Sciatic nerves were randomly assigned by the method of sealed envelopes to recive: 2 mL perineurally 1.33% liposomal bupivacaine, 1% ropivacaine or a solution of 2% lidocaine with addition of 4mg / ml of dexamethasone. Neurologic examination protocol was followed to determine motor function by extensor postural thrust and nociception by withdrawal reflex. ***Results:*** The rate of recovery of motor and sensory function after perineural administration of liposomal bupivacaine is statistically slower compared (<0.001) with perineural administration of ropivacaine or lidocaine with addition of dexamethasone. Liposomal bupivacaine significantly prolonged analgesic effect when used as a single – injection perineural sciatic block. *Conclusion:* Liposomal bupivacaine has a favorable profile when it comes to the duration of ation compared with lidocaine in combination with dexamethasone and ropivacaine.

INTRODUCTION

Regional anesthesia is widely integrated in pain therapy, during the pre / intra / and postoperative periods. Peripheral nerve blocks, as one of the methods of regional anesthesia, offer many benefits that, among other things, make a significant contribution to improving the therapeutic effects. Their use reduces blood loss during surgery and the incidence of deep venous thrombosis, reduces perioperative hypercoagulability, avoids common side effects of general anesthesia, reduces the use of opioids, and reduces overall health costs [1, 2]. Peripheral nerve blocks are the preferred choice in ambulatory settings, particularly to the isolated limb injuries[3]. One of the commonly used regional anesthesia techniques is blockade of sciatic nerve, which has gain great popularity since it was first administered in 1930, and which can be performed in all situations where surgery is required at the lower extremity or in the treatment of postoperative pain. However, one of the deficiency of the local anesthetics used in such procedures is their relatively short duration of action. The duration of postoperative pain greatly outweighs the duration of analgesia after single administration of traditional local anesthetic formulations [4]. Scientists have tried mixing local anaesthetic with adjuvant drugs in an attempt to prolong analgesia from nerve blocks. The glucocorticoid dexamethasone appears to be effective in a small number of preclinical [5] and clinical [6] studies. Why dexamethasone would prolong regional anaesthesia is a subject of much discussion. Steroids induce a degree of vasoconstriction, so one theory is that the drug acts by reducing local anaesthetic absorption. Another attempt to prolong duration of nerve blockade was introducing formulation of long lasting local anaesthetics such as ropivacaine and bupivacaine[7, 8]. By their use into clinical

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practice duration of anaesthesia was prolonged, but not sufficiently required. One way to overcome this problem is to develop anesthetic depo formulations designed to keep the anesthetic longer at the injection site and to release the drug more slowly over time [9]. Liposomal bupivacaine is a sustained-release bupivacaine formulation designed to allow drug diffusion up to 72 hours after single administration at the end of surgery. EXPAREL ® (bupivacaine liposome injectable suspension) is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks [10]. Hence, the aim of our study is to compare quality of motor and sensory peripheral nerve blockade between liposomal bupivacaine, ropivacaine and lidocaine with dexamethasone.

MATERIALS AND METHODS

The study was conducted at the Faculty of Medicine, University of Sarajevo, with the approval of the Ethic Committee of the Faculty of Medicine and in accordance with the principles of laboratory animal care and was approved by the Laboratory Animal Care and Use Committee. Thirty adult wistar rats, both sexes, with an average weight of 300 grams, were used as material in this study. Rats were housed in static microisolation cages and fed a commercial diet and provided bottles with purified water. Rooms were maintained on a 12:12 h dark : light cycle at 21 to 23 ºC and 30% to 70% relative humidity. All animals were administered general anesthesia by intraperitoneal injection with nembutamol sodium pentobarbital (50 mg / kg). Following the rules of strict asepsis we made unilaterally (right side) an incision on the skin and gluteal muscle and dorsally approached to the sciatic nerve. The rats were randomly divided in three groups by sealed envelopes. In the first one 1.33% liposomal bupivacaine (Exparel, Pacira Oharmaceutical Inc., Parisppany, NJ, USA) was administered perineurally, in the second group 1% ropivacaine (Astra Zeneca, USA) was applied perineurally and a solution of 2% lidocaine (Bosnalijek, BiH) with addition of 4mg / ml of dexamethasone (Krka, Slovenia) was applied in the third group.

