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Effects of dexmedetomidine on bupivacaine-induced myotoxicity and inflammation in rats

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ABSTRACT

Aims: The increasing use of regional anesthesia techniques has heightened concern regarding local anesthesia-related tissue damage. Bupivacaine is widely used because of its long duration of action and high potency, however it is associated with a high myotoxic potential. This study aims to evaluate whether the addition of dexmedetomidine as an adjuvant to bupivacaine during peripheral block may influence bupivacaine-induced myotoxicity and inflammation.

Methods: Twenty-eight Wistar albino rats were allocated into four equal groups. Group C received 0.2 ml of 0.9% normal saline, group B received 0.2 ml of 0.25% bupivacaine, group D received 0.2 ml of dexmedetomidine at a concentration of 0.005%, and group BD received a combination of 0.25% bupivacaine and 0.005% dexmedetomidine. All injections were administered intramuscularly into the right gastrocnemius muscle. After 48 hours, muscle tissues were harvested for histopathological evaluation using the Modified Benoit Score (MBS). Serum creatine phosphokinase (CPK) and C-reactive protein (CRP) levels were measured.

Results: No rats were lost during the study, and all animals completed the experimental protocol. Histopathological evaluation revealed that group B exhibited the highest degree of muscle damage, as assessed by the MBS, with scores significantly higher than those of all other groups ($p<0.05$). MBS values in group BD were significantly lower than those in group B but remained higher than those observed in groups C and D ($p<0.05$). CPK levels were significantly elevated in group B compared with groups C and D ($p<0.05$), whereas no significant differences were observed among the remaining groups. In contrast, CRP levels did not differ significantly between the groups ($p>0.05$).

Conclusion: Dexmedetomidine was associated with a reduction in bupivacaine-induced myotoxicity in rats, as supported by histopathological and biochemical findings. These results suggest that dexmedetomidine may have the potential to reduce muscle injury when used as an adjuvant to local anesthetics, although further experimental and clinical studies are required.

Keywords: Bupivacaine, dexmedetomidine, myotoxicity

INTRODUCTION

Peripheric nerve blocks, peripheric nerve catheters, plane blocks are applied for intraoperative anesthesia and postoperative pain control. These techniques significantly reduce the use of additional analgesics and opioids, as well as shortening the postoperative hospital stay and recovery time. The increasing popularity of them has also increased interest in tissue damage induced by local anesthetics.[1]

Bupivacaine is the most preferred agent due to its long duration of action and high potency, but it is the agent with the highest cardiotoxicity and myotoxicity. Adjuvant agents can be added to local anesthetics for the purposes of both prolonging duration of action and reducing toxic effects.[2,3]

Dexmedetomidine is a sympatholytic used as a selective alpha-2 adrenergic agonist agent for sedation. There are

studies showing that adding dexmedetomidine as an adjuvant to local anesthetics reduces local inflammation while prolonging the duration of nerve block.[2,4]

Myotoxicity might be a complication peripheral nerve blocks and bupivacaine is known to have a high myotoxic pontential.[5-7]

We hypothesized that dexmedetomidine, when used as an adjuvant to bupivacaine, might reduce bupivacaine-induced myotoxicity in a rat model, as assessed by histopathological muscle damage and serum CPK levels.

METHODS

Ethics committee approval was obtained from the Animal Experiments Local Ethics Committee of University of Health Sciences Ankara Training and Research Hospital (Date: 31.01.2023, Decision No: 0719). All procedures were conducted in accordance with the ARRIVE guidelines and the national/international guidelines for the care and use of laboratory animals. Blood samples were evaluated in Private ENA Laboratory and tissue samples were evaluated in Ankara Training and Research Hospital Pathology Department Laboratory.

