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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(2):547-53

The clinical and histopathological effects of perineural dexmedetomidine in combination with bupivacaine in sciatic nerve block in rabbits undergoing sevoflurane anesthesia

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Received 23 September 2021; Accepted 15 November 2021
Available online 06.03.2022 with doi: 10.5455/medscience.2021.09.304

Abstract

Many drugs or additives have been tried as adjuvants in the blocking of nerve blocks with local anesthetics, and it is aimed to increase the duration of action and analgesia quality of local anesthetics in this way. In this study, we aimed to see the adjuvant efficacy of Dexmedetomidine [Dex] added to bupivacaine and its effect on analgesia and histopathological effects in rabbits by administering sevoflurane anesthesia. Twenty-four rabbits were randomly allocated to 3 groups; Group S: sham [0.5 ml saline], Group B: perineural bupivacaine [0.5 mg/kg] [0.5 ml] and Group BD: perineural bupivacaine [0.5 mg/kg] combined with Dex [20 µr/kg] [0.5 ml]. Analgesia measurement was evaluated by hotplate test, the paw withdrawal response was performed for sensorial and motor blockades also were recorded at baseline, 30, 60, 90, and 120 min after drug administration. Dissected nerve tissue was also examined for histopathologic evaluation. In the hot-plate test applied for the measurement of acute thermal pain; when compared to Group S, significant prolongation was found in Group B and Group BD at 0, 30, 60, 90, and 120 minutes [$p<0.05$]. When Group BD was compared with Group B, a significant prolongation was found at 60 minutes [$p=0.012$]. No significant difference was found in other times. No significant differences were found between the groups in sensory and motor block tests. In the BD group, compared to the B group, edema and inflammation in the epineurium and surrounding tissues were significantly reduced on the 1st day [$p<0.05$]. On the 14th day, there was no difference in terms of edema. In rabbits administered sevoflurane anesthesia, the mixture of bupivacaine and Dex applied to provide analgesia in the application of sciatic block prolongs the delay time and increases the quality of analgesia in the hot-plate test evaluating acute thermal pain. Dex added to bupivacaine contributed positively when the analyzed histopathological parameters were evaluated.

Keywords: Dexmedetomidine, bupivacaine, sciatic nerve blockage, sevoflurane, rabbit model

Introduction

Adjuvant drugs applied in addition to local anesthetics in nerve blocks increase both the duration of action and the quality of action of local anesthetics, and the duration of analgesia is further extended by adding various drugs and adjuvant substances to long-acting local anesthetics. Various studies have been conducted to increase the duration and quality of analgesia and anesthesia and to reduce costs related to adjuvant drugs added to local anesthetics. Routine administration of some adjuvant drugs with local anesthetics has begun to provide better analgesia quality [1]. However, these adjuvant drugs are sometimes insufficient and sometimes cause excessive drug costs.

Dexmedetomidine [Dex] is a potent selective α2-agonist agent with sedative, analgesic, anxiolytic, cardiovascular, and central nervous system effects. It is recommended for use when sedating patients under mechanical ventilation in the intensive care unit due to its anxiolytic properties [1]. It has been reported that it reduces the need for opioids and anesthetics in various applications and that it also significantly increases analgesic efficiency [2,3].In some studies conducted in our clinic [4-6]; it has been shown in rats that the quality of analgesia increased in the perineural injection of Dex as an adjuvant added to local anesthetics.

The primary aim of this experimental study is to analyze the

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efficacy of Dex in sciatic nerve block in rabbits, which was provided anesthesia with sevoflurane, an inhaled anesthetic without analgesic activity. The secondary aim is to determine the histopathological effects of the perineural Dex-bupivacaine combination on the sciatic nerve.

Materials and Methods

This single-blinded study was carried out at the Inonu University Experimental Animal Production and Research Center and supported by the Inonu University Coordination Unit of Scientific Research Projects (Project no: TSA-2017-712). It was used 24 young male New Zealand (5-6 kg) lineage rabbits, weighing 5-6 kg, after obtaining permission from the Inonu University Animal Experiments Local Ethics Committee (2017/A-329).

