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The role of QX-314 and Capsaicin in producing long-lasting local anesthesia in the animal model of Trigeminal Neuralgia

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Introduction: Trigeminal Neuralgia (TN) consists of painful attacks often triggered with general activities, which cause impairment and disability. The first line of treatment consists of pharmacotherapy. However, the occurrence of many side-effects limits its application. Acute pain relief is crucial for titrating oral drugs and making time for neurosurgical intervention. This study aimed to examine the long-term anesthetic effect of QX-314 and capsaicin in trigeminal neuralgia using an animal model.

Materials and Methods: TN was stimulated by surgical constriction of the infraorbital nerve in rats. After seven days, anesthesia infiltration was done, and the duration of mechanical allodynia was compared. Thirty-five male Wistar rats were randomly divided into seven groups as follows: control (normal saline); lidocaine (2%); QX314 (30 mM); lidocaine (2%)+QX314 (15 mM); lidocaine (2%)+QX314 (22 mM); lidocaine (2%)+QX314 (30 mM); and lidocaine (2%)+QX314 (30 mM) +capsaicin (1µg).

Results: QX314 in combination with lidocaine significantly increased the duration of anesthesia, which was dose-dependent. The combination of lidocaine+QX314+capsaicin could significantly increase the duration of anesthesia in trigeminal neuralgia.

Conclusion: In the present study, we demonstrated that the combination of QX-314 with lidocaine and capsaicin produced a long-lasting, reversible local anesthesia and was superior to lidocaine alone in the fields of the duration of trigeminal neuropathic pain blockage.

Keywords: Capsaicin, Lidocaine, Long-lasting, Trigeminal neuralgia

Introduction

Trigeminal Neuralgia (TN) refers to a moderate to severe episode of pain attacks that are sudden and unilateral in the trigeminal nerve branches [1]. The attacks are often triggered with general activities that cause impairment and disability [2]. There is generally no pain between attacks [3]. The latest edition of the International Classification of Headache Disorders and the International Classification of Disease by the World Health Organization (WHO) classified three etiological categories of TN: idiopathic TN, which is neurovascular contact without morphological changes of the trigeminal root; classical TN due to a neurovascular compression with morphological changes of the trigeminal root; and secondary TN due to major neurological diseases such as cerebellopontine angle tumors or multiple sclerosis [4].

The first line of treatment consists of pharmacotherapy. Carbamazepine is one of the effective medicines, but its side-effects limit its use. To avoid serious side-effects, carbamazepine or other drugs must be titrated over the treatment. Studies reported that carbamazepine might have a 50% failure rate for long-term pain control [5, 6], and pain flare-ups can have personal and occupational effects. If pharmacological therapy fails, the next option is surgical interventions, such as the gasserian ganglion rhizotomy and microvascular decompression [7, 8]. Weak and challenging evidence is available on the interventions in acute exacerbations of TN [9]. Therefore, a standard approach for titrating oral drugs and making time for neurosurgical intervention is crucial.

Lidocaine is a local anesthetic acting on voltage-gated sodium channel blocking. Its advantages of low cost and side effects make it a promising pain controlling factor in TN. However, its short duration of action restricts its use [10, 11].

QX-314 is a lidocaine derivative and can be permanently charged—one of its distinctive features. Studies have reported the long duration of the nerve block by QX-314, which can

be attributed to the difficulty permeating the membrane and intracellular accumulation [12, 13].

Capsaicin is an agonist for the transient receptor potential cation receptor and has successfully treated TN pain. Capsaicin has been used in several studies as a treatment alternative for controlling neuropathic pain [14]. Few clinical trials have been done in evaluating its effectiveness when combined with QX-314.

This study's objective was to examine the long-term anesthetic effect of QX-314 and capsaicin using well-established standard TN animal models.

Materials and Methods

Animals

Thirty-five adult male Wistar rats weighing 200-250 g were purchased from the animal house center of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz City, Iran. The animals were maintained in a controlled environment with a 12/12 h light/dark cycle. Food and water were available. All experimental procedures were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Approval Number, 2015014A).

