Dexmedetomidine Enhances the Pulpal Anesthetic Effect of Lidocaine: A Pilot Study

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Dexmedetomidine hydrochloride (DEX) demonstrates analgesic, sedative, and hypotensive effects. DEX may also enhance the effect of local anesthetics used in the oral cavity, although this has not been well established in combination with lidocaine. We conducted a single-blind crossover study in 8 healthy volunteers to investigate whether DEX enhances the anesthetic effect of lidocaine in the oral cavity. DEX or DEX + lidocaine was injected into the labial gingiva corresponding to the root apex of the maxillary left central incisor and into the buccal gingiva corresponding to the root apex of the mandibular right first molar. Pain threshold, blood pressure, pulse rate, oxygen saturation, and bispectral index were measured 5 minutes after treatment and at 10-minute intervals for 60 minutes. DEX + lidocaine caused pulpal anesthesia in more subjects than lidocaine alone; this difference was significant for both central incisors and first molars up to 40 minutes after treatment. Following DEX + lidocaine treatment, blood pressure and bispectral index were significantly reduced at several time points, and pulse rate significantly reduced at all time points. Neither treatment caused changes in oxygen saturation. In conclusion, administering DEX with lidocaine for dental local anesthesia caused sedation and enhanced local anesthesia compared to lidocaine alone.

Key Words: DEX; Local anesthetic effect; Sedation; Oral infiltration.

In dentistry, some local anesthetics have poor efficacy during dental surgical procedures when used without vasoconstrictors. Vasoconstrictors such as epinephrine and felypressin inhibit the absorption of dental anesthetics into local blood vessels. The effects of local anesthetics are thus prolonged when anesthetic agents are used in combination with vasoconstrictors. The addition of epinephrine to local anesthetics is a common practice, owing to the superior anesthetic effects and satisfactory duration of action produced by the combination. However, the alpha-1 receptor-mediated vasoconstriction produced by epinephrine can be pronounced and hence care must be taken during administration to medically compromised individuals.¹ In addition, there have been cases in which epinephrine caused stimulation of beta-1 receptors and acceleration of cardiac function, which resulted in arrhythmia and myocardial ischemia.² The vasoconstrictor effect of felypressin is weaker than that of epinephrine and has

less effect on the circulatory organs; therefore, in Japan, felypressin is combined with prilocaine for use in patients for whom epinephrine is undesirable.³ However, because felypressin is a weaker vasoconstrictor than epinephrine, it may not have similar clinical efficacy when coadministered with a local anesthetic. Furthermore, felypressin, particularly in higher doses, may cause a reduction in coronary blood flow,⁴⁻⁷ making it potentially unsafe for use in patients with angina pectoris or coronary artery disease. There is a need for vasoconstrictors that can enhance the effects of local anesthetics without negative cardiovascular effects.

Dexmedetomidine hydrochloride (DEX) is an adrenergic alpha-2 receptor agonist that demonstrates analgesic, sedative, and hypotensive actions via central alpha-2A receptors. In addition, it acts on alpha-2B receptors of peripheral blood vessels, causing vasoconstriction. When coadministered with local anesthetics, DEX has been shown to enhance the anesthetic effects and prolong the duration of action of lidocaine.⁸ In addition, DEX reduces blood pressure and can cause sedation. In a recent study, DEX was examined for its ability to enhance the anesthetic effects of lidocaine in the oral cavity by measuring current perception threshold.⁹ In the present study, we sought to clarify the effect of DEX on the local anesthetic action of lidocaine in the oral cavity, using an electric pulp tester (EPT). The EPT

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has been used extensively for measuring pain threshold with various local anesthetic solutions.^{10–13} In addition, we studied changes in blood pressure, pulse rate, and degree of sedation due to combined treatment with DEX and lidocaine.

METHODS

The study was a single-blind crossover comparative study. We observed the guidelines in the Declaration of Helsinki. We received permission to perform the study from the Ethics Committee of the Nippon Dental University School of Life Dentistry at Tokyo (NDU-T2011-30), and followed the guidelines for clinical studies stipulated by the Ministry of Health, Labor, and Welfare. The exclusion criteria were individuals that had pathology such as dental caries or restorations involving any tested teeth. Furthermore, we checked that the maxillary left central incisor and the mandibular right first molar were vital teeth and that hyperesthesia was absent. The final sample size consisted of 8 students from the Nippon Dental University School of Life Dentistry at Tokyo who agreed to participate in the study and from whom consent had been obtained.

