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Intranasal lidocaine 8% spray for second-division trigeminal neuralgia

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Background. Trigeminal nerve block has been widely used for trigeminal neuralgia. This may induce paraesthesia. The second division of the trigeminal nerve passes through the sphenopalatine ganglion, which is located posterior to the middle turbinate and is covered by a mucous membrane. We examined the effectiveness of intranasal lidocaine 8% spray on paroxysmal pain in second-division trigeminal neuralgia.

Methods. Twenty-five patients with second-division trigeminal neuralgia were randomized to receive two sprays (0.2 ml) of either lidocaine 8% or saline placebo in the affected nostril using a metered-dose spray. After a 7 day period, patients were crossed over to receive the alternative treatment. The paroxysmal pain triggered by touching or moving face was assessed with a 10 cm visual analogue scale (VAS) before and 15 min after treatment. Patients used a descriptive scale to grade pain outcome, and were asked to note whether the pain returned and how long after therapy it recurred.

Results. Intranasal lidocaine 8% spray significantly decreased VAS [baseline: 8.0 (2.0) cm, 15 min postspray: 1.5 (1.9) cm, mean (SD)], whereas the placebo spray did not [7.9 (2.0) cm, 7.6 (2.0) cm]. Moreover, pain was described as moderate or better by 23 patients of the lidocaine spray and 1 of the placebo group. The effect of treatment persisted for 4.3 h (range 0.5–24 h).

Conclusions. Intranasal lidocaine 8% administered by a metered-dose spray produced prompt but temporary analgesia without serious adverse reactions in patients with second-division trigeminal neuralgia.

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Trigeminal neuralgia is a recurrent severe shooting neuropathic pain in the distribution of the trigeminal nerve, which can be triggered by light stimuli such as touch, chewing, talking and toothbrushing.[1] An attack of trigeminal neuralgia lasts only seconds to a couple of minutes, but multiple excruciating attacks may occur in a single day, which may jeopardize adequate eating or drinking. This is particularly true as the most commonly affected divisions of the trigeminal nerve are the second (maxillary) and third (mandibular), which serve the lips and teeth areas.

The treatment of trigeminal neuralgia continues to be a major therapeutic challenge. Trigeminal nerve block with a needle has been traditionally performed for the relief of trigeminal neuralgia.[2] However, this nerve block is often accompanied by excruciating pain originating from punctured nerve fibres by the needle, possibly resulting in paraesthesia. Many patients thus prefer to avoid such injections.

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 a 1.0–2.0 mm thick layer of connective tissue and mucous membrane.[3 4] Anatomically, the location of the SPG makes it easily accessible and within diffusing distance for anaesthetics that can be applied topically. Peterson and colleagues[4] succeeded in inducing SPG block with a 15 cm long cotton tip applicator soaked in lidocaine 4% inserted through the nare. The main limitation of this procedure is the difficulty in administration. Kudrow and colleagues[5] reported intranasal instillation of lidocaine 4% (0.4 ml) solution for patients with migraine. With this drip method one must be careful not to allow the solution to go down the throat. In our experience, patients with trigeminal neuralgia find it difficult to eat or drink even after pain disappears if the anaesthetic has caused temporary numbness of the

throat. As an alternative to the above procedures, we tested in this study the effect of lidocaine 8% (0.2 ml) applied as a metered-dose spray in patients with trigeminal neuralgia and examined the effectiveness of intranasal lidocaine application on an attack of trigeminal neuralgia.

Methods

Patients

Consecutive outpatients with idiopathic trigeminal neuralgia possessing the most severe pain in the second division were enrolled into a randomized, double-blind, placebo-controlled crossover study at the Kitasato University Hospital. All patients provided written informed consent after explanation of the study procedure and before randomization. The study protocol was approved by the Human Ethics Review of our university. Inclusion criteria for the selection of idiopathic trigeminal neuralgia were according to the definition of the International Headache Classification, a paroxysmal, unilateral pain that can be 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. A further inclusion criterion was that the patients had been suffering from the painful paroxysms for at least 3 months with a pain intensity of more than 4 cm according to a 10 cm visual analogue scale (VAS), with 10 cm being the worst pain and 0 cm being no pain. The patients were capable of properly assessing the severity of their pain and condition.

