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Examining the effects of lidocaine and dexmedetomidine on compound action potential in rat sciatic nerve

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ABSTRACT

Aims: Recent interest in peripheral regional blocks (PRB) has increased for surgical and nonsurgical implementations. Lidocaine is frequently preferred in PRBs because of its wide safety margin. The short duration of action limits the use of lidocaine. Dexmedetomidine is a new-generation adjuvant agent. According to our hypothesis, dexmedetomidine will prolong the duration of the action of lidocaine.

Methods: A total of 48 rat sciatic nerves were isolated and electrophysiological recordings were taken from 28. They were then randomly divided into 4 groups as group control (C), group L given 1 mM lidocaine, group D given 5 microgram/L dexmedetomidine, and group LD given 1 mM Lidocaine and 5 microgram/L dexmedetomidine. Compound action potentials (CAP) were recorded after the stimulation of the nerves. Maximum depolarization value (MD, mV), time to maximum depolarization (MDT), Area Under the CAP curve (Area, mV.ms), and conduction velocities were calculated separately for fast-conducting fibers (CVF, m/s) and medium-slow-conducting fibers (CVM, m/s).

Results: No significant effects of dexmedetomidine was detected compared to the control group for all comparisons ($p>0.05$). In the area under the curve evaluations that provide information on the number of affected fibers, a statistically significant difference was detected in group LD compared to group C ($p=0.001$). A statistically significant difference was detected in the nerve conduction velocity evaluations between group LD and group L in fast conduction velocity and medium and slow conduction velocity fibers ($p=0.002$, $p=0.009$ for fast conducting fibers and medium and slow conducting fibers, respectively).

Conclusion: When nerve conduction parameters were evaluated, dexmedetomidine alone did not exhibit a significant effect. When applied with lidocaine, it increased the effects of lidocaine on nerve conduction parameters and decreased nerve conduction velocities. Our results showed that dexmedetomidine interacts additively or synergistically with lidocaine and prolongs the duration of effect of lidocaine.

Keywords: Rat sciatic nerves, compound action potentials, lidocaine, dexmedetomidine

INTRODUCTION

Peripheral regional blocks (PRBs) are the administration of nerve inhibitory drugs (primarily local anesthetics) to the area around a specific nerve or nerve bundle[1], distal to the needle site to provide anesthesia.[2] PRBs are often preferred for patients who have a high risk of postoperative respiratory depression after general anesthesia, such as advanced age, severe obesity, obstructive sleep disorders, and acute or chronic lung diseases. In recent years, PRBs have been frequently included in multimodal analgesia regimens aimed at restricting opioid use.[3,4] When applied correctly and effectively, PRBs can provide better analgesia than opioids.[5] The widespread use of ultrasonography continues to contribute to the development of PRB techniques.

Local anesthetics (LA) are administered to the nerve periphery by single-shot or continuous injection methods in PRBs.[6] Continuous injection techniques have been associated with adverse conditions such as nerve damage, difficulty in catheter removal, infection, injection catheter displacement, local anesthetic systemic toxicity (LAST), and neurotoxicity.[4,7] The duration of benefit of single-shot PRBs is associated with the

duration of the LA effect, and strategies that will contribute to prolonging this duration are being investigated. The use of adjuvant drugs is one of the strategies applied to prolong the duration of the effect of single-shot PRBs.[8]

Lidocaine is one of the oldest and most commonly used LAs. The reason for the interest in lidocaine might be its long-term use, clinicians" habits, trust, and short onset of action. As well as these advantages, Lidocaine may also increase the cytolytic activity of natural killer (NK) cells[9], improve microvascular perfusion[10], and reduce opioid consumption.[11] Its disadvantages are considered to be short duration of action[12], neurotoxicity[13], and association with LAST.[14] Researchers are encouraged to work on adjuvant agents that aim to decrease the disadvantages of lidocaine.