A 27 G long beveled needle (LifeTech, PB-25SCS) was placed at an angle of 45° perineurally (within epineural tissue but outside perineurium). Stereomicroscopic guidance was used to ensure precise perineural placement of the needle, after which the needle was stabilized with a suitable instrument (Activational System Inc., Scientific Instrumentation, SAS-1451AP, Small Animal Stereotaxic Frame, USA). Using an automatic syringe (PHD2000, Harvard Apparatus, Holliston, MA), we applied 2 ml of the tested solutions, with the speed of 5 ml / min, to the experimental groups mentioned above. After the injection was performed, the wound was sutured and we awaited for the waking of the animals from the general anesthesia. After waking the animals from the general anesthesia, a methodological neurological examination was performed at appropriate time intervals (every hour for the first 6 hours after waking, and once a day for the next three days). Neurological examination was performed with a modified Thalhammer neurological examination [11] for the assessment of neurological status for small animals, and included the following parameter:

- **Nociception** was assessed by observing limb withdrawal in response to noxious stimuli. The force of the calibrated forceps, with a tip diameter of 2 mm, was applied to the skin fold of the lateral metatarsus. Nociception is graduated according to the following criteria:

  - ***score 4*** **-** normal reaction, strong and rapid withdrawal of the entrapped part of the hind limb, vocalization and forceps bite attempt
  - ***score 3*** **-** slower withdrawal of the entrapped part of the hind limb, vocalization without trying to bite the forceps
  - ***score 2*** **-** slow withdrawal of the entrapped part of the hind limb, without vocalization, without attempting to bite the forceps
  - ***score 1*** **-** very poorly expressed attempt to pull the hind limb
  - ***score 0*** **-** none of the above mentioned reactions are present

A return to value 3 was considered a recovery of function.

Motor function was estimated by extensor postural thrust. The whole body of the rat with the exception of the hind limb was wrapped in a surgical towel and lifted from the surface. When the anterior limbs are lifted, their tibitarsal joint is expanded to maintain an upright posture, and in this case the body weight is maintained by the distal metatarsus and fingers. By supporting the animal thorax and lowering it, extensor postural thrust was tested as a force that resists the contact of the platform with the heel. As the animal was lowered the posterior extremity extended to the surface of the scale (digital scale from 0 to 500 grams) (model TM 560; Giberini, Milano, Italy). This method measures the strength in grams produced with the foot opposite the surface of the scale, as a result of the extension of the gastrocnemius muscle. The strength in grams applied to the digital scale platform was recorded before the application of local anesthetic as normal extensor postural thrust (NEPT) value and after injection of local anesthetic - experimental value (EEPT). Both values are incorporated into the formula for calculating the functional deficit percentage:

Percentage of the functional deficit = (NEPT – EEPT) / NEPT × 100

The duration of a motor blockade is defined as the time required to recover to a 25 % motor deficit.

Statistical analysis

All data analyses were performed using Statistical Package for the Social Sciences version 13.0 (IBM SPSS, Chicago, IL, USA). The Shapiro-Wilk test of normality was performed to evaluate the normality of the continuous variables. Continuous variables with normal distributions were compared by applying one-way analysis of variance (ANOVA) followed by Tukey's post hoc test and data were expressed as the mean ± standard deviation (SD). A one-way analysis of variance (ANOVA) for repeated measures with the Bonferroni post-hoc correction was used to compare the intragroup motor deficit scores during the 72 hours follow-up period. The Kruskal-Wallis test for independent samples with post-hoc a Mann Whitney U test was performed for non-normally distributed variables and data were reported using the median and interquartile range (IQR: 25-75th percentile). Probability (*P*) values less than 0.05 were considered as statistically significant.