Excluded from the study were patients with other neurological diseases, psychological diseases and/or other serious acute or chronic diseases. Also excluded were patients for the following reasons: surgery for trigeminal neuralgia within the last year, change of oral medications within 1 week before the study, past history of allergy or hypersensitivity to the anaesthetic being used or to the preservative agents contained in the anaesthetics.

Study protocol

Patients were randomized to receive two sprays (0.1 ml of one spray twice) of either lidocaine 8% (LDC/PBO group) or saline placebo (PBO/LDC group) in the affected nostril with a metered-dose spray bottle in the first arm of the study. After a 7 day period, patients crossed over to receive the alternative treatment. Patients were randomized by blindly taking a number from a closed container. Thirteen patients received lidocaine first and twelve patients received placebo first. Commercially available lidocaine was selected. Lidocaine, but not placebo, included preservative agents. When receiving the spray, patients were asked to lie in the supine position with their necks extended 30–45°, and maintained the position for 30 s. The paroxysmal pain triggered by touching or moving face was assessed with VAS before and 15 min after the treatment. Physical examination including measurement of arterial pressure and heart rate was conducted at the pretreatment visit and on completion of, or withdrawal from, the spray. Patients were observed for 30 min in supine position with their head flat, and used a descriptive scale (unchanged, moderately better, markedly better or worse) to grade the outcome. Thirty minutes after the spray, 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. Especially, patients were asked to rate 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. Previous conventional agents were discontinued 12 h before the spray to avoid reinforced analgesia with the previous agents after the spray, and resumed when the pain recurred or failed to relieve. The investigators were not informed of the patient background or the content of spray treatment.

Statistical analysis

A difference of at least 3 cm of VAS score was considered clinically significant. Based on a preliminary examination, we estimated the within group standard deviation for VAS score to 2.5 cm. For a power of 0.8 and α=0.05, a sample size of 12 patients in each group was calculated to be appropriate. Therefore, we determined that the appropriate sample size was $\sim$24 patients in this study, as these patients were studied in a crossover design.

Data are expressed as mean (SD). For statistical analysis of the data, differences between means of VAS score in patients before and after spray were assessed with a paired Student's *t*-test. A repeated measures analysis of variance (ANOVA) with the sequence of spray (lidocaine spray then placebo spray or placebo spray then lidocaine spray) as the independent factor was used to investigate the carry-over effect and period effect. If significant differences were detected by ANOVA, individual means were compared by using the Student–Newman–Keuls test. Categorical variables were compared using χ^2-test with Yates' correction. Differences were assessed with two-sided tests, with an α concentration of 0.05.

Results

Patient characteristics

Twenty-five consecutive outpatients (20 females, 5 males) were enrolled in the study. We observed no morbidity related to placement of either lidocaine or saline sprays. No patient was lost to follow-up review during the study period, and all patients provided the required follow-up information.

All patients had received previous treatment with carbamazepine. However, 11 patients had to discontinue

Table 1 Patient characteristics

Patient characteristics	LDC/PBO	PBO/LDC	Total
Number	13	12	25
Female:male	11:02	9:03	20:05
Mean (range) age (yr)	65 (45–77)	63 (44–85)	63 (44–85)
Median duration of illness (yr)	3	4	4
No. of patients on carbamazepine	7	7	14
VAS score at entry (cm)			
Mean	8.1	7.9	8
SD	2	2	2
Pain location			
Right:left	9:04	7:05	16:09
V2	3	4	7
V2, 3	6	6	12
V1, 2	2	0	2
V1, 2, 3	2	2	4

Table 2 Visual analogue scale; LDC *vs* PBO. *P<0.01 *vs* PBO

VAS score	LDC	PBO
Unchanged	00*	18
Decreased within 2 cm scale	1	3
Decreased more than 2 cm	14*	3
Pain gone (VAS score 0 cm)	10*	0
Increased	0	1
Total	25	25

it because of unwanted effects. Of these 11 patients, 3 received no drugs for trigeminal neuralgia at the time of the study, 6 patients were on mexiletine only, 1 patient received a combination of mexiletine and phenytoin and 1 patient was on mexiletine and clonazepam. The remaining 14 patients had been receiving carbamazepine for at least 1 month before study entry. Nine of the fourteen patients were on carbamazepine only; the other 5 patients were being treated with phenytoin, clonazepam, baclofen or mexiletine in combination with carbamazepine. The pain intensity in the second division of the trigeminal nerve was more than 4 cm of VAS score despite treatment in all 25 patients. The mean age at entry was 64 yr (range 35–85 yr). The duration of trigeminal neuralgia ranged from 3 months to 28 yr (median 4 yr). The two groups appeared to have broadly comparable histories of trigeminal neuralgia (Table 1).