The rats were housed in temperature-controlled [20°C] rooms with a 12-hour light-dark cycle for 10 days before the beginning of the study. During this process, the rats were provided with unlimited access to food and water. On the day of the experiment, the rats were randomly divided and assigned into three groups, consisting of 8 rats each: Group S: sham (0.5 ml saline), Group B: perineural bupivacaine (0.5 mg/kg) (0.5 ml) and Group BD: perineural bupivacaine (0.5 mg/kg) combined with Dex (20 µr/kg) (0.5 ml).

To administer inhalation anesthesia with sevoflurane, first of all, anesthesia induction was provided with a mixture of 100% oxygen + 8% sevoflurane (fresh gas flow: 4 L/min) with the help of an anesthesia mask to support spontaneous respiration in rabbits (Figure 1). After testing the reflex responses with paw pulling, the dose of sevoflurane was adjusted to the range of 2-3% and was administered at this dose to preserve spontaneous breathing throughout the surgery. At the end of the surgery, sevoflurane was completely turned off and oxygen support with the mask was continued until the rabbit gave a pawing response. No additional oxygen was given to the rabbits after recovery (Ozkan's sevoflurane inhalation anesthesia method).

After inhalation anesthesia with sevoflurane, the sciatic nerve of the right posterior extremity; exposed using a lateral incision (5 cm) on the calf and separating the superficial fascia. After visualization of the sciatic nerve, the study drug was injected perineurally and the skin was closed at 0.5 cm intervals using a non-absorbable suture [4.0 prolene]. Since samples will be taken from the sciatic nerve at the end of the experiment, the nerve area where the drug was applied was marked with sutures. Following the surgery, each of the rats was given 20 mg/kg of paracetamol (Perfalgan, Bristol-Myers Squibb, NY, USA) with a 28 G-insulin needle as an IP for analgesia [7]. After the skin was closed in all groups, the test animal was allowed to recover [approximately 5 minutes] and the pawing response was monitored every 30 minutes and recorded for 120 minutes. A hot-plate test was used for analgesia evaluation. In addition, for the histopathological evaluation of the injected area, samples (3 cm sciatic nerve) were taken from the sciatic nerve in the area where the drug was administered from half of each group on the 1st day of the experiment and from the other half on the 14th day of the experiment, and the experimental animals were euthanized.

The same anesthesiologist prepared drug solutions, while drug injections were administered to the rabbits by a surgeon who did not know the drug ingredients. All surgical procedures were performed by the surgeons who did not know from which group the rabbits belonged under aseptic conditions. A total of 0.5 ml of the study drug were prepared for each experimental animal.

Figure 1. Administration of sevoflurane inhalation anesthesia with a mask to rabbits

Histological evaluation

Sciatic nerve segments of approximately 1-1.5 cm in length were removed. They were placed in 10% neutral formaldehyde solution for 24-48 hours for fixation. It was sampled by making incisions in the horizontal and vertical axis. Tissue tracking was applied to the tissues in a closed tissue tracking device. After follow-up, tissues were paraffin-blocked at the tissue-embedding center. Paraffin sections of 4-5 µm thickness were prepared in a rotary microtome and deparaffinized in an oven at 60ºC. After deparaffinization, the following routine hematoxylin-eosin (H&E) staining method was applied to the tissues. Prepared H&E samples were evaluated with an Olympus BX-51 light microscope and photographed with an Olympus DP-70 digital camera. The sham, bupivacaine, and bupivacaine+Dex groups were evaluated on the 1st and 14th days with H&E dye under the light microscope. The presence of edema in the sciatic nerve, inflammation in the epineurium and surrounding tissues, degeneration, and fibrosis in myelin fibers were evaluated semiquantitatively. Edema, inflammation in the epineurium and surrounding tissues, presence of fibrosis (0 = no edema, no inflammation and no fibrosis, 1 = mild edema / mild inflammatory infiltrate / mild fibrosis in small foci, 2 = edema in local areas / moderate inflammatory infiltrate / moderate fibrosis presence, 3=significant edema/severe inflammatory infiltrate/ severe fibrosis) (8), sciatic nerve damage (0=no lesions, 1=1-2%

axon and myelin fiber damage, 2=2-5% axon and myelin fiber damage, 3=more than 5% axon and myelin fiber damage] was evaluated (9).

