

学位論文

**Immediate analgesic effect of 8% lidocaine
applied to the oral mucosa in patients
with trigeminal neuralgia**

(三叉神経痛の口腔粘膜の痛みに対する
8%リドカインの即効性鎮痛作用)

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著者の宣言

本学位論文は、著者の責任において研究を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

ABSTRACT

Background.

Trigeminal nerve block is widely used for trigeminal neuralgia (TN), though with much painful procedure and potential serious complications. The pain of TN occurs most frequently in the second and the third divisions of the trigeminal nerve, which are distributed in intraoral mucous membrane. Here, we examined the response to intraoral application of 8% lidocaine in patients with oral TN pain in a double-blind, placebo-controlled crossover study.

Methods.

Twenty-four outpatients with oral TN pain were randomized to receive intraoral application of either 8% lidocaine (LDC) or saline placebo (PBO) to the painful area. Following 7-days period, patients were crossed over to receive the alternative treatment. The pain was assessed with a numerical rating scale (NRS) before and 15 min after treatment. Patients used a descriptive scale to grade pain outcome and were asked to note any recurrence and the latency for recurrence after therapy.

Results.

Intraoral LDC, but not PBO, significantly decreased the NRS from 5 (4, 8) [median (25, 75 percentiles)] to 1 (0, 4) ($P=0.001$). Of the 24 patients, 19 described marked or moderate relief of pain after LDC but only 3 described the same after PBO application. The effect of LDC and PBO persisted for 2.8 (0.3, 3.0) and 0 (0, 0) hours, respectively.

Conclusions.

Intraoral application of 8% lidocaine produced prompt analgesia without serious side effects in patients with trigeminal neuralgia who presented with severe intraoral pain.

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1. Background

Trigeminal neuralgia (TN) is characterized by recurrent severe shooting neuropathic pain in the distribution of the trigeminal nerve, which is triggered by innocuous stimuli such as touch, chewing, talking, and tooth brushing. An attack of trigeminal neuralgia lasts only seconds to a couple of minutes, but multiple excruciating attacks may occur in a day, which could jeopardize adequate eating or drinking.¹

The guidelines on TN management by the American Academy of Neurology and the European Federation of Neurological Societies recommend oral administration of carbamazepine or oxcarbazepine as the first-line treatment for pain control.² These anticonvulsants do not only produce prompt analgesia for TN pain, but also have adverse effects such as sleepiness, staggering, nausea, vomiting, and drug eruption. It is also difficult, at least in some cases, to continue the use of these medications orally.³ When the medical therapy is difficult to be adapted for the pain relief, the guidelines recommend surgical treatment.² Surgery has proved quite effective in TN. Nevertheless some patients refuse to undergo it due to potential serious complications.⁴ While trigeminal nerve block using a needle has been traditionally performed for the relief of TN, such nerve block is usually or sometimes always accompanied by excruciating pain from the nerve fibers damaged during needle puncture, which in some cases leads to persistent nerve injury including dysesthesia.⁵ Thus, many patients prefer to avoid injections, despite the more rapid relief.

This is particularly true as the most commonly affected divisions of the trigeminal nerve are the second (maxillary) and third (mandibular), which serve the mucous membranes of the lips, gum, palate, and tongue as well as face skin. Based on this relationship, we hypothesized that intraoral pain associated with TN can be relieved by a small dose of local anesthetic applied to the painful mucous membrane. A metered-dose pump of 8% lidocaine (LDC; Xylocaine pump spray[®], Astra Zeneca) is commercially available and mainly used for anesthetizing mucosal membranes, e.g., preparation of the upper airway for endoscopy. This preparation includes flavor and fragrance, and can be easily used for intraoral applications.^{6,7} To test our hypothesis, we examined in a double-blind, placebo-controlled crossover study the efficacy of intraoral LDC in the relief of oral pain in patients with trigeminal neuralgia.

