Effect of Topical Anesthesia Using an Adhesive Patch and Anesthetic Solution

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We analyzed trigeminal somatosensory evoked potentials (TSEP) to the alveolar mucosa to investigate the efficacy of an amide local anesthetic, 2% lidocaine hydrochloride with 12.5 µg/mL epinephrine (Lido treatment) as a topical anesthetic. Eighteen consenting healthy adult volunteers were enrolled. A volume of 0.06 mL of Lido, 0.06 g of 20% benzocaine, or 0.06 mL of physiological saline (control) was instilled onto a hemostatic adhesive patch, which was then applied to the alveolar mucosa at the maxillary right canine for 5 minutes. An electrical stimulus approximately 5 times that of the sensory threshold was applied using a surface stimulation electrode. The trigeminal somatosensory evoked potential was recorded immediately, 5 minutes, and 10 minutes after removal of the patch. Positive P125 and P310 peaks and negative N100 and N340 peaks were observed as a result of the electrical stimulation. A significant decrease in the percentage change in amplitude of N100-P125 was observed in the Lido treatment immediately, 5 minutes, and 10 minutes after patch removal. In the Lido treatment, trigeminal somatosensory evoked potential amplitude at N100-P125 decreased significantly, suggesting that topical anesthesia produced by an amide local anesthetic may have a topical anesthetic effect as potent as that produced by an ester local anesthetic.

Key Words: Benzocaine; Lidocaine; Somatosensory evoked potential; Pain; Adhesive patch.

Infiltration anesthesia is commonly performed for pain relief in clinical dentistry. However, the pain caused by this procedure itself is stressful for patients. Although various methods to alleviate pain during the injection of infiltration anesthesia have been compared, including slow injection speed, heating the cartridge, and using a refrigerant at the injection site, none provide consistent pain relief.^{1–3} Topical anesthesia is often used to reduce the pain of infiltration anesthesia. Commonly used topical anesthetics with an indication exclusively for dental use in Japan are ester-type local anesthetics, many of which produce a less potent anesthetic effect than amide-type local anesthetics and have a higher incidence of allergic reactions.⁴ In addition, because topical anesthetics are formulated as gels or pastes, they may not produce sufficient anesthesia when they become diluted with saliva or diffuse inside the mouth.⁵

Nakamura et al⁶ instilled an amide or ester local anesthetic onto hemostatic adhesive patches and applied the patches to the gingiva for 5 minutes. A visual analogue scale (VAS) score was used to measure pain at the insertion of 30- or 33-G needles. The results showed that the amide local anesthetic was a highly effective topical anesthetic. Because 2% lidocaine hydrochloride with 12.5 µg/mL epinephrine cartridges is most commonly used for dental infiltration anesthesia in Japan, we studied this solution as a topical anesthetic agent. We analyzed trigeminal somatosensory evoked potential (TSEP) when electrical stimulation was applied to alveolar mucosa and compared the topical anesthetic effects of this amide with an ester local anesthetic, 20% benzocaine, to clarify the effectiveness of the amide local anesthetic as a topical anesthetic.

METHODS

This study was approved by the Tokyo Dental College Ethics Committee (approval No. 392). The objective of

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(A) Front view

(B) Side view

Figure 1. Surface stimulation electrode (NM-990W, Nihon Kohden Corporation, Tokyo, Japan).

the study was explained to the subjects by using a written summary, and informed consent was obtained from 18 healthy adult volunteers (11 males, 7 females).

We used 2% lidocaine hydrochloride solution with 12.5 µg/mL epinephrine (Xylestesin-A, 3M Health Care Limited, Tokyo, Japan; Lido treatment) and 20% benzocaine (Gingicaine gel 20%, Hakusui Trading Co, Ltd, Tokyo, Japan; Benzo treatment). Physiological saline solution was used as a control (Control treatment). For the topical anesthetic, we applied the drug for each treatment onto the gauze section (10 × 10 mm) of a hemostatic adhesive patch (Medipatch, Hakujuji Co, Ltd, Tokyo, Japan) following the method used in a study by Nakamura et al.⁶

The subjects rested in the dental chair in a horizontal supine position. Air was used to fully dry the alveolar

Figure 2. An adhesive patch was applied for 5 minutes to the dried gingivobuccal fold of the maxillary right canine.