Statistical analysis

Sample size value was determined in our study with statistical power analysis and was accounted as a power of 0.80. Statistical analysis was performed using the SPSS program (Statistical Package for Social Sciences 21.0; SPSS, Chicago, IL, USA). The guess of a standard distribution was supported with the Kolmogorov– Smirnov test. Mann-Whitney U test was used for comparison between groups. For histological analysis, the statistical significance was detected at $p<0.01$, and similarly, the Mann-Whitney U test was preferred when multiple comparisons were needed. All records are given as median (minimum - maximum). $P<0.05$ was considered significant.

Results

All rabbits enrolled in this experimental investigation completed the study. Rabbits were evaluated for thermal analgesia and neurobehavioral examination by the hotplate and the paw withdrawal responses, respectively.

Results of hotplate test, sensory and motor blockades

In the hot-plate test applied for the measurement of acute thermal pain; significant prolongation was found in Group B and Group BD at 0, 30, 60, 90, and 120 minutes when compared to Group S ($p<0.05$). When Group BD was compared with Group B, a significant prolongation was found at 60 minutes ($p=0.012$). No significant difference was found in other times (Table 1). No significant differences were found between the groups in sensory and motor block tests (Table 2, 3).

Table 1. Hot-plate test and extension time results for drugs by groups. ᵖ

Time (min)	Group S (n : 8)	Group B (n : 8)	Group BD (n : 8)	P value
Basal	11(8-16)	11(8-16)	13(7-20)	0.554
0	20(9-24)	40(10-50)α	35(35-48)β	α=0.008. β<0.001
30	11(7-23)	42(31-56)α	44(32-52)β	α<0.001. β<0.001
60	12(9-17)	39(38-58)α	54(20-55)β.*	α<0.001. β<0.001.*=0.012
90	9(5-20)	34(16-60)α	47(28-54)β	α<0.001. β=0.001
120	7(5-17)	30(28-50)α	46(20-60)β	α<0.001. β<0.001

π Group S: sham, Group B: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg)) Group BD: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg) + dexmedetomidine (20 µr/kg)
α: significant difference, compared with Group S. β: significant difference, compared with Group S
* significant difference compared to Group B

Table 2. Sensory blockade scores* by group, for drugs. ᵖ

Time (min)	Grup S (n : 8)	Grup B (n : 8)	Grup BD (n : 8)	P value
0	0(0)	1(0-2)	2(0-3)	0.217
30	0(0)	1(0-1)	1(0-1)	0.219
60	0(0)	2(0-3)	2(0-3)	0.056
90	0(0)	1(0-2)	1(0-2)	0.163
120	0(0)	1(0-1)	1(0-2)	0.135

π Group S: sham, Group B: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg)) Group BD: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg) + dexmedetomidine (20 µr/kg)
* Sensory blockade scores (complete sensory blockade score = 3; normal sensory function = 0)

Table 3. Motor blockade scores* for drugs by groups. ᵖ

Time (min)	Grup S (n : 8)	Grup B (n : 8)	Grup BD (n : 8)	P value
0	0(0-0)	2(1-2)	1(0-2)	0.667
30	0(0-0)	1(0-2)	2(0-3)	0.061
60	0(0-0)	2(1-2)	1(0-1)	0.311
90	0(0-0)	1(0-2)	1(0-3)	0.070
120	0(0-0)	1(0-1)	2(0-3)	0.352

π Group S: sham, Group B: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg)) Group BD: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg) + dexmedetomidine (20 µr/kg)
* Motor blockade scores (complete motor blockade score = 3; normal motor function = 0)

Results of histopathological evaluation

Each group was separately evaluated for the histopathological evaluation concerning the presence of edema, inflammation at epineurium and surrounding tissues, axon-myelin fiber degeneration, and fibrosis.