2. Methods

2-1. Patients

A trial steering committee and an independent data monitoring and ethics committee oversaw the conduct of the trial. The study was approved by Kitasato University Medical Ethics Committee and written informed consent was obtained from each patient.

Consecutive outpatients with classic trigeminal neuralgia were enrolled into a randomized, double-blind, placebo-controlled, crossover study at Kitasato University Hospital. The inclusion criteria for the selection of classic trigeminal neuralgia were based on the definition of the International Headache Classification: paroxysmal unilateral pain triggered in the anatomical region of the trigeminal nerve, without any sensory or motor focal symptoms in this region. Extensive tests including magnetic resonance imaging showed no cause for the trigeminal neuralgia. Patients were eligible for inclusion if they had the most severe TN pain in the mouth, aged 20 years or older, were capable of proper assessment of the severity of pain and their condition, and had experienced multiple episodes of intraoral pain for at least 3 months with a pain intensity of more than 4 points on the Numerical Rating Scale (NRS; scale 0-10; 0 = no pain, 10 = worst pain). Excluded from the study were patients with other neurological diseases, psychological diseases, serious chronic diseases, such as ischemic heart disease, pulmonary emphysema, and those with history of severe drug allergy. We also excluded patients treated with orally-applied lidocaine, allergy to local anesthetics, and those with alcohol intolerance.

2-2. Study protocol

In the first arm of the study, patients were randomized to receive either 8% lidocaine (LDC/PBO group) or saline placebo (PBO/LDC group) applied to the oral mucosa. After a 7-day period, patients were crossed over to receive the opposite treatment. The investigator sprayed 0.2 ml of lidocaine (LDC) or saline (PBO) (0.1 ml of 1 spray twice) in the patient palm from a blinded metered-dose spray bottle, then the patient applied the liquid to their painful mouth area by the finger.

Paroxysmal oral pain triggered by mouth opening or chewing was assessed with NRS before and 15 min after the treatment. Physical examination, including measurement of blood pressure and pulse rate, was conducted at the pretreatment visit and on completion of, or withdrawal from, the treatment. Patients were observed for 30 min in sitting position, and asked to use a description of pain intensity (markedly better, moderately better, unchanged or

worse) to grade the outcome. Thirty minutes after the application, patients were asked to describe their overall pain response as either unchanged, improved throughout the observation period or temporarily improved with subsequent deterioration. Furthermore, patients were asked to keep a diary of their pain scores in order to note whether the pain returned and how long after therapy it recurred, and to describe it in detail during the medical follow-up examination at the hospital 7 days after therapy.

Any medications used previously were discontinued 12 hours before the therapy to avoid reinforced analgesic effect with such agents after the therapy, but resumed when the pain recurred or failed to relieve. The investigators were blinded to the clinical background and the content of the spray used for treatment.

2-3. Statistical analysis

For analysis of the results, we classified patients with NRS data into three groups: the markedly effective group (pain-free), effective group (less pain), and ineffective group (no change or worse pain). Furthermore, to compare the effects of LDC with PBO by the description of pain intensity to grade the outcome, we divided the subjects into two groups; the responders group of patients with markedly better and moderately better outcomes, and the non-responders group of patients with unchanged and worse outcomes.

A difference of at least 3 points of NRS score was considered clinically significant. Based on preliminary tests, we estimated the within-group standard deviation for NRS score of 2.5 points. For a power of 0.8 and $\alpha = 0.05$, a sample size of 12 patients in each group was calculated to be appropriate. Therefore, the appropriate sample size was about 24 patients in this study, since these patients were studied in a crossover design.

