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The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia

A randomized double-blind placebo-controlled trial

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To evaluate the reported benefit of ipsilateral single-application ophthalmic anesthetic eyedrops in patients with typical trigeminal neuralgia, a randomized double-blind placebo-controlled trial was performed. Forty-seven patients were randomly assigned to receive two drops of either proparacaine (25 cases) or saline placebo (22 cases). The experimental and placebo groups were equivalent in regard to patient age, distribution of trigeminal neuralgia pain, duration of pain, current medication regimens, and number of prior procedures performed. Pain response was assessed at 3, 10, and 30 days after instillation using two pain rating scales and a measure of pain frequency. Treatment failure was defined in advance as any of the following: a lack of clinical response, the need for an increase in medication, or the need for surgery. No significant difference in outcomes was found between the two groups either when using a verbal pain rating scale ($p = 0.24$) or when comparing overall pain status (unchanged, improved throughout the study period, or temporarily improved) ($p = 0.98$). No difference in the frequency of trigeminal neuralgia attacks between the two treatment groups (scaled within five levels of pain frequency) was detected ($p = 0.09$). During follow-up monitoring, 11 patients in the test drug group and 14 in the placebo group required surgery because of persistent pain ($p = 0.24$). The results of this study indicate that single-application topical ophthalmic anesthesia reduces neither the severity nor the frequency of pain in comparison to placebo administration. Although a simple and safe treatment, the single application of topical ophthalmic eyedrops provides no short- or long-term benefit to patients with trigeminal neuralgia.

KEY WORDS • **trigeminal neuralgia** • **local anesthesia** • **randomized trial** • **facial pain**

THE management of trigeminal neuralgia has intrigued physicians for several hundred years. Recently, letters to the editor in both the *Journal of the American Medical Association*[10,11] and the *Journal of Neurosurgery*[7] described the long-term value of single-application topical ophthalmic anesthesia (two drops of 0.5% proparacaine hydrochloride) onto the cornea ipsilateral to the trigeminal neuralgia. Reportedly, this observation was made by a physician with trigeminal neuralgia who had a topical anesthetic agent applied to his eye during an ophthalmological examination.[10] Subsequently, Zavon and Fichte[10,11] described symptomatic relief in a total of nine similarly treated patients. Spaziante, *et al.*,[7] reported pain improvement in 15 of 25 patients treated with the same anesthetic agent and dose. Interestingly, lasting symptomatic improvement was noted in patients regardless of the trigeminal distribution of their pain. We sought to evaluate the reported benefits of topical ophthalmic anesthesia using a randomized double-blind placebo-controlled trial. We hypothesized that a single ipsilateral application of a topical ophthalmic anesthetic agent would result in early and perhaps prolonged improvement in the symptoms of trigeminal neuralgia compared to placebo (saline drops) administration.

Clinical Material and Methods

Study Eligibility Criteria

All patients eligible for the trial suffered typical trigeminal neuralgia, defined as sharp, lancinating pain

in one or more trigeminal nerve branch distributions, either spontaneous or aggravated by trigger factors. Any trigeminal distribution of pain was acceptable for the study, as was a diagnosis of multiple sclerosis. Patients could vary in age from 20 to 85 years; they could not have deafferentation pain, and had to be mentally cognizant to describe any treatment effects during a follow-up telephone conversation. Patients who had undergone previous surgical procedures were eligible for entry into the study, as were those on any medication regimen, as long as that regimen had been unchanged for 7 days prior to entry into the study and no alterations were made on the day of study entry. Patients considered ineligible for the study included those scheduled for surgery within 3 days of the ophthalmic treatment, those with atypical trigeminal neuralgia, patients with hyperthyroidism, those who were or could have been pregnant, or those with a known allergic reaction to any local anesthetic agent.