mucosa at the gingivobuccal fold around the maxillary right canine. A surface stimulation electrode (NM-990W, Nihon Kohden Corporation, Tokyo, Japan) was placed in close contact with this area and covered by the buccal mucosa (Figure 1). Electrical stimulation was applied and TSEP was observed as an initial reference for comparison. The TSEP observations were made using an electromyogram/evoked potential measuring system (Neuropack S1, Nihon Kohden). The sensory threshold for electrical stimulation was determined for each subject. Electrical stimulation 5 times that at the sensory threshold was applied, and the TSEP was recorded from the contralateral scalp. The stimulation was 0.2 ms in duration and applied a total of 200 times at a frequency of 2 Hz. In accordance with the international 10-20 system, the lead was placed at C5/C6 (the midpoint on a line from the crown of the head to the external acoustic opening), which corresponds to the first sensory region of the trigeminal nerve, and the reference electrode was attached at Fpz. The ground electrode was attached to the chest. The band-pass filter was set at 1–500 Hz. These experimental conditions were based on previous studies.^{7–10}

The patch was applied to the canine gingivobuccal fold for 5 minutes (Figure 2). After removal of the patch, the area was dried fully with air, an electrode was immediately placed on the area, and TSEP was measured. TSEP was then measured in a similar fashion after 5 and 10 minutes. After the measurement at 10 minutes, the stimulation site was washed with water and left alone for 10 minutes. The TSEP was then measured at the same site to confirm that the TSEP had fully recovered in comparison with the initial reference measurement. The same procedure was performed for

Comparison of TSEP Latency Among Treatments*

	Latency, ms (mean $\pm$ SD)			
	N100	P125	P310	N340
Control				
Baseline	102.6 $\pm$ 6.76	124.1 $\pm$ 7.37	300.9 $\pm$ 16.3	338.9 $\pm$ 16.8
Immediately	105.9 $\pm$ 8.90	126.3 $\pm$ 6.50	301.1 $\pm$ 16.8	343.0 $\pm$ 20.7
5 min	101.3 $\pm$ 9.32	125.5 $\pm$ 8.74	308.1 $\pm$ 20.1	349.8 $\pm$ 17.6
10 min	106.8 $\pm$ 8.38	129.0 $\pm$ 7.48	303.5 $\pm$ 14.8	351.8 $\pm$ 17.8
Lido				
Baseline	102.8 $\pm$ 9.12	128.2 $\pm$ 5.78	304.0 $\pm$ 19.1	339.4 $\pm$ 19.6
Immediately	105.8 $\pm$ 8.64	124.6 $\pm$ 6.87	315.2 $\pm$ 19.9	351.6 $\pm$ 21.9
5 min	104.3 $\pm$ 7.03	125.8 $\pm$ 7.23	309.0 $\pm$ 23.3	344.6 $\pm$ 20.9
10 min	102.6 $\pm$ 10.4	129.2 $\pm$ 7.33	311.4 $\pm$ 22.7	352.5 $\pm$ 19.9
Benzo				
Baseline	102.2 $\pm$ 8.97	124.7 $\pm$ 7.37	304.7 $\pm$ 17.7	348.9 $\pm$ 19.5
Immediately	104.5 $\pm$ 7.94	126.6 $\pm$ 8.31	311.7 $\pm$ 21.1	353.0 $\pm$ 17.9
5 min	103.9 $\pm$ 8.90	128.6 $\pm$ 8.37	312.0 $\pm$ 15.9	352.2 $\pm$ 18.1
10 min	104.7 $\pm$ 9.87	127.6 $\pm$ 5.01	301.7 $\pm$ 22.9	338.2 $\pm$ 24.1

* Lido indicates treatment with 2% lidocaine hydrochloride with 12.5 μ g/mL epinephrine; Benzo, treatment with 20% benzocaine.

the 3 treatment groups. This study was conducted according to a double-blind crossover design. To maintain consistency of the anesthesia technique, one individual administered all anesthetics.

For each treatment, the following were evaluated: TSEP latency, percentage change in amplitude with a reference amplitude of 100%, and pain after electrical stimulation assessed using a 100-mm VAS (0 mm = no sensation, 100 mm = most intense pain imaginable). The topical anesthesia was evaluated using percentage change because the waveform of the TSEP amplitude differed for each individual. Data are expressed as mean $\pm$ SD. Repeated-measures analysis of variance was used for statistical analyses of latency and percentage change in amplitude in each treatment, and the Dunnett test or the Student-Newman-Keuls test was used for multiple comparisons. VAS scores were analyzed using the Friedman chi-square test and multiple comparisons were made using the Wilcoxon *t* test with Bonferroni correction. $P < .05$ was considered statistically significant. The Origin 8.6 software (OriginLab Corp, Northampton, MA) was used for data analysis.