Dexmedetomidine is one of the novel adjuvant agents that has attracted attention in recent years[8] as a selective α2-adrenergic receptor agonist that can provide analgesia, anti-anxiety, sympathetic system inhibition, mild respiratory inhibition and has little effect on hemodynamic stability.[15] Previous studies reported that the use of dexmedetomidine as an adjuvant agent in PRBs shortens the onset of anesthesia and prolongs the duration of sensory and motor blockade.[16,17] Various theories were put forward as to how dexmedetomidine exerts these effects. However, its mechanism of action has not been fully elucidated. The peripheral effect is among the strong mechanisms proposed[4], which may occur because dexmedetomidine maintains the cells in a depolarized state[18,19] or by delaying the absorption of LA through its vasoconstrictor effect in blood vessels close to the peripheral nerve.[4,20]

Compound action potentials (CAPs) are the sum of single-fiber action potentials from all fibers in a nerve.[21] They are obtained by recording the depolarization of a motor nerve after stimulation.[22] The rat sciatic nerve has nerve fibers that have different conduction velocities and sensory and motor nerve fibers.[23,24] CAPs recorded after stimulation of the nerve provide information about the activities of sensory and motor fibers with different conduction velocities.[23] In the present study, the CAP recordings were examined on the rat sciatic nerve to investigate the effects of using dexmedetomidine as an adjuvant agent. According to the hypothesis established here, dexmedetomidine, which is of interest as a new adjuvant, will prolong the effect of lidocaine.

METHODS

This article was produced based on a thesis that was completed in 2012. Approval was obtained from the Selçuk University Experimental Research and Application Center (SUDAM) Experimental Animal Ethics Committee (Date: 28.11.2011, Decision No: 2011-123). Experiments were performed in the laboratories of the Biophysics Department of the Selçuk University Meram Medical Faculty. Surgical and experimental procedures were applied to rats obtained from the Selçuk University Experimental Medical Research and Application Center. The rules determined by the Selçuk University Meram Medical Faculty Experimental Animal Ethics Committee were followed in these procedures.

A total of 24 Wistar albino adult female rats weighing 200-300 g were used in the study. These rats had not been included in any previous study and were not exposed to any drug. Rats whose food and water needs were met and who were provided with appropriate temperature (22±2^{0}C) and humidity conditions were used in the experiments.

The rats were divided randomly into 4 groups as group C (Control) which was not given any drug, group L (1 mM lidocaine), group D (5 microgram/L dexmedetomidine), and group LD (1 mM lidocaine and 5 microgram/L dexmedetomidine). Anesthesia was induced in the rats with intraperitoneal 100 mg/kg ketamine and 5 mg/kg xylazine. The sciatic nerve was carefully isolated from the left hind leg of each rat. The sciatic nerves were taken to the nerve chamber containing Krebs solution (pH 7.4, 20 mM $NaHCO_3$, 10 mM glucose, 119 mM NaCl, 1.2 mM $MgSO_4$, 4.8 mM KCl, 1.8 mM $CaCl_2$, 1.2 mM KH_2PO_4). The nerves were rested for 5 minutes, drug implementations were made, and CAP recordings were taken after 20 minutes. Supramaximal square pulses were given from the proximal end of the nerve and the distal end was placed in the electrode to transfer the CAP recordings to the computer. Supramaximal square pulses were applied from the proximal end of the nerve with a GrassSIU5 stimulus isolation unit with a Grass S88 stimulator at a frequency of 1 Hz and was repeated for 200 microseconds. CAP recordings were converted to digital data with an Analog/Digital converter (AdvantechPCL-717 A/D Converter) and transferred to the computer for further analysis. From the CAP recordings, the maximum depolarization value (MD, mV), the area under the CAP curve (Area, mV.ms), and conduction velocities were calculated separately for fast-conducting fibers (CVF) and medium-slow-conducting fibers (CVM).

Primary Outcome

To examine the effects of lidocaine and dexmedetomidine separately on CAP potentials in the rat sciatic nerve.

Secondary Outcome

To examine the contribution of dexmedetomidine to the local anesthetic efficacy of lidocaine when used as an adjuvant agent.

Statistical Analysis

The SPSS 16.0 (SPSS IL 16.0 Chicago, USA) package program was used to evaluate the recorded data. The difference between the data obtained from the experimental groups was evaluated by one-way analysis of variance (ANOVA). The Tukey Multiple Comparison Test was used between the parameters where the difference between the groups was significant ($p<0.05$). It was found that the groups differed from each other at a 95% Confidence Interval. The difference between the groups less than $p<0.05$ was accepted as statistically significant. All experimental parameters are given as mean±standard error throughout the text.

RESULTS

The study was conducted in the Nerve Electrophysiology Laboratories of the Department of Biophysics of the Meram Medical Faculty of Necmettin Erbakan University. 48 sciatic nerves were isolated from 24 rats included in the study. Electrophysiological recordings of 28 sciatic nerves could be used for the study. Nerves that were crushed during their removal and placement for recording were not included in the study.