The study was carried out using 28 male Wistar-albino type rats with an average weight of 250 grams, in accordance with the standards recommended by the Council of Europe (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes) (ETS123). The room temperature was 22-25^{0}C and the environment including 12 hours light/dark cycles was provided before the experiment. Experimental animals were fed ad libitum (23% protein, 5% fat, 15% fiber, 50% carbohydrate) standard rat chow and drank tap water. Experimental animals were randomly divided into four groups of 7 rats each. The right legs of the rats were marked and the gastrocnemius muscles were injected.

- **Group C:** 0.2 ml 0.9% normal saline
- **Group B:** Bupivacaine 0.25% concentration; 0.1 ml 0.5% bupivacaine diluted with 0.1 ml 0.9% saline
- **Group D:** 0.1 ml of 0.01% dexmedetomidine, diluted with 0.1 ml of 0.9% saline, at a concentration of 0.005%
- **Group BD:** 0.1 ml of 0.5% bupivacaine was diluted with 0.1 ml of 0.01% dexmedetomidine and injected intramuscularly at a concentration of 0.25% bupivacaine and 0.005% of dexmedetomidine (Figure 1).

The right gastrocnemius muscle of the rats was used for injection. Injection of medications was administered with a 30 G tuberculin needle after negative aspiration. For the B and BD groups, as a commercial preparation, Buvicaine^{Ò} 0.5% in 20 ml vial, Polifarma, was diluted 1:1 with a concentration of 0.25%. Dekstomid^{Ò} 200mcg/2ml, Polifarma was used as a commercial preparation for dexmedetomidine injected into groups D and BD by diluting it 1:1 with a concentration of 0.005%.

After injections, the rats were placed in separate cages for each group. At the 48th hour after the injection, the injected

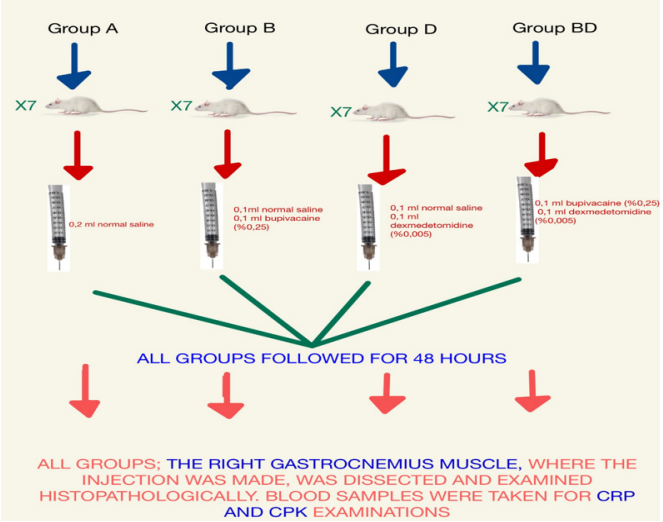

Figure 1. Schematic illustration of the experimental design and study groups

extremities of the rats were removed after skin tissue dissection under ketamine anesthesia and fixed in 10% formalin solution that was previously labeled. After this procedure, the gastrocnemius muscle was separated from the extremities that were fixed as a whole and placed in 10% formaline solution again. Blood samples were taken from the inferior vena cava from the rats for biochemical analysis. At the end of the procedure, the rats were sacrificed by intracardiac blood collection method.

After the tissues were fixed in 10% formalin for 24 hours in the Pathology Department of Ankara Training and Research Hospital, they were dehydrated by passing through a series of 50%, 70%, 80%, 96% and 100% alcohol. Afterwards, the tissues, which were made transparent by passing through xylene, were placed in paraffin blocks by keeping them in paraffin overnight. 5 micron thick sections were taken from paraffin blocks with a microtome (Leica RM 2155), stained with hematoxylin-eosin and examined under a light microscope (Olimpus BX51). Microphotographs of tissue sections (Zeiss Axio Imager M2) were taken. Damage-based scoring was performed and evaluated using the "Benoit, Yagiela, and Ferrell" scoring system[8] (Table 1).