Patient Characteristics

During a consecutive 6-month period, 47 patients with typical trigeminal neuralgia were randomly assigned to receive either the test drug (0.5% proparacaine hydrochloride) or a placebo (buffered saline). After consent had been obtained for the study, patients were randomly assigned to a group using a coin toss (heads = Group A, tails = Group B). This study was approved by the Institutional Review Board for Biomedical Research at the University of Pittsburgh (IRB #921010). The code was not broken until the study was completed (double-blind design). Twenty-five patients were randomly assigned to Group A (test drug) and 22 to Group B (placebo). In the test drug group there were seven men and 18 women, and in the placebo group seven men and 15 women. The mean patient age in the test drug group was 59 years (range 26 to 82 years) and in the placebo group 63 years (range 46 to 85 years).

Table 1 details the clinical characteristics for the test drug and control groups. The distribution of involved trigeminal divisions and the number of patients who had undergone prior surgery were similar in both groups. Medications being received at the time of entry into the study included (number of patients in the test drug group, number of patients in the placebo group): carbamazepine (thirteen, nine), phenytoin (one, three), baclofen (one, none), clonazepam (one, none), carbamazepine and baclofen (two each), phenytoin and baclofen (one each), and carbamazepine, phenytoin, and baclofen (one, none). Five patients in the test drug group were not taking medication compared with seven in the placebo group.

TABLE 1

Clinical characteristics of randomized patients with trigeminal neuralgia

Characteristic	Test Drug Group	Control Group
no. of cases	25	22
pain duration (yrs)		
mean	6.8	6.5
range	0.25–25	0.2–25
side of pain		
left	9	11
right	16	11
divisions affected		
V_1	2	1
V_2	0	4
V_3	6	4
V_1, V_2	1	2
V_1, V_3	0	1
V_2, V_3	11	9
V_1, V_2, V_3	5	1
prior surgery		
none	13	13
microvascular decompression	3	3
glycerol rhizotomy	3	2
thermal rhizotomy	1	0
other	5	4

Instillation Method

Two drops of test drug or placebo were instilled onto the cornea ipsilateral to the trigeminal neuralgia by an individual blinded to the agent selected. After instillation, the eye was closed and an eye patch placed (with the patch applied, patients could not distinguish between agents). The patient remained in the office with the patch applied for a 20-minute observation period, which matched the approximate length of ophthalmic anesthesia. The patch was then removed, the eye examined, and the patient discharged home.

Follow-Up Evaluation

The patients were asked to keep a log of the frequency of pain attacks after discharge home. The patient was contacted by telephone 3, 10, and 30 days after instillation. The change in severity of pain was assessed in comparison with information given during the previous telephone conversation. Patient name, age, date of assessment, trigeminal division of pain, current medications and dosages, and prior surgical procedures (if any) were recorded on data sheets. The patients were assessed in regard to frequency of attacks and to the severity of pain rated via two scales. For the first scale (verbal pain rating), patients were asked to rate the severity of their current pain from 0 to 10 based on their experience with trigeminal neuralgia, with 10 being the worst pain and 0 being no pain.[3] The patients also used a descriptive scale (unchanged, moderately better, markedly better, or worse) to grade outcome. End-point criteria included clinical response (defined as improved, worsened, or unchanged pain in comparison to pain level before instillation) and the need for an increase in oral medication or for surgical intervention during the observation period.

Statistical Analysis

Because Spaziante and associates[7] reported that 15 of 25 patients experienced improved pain control in their nonrandomized series, we sought to confirm this improvement in 60% of our patients receiving the test

TABLE 2

*Results of proparacaine versus placebo treatment for trigeminal neuralgia according to pain rating scale**

Outcome	Test Drug Group	Placebo Group
no change	17	15
decrease in pain (≥ 2 levels)	1	4
pain gone or rare	5	1
temporary relief only	2	2
totals	25	22

* Pain scaled from 0 to 10, with 10 = worst pain.