Visual analogue scale

Intranasal lidocaine spray significantly decreased the VAS score from 8.0 (2.0) cm before spray to 1.5 (1.9) cm at 15 min postspray, whereas the placebo spray did not change the VAS score [from 7.9 (2.0) to 7.6 (2.0) cm]. Table 2 details the VAS results for the lidocaine and placebo sprays. In the 25 patients, the number of patients whose VAS score decreased more than 2 cm was 3 (12%) after the saline spray and 24 (96%) after the lidocaine spray. Ten patients (40%) of the lidocaine spray group were pain-free. In this double-blind, crossover study, neither carry-over effect nor period effect was found. The lidocaine spray, but not the saline placebo, significantly reduced VAS score at 15 min after the administration in the two groups.

Table 3 Description of pain intensity. †Includes patients who described their pain as moderately better or markedly better, with relief that lasted the full length of observation. *P<0.01 *vs* PBO

Pain intensity	LDC	PBO
Unchanged	01*	21
Improved†	23*	1
Temporary relief only	1	3
Total	25	25

Description of pain control

Table 3 compares the results for both the test drug and placebo groups. When the number of patients with unchanged pain control was compared with those with any improvement (permanent or temporary), a significant difference was also found between the two groups (P<0.01). The effect of lidocaine persisted for a median duration of 4.3 h (range 0.5–24 h).

Side-effects

Side-effects were reported in 15 patients with the lidocaine spray. All side-effects were limited to local irritation; burning, stinging or numbness of the nose and eye (n=15), and bitter taste and numbness of the throat (n=1). No potential serious side-effects were reported, and none had difficulty in phonation or swallowing. No substantial changes in arterial pressure or heart rate were detected in any subject of the two treatment groups.

Discussion

Our results suggest that intranasal lidocaine spray provides effective analgesia for idiopathic second-division trigeminal neuralgia. The paroxysmal pain relief at 15 min was markedly superior to placebo. The fact that the relief is clinically meaningful is shown by the immediate improvement of disability in responders with a longitudinal paroxysmal pain refractory to treatments.

The results of this study indicate that ~90% of the patients treated with intranasal lidocaine 8% spray reported a significant reduction of pain intensity. This rate is comparable with that reported for oral carbamazepine.[16] The onset of effect with intranasal lidocaine, however, appeared within 30 min, while with oral carbamazepine only within 48 h. The rapid relief and rapid relapse in all patients is consistent with the pharmacological properties of lidocaine.

Systemic lidocaine has been shown to relieve neuropathic pain with a significant plasma concentration-dependent decrease in pain intensity starting at 1.5 $\mu g\ ml^{-1}$.[7] Scott and colleagues[8] measured plasma concentration of lidocaine in patients after spraying of the trachea and larynx with 50 mg of lidocaine. Mean maximum plasma concentration

of lidocaine in the patients was 0.6 $\mu g\ ml^{-1}$. Therefore, it can be considered that the basic mechanism for the rapid effect of intranasal spray with 16 mg of lidocaine in trigeminal neuralgia is the anaesthetic effect on the SPG. Spray infusion of lidocaine 8% (0.2 ml) is thought to allow lidocaine to infiltrate in the region of the SPG, which contains sensory nerve fibres of the maxillary division. In addition, the SPG includes parasympathetic nerve fibres, some of which innervate the superior and anteroinferior cerebellar arteries.[9] Cerebral vasodilation caused by stimulation of the trigeminal ganglion is mediated by the SPG,[10] and is dependent on nitric oxide synthase present in 70–80% of SPG cells.[11] In the cat, blockade of nitric oxide synthase activity reduces the cerebral vasodilator response to facial nerve stimulation.[12] Mechanical compression of the trigeminal root adjacent to the pons by an artery such as the superior and anteroinferior cerebellar artery has been generally thought to cause trigeminal neuralgia.[13] Therefore, intranasal lidocaine may produce, in addition to sensory blockade, parasympathetic nerve blockade, resulting in inhibition of vasodilation and compression of the trigeminal root.