Table 1. Histopathological scoring of muscle damage among study group

Score	Damage status
0	No fiber damage
1	Localized and/or sparse fiber destruction and localized inflammatory cell accumulation
2	Necrosis of several muscle fibers
3	Destruction and necrosis of most of the muscle mass (more than 5 fibers)

Legend: Histopathological muscle injury was graded using the Modified Benoit Score. Higher scores indicate more severe muscle damage.

The primary outcome of the study was histopathological muscle damage, assessed using the Modified Benoit Score (MBS) based on the degree of muscle fiber degeneration, necrosis, and inflammatory cell infiltration in the gastrocnemius muscle.

The secondary outcomes included biochemical markers of muscle injury and inflammation, namely CPK and CRP levels, measured from blood samples obtained at 48 hours after injection.

Statistical Analysis

Data analysis was performed using the IBM SPSS 25.0 (Armonk, NY: IBM Corp.) statistical package program. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min-max) were used when evaluating study data. The conformity of the data to the normal distribution was evaluated using the Shapiro-Wilk test, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). In the study, Kruskal-Wallis test was used for the comparison of quantitative that did not show normal distribution between groups. In cases where there was a difference, a post-hoc Bofferroni correction was applied to find the source of the difference. Relationships between variables were evaluated with Spearman's Rho Correlation test. Statistical significance level was accepted as α=0.05.

RESULTS

This study was performed during a two-day period in March 2023. A total of 28 rats were included in the study, and all animals completed the experimental protocol; no rats were lost during the study. Macroscopic examination performed during dissection revealed mild edema at the injection site in all groups, without evidence of gross necrosis or abscess formation. Histopathological evaluation of muscle samples obtained from the injection sites was performed using light microscopy. Representative photographs and histopathological scores are presented in Figure 2-6.

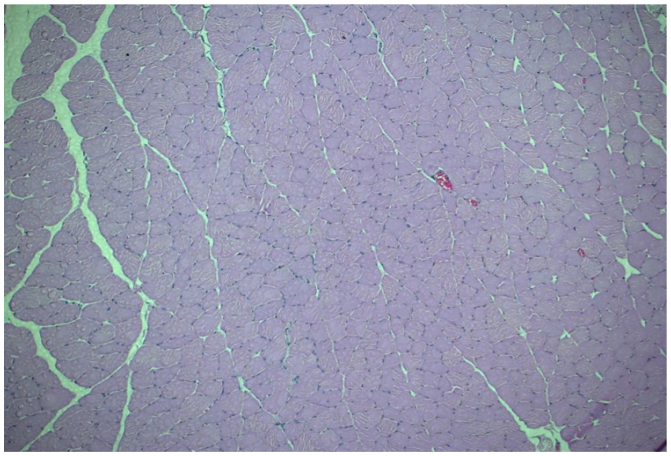

Figure 2. Histopathological appearance of the gastrocnemius muscle in the control group

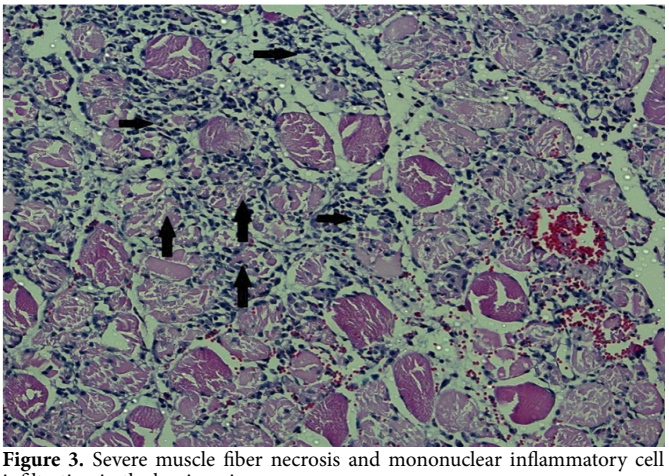

Figure 3. Severe muscle fiber necrosis and mononuclear inflammatory cell infiltration in the bupivacaine group