The study was conducted in a quiet private room with a dental chair installed, and the ambient temperature was maintained at 22°C. A blood pressure and oxygen saturation (SpO₂) monitor (BP-508, Omron Colin Co, Ltd, Tokyo, Japan) and a bispectral index (BIS) monitor (BIS VISTA, Covidien, Minneapolis, Minn) were attached to subjects in the semi-Fowler position to measure the depth of anesthesia. We measured blood pressure, pulse rate, SpO₂ (BP-608EV, Omron Colin), and BIS baseline values after keeping subjects at rest for 5 minutes.

Local anesthetic effect was measured using an Electric Pulp Test (Pulp Tester, Yoshida Dental Trade Distribution Co, Ltd, Tokyo, Japan) coated with electrocardiogram gel (Cardio Cream, Nihon Kohden Co, Tokyo Japan). The probe of the EPT was brought into contact with the healthy enamel at the center of the buccal face, the gingival margin of the maxillary left central incisor, and the mandibular right first molar.¹⁴ Next, stimulus intensity was elevated from 0 to 80 over 20 seconds. When the subjects felt some sensation or the presence of the stimulus, they were asked to raise their hand, after which the stimulus intensity at that time was measured. Two measurements were taken for each target tooth and the mean value was used as the baseline for pain threshold. A 32-gauge needle (Misawa Medical Industry Co, Ltd, Ibaraki, Japan) and a disposable syringe (Terumo Corporation, Tokyo, Japan) were then used

to administer aliquots of the test solution. A 0.5-mL aliquot was administered into the part of the labial gingiva corresponding to the root apex of the maxillary left central incisor. A 1.0-mL aliquot was administered into the buccal gingiva at the midpoint of the line connecting the mesial and distal roots, corresponding to the root apex of the mandibular right first molar. Each treatment was administered over a 30-second period. The test solution contained 2% lidocaine (1 mL of 4% xylocaine solution [AstraZeneca, Osaka, Japan] + 1 mL of physiological saline) or 12.5 µg/mL DEX added to 2% lidocaine (DL) (1 mL of Precedex Intravenous Solution 200 µg [Maruishi Pharmaceutical Co, Ltd, Osaka, Japan] + 3 mL of physiological saline + 4 mL of 4% xylocaine solution). The doses of DEX and lidocaine used were based on the data from previous animal studies.¹⁵

Subjects were evaluated for injection pain at the time of test solution administration, based on a 4-step scale as follows: 0 for no pain, 1 for mild pain (felt pain but were comfortable), 2 for moderate pain (uncomfortable but tolerable pain), and 3 for strong pain (intolerable pain).¹⁶ We measured the EPT value at which the stimulus or first sensation was experienced as described above, as well as blood pressure, pulse rate, SpO₂, and BIS value at 10-minute intervals from the time of test solution administration until 60 minutes. We defined *pulpal anesthesia* as the state in which the EPT reached the maximum stimulus intensity of 80 without any reaction from the subject. All the subjects received both test solutions, with at least a 2-day interval between treatments. Anesthesia was administered by the same dental anesthesiologist. In this single-blinded study, the type of anesthetic solution was concealed from the subjects.

The lidocaine and DL groups were compared using a chi-square test for pain at time treatment was administered and a Fisher exact test for anesthetic efficacy. Because of the crossover nature of this study, we used the McNemar test in cases where the result was limited to 2 values in a paired 2-group comparison. A paired *t* test was used for blood pressure, pulse rate, SpO₂, and BIS measurements. The significance level in all cases was set at .05.

RESULTS

The study subjects were 4 males and 4 females, aged 29.2 ± 2.2 years (height, 167.5 ± 5.5 cm; weight, 61 ± 13.8 kg). We did not observe any significant difference in injection pain perception between the lidocaine and DL groups for either the central incisors or the first molars at the time of injection (Table 1). We then examined the

Table 1. No. of Patients Reporting Different Levels of Discomfort at the Time of Solution Deposition*

	Pain Threshold				Total	p
	0	1	2	3		
Central incisor						
Lidocaine	0	2	6	0	8	.261
DEX + lidocaine	0	6	2	0	8	
First molar						
Lidocaine	3	4	1	0	8	.774
DEX + lidocaine	3	5	0	0	8	

* DEX indicates dexmedetomidine hydrochloride.

percentage of subjects who experienced pulpal anesthesia, which was significantly higher in the DL group than in the lidocaine group for both the central incisors and the first molars (Table 2). Pulpal anesthesia was consistently observed in a higher percentage of subjects in the central incisor (Figure 1) than in the first molar (Figure 2) for up to 50 minutes postinjection.