Continuous parameters were summarized as median (plus 25 and 75 percentiles), and categorical data were presented as numbers. In this study, in order to confirm the carryover and period effects, we evaluated the difference in the pre-NRS score between the first and second arms using Wilcoxon Signed-Rank test. With respect to statistical analysis of the treatment data, differences in the NRS score were evaluated before and after application with Wilcoxon Signed-Rank test. The rate of change in NRS score between LDC/PBO and PBO/LDC groups was assessed with Mann-Whitney U-test. Pain control by NRS data and the effects of LDC with PBO by the description of pain intensity to grade the outcome were evaluated the data with Chi-squared test Fisher's exact test for $n \times m$ tables. Differences were

assessed with two-sided tests, with an alpha level of 0.05. Analyses were performed with JMP® Pro Ver. 10.0.2 software (SAS Institute, Inc., Cary, NC).

3. Results

3-1. Patients population

Twenty-four consecutive outpatients (18 females, 6 males) were enrolled in this study (Table 1). We observed no morbidity related to either lidocaine or saline application throughout the study. None of the patients was lost to follow-up during the study period, and all patients provided the required follow-up information.

Table 1 presents the demographic and baseline clinical features of the patients. All patients had received previous treatment with carbamazepine. However, 3 patients had to discontinue it because of unwanted effects, and had been using no drugs, zonisamide, and a combination of baclofen, gabapentin and Gorei-san (traditional Chinese herbal medicine), respectively, at study entry. The remaining 21 patients had been receiving carbamazepine (100-800 mg) for at least 1 month before study entry. Eleven of these 21 patients were on carbamazepine only, while the other 10 patients were being treated with baclofen or mexiletine in combination with carbamazepine. The pain intensity in mouth mucosa area of TN was more than 4 points of NRS score despite all medical attempts at pain relief.

3-2. Changes in numerical rating scale

There were no differences in pre-NRS score between patients of the first arm and the second arm ($P = 0.949$). Namely, in this double-blind crossover study, no carryover effect or period effect was noted.

LDC significantly reduced the NRS score from 5 (4, 8) points just before application to 1 (0, 4) points at 15 min post-application ($P = 0.001$), whereas PBO did not change the NRS score [from 5 (4, 8) points, to 5 (4, 8) points] ($P = 0.093$). The difference in the Δ change in the NRS scores between LDC and PBO was significant ($P < 0.001$). Analysis of data of the 24 patients showed that the number of patients whose NRS score decreased by > 3 points was 16 (67%) after LDC and 1 (4%) after PBO (Table 2). Eleven patients (46%) became pain-free after LDC. Table 3 summarizes the changes in NRS score in the two treatment groups. LDC, but not PBO, significantly reduced the NRS score at 15 min after application.

3-3. Description of pain intensity

Table 4 compares the results of both the test drug and placebo groups. A significant difference in parameters of pain control was found between the two groups ($P < 0.001$). Furthermore, the effect of LDC and PBO persisted for a median of 2.8 (0.3, 3) hrs and 0 (0, 0) hrs, respectively.

3-4. Adverse effects

None of the patients experienced serious side effects, such as acute lidocaine intoxication or aspiration pneumonia. Numbness of the application area was reported in 9 patients with LDC and 3 patients with PBO. One patient felt bitterness following LDC application. No substantial changes in blood pressure or heart rate were found in any patient of the two treatment groups. All adverse events were mild, and disappeared without medication within a few hours.

4. Discussion

Our results demonstrated that oral application of LDC produced prompt analgesia without serious side effects in patients with TN who reported lack of response to previous treatment with carbamazepine. The paroxysmal pain relief at 15 min was markedly superior to placebo.

The results of this study indicate that approximately 80% of patients treated with LDC reported a significant reduction of pain intensity. This rate is comparable with that reported for oral carbamazepine.^{1,3} The onset of effect of intraoral lidocaine, however, appeared within 15 min, while that with oral carbamazepine is 24-48 h.⁶ The rapid relief and relapse in all patients is consistent with the pharmacological properties of lidocaine.