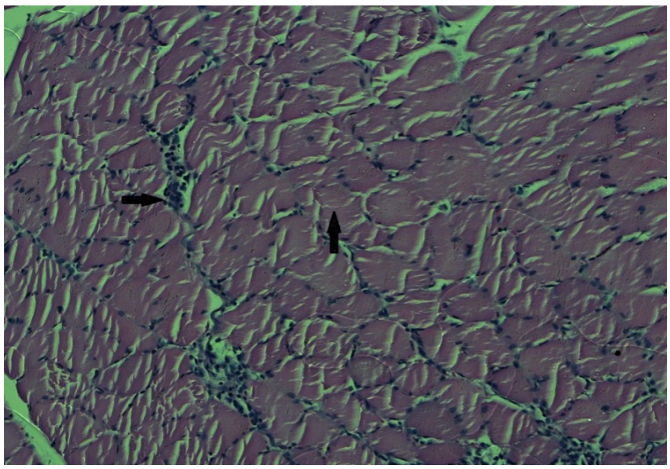

Figure 4. Minimal inflammatory changes in the dexmedetomidine-only group

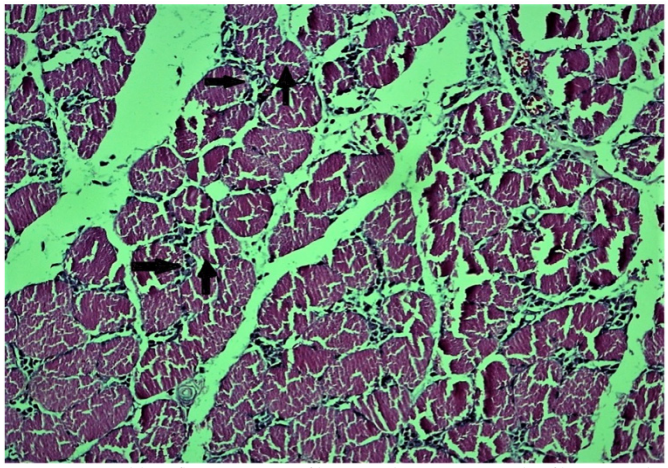

Figure 5. Mild inflammatory infiltration between muscle fibers in the bupivacaine–dexmedetomidine group

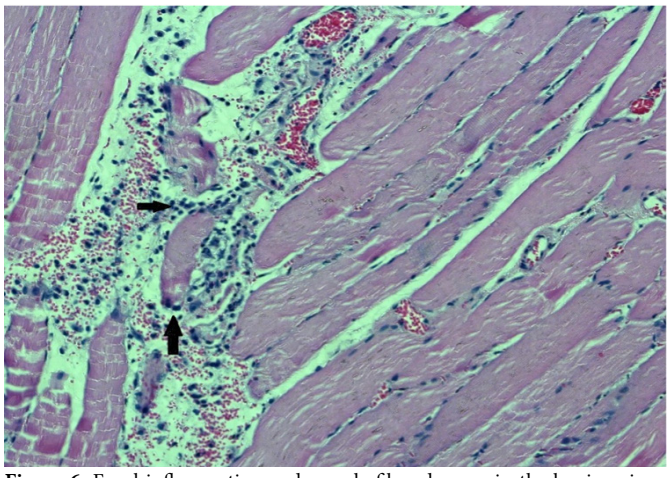

Figure 6. Focal inflammation and muscle fiber damage in the bupivacaine–dexmedetomidine group

In the microscopic evaluation, no damage to the muscle fibers and inflammatory cell infiltration were observed in any of the samples in the 0.9% saline injection group (group C) (Figure 2). In between myofibrillary areas diffuse mononuclear leukocyte infiltration, diffuse necrobiotic change and degeneration were observed in most of the samples in group B (Figure 3). In group group D, the appearance was generally similar to the group C. In some samples, only focal and light density mononuclear cell accumulation was observed between muscle fibers (Figure 4). In the group BD, mild inflammation was observed between muscle fibers (score 1) in only three

samples (Figure 5). Focal inflammation and damage to some muscle fibers (score 2) were observed in some samples in the group BD. Inflammatory cells were predominantly composed of lymphocytes. In some cases, eosinophils were also seen in the infiltrate (Figure 6).