Spaziante and colleagues[14] reported pain improvement in 15 out of 25 patients with trigeminal neuralgia after single-application topical ophthalmic anaesthesia (two drops of proparacaine hydrochloride 0.5%) onto the ipsilateral cornea to the trigeminal neuralgia. Interestingly, lasting pain improvement was noted in their patients regardless of the trigeminal distribution of their pain. In contrast, Kondziolka and colleagues[15] applied the same treatment in a randomized double-blind, placebo-controlled trial, and concluded that this procedure provides no benefit to patients with trigeminal neuralgia. They contacted the patients by telephone on 3, 10 and 30 days after the treatment in order to evaluate severity and frequency of their current pain. Thus, the effect on the treatment day was not clear. In this study, paroxysmal pain triggered in all patients recurred within 24 h. In patients whose paroxysmal pain was triggered by talking or opening mouth, pain reduction may contribute to the first and third divisions and also the second. The possibility that lidocaine spray relieves not only paroxysmal pain in the second division of the trigeminal nerve but also in the first and the third area cannot be completely excluded. A further trial is required to assess the efficacy of intranasal lidocaine in patients with trigeminal neuralgia in which the most severe pain is triggered in the first or third division of the trigeminal nerve.

That most patients responded rapidly and completely to lidocaine while two patients did not respond at all suggests that failure of response is related to anatomical variation and poor access to the SPG. The SPG may lie as deep as 7.0–9.0 mm in a few instances.[3,4] In the patients without response, other approaches such as a long cotton tip applicator presented by Peterson and colleagues[4] could be necessary. In comparison with the lidocaine solution used by Kudrow and colleagues,[5] smaller volume and higher concentration of lidocaine was used in this study. Kudrow and colleagues presented that oropharyngeal numbness was noted by half of the patients, whereas only 1 out of 25 patients was reported in our study. Patients should be warned not to eat or drink if the anaesthetic causes temporary numbness in the throat. The optimum conditions to avoid such complications, including patient position, concentration and volume of lidocaine, require elucidation through further research.

In the light of other current therapies for trigeminal neuralgia, intranasal lidocaine spray has some advantages. The first advantage is the rapid relief. Patients with trigeminal neuralgia desire prompt pain relief and to start eating, drinking, talking and washing their faces as soon as possible. Intranasal lidocaine 8% spray may offer the fastest relief of any known agent. The second advantage is non-oral therapy. Patients often cannot take oral medications because the pain intensity is aggravated upon mouth opening. The third advantage is therapy with a portable device. The patient can carry a metered-dose spray bottle and use it whenever pain appears. The fourth advantage is no serious adverse reactions. Patients are commonly more than 50 yr of age, and sometimes have complications such as cardiopulmonary disease and cerebral infarction. Although these patients were excluded in this study, intranasal lidocaine therapy should have even lesser side-effects than the traditional antiepileptic drugs.

There are some limitations to our study. In our study, 15 of the patients who received intranasal lidocaine 8% spray felt burning or stinging sensation in the treated nostril. One of the criticisms of this study is the possibility that the patients distinguished lidocaine from placebo as saline did not mimic the local irritant 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 VAS score did not change before and after the saline spray, in agreement with previous studies that showed a lack of placebo response in trigeminal neuralgia,[16,17] possibly explaining the distinctness in perception (shooting, stating or electric shock-like) of the paroxysmal pain. Criticisms of this study include the limitation in treating only a single paroxysmal pain episode, and the early relapse (within 24 h) that was recognized by all patients. It is possible that patients with new-onset trigeminal neuralgia respond differently to the treatment. In this regard, Maizels and Geiger[18] demonstrated that the response rate does not change over time; there is no tachyphylaxis with repetitive use (intranasal drip) of lidocaine 4% (0.5 ml) in patients with migraine. At this stage, it is important to verify the repetitive effect of intranasal lidocaine 8% spray on trigeminal neuralgia.

In conclusion, intranasal spray of lidocaine 8% (0.2 ml), but not that of placebo, significantly reduced the VAS score of paroxysmal pain triggered by touching or moving face in patients with trigeminal neuralgia, in which the most painful pain is in the second division of the nerve. Twenty-three of twenty-five patients treated with intranasal lidocaine spray reported relief of pain, and the analgesic effect lasted for

a median period of 4.3 h. Our findings suggest a role for SPG in trigeminal neuralgia.

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