Histopathological results of the first day of the experiment

In the Sham group; edema, inflammation, and mast cell presence in the epineurium and surrounding tissues were not observed. Inflammation in the epineurium and surrounding tissue was observed as neutrophil-dominated acute inflammation on the 1st day. When compared with the sham group in terms of edema and inflammation, a significant difference was observed in the B and BD groups. In the bupivacaine+Dex group, edema, inflammation in the epineurium and surrounding tissues were significantly reduced on the 1st day compared to the bupivacaine group (Figure 2 A-D) (Table 4,5).

When the number of mast cells was compared with the control group, a significant difference was observed in the Bupivacaine and Bupivacaine+Dex groups. The number of mast cells was significantly increased in the bupivacaine+Dex group compared to the bupivacaine group (Figure 3 A-D) (Table 4,5).

Histopathological results of the 14th day of the experiment

In the sham group, there was no edema, inflammation in the epineurium and surrounding tissues, and the presence of mast cells. On the 14th day, inflammation was observed in the lymphohistiocytic character. In the bupivacaine+Dex group, edema decreased on the 14th day in the epineurium when compared with the bupivacaine group. In the bupivacaine+Dex group, inflammation in the epineurium and surrounding tissues had a lymphohistiocytic character and slightly decreased. Lymphohistiocytic changes were observed in the intraneural area in the bupivacaine and bupivacaine+Dex groups. When the bupivacaine group and the bupivacaine+Dex group were compared with the sham group, the increase in edema, epineurium, and inflammation in the surrounding tissues was statistically significant (Figure 2 E-H) (Table 4, 5). The number of mast cells was significantly increased in the bupivacaine+Dex group compared to the bupivacaine group (Figure 3 E-H) (Table 4 and 5).