There was a statistically significant difference ($p<0.05$) between the groups in MBS values. Multiple comparison (post-hoc) tests were applied to find out from which groups the difference originated. There was a difference between group B and other groups, group B MBS values were higher than the other groups. In addition, there was a difference between group BD and other groups, group BD MBS values were found to be higher than group C and group D MBS values, and lower than group B values (Table 2).

There was a statistically significant difference between the groups in CPK values ($p<0.05$). When multiple comparison (post-hoc) tests were applied to it, there was a difference between group B and group C and D. group B values were found to be the highest (Table 3).

In the comparisons between the groups; It was found that there was no statistically significant difference between the groups in terms of CRP values ($p>0.05$) (Table 4).

Relationships between the MBS–CPK–CRP are:

- A positive correlation was found between the MBS and CPK, at the level of r=0.827 (it can explain approximately 68% of the variation in MBS (R^2=0.684)),
- A positive correlation was found between the MBS and CRP, at the level of r=0.471. (which can explain approximately 22% of the variation in MBS (R^2=0.222)),
- A positive correlation was found between CPK and CRP at the level of r=0.669. (explains approximately 45% of the variation in CPK (R^2=0.448)),
- These relationships were found to be statistically significant ($p<0.05$) (Table 5).

Table 5. Relationships between Modified Benoit Score–CPK–CRP

	Modified Benoit Score		CPK		CRP	
	r	p*	r	p*	r	p*
Modified Benoit Score	1.000	--	0.827	<0.001	0.471	0.011
CPK	0.827	<0.001	1.000	--	0.669	<0.001
CRP	0.471	0.011	0.669	<0.001	1.000	--

Legend: Correlations were assessed using Spearman's rho correlation test. CPK: Creatine phosphokinase, CRP: C-reactive protein

DISCUSSION

In this experimental study, we investigated the histopathological and biochemical effects of dexmedetomidine on bupivacaine-induced myotoxicity in a rat model. The main findings of the study demonstrated that bupivacaine caused significant myotoxic muscle damage, as evidenced by high MBSs and elevated serum CPK levels. The addition of dexmedetomidine to bupivacaine resulted in a significant reduction in histopathological muscle damage and lower CPK levels compared with bupivacaine alone, while dexmedetomidine administered alone did not induce myotoxic changes. No significant differences were observed among the groups with respect to CRP levels. These findings suggest that dexmedetomidine may attenuate bupivacaine-

Table 2. Comparison of Modified Benoit Score between groups

		Group A (n=7)	Group B (n=7)	Group D (n=7)	Group BD (n=7)	p*	Difference
Modified Benoit Score*		0.00±0.00 0 (0.0-0.0)	2.57±0.79 3.0 (1.0-3.0)	0.43±0.53 0.0 (0.0-1.0)	1.57±0.53 2.0 (1.0-2.0)	<0.001[a]	B with A-D-BD BD with A-B-D
	0**	7 (100.0%)	--	4 (57.1%)	--	--	--
	1**	--	1 (14.3%)	3 (42.9%)	3 (42.9%)		
	2**	--	1 (14.3%)	--	4 (57.1%)		
	3**	--	5 (71.4%)	--	--		

Legend: Data are presented as mean±SD and median (min–max). Comparisons were performed using the Kruskal–Wallis test. Abbreviations: C: Control, B: Bupivacaine, D: Dexmedetomidine, BD: Bupivacaine+ Dexmedetomidine

Table 3. Comparison of CPK between groups

	Group A (n=7)	Group B (n=7)	Group D (n=7)	Group BD (n=7)	p	Difference
CPK*	894.7±270.6 844.0 (514.0–1.196,0)	1.784,9±535,5 1.731,0 (1.110,0–2.562,0)	885.9±258.3 753.0 (687.0–1.308,0)	1.207,0±428.2 1.462,0 (522.0–1.591,0)	0.007[a]	B with A-D