4-1. Lidocaine

Systemic administration of lidocaine has been shown to relieve neuropathic pain with a significant plasma concentration-dependent decrease in pain intensity starting at $1.5 \mu\text{g ml}^{-1}$.⁸ Scott and colleagues⁹ measured plasma concentrations of lidocaine in patients after spraying of the trachea and larynx with 50 mg of lidocaine. The mean maximum plasma concentration of lidocaine in their patients was $0.6 \mu\text{g ml}^{-1}$. Another study described the application of a mucoadhesive patch containing 46 mg of lidocaine to the buccal mucosa for dental anesthesia. The resultant plasma concentration of lidocaine in their patients was approximately $0.2 \mu\text{g}$

ml⁻¹ at 15 min assessment.¹⁰ Therefore, it can be considered that the basic mechanism for the rapid effect of oral application of LDC in trigeminal neuralgia is the local anesthetic effect, through a decrease of mechanical allodynia on the mucous membrane. Oral application of 8% lidocaine (less than 0.2 ml = 16 mg) is probably followed by infiltration of lidocaine into the oral mucous membrane, which contains sensory nerve fibers of the maxillary and mandibular divisions of the trigeminal nerves.

4-2. Mechanism

TN is considered to be due to mechanical compression of the trigeminal root at the pons by a neighboring artery.¹¹ Peters et al. reported that expertly performed ganglion-level procedures are more effective than peripheral procedures, but are neuro-destructive, causing sensory loss and paresthesia.¹² The second division of the trigeminal nerve passes through the sphenopalatine ganglion (SPG), which is located posterior to the middle turbinate, and is covered by 1.0-2.0 mm thin layer of connective tissue and mucous membrane. Thus, application of intranasal lidocaine spray onto the affected side provides effective analgesia for classic second-division TN.¹³ Intranasal lidocaine spray is reported to produce no serious adverse reactions, but about 60% of patients reported burning or stinging sensation in the treated nostril.¹³ In patients with TN-related pain limited to the area of the oral mucous membrane, oral application of LDC may be easier and well-tolerated than the above procedures.

The analgesic effect of peripheral nerve block on TN pain often continues for a long period of time after the disappearance of the initial hypesthesia.^{13,14} To establish the clinical value of oral LDC in repeated application for TN pain, a randomized controlled trial with a longer follow-up period is needed. Furthermore, it is important to elucidate the optimal dose of this drug for effectiveness and reducing adverse events in patients on long-term treatment for TN.

4-3. Advantages

Compared with other currently available therapies for TN, oral application of 8% lidocaine has certain advantages. The first advantage is the immediate therapeutic effect. It is advantageous to induce prompt relief of pain and to be able to start eating, drinking, and talking as soon as possible. Oral application of 8% lidocaine may offer the fastest relief compared to any known agent. The second advantage is treatment with a portable device. The

patient can carry a metered-dose spray bottle and use it whenever pain appears. The third advantage is the lack of serious adverse reactions. Patients with TN are commonly older than 50 years of age, and sometimes have complications such as ischemic heart disease and pulmonary emphysema. Although these patients were excluded in this study, intraoral lidocaine therapy should have lesser side-effects than the traditional antiepileptic drugs.

4-4. Study Limitation

Our study has certain limitations. In our study, 9 of the patients who received oral application of 8% lidocaine felt numbness in the mouth. One of the criticisms of this study is the possibility that the patients distinguished lidocaine from placebo since saline did not mimic the local anesthetic effect of lidocaine. However, the difference in the analgesic effect between lidocaine and saline was evident in the first arm of the crossover study. The NRS score did not change before and after the saline application, in agreement with previous studies that showed a lack of placebo response in TN,^{15,16} possibly explaining the distinctness in perception (shooting, stinging or electric shock-like) of the paroxysmal pain. Furthermore considering that 8% lidocaine pump spray contains other agents, we cannot exclude the analgesic effect of other chemicals present in the liquid spray. For example, ethanol in the spray commonly used for trigeminal nerve block, which may provide an analgesic effect on TN pain.¹⁷ Another limitation is that treatment was applied only once for a single episode of paroxysmal pain, and early relapse (within 24 h) was recognized by all patients. It is also possible that patients with new-onset TN respond differently to the treatment. At this stage, it is important to verify the repetitive effect of intraoral 8% lidocaine application on TN. In the present study, intraoral LDC was only proposed for pain triggered by intraoral stimuli such as opening the mouth or chewing. We need to explain clearly whether the treatment is successful also on spontaneous pain or not in the next study.