The data of the control group (C), lidocaine (L) group, dexmedetomidine (D) group and lidocaine+dexmedetomidine

(LD) Group were compared for MD, time to maximum depolarization (MDT), conduction velocity of CVF, conduction velocity of CVM and area under the curve (Area) (Table 1). The differences between the groups were found to be significant for all data (p<0.05).

The highest peak of CAPs during depolarization was defined as MD. The groups were compared for MDs (Table 2). In the comparisons of MD values between groups, significant differences were detected for the control group, group L, and group LD (p=0.000). Significant differences were detected between group L and group D (p=0.000). However, there was no significant difference between group L and group LD. MDT was defined as the time from the moment the stimulation was given from the proximal end of the rat sciatic nerve to the time MD was reached. In the comparisons of MDT values between groups, significant differences were detected for group C and group LD (p=0.000). Also, significant differences were detected between group L and group D (p=0.000). However, there was no significant difference between group L and group LD (Table 3).

For field evaluations, the areas under the curve of the recorded CAPs were calculated as a parameter associated with the depth of sensory and motor blockade. In the comparison of the area under the curve values between the groups, significant differences were detected for group C and group LD (p=0.001). This result may show that the highest difference for the area under the curve was achieved with the LD group (Table 4).

The data on conduction velocities of CVF with CAP recordings were defined as CVF, which was calculated based on the time from the moment the stimulus was given from the proximal end of the rat sciatic nerve to the moment of CAP onset. In the comparison of CVF values between the groups, significant differences were detected for the control group, group L, and group LD (p=0.007, p=0.000, respectively). Significant differences were detected between group L and group D and group LD (p=0.002, p=0.002, respectively). Significant differences were detected between group D and group LD (p=0.000). This result may show us that lidocaine is effective on CVF and that it is effective on CVF when applied with dexmedetomidine (Table 5).

The data on conduction velocities of medium and slow conducting fibers with CAP recordings were defined as CVM, which was calculated based on the time from the moment the stimulus was given from the proximal end of the rat sciatic nerve until reaching MD. In the comparison of CVM values between the groups, significant differences were detected for the control group, group L, and group LD (p=0.000, p=0.000, respectively). Significant differences were detected between group L, group D, and group LD (p=0.000, p=0.009, respectively). Significant differences were detected between group D and group LD (p=0.000). This result may show us that lidocaine is effective on CVF, and when applied with dexmedetomidine, it is effective on fibers with medium and slow conduction velocities (Table 6).

DISCUSSION

In the present study, the effects of perineural lidocaine and dexmedetomidine on CAP recordings in rat sciatic nerve were investigated when applied alone and together and it was found that dexmedetomidine reduces the conduction velocity of fibers

Table 1. Comparison of parameters between groups (mean±SD)

	Group C (n=6)	Group L (n=6)	Group D (n=6)	Group LD (n=6)	p
MD (mV)	9.00±1.33 (8.08-11.89)	3.92±1.15 (2.83-6.12)	8.59±2.31 (6.70-13.57)	1.97±1.05 (0.60-3.96)	<0.05*
MDT (ms)	0.20±0.03 (0.18-0.28)	0.36±0.11 (0.26-0.60)	0.17±0.02 (0.16-0.22)	0.45±0.05 (0.38-0.56)	<0.05*
Area (mVxms)	3.26±0.52 (2.39-4.00)	2.65±0.38 (2.17-3.32)	3.64±0.89 (2.85-5.51)	1.67±0.77 (0.55-3.03)	<0.05*
Conduction velocity of fast conductive fibers (CVF) (m/s)	46.29±5.39 (38.46-52.63)	37.11±4.34 (30.30-41.66)	47.73±4.53 (40.00-52.63)	26.88±4.55 (20.00-34.48)	<0.05*
Conduction velocity of medium-slow conductive fibers (CVM) (m/s)	31.63±3.58 (25.00-35.71)	22.45±3.67 (15.87-26.31)	33.28±2.10 (30.30-37.03)	16.73±2.43 (12.82-20.83)	<0.05*

SD: Standard deviation, MD: Maximum depolarization, MDT: Time to reach maximum depolarization, Area: Area under the curve, CVF: Conduction velocity of fast conductive fibers, CVM: Conduction velosity of medium-slow conductive fibers. * p value is below the threshold of <0.05

Table 2. Comparison of maximum depolarization values between groups

	Group C Group L	Group C Group D	Group C Group LD	Group L Group D	Group L Group LD	Group D Group LD
MD (mV)	9.00±1.33	9.00±1.33	9.00±1.33	3.92±1.15	3.92±1.15	8.59±2.31
	3.92±1.15	8.59±2.31	1.97±1.05	8.59±2.31	1.97±1.05	1.97±1.05
p	0.000*	0.961	0.000*	0.000*	0.112	0.000*