Legend: Serum CPK levels were compared using the Kruskal–Wallis test. Abbreviations: CPK: Creatine phosphokinase

Table 4. Comparison of CRP between groups

	Group A (n=7)	Group B (n=7)	Group D (n=7)	Group BD (n=7)	p
CRP*	0.16±0.10 0.10 (0.10–0.30)	0.21±0.09 0.20 (0.10–0.30)	0.14±0.05 0.10 (0.10–0.20)	0.17±0.05 0.20 (0.10–0.20)	0.343[a]
0.1**	5 (71.4%)	2 (28.6%)	4 (57.1%)	2 (28.6%)	
0.2**	--	2 (28.6%)	3 (42.9%)	5 (71.4%)	--
0.3**	2 (28.6%)	3 (42.9%)	--	--	

Legend: Serum CRP levels were compared using the Kruskal–Wallis test. Abbreviations: CRP: C-reactive protein

induced myotoxicity without causing additional muscle injury.

Bupivacaine is the local anesthetic that is frequently preferred in peripheral blocks due to its duration of action and high potency.[9] Bupivacaine has the highest known myotoxic potential.[3,10] Due to the advantages and comfort of peripheral blocks, the toxic effect profile of local anesthetics has started to be seen more frequently as a result of the increased frequency of use. Myotoxicity due to local anesthetics has been argued to be clinically insignificant due to its rarity and reversible nature, but myonecrosis and severe muscle dysfunction have been reported with increasing frequency of use.[11] In our study, we investigated how dexmedetomidine affects bupivacaine-induced myotoxicity histopathologically and biochemically.

Bupivacaine causes damage by causing intracellular calcium release via ryanodine receptors. It's also known that bupivacaine inhibits calcium absorption into the sarcoplasmic reticulum. As a result, the intracellular calcium concentration reaches toxic levels.[12,13] Bupivacaine-induced myotoxicity has been closely associated with mitochondrial dysfunction.[5] It affects energy metabolism by disrupting mitochondrial functions and increases its effects on calcium.[13] Nouette-Gaulain et al.[14,15] showed that the preservation of mitochondrial functions with the effect of human recombinant erythropoietin (rhEPO) in rats treated with rhEPO can reduce the myotoxic effects of bupivacaine.

Oz Gergin et al.[16] investigate the myotoxic effects of bupivacaine, ropivacaine and levobupivacaine on rats, showed that bupivacaine caused more myotoxic damage than other agents. Histopathology detected myonecrotic debris and inflammatory cells. In electron microscopy, they observed vacuolization and mitochondrial swelling in the sarcoplasmic reticulum. These findings were consistent with studies describing pathophysiology in the literature. In histopathology, the highest level of myocnecrosis and all indicators of necrobiotic changes are best observed 48 hours after bupivacaine injection.[17,18] Foster et al.[19] they administered local anesthetics in 200 µl volume by i.m. injection in rats and reported that this volume did not cause pressure damage. Nouette-Gaulain et al.[15] showed that toxic damage increased in direct proportion with exposure time. In addition, a dose-related relationship between bupivacaine-induced myotoxicity has been shown in the literature. It has been shown that as the concentration increases, it can cause longer lasting myotoxicity and even permanent damage.[20]

In our study, we examined the histopathological changes on the myocytes at 48th hour by injecting 200 µl of 0.25% concentration of bupivacaine into the gastrocnemius muscle of rats in group B, based on the information in the literature. We observed statistically significant high ($p<0.001$) myonecrotic changes in the bupivacaine group only when compared to all other groups histopathologically. We observed these changes in 71.4% of the rats in the bupivacaine group, the highest score of 3 when scored on myonecrotic muscle fibrils and mononuclear inflammatory cell deposition. Histopathological score of 3 was not observed in rats in other groups.