5. Conclusion

Intraoral application of 8% lidocaine, but not that of placebo, significantly reduced the NRS score of paroxysmal pain triggered by opening the mouth or chewing in patients with trigeminal neuralgia. Topical application with a metered-dose 8% lidocaine pump spray may simplify treatment of TN pain based on prompt analgesia, lack of systemic side effects and convenience of use.

6. Acknowledgement

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8. Achievements lists

I) 主学術論文 (英文原著)

- ◎1. Niki Y, Kanai A, Hoshi K, Okamoto H: Immediate analgesic effect of 8% lidocaine applied to the oral mucosa in patients with trigeminal neuralgia. Pain Medicine, In press

II) 原著論文 (主学術論文を除く)

- 1. Kanai A, Okamoto T, Suzuki K, Niki Y, Okamoto H: Lidocaine Eye Drops Attenuate Pain Associated with Ophthalmic Postherpetic Neuralgia. Anesthesia & Analgesia, Vol110(5): 1457-1460, 2010
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9. Tables

Table 1. Clinical characteristics of the participating patients.

	LDC/PBO	PBO/LDC	Total
Number	12	12	24
Females:males	9:3	9:3	18:6
Age (years)	73 (66, 77)	68 (63, 80)	69 (65, 77)
Body weight (kg)	50 (49, 60)	53 (43, 63)	50 (47, 62)
Duration of illness (years)	4.8 (3.9, 15.3)	8.7 (4, 15.8)	6.7 (3.9, 15.8)
No. of patients on carbamazepine	11	10	21
Dose of carbamazepine (mg)	300 (100, 400)	400 (300, 600)	350 (125, 600)
Pain distribution			
Right:Left	7:5	10:2	17:7
V2	2	4	6
V2, 3	3	5	8
V3	7	3	10

Data are number of patients or median values (25, 75 percentiles).

NRS: numerical rating scale; LDC: lidocaine; PBO: placebo

Table 2. Numerical Rating Scale; LDC versus PBO

Pain Control	LDC	PBO
(NRS score)		
Markedly effective group	11	1
(NRS score 0 point)		
Effective group	8	4
(Reduction by > 3 points / Reduction with 3 points)	(5 / 3)	(0 / 4)
Ineffective group	5	19
(No change / Increased pain)	(5 / 0)	(18 / 1)

Data are number of patients.

$P < 0.001$, comparison between LDC and PBO treatments using Fisher's Exact test.

Abbreviations as in Table 1.

Table 3. Numerical Rating Scale; LDC/PBO versus PBO/LDC

	Period 1			Period 2		
	Baseline	After 15 min	P value	Baseline	After 15 min	P value
LDC/PBO (n=12)	4.5 (4.0, 7.0)	0.5 (0, 2.8)*	0.004	5.0 (4.0, 6.0)	4.5 (4.0, 6.0)	0.180
PBO/LDC (n=12)	5.5 (4.0, 8.0)	5.5 (4.0, 8.0)	0.202	5.5 (4.0, 8.8)	2.0 (0, 4.8)*	0.008

Data are median (25, 75 percentiles).

**P* < 0.001 versus the baseline value.

Abbreviations as in Table 1.

Table 4. Description of pain intensity

Group	LDC	PBO
(Pain intensity)		
Responders group	19	3
(Markedly better / Moderately better)	(12 / 7)	(0 / 3)
Non-responders group	5	21
(Unchanged / Worse)	(5 / 0)	(20 / 1)
Total	24	24

Data are number of patients.

$P < 0.001$, comparison between LDC and PBO treatments using Fisher's Exact test.

Abbreviations as in Table 1.