RESULTS

The mean age of the subjects was 27.7 ± 1.5 years. The mean sensory threshold was 0.87 ± 0.13 mA and the mean stimulation intensity was 4.39 ± 0.59 mA. None of the subjects experienced regional complications such as reddening, ulceration, or delayed allergic reaction to the local anesthetic at the site where the patch was

applied. In addition, systemic complications such as local anesthetic toxicity or vasovagal syncope were also not recognized.

In each treatment, electrical stimulation produced negative peaks at N100 and N340 and positive peaks at P125 and P310. The Table shows the mean peak latency in each treatment. No significant differences were observed in latency immediately after patch removal or after 5 and 10 minutes in any of the 3 treatments.

Figure 3 shows the percentage change in amplitude in each treatment. No significant difference was observed for either N100-P125 or P310-N340 in the Control and Benzo treatments. In contrast, significant differences were observed for N100-P125 in the Lido treatment immediately, 5 minutes, and 10 minutes after patch removal. A comparison of the 3 treatments showed a significant difference for P310-N340 in the Lido and Benzo treatments compared with the Control treatment after 5 minutes. No significant difference was observed between the Lido and Benzo treatments.

Figure 4 shows the VAS scores in each treatment. Although the VAS score in the Lido treatment tended to be lower immediately after patch removal, no statistically significant differences were observed in the 3 treatments immediately, 5 minutes, or 10 minutes after patch removal.

DISCUSSION

There are many studies on the effects of local anesthetics, including studies that have evaluated VAS scores when a needle was inserted into a site where

Figure 3. Comparison of trigeminal somatosensory evoked potential percentage change in amplitude N100-P125/P310-N340. (A) Control treatment, (B) Lido treatment, and (C) Benzo treatment. Significant differences were observed for N100-P125 between baseline and immediately, 5 minutes, and 10 minutes after patch removal in the Lido treatment. Significant differences were observed for P310-N340 in the Lido and Benzo treatments compared with the Control treatment 5 minutes after patch removal. Lido indicates 2% lidocaine hydrochloride with 12.5 $\mu\text{g/mL}$ epinephrine; Benzo, 20% benzocaine.

topical local anesthetic had been applied and those that have evaluated TSEP waveform, as in this study.^{5,6,11–13} TSEP is used to test nerve function and is considered suitable for the quantitative evaluation of many agents such as analgesics, narcotic drugs, and anesthetics.^{12,14,15} Decrease in TSEP amplitude seen in this study is consistent with that in reports by Sasao and Amemiya¹² and by Narita et al,¹³ and is presumably because of the effectiveness of local anesthetic.

Figure 4. A comparison of visual analogue scale scores. (A) Control treatment, (B) Lido treatment, and (C) Benzo treatment. Box plots show the median, lower and upper quartiles (25–75%), and minimum and maximum values. Lido indicates 2% lidocaine hydrochloride with 12.5 $\mu\text{g/mL}$ epinephrine; Benzo, 20% benzocaine.

According to Matsuura et al,¹⁶ it takes between 40 and 50 ms for a nociceptor to receive stimulation until that generates nerve impulses. The distance from the tooth pulp and skin on the lower jaw to the cerebral cortex has been estimated to be about 30–40 cm.^{16,17} This suggests that the N100-P125 amplitude obtained in this study should be an A δ fiber response traveling at 10 m/s, and that similarly, the P310-N340 amplitude should be a C fiber response traveling at 1 m/s. A δ fibers transmit the “first pain” as a pricking or sharp sensation.¹⁸ According to Chen et al,¹⁹ the amplitude at about 100 ms is correlated with stimulus intensity and may reflect sensory transmission. Decrease in the

amplitude of these responses may be due to the effective topical anesthesia.

In this study, no statistically significant differences in TSEP latency were observed in 3 treatments, though TSEP amplitude tended to be lower in the Lido and Benzo treatments compared with the Control treatment. There was a significant decrease of percentage change in amplitude for N100-P125 in the Lido treatment immediately, 5 minutes, and 10 minutes after patch removal. Furthermore, a comparison of the 3 treatments showed a significant decrease for P310-N340 in the Lido and Benzo treatments compared with the Control treatment after 5 minutes. A comparison of VAS scores revealed no statistically significant changes in the 3 treatments, though the scores tended to be lower immediately after patch removal in the Lido treatment. These results suggest that 2% lidocaine hydrochloride solution containing epinephrine may have a topical anesthetic effect as potent as that of 20% benzocaine. The reason we used 2% lidocaine hydrochloride solution containing epinephrine is that this agent is most commonly used for dental infiltration anesthesia in Japan and it is quite simple for dentists to use a small volume of this solution as a topical anesthetic agent.