Adjuvant agents are added to reduce the toxic effects of local anesthetics and to prolong their duration of action. It has been reported that steroid and epinephrine added to local anesthetics increase myotoxicity.[21,22] Guttu et al.[22] showed that adding steroids to bupivacaine significantly increased myotoxicity. Padera et al.[23] In their study on rats, they showed that tetradotoxin added to bupivacaine as a Na channel blocker significantly prolonged the blocking time, but had no reducing effect on myotoxicity. Plank et al.[7] conducted in mouse muscle cell culture, found that dantrolene reduced the damage due to its effect on calcium metabolism, while caffeine increased it. Although clonidine, found to not have an effect on the duration of action of long-acting local anesthetics such as bupivacaine in peripheral blocks.[24–26] Erdivanli et al.[27] showed that dexmedetomidine added to intrathecal bupivacaine increased the quality and duration of analgesia in a dose-dependent manner, and dexmedetomidine didn't cause any neurotoxicity and inflammation. Brummet et al.[2] showed that perineural administration of dexmedetomidine combined with bupivacaine increased the duration of sensory and motor blockade without causing neurotoxicity, while dexmedetomidine alone did not cause significant motor and sensory blockade. They concluded that dexmedetomidine exerts these effects presynaptically by inhibiting nociceptive transmission and by hyperpolarizing postsynaptic a-2a receptors.[2] Addition of dexmedetomidine to bupivacaine has been shown to reduce postoperative pain scores and significantly prolong the duration of the block in supraclavicular block, abdominal facial plane blocks, and thoracic wall facial plane blocks.[28–30] Jin et al.[31] reported that dexmedetomidine added to bupivacaine reduced cardiac toxicity by reducing bupivacaine-induced vasopermeability-related protein production. The effects of dexmedetomidine and dexamethasone added to liposomal bupivacaine were compared and the block times were prolonged, but there was less inflammation in the samples added dexmedetomidine.[4] In a recent review of the myotoxic effects of local anesthetics, it was mentioned that there is no study on the effects of dexmedetomidine or dexamethasone added to local anesthetics on myotoxicity, and it was stated that there is a need for experimental studies on this subject. There are no experimental studies on the myotoxicity of dexmedetomidine.[11]

We aimed to show whether dexmedetomidine, which has been shown to prolong the block time and reduce tissue inflammation in previous studies, has an effect on myotoxic damage. The dose of dexmedetomidine was calculated for rats according to the publications and injected at a concentration of 0.005% and in a volume of 200 µl.[32] In group D, we found histopathologically similar scores to the control group. While 57.1% of the muscle samples of the rats in group D had the same findings as the control group, localized myofibril damage and localized inflammatory cell accumulation were observed in 42.9% of them. In the BD group, the scores were higher than groups A and D, but lower than group B. As a result of our histopathological evaluations, it was observed that dexmedetomidine alone did not cause myotoxicity and it statistically significantly reduced bupivacaine-induced myotoxicity ($p<0.001$).

We think that dexmedetomidine can reduce the required concentrations of bupivacaine with its analgesic feature alone, and it will also reduce bupivacaine-induced myotoxicity.

In a randomized controlled study, it was shown that premedication of low-dose intramuscular dexmedetomidine (1 μg.kg-1) caused preoperative sedation without clinically significant bradycardia or hypotension.[33] Similarly, in our study, we observed the sedation effect in D and BD group rats to which we applied dexmedetomidine.

Nosaka et al.[34] showed that plasma creatine phosphokinase (CPK) levels increased after bupivacaine injection into the human biceps muscle, and this increase was directly proportional to the dose of bupivacaine administered and thus the amount of muscle damage. In our study, a statistically significant difference ($p<0.05$) was found between the groups in terms of CPK values, parallel to similar studies. There was a difference between group B and group C and D, and group B values were the highest. In the BD group to which we added dexmedetomidine, the CPK value was not as high as in the B group.

