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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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 with a concentration of 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 ~24 patients in this study, as these patients were studied in a crossover design.

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 \( \alpha = 0.05 \), a sample size of 12 patients in each group was calculated to be appropriate. Therefore, we determined that the appropriate sample size was ~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 \( \chi^2 \)-test with Yates’ correction. Differences were assessed with two-sided tests, with an \( \alpha \) 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...
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The lidocaine spray, but not the saline, significantly reduced VAS score at 15 min after the administration in the two groups.

**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. 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 \( \mu g \) \( ml^{-1} \). Scott and colleagues 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 colleagues14 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 colleagues15 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 colleagues5 could be necessary. In comparison with the lidocaine solution used by Kudrow and colleagues,3 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 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 Geiger18 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.

References
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