MD: Maximum depolarization, * p value is below the threshold of <0.05

Table 3. Comparison of the groups for the time to reach maximum depolarization

	Group C Group L	Group C Group D	Group C Group LD	Group L Group D	Group L Group LD	Group D Group LD
MDT (ms)	0.20±0.03	0.20±0.03	0.20±0.03	0.36±0.11	0.36±0.11	0.17±0.02
	0.36±0.11	0.17±0.02	0.45±0.05	0.17±0.02	0.45±0.05	0.45±0.05
p	0.001	0.885	0.000*	0.000*	0.100	0.000*

MDT: Time to reach maximum depolarization, * p value is below the threshold of <0.05

Table 4. Comparison of groups for area under the CAP curve

	Group C Group L	Group C Group D	Group C Group LD	Group L Group D	Group L Group LD	Group D Group LD
Area (mVxms)	3.26±0.52	3.26±0.52	3.26±0.52	2.65±0.38	2.65±0.38	3.64±0.89
	2.65±0.38	3.64±0.89	1.67±0.77	3.64±0.89	1.67±0.77	1.67±0.77
p	0.354	0.714	0.001*	0.051	0.056	0.000&

* p value is below the threshold of <0.05, CAP: Compound action potentials

Table 5. Comparison of groups for CVF

	Group C Group L	Group C Group D	Group C Group LD	Group L Group D	Group L Group LD	Group D Group LD
CVF (m/s)	46.29±5.39	46.29±5.39	46.29±5.39	37.11±4.34	37.11±4.34	47.73±4.53
	37.11±4.34	47.73±4.53	26.88±4.55	47.73±4.53	26.88±4.55	26.88±4.55
p	0.007*	0.940	0.000*	0.002*	0.002*	0.000*

CVF: The velocity of fibers with fast conduction velocity * p value is below the threshold of <0.05

Table 6. Comparison of groups for CVM

	GroupC Group L	Group C Group D	Group C GroupLD	Group L Group D	Group L GroupLD	Group D Group LD
CVM (m/s)	31.63±3.58	31.63±3.58	31.63±3.58	22.45±3.67	22.45±3.67	33.28±2.10
	22.45±3.67	33.28±2.10	16.73±2.43	33.28±2.10	16.73±2.43	16.73±2.43
P	0.000	0.740	0.000	0.000	0.009	0.000

CVM: Conduction velosity of medium-slow conductive fibers, * p value is below the threshold of <0.05

with both fast and medium and slow conduction velocities. These results may show that dexmedetomidine shortens the onset of the block and prolongs the duration of the block when applied with lidocaine as an adjuvant agent. MD value and area under the curve are proportional to the number of nerve fibers stimulated in that nerve.[23] Although not statistically significant in the present study, a greater decrease was observed in group LD compared to group L for MD value. This result may indicate that dexmedetomidine provides blockade of more nerve fibers when used with lidocaine. The other result showing blockade of more nerve fibers with dexmedetomidine added to lidocaine is the decrease in the area under the curve. When compared with group C, a statistically significant difference was shown only in group LD. This may indicate that the number of fibers developing block increased in group LD and that dexmedetomidine deepened the blockade caused by lidocaine.

The conduction speed of fibers with fast conduction speed is determined by the time from the moment when the stimulus is applied from the proximal end of the rat sciatic nerve to the moment when the CAP is started. In fibers that have medium and slow conduction speeds, the conduction speed is determined by the time from the moment when the stimulus is given from the proximal end of the rat sciatic nerve to the moment when the MD is reached.[25] In our study, the specified times were prolonged in each fiber group. The CVF and CVM values between group L and group LD are statistically significant. However, the difference is greater in CVF. This shows the conduction speed of CVF. Our results are consistent with the findings of the previously presented study.[23] Our results may show that the effect of dexmedetomidine is stronger in fibers with fast conduction speed when added to lidocaine. In previous clinical studies, clinical data were presented indicating that dexmedetomidine shortens the onset time of the block and prolongs the block duration.[16] It has been reported that dexmedetomidine added to perineural ropivacaine in the canine sciatic nerve increases the duration of sensory block.[26] The decrease we found in CVF and CVM supports the fact that dexmedetomidine shortens the time to onset of the block and prolongs the duration of the block when applied as an adjuvant agent.