Ethic statement: The procedures used and the care of animals were approved by Ethic Committee of the Faculty of Medicine (approval No. 02-3-4-2819/17)

RESULTS

Mean motor deficit values in the Liposomal Bupivacaine, Lidocaine + Dexamethasone, and Ropivacaine groups during the 72-hour experimental monitoring period are shown in Table 1. This trend of recovery of motor deficit was maintained until the 24th hour of prevention, when only in the Liposomal Bupivacaine group the motor deficit was present (6.5 ± 9.1%), while in the other two experimental groups it was absent (0.0 ± 0.0%), which indirectly indicates prolonged effect of this anesthetic in relation to the other two. The results of testing the differences in the effect of the three observed drugs on motor deficits during the 72-hour experimental monitoring period are shown in Figure 1. After 24 hours of the experiment, the motor deficit remained only in the Liposomal Bupivacaine group and amounted to 6.5 ± 9.1%, whereas in the Lidocaine + Dexamethasone and Ropivacaine groups no motor deficit was recorded in the 24 hour of the experiment (0.0 ± 0.0%). The results of examining the differences in the effects of the three groups of anesthetics on the nociception score during the 72-hour experimental monitoring period are shown in Table 2. The first differences in nociception scores between the experimental groups were determined at 3 hours of the experiment, with only the difference between the Ropivacaine and Lidocaine + Dexamethasone groups being statistically significant (*P = 0.008).

Table 1. Motor deficit data at baseline and over the 72 hours follow-up period for each drug group

Motor deficit (%)			
Time (hours)	Liposomal Bupivacaine	Lidocaine + Dexamethasone	Ropivacaine
0 (baseline)	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
1	97.5 ± 3.1	98.0 ± 3.2	97.2 ± 1.9
2	91.0 ± 1.9	93.5 ± 3.8	88.6 ± 3.1
3	84.7 ± 4.4	80.5 ± 4.3	75.5 ± 4.0
4	76.3 ± 5.1	69.6 ± 5.0	59.1 ± 5.4
5	67.5 ± 5.0	57.8 ± 4.4	47.6 ± 3.5
6	57.0 ± 4.6	46.4 ± 4.4	37.9 ± 2.7
24	6.5 ± 9.1	0.0 ± 0.0	0.0 ± 0.0
48	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
72	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Data are presented as mean ± SD;

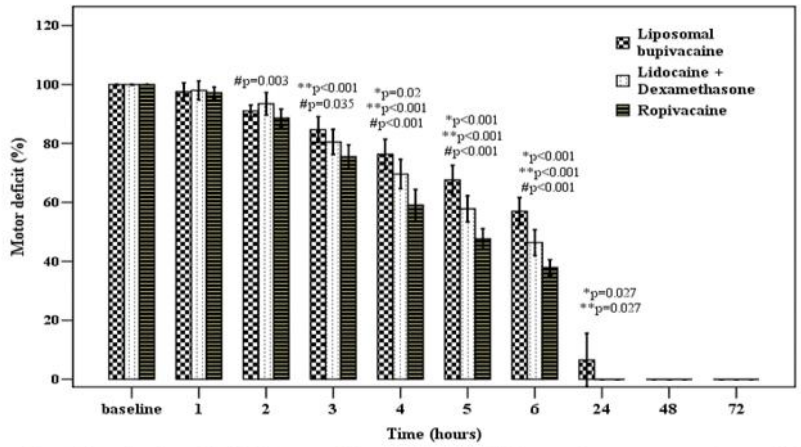

Figure 1. Recovery of motor function during the 72 hours follow-up period; Bars show mean values ± SD (n=10/group); *Liposomal Bupivacaine *vs.* Lidocaine +Dexamethasone; **Liposomal Bupivacaine *vs.* Ropivacaine; #Lidocaine + Dexamethasone *vs.* Ropivacaine

Table 2. Differences in nociception score between drug groups over the 72 hours follow-up period