TABLE 3

Results of proparacaine versus placebo treatment for trigeminal neuralgia according to description of pain control

Pain Control	Test Drug Group	Placebo Group
unchanged	18	15
improved*	5	5
temporary relief only	2	2
totals	25	22

* Includes patients who described their pain as moderately better or markedly better, with relief that lasted the full length of study.

drug. We assumed that 20% of the patients in the placebo group would improve spontaneously, an improvement possible in this disorder. To confirm a statistically significant difference between the two agents at a p value of 0.05 with a power of 0.8, the number of subjects necessary for randomization was calculated to be 23 patients per group (46 total). Parameters compared in the test drug and placebo groups included severity of pain using both the rating scale and the descriptive indices and frequency of pain. Proportions were compared using chi-squared analysis or Fisher's exact test for small samples. Mean values were compared using a t-test for independent means. A p value of 0.05 or less was considered statistically significant.

Results

We observed no morbidity related to placement of either proparacaine or saline eyedrops. No patient was lost to follow-up review during the study period, and all patients were able to provide the required follow-up information. Within the study period, 11 patients in the test drug group underwent surgery because of persistent pain (seven underwent microvascular decompression and four percutaneous glycerol rhizotomy).[5,9] In the placebo group, 14 patients underwent surgery (11 underwent microvascular decompression, two glycerol rhizotomy, and one stereotactic radiosurgery). The difference in the number of patients undergoing surgery in each group was not statistically significant (p = 0.24, Fisher's exact test). Two patients in the placebo group required an increase in medication during the follow-up interval (at 10 days after instillation of eyedrops) and thus were followed only to that point.

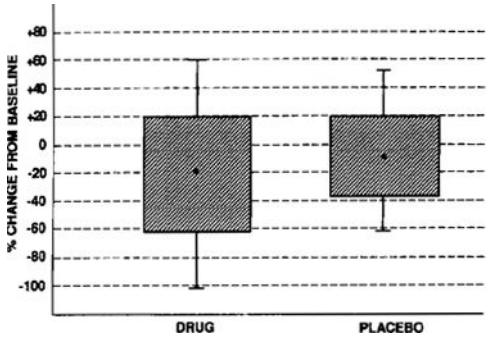

FIG. 1. Box-and-whisker plot showing percentage changes in numerical level of pain compared with baseline for patients receiving proparacaine or placebo. The mean reduction is noted by the *dot* in the center of the box, 1 standard deviation is represented by the size of the *box*, and 1.96 standard deviations (the 95% confidence interval) by the *vertical bars*.

Verbal Pain Rating

Patients recorded their pain on a scale from 0 to 10, with 10 being the worst pain and 0 being no or extremely rare pain. Table 2 details the verbal pain rating results for the test drug and placebo groups. The results were stratified according to the following outcomes: no change; a decrease of two or more levels; pain gone or occurring only rarely; and temporary relief, then return to baseline. There was no significant difference between the two groups (p = 0.24, Fisher's exact test).

We also compared the percentage change from baseline in the numerical level of pain between the drug and placebo groups. For example, an improvement in pain level from 10 to 6 represented a 40% improvement in level of pain, and from 10 to 0 a 100% improvement. A box-and-whisker plot showing the distribution of percentage change in the numerical level of pain for the two groups is shown in Fig. 1. There was a mean improvement in the level of pain of 21% in the test drug group and 6% in the placebo group. These percentage changes were not significantly different (p = 0.17, t = 1.39).

Description of Pain Control

The patients were asked to describe their overall pain response as either unchanged, improved throughout the study period, or temporarily improved with subsequent deterioration. Table 3 compares the results for both the test drug and placebo groups; these were not significantly different (p = 0.98, Fisher's exact test). When the number of patients with unchanged pain control was compared to those with any improvement (permanent or temporary), again no significant difference was found between the two groups (p = 0.77, chi-squared analysis = 0.08).

TABLE 4

Results of proparacaine versus placebo treatment for trigeminal neuralgia according to frequency of pain attacks

Frequency	Test Drug Group	Placebo Group
unchanged	19	16
decreased*	1	5
pain gone	5	1
totals	25	22

* Refers to a decrease in frequency of one group or more (frequency groups: ≤ 10 min, 10–60 min, 1–4 hrs, or 4–24 hrs with triggers).