A drop in blood pressure was noted in the DL group (Figure 3). Significant differences in blood pressure were observed between the 2 groups at 20, 40, and 50 minutes after test solution administration. The pulse rate was found to decrease in the DL group (Figure 4). Significant differences were found in pulse rate between the groups starting from 5 minutes up to 60 minutes after administration of the test solutions.

The BIS values decreased in the DL group (Figure 5). Between the 2 groups, significant differences in BIS were found at 20, 30, 40, and 50 minutes. There were no significant changes observed in SpO₂ in either group (data not shown).

DISCUSSION

The results from this study demonstrated that the incidence of pulpal anesthesia caused by lidocaine was significantly improved by the addition of DEX. Several possible mechanisms may underlie the anesthetic action produced by the combined treatment. The oral cavity has an abundant blood supply, which allows for the systemic absorption of administered anesthetics by local blood vessels. This results in insufficient anesthetic effects and short duration of action of some anesthetic

Table 2. Percentage of Subjects Who Experienced Pulpal Anesthesia Due to the Test Solutions*

	Lidocaine, % (No./Total)	DEX + Lidocaine, % (No./Total)	p
Central incisor	37.5 (3/8)	100 (8/8)	.0135
First molar	12.5 (1/8)	100 (8/8)	.0007

* DEX indicates dexmedetomidine hydrochloride.

Figure 1. Incidence of anesthesia in the central incisor. The graph depicts the percentage of subjects with no response to electric pulp tester (EPT) at the maximum setting for the 2 anesthetic formulations. The dotted line represents dexmedetomidine hydrochloride + lidocaine (DL) and the solid line represents lidocaine (L) alone.

agents. In dental practice, vasoconstrictors are often administered with local anesthetics to increase the effect of the latter. The localization of lidocaine may be prolonged by the vasoconstrictor effect of DEX via its agonistic activity on peripheral alpha-2 blood vessel receptors.^{17–19}

Another possible mechanism for the action of DEX administered with lidocaine may be through the inhibition of neurotransmission. Clonidine is an alpha-2 receptor agonist, which has been shown to inhibit neurotransmission,^{20,21} and thereby enhances the effects of local anesthetics.^{22–25} Furthermore, Yoshitomi et al⁸ have suggested that DEX may have inhibitory effects on

Figure 2. Incidence of anesthesia in the first molar. The graph depicts the percentage of subjects with no response to electric pulp tester (EPT) at the maximum setting for the 2 anesthetic formulations. The dotted line represents dexmedetomidine hydrochloride + lidocaine (DL) and the solid line represents lidocaine (L) alone.

Figure 3. Change in blood pressure caused by the 2 anesthetic formulations. There was a decrease in systolic and diastolic blood pressure when dexmedetomidine hydrochloride + lidocaine (DL) was administered. The lower set of lines represents diastolic blood pressure, whereas the upper set represents systolic blood pressure. The dotted line represents DL and the solid line represents L alone. * indicates $p < .05$.

neurotransmission. In addition, DEX has spinal α -2A receptor-mediated central analgesic action.²⁶ However, pain in the oral cavity is mediated via the trigeminal nucleus rather than the spinal cord. The spinal trigeminal nucleus is embryologically an extension of the dorsal horn of the spinal cord, and, reportedly, α -2A receptors are present in the trigeminal system as well.²⁷ Thus, it is difficult to clearly delineate the central analgesic effect of DEX mediated via the α -2A receptors of the trigeminal nucleus from the local effects within the oral cavity.