Nociception score				
Time (hours)	Liposomal Bupivacaine	Lidocaine + Dexamethasone	Ropivacaine	p-value
0 (baseline)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-
1	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-
2	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-
3	0.5 (0.0 - 1.0)	0.0 (0.0 - 1.0)	1.0 (1.0 - 1.0)	#0.008;
4	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.25)	2.0 (2.0 - 2.25)	**<0.001; #<0.001;
5	2.0 (1.0 - 2.0)	2.0 (2.0 - 2.25)	3.0 (2.75 - 3.0)	*0.028; **<0.001; #0.009;
6	2.0 (2.0 - 3.0)	2.0 (2.0 - 2.25)	3.0 (2.75 - 3.0)	**<0.001; #0.001
24	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	1.0
48	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	1.0
72	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	4.0 (4.0 - 4.0)	1.0

DISCUSSION

The selection of optimal long-acting local anesthetic and concentration for sciatic nerve block must take into consideration the available anesthetics, the time to onset, duration of blockade and side effects of each drug and dose. It is demonstrated that regional anaesthesia to lower extremity is a suitable alternative to general anaesthesia and confers significant benefit to the improvement of patient safety [12, 13]. It minimizes the stress response, and avoids opioid-related complications. Among various approaches to neural block of the lower extremity, sciatic nerve block is a common regional anaesthetic technique for leg and foot surgery. It is performed in a variety of orthopedic and soft tissue surgical procedures of the lower extremity [14]. Our results demonstrate that liposomal bupivacaine significantly prolonged analgesic effect in comparing to plain ropivacaine or lidocaine with dexamethasone when used as a single-injection perineural sciatic block in Wistar rats. This finding is generally consistent with previous studies, but direct comparisons are difficult because of the variety of local anesthetic mixtures used, different blocks studied, and different methods of evaluating block duration. This study is the first to directly compare duration of action of these three local anesthetics. Longer duration of motor and sensory blockade after perineural injection of liposomal bupivacaine can be explained by longer exposure of nerves to a relatively higher concentration of local anesthetic. Pharmacokinetic studies showed that liposomal bupivacaine exhibited bimodal kinetics with rapid uptake during first few hours and prolonged release over 96 h[15].

Such drug characteristics can be useful in peripheral nerve blocks as an alternative to indwelling catheters. Our results are in agreement with other that found also longer duration of sensory and motor blockade using liposomal bupivacaine with no persistent neurological deficit [16, 17]. We did not evaluate potential neurotoxicity and consequential neurologic deficit of these three local anesthetics, since primary aim of these study was to compare duration of action of these local anesthetics.
Other dose-response study suggests that deposition of a liposomal bupivacaine formulation adjacent to the femoral nerve results in a partial sensory and motor block of over 24 hours for the highest doses examined, with a very high degree of intersubject variability [18]. The average duration of sensory block after liposomal bupivacaine injection was approximately 12 hours shorter in comparison to some clinical studies [18, 19]. Recent case report showed intercostal block with duration up to 96 h after liposomal bupivacaine administration [20]. Also partial sensory and motor blockade that lasted more than 24 h were found in dose dependent study, after application of high doses of liposomal bupivacaine [18]. In contrary to our results where perineural application of liposomal bupivacaine resulted in sensory and motor blockade that lasted lesser than 24 hours. We used an open model to ensure exact perineural position of the needle under the direct visual control, and thus to ensure that in all applications the needle position was the same. Longer exposure of the nerve in a closed model may be essential for prolonged blockade. Open model probably resulted in leakage of liposomal bupivacaine in surrounding tissues, decreasing the concentration of liposomal bupivacaine. Moreover, in animals it may be difficult to detect subtle neurological impairment such as transient parasthesia. Studies with rat incisional pain model also demonstrated that infiltration of a single dose of liposomal bupivacaine effectively attenuates both mechanical and thermal hypersensitivity for 4 days [21]. Other studies similarly reported that liposomal bupivacaine effectively attenuated both mechanical (from 2 to 4 days) and thermal hypersensitivity (up to 3 days) [22]. Recent study showed that plain bupivacaine compared with ropivacaine showed longer duration of sensory and motor blockade. Onset of action of sensory, motor block was early in ropivacaine group with faster recovery of motor functions as compared to bupivacaine group [23]. Bupivacaine is frequently used as the local anaesthetic for nerve blocks anaesthesia because it offers the advantage of providing a long duration of action and a favorable ratio of sensory to motor neural block [24, 25]. However, its toxicity is a concerning issue especially when larger doses are used as with peripheral nerve blocks and/or prolonged infusions for postoperative analgesia. Liposomal bupivacaine, as depo formulation of bupivacaine, allows usage of higher doses in one application with less side effects and longer duration of action, as showed in our study. Comparing the quality of sensory and motor blockade at specific time intervals, our results showed that liposomal bupivacaine showed a higher quality of sensory and motor blockade in each time period. These manifest themselves as a slower recovery of a particular function at a given time point, which was statistically significant comparing to lidocaine or ropivacaine.