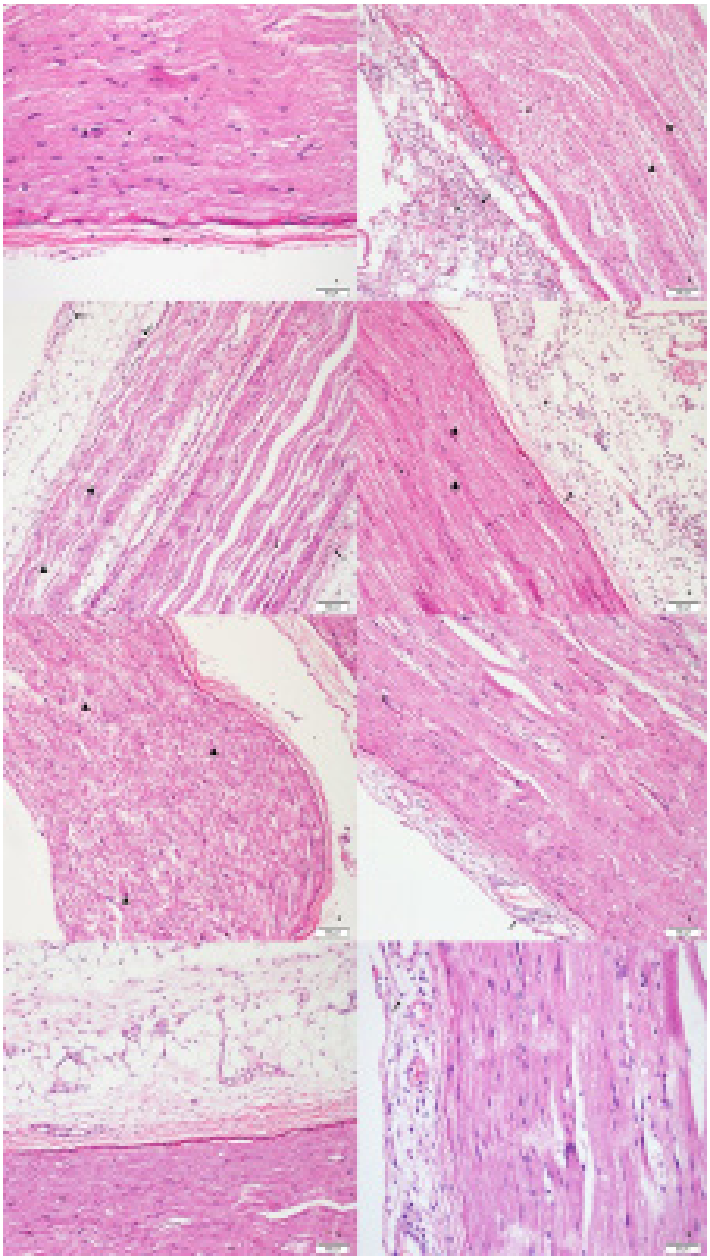

Figure 2. Histopathological changes in the sciatic nerve tissue: epi, epineurium; e, edema; s, swollen Schwann cells; v, vacuolization; thick arrow, inflammation; arrowhead, degenerate axons, and myelin degeneration; hematoxylin-eosin staining, HE×40 (A, B, D, E), HEx20 (C, F, G, H)

Table 4. Histopathological Scores and Mast cell count, by group, for drugs.[π]

		Degeneration	Edema	Number of mast cells
	Group S	0	0	0
First day	**Group B**	2.5 ±0.5	2.75±0.43	1.25 ±0.43
	Group BD	1.75±0.43	1.5±0.5	2.5±0.5
	Group S	0	0	0
14th day	**Group B**	1.75±0.43	1.5±0.5	1.75±0.82
	Group BD	1.5±0.5	0.25±0.43	2.75±0.43

π Group S: sham, Group B: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg)) Group BD: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg) + dexmedetomidine (20 μr/kg)

Table 5. P-values for histopathological evaluation, by groups, for drugs. [π]

		Degeneration	Edema	Number of mast cells
First day	**Group S & Group B**	<0.001	<0.01	<0.01
	Group S & Group BD	<0.01	<0.01	<0.01
	Group B & Group BD	<0.01	<0.05	<0.01
14th day	**Group S & Group B**	<0.01	<0.001	<0.05
	Group S & Group BD	>0.05	<0.01	<0.001
	Group B & Group BD	<0.01	>0.05	<0.05

π Group S: sham, Group B: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg)) Group BD: perineural bupivacaine (0.5 mL 0.5% (0.5 mg/kg) + dexmedetomidine (20 µr/kg)