Frequency of Pain

The effect of test drug or placebo administration on the frequency of trigeminal neuralgia attacks was evaluated via the following stratification: pain occurred every 10 minutes or less, every 10 to 60 minutes, every 1 to 4 hours, or every 4 to 24 hours. We arbitrarily stipulated that for a patient to have a significant decrease, the pain frequency had to decrease at least to the next category. When the two groups were compared as to whether the pain was unchanged in frequency, decreased in frequency, or completely relieved, no significant benefit of proparacaine was observed (Table 4, $p = 0.09$, Fisher's exact test). When the groups were compared according to unchanged versus improved (decreased frequency or complete relief of pain), no significant difference was found ($p = 0.80$, chi-squared analysis = 0.07).

Discussion

The possibility that two drops of topical ophthalmic anesthesia might provide prolonged and significant pain relief for trigeminal neuralgia patients was attractive. A quick, easily obtained therapy might benefit many patients who suffer the side effects of medical therapy, or others in whom the results of medical or surgical therapy are incomplete or short-lived.

Why Might Topical Ophthalmic Anesthesia Be Effective?

That 15 to 20 minutes of local ocular (corneal) anesthesia was reported to provide long-lasting relief of trigeminal neuralgia regardless of the divisions affected was perplexing. Prior investigators were unable to provide a cogent explanation for pain relief. Spaziante, *et al.*,[7] suggested that peripheral suppression of corneal trigger zones might influence pain affecting the first division of the trigeminal nerve; relief in lower-division pain was unexpected. They rejected the concept of a "central" action of the drug.

Stajčic, *et al.*,[8] found that subcutaneous injection of lidocaine (directed at the affected division) was initially effective in the treatment of trigeminal neuralgia, but recurrence of pain was observed in most patients. Interestingly, relief of cluster headache has been reported after the application of a local anesthetic agent (lidocaine) to the nasal mucosa.[4,6] If the application of a peripheral anesthetic agent could be of potential benefit in cluster headache (and if there were perhaps some peripheral or central similarity in the etiology or triggering of these disorders[2]), perhaps a similar response could be elicited in trigeminal neuralgia patients treated by brief corneal anesthesia.

A central mechanism can be invoked if retrograde transport of the anesthetic agent to the gasserian ganglion (or even more proximally) occurred. A central effect is thought to be the mechanism of action of medication (carbamazepine, phenytoin, or baclofen), as documented in animal models.[1] However, unlike continuous oral administration that maintains an effective blood level of a drug, a single application of topical anesthesia would be unlikely to maintain such a neuronal effect for any length of time.

Failure of Proparacaine Therapy

The simplest explanation for the lack of significant benefit of proparacaine in this study was that this agent in fact provided no persistent pharmacological benefit. Trigeminal neuralgia patients who received proparacaine did no better than those who received saline placebo, when evaluated using either a pain rating scale or descriptive ratings. Similarly, no reduction was observed in the overall frequency of trigeminal neuralgia attacks.

Several criticisms are appropriate concerning the present study design. First, patients in both groups had suffered trigeminal neuralgia for a mean duration of approximately 6 years, and many had undergone prior surgery. It is possible that patients with new-onset trigeminal neuralgia (a "less-refractory" group) might respond differently. However, in the nine patients entered in the trial who had trigeminal neuralgia for 1 year or less, no difference was observed. Fromm, *et al.*,[1] successfully used a similar patient cohort to demonstrate the value of baclofen; those patients had a history of trigeminal neuralgia for a mean of 7.9 years, with 42% of patients having undergone prior surgery. The total number of patients entered into that trial was selected in order to demonstrate an improvement in 60% of patients treated. Perhaps a larger study could have shown a significant but smaller level of benefit.

The present study fails to confirm that topical ophthalmic anesthesia benefits patients with typical trigeminal neuralgia. Neither the severity nor the frequency of pain was significantly affected. Thus, our evidence does not support the concept that topical proparacaine instillation, although simple and safe, is a useful therapeutic agent to manage patients with trigeminal neuralgia.

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