Intravenous administration of DEX causes transitory fluctuations in blood pressure. This is because DEX first stimulates α -2B receptors in the walls of peripheral blood vessels, which results in vasoconstriction. Following this, excitation of α -2A receptors occurs in the medulla solitary nucleus, which is the cardiovascular regulation center. The excitation of the central α -2A receptors leads to inhibition of the sympathetic nervous system, which results in a decreased release of noradrenaline from the ends of postganglionic sympathetic nerves.^{28,29} Yamane et al⁹ have shown that the administration of 1 μ mol/L (0.2 mcg/mL) DEX with 0.7% lidocaine in the oral cavity does not influence blood pressure or heart rate. In the present study, we administered a combination of 12.5 μ g/mL DEX and 2% lidocaine to the subjects. Our results showed a clear drop in blood pressure from 20 to 50 minutes after administration of the test solution. We believe that the

Figure 4. Change in heart rate caused by the 2 anesthetic formulations. The heart rate in subjects administered dexmedetomidine hydrochloride + lidocaine (DL) was significantly decreased as compared to that in subjects administered only lidocaine (L). The dotted line represents DL and the solid line represents L alone. * indicates $p < .05$.

observed effect may be because, during administration of the test solution, only the blood vessels closest to the administration site were constricted. Consequently, blood pressure was not affected until after about 20 minutes, when sufficient amounts of DEX had been absorbed from the oral mucosa into the blood and then to the central nervous system. It was also observed that a decrease in pulse rate occurred earlier than a drop in blood pressure. This may be due to a lower threshold for the activation of sympathetic receptors that regulate pulse rate, as compared to those that regulate blood pressure. Changes in the aforementioned circulatory dynamics may have significantly improved the effects of local anesthetic vasoconstrictors in patients with hypertension, ischemic heart disease, or hyperthyroidism.

The BIS monitor determines the degree of sedation due to changes in brain waves.³⁰ A BIS value of 60 or

Figure 5. Change in bispectral index (BIS) values caused by the 2 anesthetic formulations. BIS significantly decreased in subjects administered dexmedetomidine hydrochloride + lidocaine (DL) compared to that in subjects administered lidocaine (L) alone. The dotted line represents DL and the solid line represents L alone. * indicates $p < .05$.

less indicates that consciousness has been lost, 60 to 90 indicates a state of sedation, and 90 or more indicates a state of unimpaired consciousness. The sedative effect of DEX after its local administration has not been clarified yet. In this study, we measured changes in the level of consciousness, using BIS as a guide. Local administration of DEX resulted in a sedative effect, and the duration of action lasted from 20 to more than 50 minutes. For the usual intravenous administration of DEX, a bolus dose of approximately 50 μg (1 $\mu\text{g}/\text{kg}$ over 10 minutes) is initially administered, followed by a continuous infusion of 20–35 $\mu\text{g}/\text{h}$ or more.³¹ Because DEX was locally administered in this study, we used approximately one quarter of its usual intravenous bolus dose. Local tissue administration combined with a lower dose produced a slower onset of central effects compared with intravenous infusion. A major feature of DEX observed in this study was that it produced sedation without causing respiratory depression. In addition, no changes in SpO_2 were observed. These may be particularly beneficial as sedation was achieved without respiratory depression in about 30 minutes after DEX administration. On the other hand, in the case of outpatients who do not require sedation, at least a 1-hour observation period following DEX administration may be required prior to discharge. Additionally, the safety of discharge without an escort to drive or attend the patient home would need to be clarified. In conclusion, this study demonstrated that adding 12.5 $\mu\text{g}/\text{mL}$ DEX to lidocaine enhanced the local anesthetic effect when compared to lidocaine alone and produced a sedative effect without respiratory depression.

There were several limitations in this study. First, the blood concentration of lidocaine was not measured after administration of the study solutions. This would have helped determine if the local anesthesia-enhancing effect of DEX was through an effect on vasoconstriction, thus increasing local tissue lidocaine concentrations. Second, we did not determine the effects of DEX alone on anesthetic effect. A rise in anesthetic effect due to intravenous administration of DEX would likely be indicative of a central anesthetic action. However, it is not possible to rule out inhibition of peripheral nerve transmission. Comparison of plain lidocaine to lidocaine with any vasoconstrictor is likely to produce a significant difference, as it is known that plain lidocaine has poor efficacy in the oral cavity. Future studies should compare lidocaine with epinephrine to lidocaine with DEX, which would be a more appropriate clinical comparison. Finally, this was a pilot study, and hence the sample size was small. However, these data can be used for power analysis in future studies to allow for adequate sample size to detect clinically relevant differences when using DEX as a vasoconstrictor added

to local anesthetics. Further studies are required in a larger number of subjects to detect the clinical usefulness of dexmedetomidine added to lidocaine for dental local anesthesia.

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