Dexamethasone was found to prolong analgesia when combined with ropivacaine or bupivacaine for single-injection interscalene block. The combination of dexamethasone with the local anesthetic provided nearly the same (twenty-two hours) of analgesia [26]. Our results are in agreement with previous studies, because lidocain in combination with dexamethasone showed longer duration of sensory and motor blockade in comparison to plain ropivacaine, but not when compared to liposomal bupivacaine, which clearly shows advantage of liposomal bupivacaine. On the other hand, adding a glucocorticoid, steroid medication, to all local anesthetics may not be warranted for every patient. For example, diabetic patients may experience hyperglycemia. Glucocorticoids in the periphery decrease glucose utilization, increase protein break down, and activate lipolysis, as a mechanism of protection of glucose-dependent tissues from starvation. A single perioperative dose of dexamethasone has been shown to elevate intraoperative glucose for approximately four hours. It has also been thought that patients with an infectious process may be adversely affected by the anti-inflammatory effects of steroid medication. This was studied in a meta-analysis by Waldron et al. [27], in 2013, that evaluated the impact of perioperative single dose systemic dexamethasone for postoperative pain. Patients treated with dexamethasone did not demonstrate a significantly increased risk of infection or wound healing [25]. Another area of concern, and need for investigation, is the amount of dexamethasone that should be added to peripheral nerve blocks to be efficacious in prolonging analgesia. Dose finding studies are needed to define the dose, effect (is there prolongation of analgesia), and side effect when dexamethasone is added to local anesthetic for peripheral nerve blockade.

Particular attention and study needs to be given to dexamethasone dosing less than four milligrams and greater than ten milligrams in conjunction with the local anesthetic to determine if there is an average dose that should be utilized for optimal prolongation of analgesia. It is important to know that dexamethasone has not been approved for use in conjunction with local anesthetic medications. Thus, as a result, it is an

"off-label" use of the medication. In addition to potential neurological toxicity, "off-label" use of analgesic drugs in regional anesthesia can expose the patient to neurotoxic properties [28]. Most clinical studies to date that evaluated the duration of the analgesic effect of liposomal bupivacaine have been performed after infiltration of liposomal bupivacaine into the soft tissue at the end of surgery [29, 30, 31], with very little data on the duration of analgesia after peripheral nerve blocks [18]. Studies in dogs, pigs and rabbits have demonstrated a favorable safety profile for liposome bupivacaine [16, 32]. We believe that the results of our study provide valuable preclinical data on the benefits of using liposomal bupivacaine compared to the formulations of topical anesthetics available so far. Furthermore, it would be useful to provide additional studies with liposomal bupivacaine to determine a range of appropriate infiltration volumes, to examine usage in different surgical animal models and to define dosages for larger surgical sites.

Conclusion

Combined with the relatively rapid onset time and longer duration of action, liposomal bupivacaine has a favorable profile compared with lidocaine in combination with dexamethasone and ropivacaine. On the basis of these preclinical data, we conclude that liposomal bupivacaine pose no risk beyond that of lidocaine or plain ropivacaine.

Declaration of interest: All authors have no potential conflicts of interest.

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