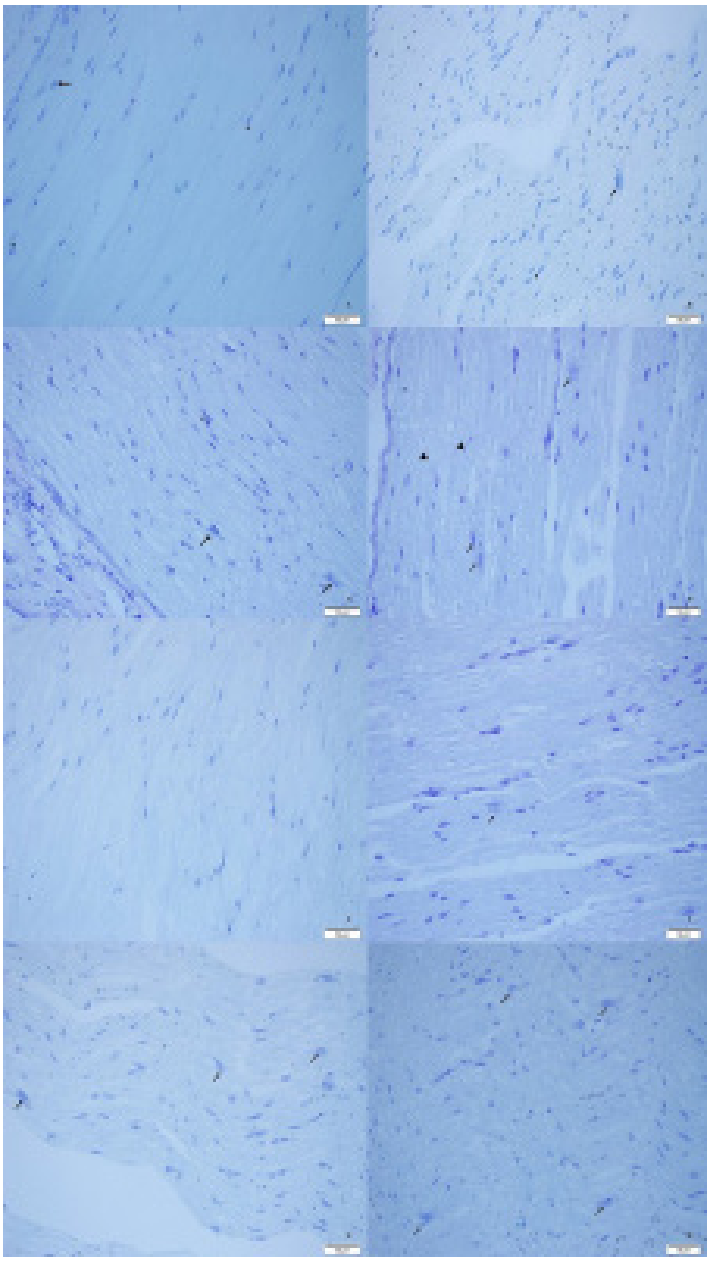

Figure 3. Histopathological appearance in toluidine blue staining in sciatic nerve tissue: s, swollen Schwann cells; arrowhead, degenerate axons, and myelin degeneration; toluidine blue staining, HE×40 (A, B, C, E, F), HEx20 (D, G, H)

Discussion

In this placebo-controlled experimental study, we showed that the mixture of bupivacaine and Dex applied to provide analgesia in the application of sciatic block prolongs the delay time and increases the quality of analgesia in the hot-plate test evaluating acute thermal pain in rabbits administered sevoflurane anesthesia. Dex added to bupivacaine have contributed positively when the analyzed histopathological parameters were evaluated.

In the literature, there are many studies in which Dex was added to local anesthetics to prolong the duration of the block or increase the quality of analgesia in sciatic block applications [5,10,11]. In the study of Erdoğan et al. in which dex was used in a sciatic block in rats, it was shown that there was a significant prolongation in the latency time at the 30th and 60th minutes after drug administration in the group with local anesthetic and dex combination compared to the group with an only local anesthetic, and these results were interpreted as an increase in analgesic quality. It has also been shown that there are significant similar stretches in the tail-flick test at the same times [5]. In this study, measurements were made at 0 to 240 minutes concerning drug administration. However, since recovery may be prolonged in rats anesthetized with ketamine, we think that the use of techniques that allow earlier recovery and shorter measurement time will affect the data of the study less. The mean recovery time in rabbits after discontinuation of sevoflurane administration did not exceed 2-3 minutes. This allowed measurements to start earlier and to create a condition similar to that in humans. In our study, it was shown that there were significant prolongations in hot plate times in the bupivacaine and bupivacaine+dex groups compared to the control group at all times after recovery. When the bupivacaine and bupivacaine+dex groups were compared with each other, a significant prolongation was detected in the bupivacaine+dex group at the 60th minute, and these results were interpreted as dex added to bupivacaine increased the analgesic effect.