He et al.[35] observed that oxidative stress and apoptosis were less in the group supplemented with dexmedetomidine from doxorubucin-induced myocardial cell cultures. We examined CRP values biochemically to evaluate the inflammatory response. In the comparisons between the groups, there was no statistically significant difference between the groups in terms of CRP values ($p>0.05$). This result is consistent with studies in the literature showing that the myotoxic effect of bupivacaine is local and does not cause systemic inflammation. In the literature, the inflammatory response-reducing effects of dexmedetomidine have been observed in cases with a stress factor such as surgery or cancer. Since there was no stress factor in our study, a statistically significant difference may not have been observed.

When the relations between MBS–CPK–CRP are examined, with MBS; While there was a strong correlation between CPK, a weak correlation was found between CRP. This made us think that high CPK values are closely related to high histopathological damage and that we can use it to predict myocyte damage.

If we talk about the limitations of our study, we do not have any factors such as incision or surgical stress exposure that will cause systemic inflammation when evaluating CRP. Therefore, we think that we did not find a significant change in CRP values. In addition, we could not compare because the rats did not have CRP and CPK values before intramuscular drug injection.

Although myotoxicity due to local anesthetics is seen as a rare and reversible side effect of these drugs, it can cause serious clinical problems especially in low-volume muscles such as ocular muscles, previously damaged muscles and in those with existing muscle disease. Continuous infusions and repeated injections of local anesthetics can also cause serious clinical damage.

Regional blocks are preferred in the geriatric age group to avoid the risks of general anesthesia due to comorbidities. Peribulbar and retrobulbar blocks are preferred especially in ophthalmic surgeries. Myotoxic damage to the extraocular muscles due to local anesthetics used in these blocks presents as diplopia and strabismus.[36,37] Parris et al.[38] reported that atrophy of the trapezius muscle, characterized by pain in the pericapsular region, developed as a result of trigger point injections using bupivacaine for the treatment of myofascial pain syndrome.

Therefore, clinicians should not forget the fact of myotoxicity and aim for longer duration of anesthesia and analgesia with single-dose injections. For this purpose, adjuvant agents thought to reduce myotoxicity should be used.

Limitations

This study has certain limitations. First, the experimental design was based on a rat model, and therefore the findings have limited direct applicability to clinical practice. In addition, only a single dose and administration protocol were evaluated, and the effects of different dosing regimens or repeated applications were not examined.

Furthermore, the assessment of myotoxicity was limited to histopathological findings at a single time point, without evaluation of functional outcomes or underlying molecular mechanisms. Accordingly, further experimental and clinical studies are needed to better clarify the potential protective effects of dexmedetomidine against bupivacaine-induced myotoxicity.

CONCLUSION

The growing use of plane blocks and peripheral nerve blocks for intraoperative anesthesia and postoperative analgesia has increased the clinical relevance of potential toxic effects associated with local anesthetics. Bupivacaine, which is widely preferred in clinical practice due to its long duration of action and high potency, has a pronounced myotoxic potential related to its high lipophilicity.

In this study, we aimed to test the hypothesis that dexmedetomidine, which is known to reduce local inflammation, may attenuate bupivacaine-induced myotoxicity when used as an adjuvant to bupivacaine in a rat model. Our findings suggest that dexmedetomidine does not exhibit myotoxic effects when administered alone and may reduce bupivacaine-induced myotoxicity when used in combination with bupivacaine. Nevertheless, further experimental and clinical studies involving different doses and administration protocols are required to clarify the clinical implications of these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from the Animal Experiments Local Ethics Committee of University of Health Sciences Ankara Training and Research Hospital (Date: 31.01.2023, Decision No: 0719).

Informed Consent

Informed consent is not required because it is an animal experiment.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept or Design of the Manuscript: G.Y.Y., Z.N.A.; Acquisition, Analysis and Interpretation of Data: M.S.D., M.C.Y.; Writing–Drafting the Manuscript: All authors; Critical Revision for Important Intellectual Content: E.Y.A., G.Y.Y.; Final Approval of the Version to be Published: All authors

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