We also showed a decrease in the percentage change in amplitude in the Lido treatment immediately after patch removal, and this anesthetic effect continued through to 10 minutes after patch removal. Consequently, we confirmed that lidocaine hydrochloride with epinephrine showed more rapid onset than benzocaine. A previous study has shown that the onset time of lidocaine is 2 minutes and duration is 15 minutes but that benzocaine administered on the mucosa produced a more rapid effect than lidocaine.²⁰ Because benzocaine has a pKa of 2.5 compared with 7.9 for lidocaine, lidocaine would be expected to enter the nerve fibers more rapidly and exert anesthetic effects more quickly.^{4,21,22} Konráðsdóttir et al²³ reported that lidocaine has a higher permeating potency through fish skin than benzocaine. Results obtained in this study agree with these findings. Although median VAS scores tended to be lower in the Lido treatment immediately after patch removal than in the Benzo treatment, there was no statistically significant difference between these 2 treatments.

Currently, one of the most commonly used topical anesthetics in Japan is 20% benzocaine. Studies have shown that 20% benzocaine is more effective than placebo for topical anesthesia, though other studies have shown that benzocaine causes discomfort because of its bitterness and does not produce sufficient pain relief.^{11,21,24,25} Because ester local anesthetics may induce local anesthetic allergies and, at least in high

doses, methemoglobinemia, it would be beneficial if an easy topical anesthetic technique using amide local anesthetics would be an option in Japan.^{4,26,27} Conventionally, lidocaine had been thought to produce topical anesthesia at a concentration of 5% or more.²⁸ However, Nakamura et al⁶ showed that a lower concentration of 2% could also be effective for topical anesthesia. We investigated the possibility of the topical anesthetic effect of the 2% lidocaine hydrochloride solution containing 12.5 µg/mL epinephrine in this study. Vasoconstrictor contained in local anesthetic solution impedes anesthetic uptake in oral mucosal tissue. However, Adriani et al²⁰ reported that epinephrine did not influence a topical anesthetic effect of cocaine and tetracaine. Results of this report and the present study suggest that epinephrine does not affect topical anesthetic effect. This may be because epinephrine administered to the mucosal surface hardly infiltrates into mucosal tissue. In contrast, benzocaine is highly lipophilic and easily infiltrates into mucosal tissue.^{4,29,30}

The present method is simple to perform, without requiring any special equipment or procedure other than a patch and the same amide local anesthetic commonly used for infiltration anesthesia. It also appears to be a highly safe procedure, given that no complications such as reddening or ulceration were observed at the site of topical anesthetic application. However, these complications are rare and our study included only a small number of individuals. In the Lido treatment, TSEP amplitude and VAS scores trended to be lower, suggesting that it may be possible to use this method instead of ester local anesthetics for topical anesthesia of the gingiva.

Possible issues with the study design include the use of a low dose of benzocaine. The package insert supplied with benzocaine does not give clear guidance on dosage, and a suitable dose is often subjectively decided. In this study, we used 0.06 g, based on the dose actually used in clinical practice and the gauze area of the patch used in the study. Further investigation on the appropriate dose may be necessary. Furthermore, even if application of the patch results in topical anesthesia, the electrical stimulation after patch removal may cause a short circuit to the surrounding tissues because the inside of the mouth is wet with saliva, and the participants may have felt a sensation of pain at another site. This may be why no significant differences in VAS scores were observed between the Lido and Benzo treatments. This might be clarified through a comparison of amplitude and VAS scores in research designed to better exclude factors such as saliva. Lastly, subjective pain responses, as indicated from the VAS scores, were lower in the Lido

group but not statistically significant. A larger sample size may be needed in the future to assess whether the percentage change in amplitude of the N100-P125 in the Lido treatment will correlate with subjective pain response.

CONCLUSION

When 2% lidocaine hydrochloride solution with 12.5 µg/mL epinephrine was applied to an adhesive patch for topical anesthesia of maxillary alveolar mucosa, the percentage amplitude change in TSEP at N100-P125 decreased. Median VAS reported pain scores in the Lido group tended to be lower than in the Benzo group, though the VAS score difference did not reach statistical difference. The results suggest that 2% lidocaine hydrochloride solution containing 12.5 µg/mL epinephrine applied to an adhesive patch may have a topical anesthetic effect as potent as that of 20% benzocaine.

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