One of the important results of our study is that dex added to bupivacaine did not affect motor and sensory blockade times in rabbits. Some studies have shown that dex has central analgesic activity at 144 microgram/kg doses [12,13]. Again, some studies have reported that sensory and motor blockade times are prolonged in rats with perineural dex at doses ranging from 28–40 micrograms/kg added to ropivacaine and bupivacaine [8,14]. In

our study, dex was applied at a dose of 20 microgram/kg to prevent central analgesic activity and not affect the study. Contrary to these studies, the fact that motor and sensory blockade times were not affected in our study was thought to be related to the dose of dex. Further studies are needed on whether higher doses of dex will prolong motor and sensory blockade times, similar to clonidine [15].

A combination of ketamine and xylazine is generally preferred in anesthesia applications of rats, and recovery can sometimes take up to 30 minutes. Standardization of the measurements may not be achieved due to delayed recovery and differences between rats. Inhalation anesthesia with sevoflurane, which allows quick recovery, can be preferred as an alternative anesthetic application since rabbits weigh more than rats and recovery may be prolonged in rabbits after intraperitoneal or intravenous anesthetic administration. In addition, the analgesic efficacy of preferred anesthetic drugs may affect the measurements. For this reason, we preferred to apply sevoflurane anesthesia, which allows early recovery and does not have analgesic activity, since the strong analgesic activity of ketamine affects the study and recovery may take up to 60 minutes in rabbits in anesthesia applications with ketamine xylazine. In addition, paracetamol, which has a lower analgesic efficiency than ketamine, was used as a postoperative analgesic.

Local anesthetic drugs are known to have neurotoxic effects. Although it has been shown that adjuvant drugs added to local anesthetic drugs increase this neurotoxicity [16], it has been shown that Dex reduces the inflammatory response due to local anesthetics and has protective effects against neural damage thanks to its anti-inflammatory property [17,18]. According to the histopathological results in our study, when compared with the sham group in terms of edema and inflammation, a significant difference was observed in the B and BD groups. In the bupivacaine+Dex group, edema, inflammation in the epineurium and surrounding tissues were significantly reduced on the 1st day compared to the bupivacaine group (Figure 2 A-D) (Table 4,5). Additionally, in the bupivacaine+Dex group, edema decreased on the 14th day in the epineurium when compared with the bupivacaine group. When the bupivacaine group and the bupivacaine+Dex group were compared with the sham group, the increase in edema, epineurium, and inflammation in the surrounding tissues was statistically significant (Figure 2 E-H) (Table 4,5). Since even dexamethasone, which has been shown to have positive effects on wound healing, has been reported to have negative effects on wound healing at high doses, the dosage of preferred drugs is one of the important factors affecting the results of the study [19]. Similar to other studies, in our study, Dex was added as an adjuvant to bupivacaine at a dose of 20 mcg/kg reduced bupivacaine-induced neurotoxicity and toxic effects on surrounding tissues. In addition, it was shown in our study that these results were also effective on the 14th day. Although Dex is beneficial in reducing the negative effects of local anesthetics, further studies are needed in terms of the appropriate dose and method of administration.

Limitations

Our study has some limitations. First, the effects of Dex that may develop due to systemic absorption could not be excluded. This limitation can be overcome by measuring serum drug levels. Second, it is unknown how much paracetamol administered for postoperative analgesia affected study results. Finally, the tests used to measure sensory and motor block levels are subjective. For more objective data, it should be supported by electrophysiological measurements.

Conclusion

In rabbits administered sevoflurane anesthesia, the mixture of bupivacaine and Dex applied to provide analgesia in the application of sciatic block prolonged the delay time and increased the quality of analgesia in the hot-plate test evaluating acute thermal pain. Dex added to bupivacaine contributed positively when the analyzed histopathological parameters were evaluated.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

This study was supported by the Inonu University Coordination Unit of Scientific Research Projects [Project no: TSA-2017-712].

Ethical approval

This study was approved by the Inonu University Animal Experiments Local Ethics Committee [2017/A-32].

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