Dexmedetomidine was reported to increase the effect of LA in a dose-dependent manner in previous studies.[27] Kosugu et al.[28] examined the CAPs recorded from frog sciatic nerves by different adrenoceptor agonists, including dexmedetomidine, and reported that dexmedetomidine reduced the CAP peak amplitude at high concentrations and that this effect was reversible.

The mechanism of action of dexmedetomidine, which is a selective α2-adrenergic receptor agonist, on ion channels and membrane potentials has not been fully elucidated. Previous studies speculated that dexmedetomidine might have effects on different ion channels. Chen et al.[29] reported evidence that dexmedetomidine had effects on sodium and potassium channels in differentiated neurons. Ishii et al.[30] argued that dexmedetomidine hyperpolarizes membrane potentials in spinal dorsal horn neurons through G-protein-mediated activation of K^+ channels. Oda et al.[31] reported that dexmedetomidine suppresses voltage-gated Na+ channel currents together with lidocaine, and creates an additive effect when used in regional anesthesia. In the present study, it was found that dexmedetomidine had no significant effects on rat sciatic nerve membrane potentials when applied alone. However, it increased the effects of lidocaine when used with lidocaine. Our findings are consistent with the results of Dalkılıç et al.'s[32] study. Our results support the opinion that dexmedetomidine provides its additive or synergistic effect when used with lidocaine through its effect on ion channels.

It is already known that conduction velocity increases with fiber diameter[33] and myelin thickness.[34,35] Previous studies reported that clonidine, which is an α2 agonist like dexmedetomidine, inhibits CAP amplitude and that this inhibition is dominant on myelinated Aα and unmyelinated C fibers.[36,37] The fact that the

effect on CVF is greater in the results of our study suggests that type A fibers may have been affected more.

The use of dexmedetomidine as an adjuvant agent in PRBs was evaluated previously in clinical studies. Ghaderi et al.[38] reported that they created a longer sensory block by adding dexmedetomidine to lidocaine in forearm bier block applications. Hu et al.[39] argued that perineural dexmedetomidine added to lidocaine and ropivacaine provided a faster onset time and a longer duration of effect in popliteal block. Abdullatif et al.[40] reported that perineural dexmedetomidine shortened the onset time of bupivacaine-induced femoral nerve block and prolonged the duration of block. The possibility that perineural dexmedetomidine passes into the systemic circulation cannot be excluded in clinical studies. It is important to demonstrate the effects of dexmedetomidine on membrane potentials. Our results can be considered as an experimental study supporting the clinical studies that evaluated the use of dexmedetomidine as an adjuvant agent in PRBs in the literature.

Lidocaine blocks voltage-gated sodium channels[13] and is not used only as LA. Systemic Lidocaine has antinociceptive effects in acute and chronic pain. These effects cannot be explained solely by its voltage-gated sodium channel-blocking properties, but the responsible mechanisms are still unclear.[32] Recently, clinicians have shown great interest in PRBs, especially fascial plane blocks, and, likely, PRBs are widely used with systemic lidocaine[14], which may be associated with increased LAST. One of the interventions aimed at limiting the use of Lidocaine in high-dose PRBs is the use of dexmedetomidine as an adjuvant agent.

Limitations

The small number of experimental animals in our study is our limitation. In the present study, not evaluating the dose and concentration differences of the agents, not evaluating their reversibility, and not being able to present data associated with neurotoxicity were considered as limitations.

The peripheral and systemic mechanisms of action of lidocaine and dexmedetomidine and their relationships with each other have not been fully explained. We believe that our study provides important findings for future studies. Considering the increasing PRBs, we believe that studies on dexmedetomidine and lidocaine will be presented in the literature in the future.

CONCLUSION

The study was conducted to evaluate the hypothesis that dexmedetomidine would prolong the duration of lidocaine effect when added to lidocaine. As a result of the study, it was found that dexmedetomidine could achieve the block duration achieved with lidocaine by slowing down conduction velocities. As an experimental study, the present research contributed and supported clinical studies concluding that dexmedetomidine prolongs the duration of sensory and motor block when added to lidocaine as a perineural adjuvant agent. To support our results and improve safety and clinical outcomes, studies using more experimental animals to eliminate our limitations are needed. In conclusion, this study provides important contributions that dexmedetomidine increases the effects of lidocaine when used perineurally with lidocaine.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Selçuk University Experimental Research and Application Center (SUDAM) Experimental Animal Ethics Committee (Date: 28.11.2011, Decision No: 2011-123).

Informed Consent

As this study is an animal experiment, informed consent is not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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