Surgical Procedures

The surgical procedure consisted of ligation of a distal segment of the infraorbital nerve outside the orbital cavity through a facial incision model, distal infraorbital nerve (dIoN-CCI) [15], to induce TN pain pattern. Therefore, all rats were anesthetized with ketamine/xylazine (75 mg/kg; 5 mg/kg), and the facial surface between the eye and whisker pad was shaved and scrubbed with iodine and alcohol. A 0.5-cm incision parallel to the mid-line was made starting at the caudal end of the third row of whisker lines towards the ipsilateral orbit. The infraorbital trunk was exposed at its distal segment outside the orbital cavity. Two chromic catgut ligatures (4–0) were loosely tied around the distal part 2 mm apart. The ligatures were tightened so that the circulation through the superficial vasculature was retarded but not cut off. The incision was sutured with a 4-0 nylon suture. Orofacial sensitivity to mechanical stimulation was tested using von Frey filament. The filament was applied within the infraorbital nerve territory, near the center of the vibrissal pad. A positive response was defined as observing reactions such as an immediate withdrawal reaction, attacking the filament by biting and grabbing, escaping by moving away from the filament, or asymmetric face stroke in the stimulated facial area.

After one week, the rats exhibited a significant decrease in the threshold toward mechanical stimuli on the ipsilateral side compared to the contralateral.

The rats were randomly assigned to seven groups: 1) control: (normal saline); 2) lidocaine (2% 100 µL); 3) Qx314 (Sigma-Aldrich, L5783) alone (30 mM); 4) lidocaine (2%, 20 µL) + QX_1 (15 mM); 5) lidocaine (2%, 20 µL) + QX_2 (22 mM); 6) lidocaine (2%, 20 µL) + QX_3 (30 mM); and 7) lidocaine (2%, 20 µL) + QX_3 (30 mM) + capsaicin (1 µg).

The drug was infiltrated in the area of surgery, and a behavioral test was applied immediately until achieving a positive response at the ipsilateral side of surgery.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism software (version 8.4). The statistical significance of differences was calculated by the t test when comparing two groups and one-way ANOVA when comparing more than two groups. Data are expressed as mean±SEM. Differences were considered statistically significant at $P<0.05$.

Results

Duration of trigeminal nerve block

QX314 in combination with lidocaine

As indicated in Figure 1, lidocaine (2%, 100 µL) induced anesthesia in the orofacial area for 46.6±13.3 minutes (Table 1). QX314, in combination with lidocaine significantly ($P<0.001$), prolonged the duration of anesthesia dose-dependently (Table 1). QX314 alone did not show a significant effect on the trigeminal nerve block in comparison to lidocaine (data not shown).

Table 1. The effect of Qx314 in combination with lidocaine on the duration of trigeminal nerve block

Groups	Duration of Anesthesia (Min)
Lid	46.6±13.3
Lid-QX1	75±3.46
Lid-QX2	186.6±8.8
Lid-QX3	273.3±17.6

Abbreviations: Lid: Lidocaine; Lid+QX1: Lidocaine in combination with Qx314 (15 mM); Lid+QX2: Lidocaine in combination with Qx314 (22 mM); Lid+QX3: Lidocaine in combination with Qx314 (30 mM).

Values are presented as the Mean±SEM (n=5).

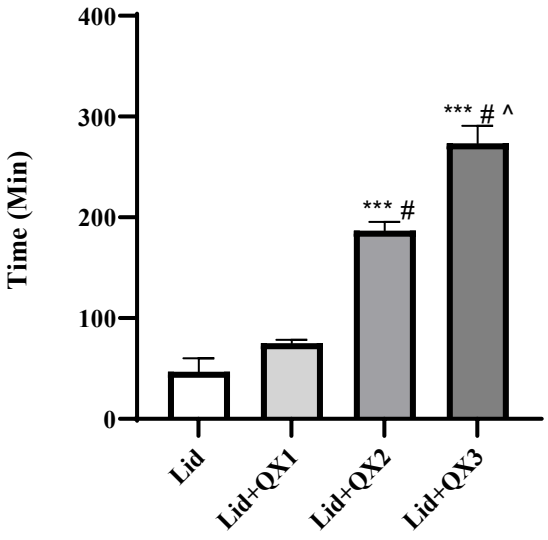

Figure 1: The effect of Qx314 in combination with lidocaine on the duration of trigeminal nerve block

Abbreviations: Lid: Lidocaine; Lid+QX1: lidocaine in combination with Qx314 (15 mM); Lid+QX2: Lidocaine in combination with Qx314 (22 mM); Lid+QX3: Lidocaine in combination with Qx314 (30 mM).

Values are presented as the Mean±SEM (n=5). Differences were considered statistically significant at $P<0.05$.

*****$P<0.001$ vs Lid group, #$P<0.001$ vs Lid+QX1group and ^$P<0.01$ vs Lid+QX2 group.**

QX314 in combination with lidocaine and capsaicin

As demonstrated in Figure 2, the combination of QX314 (33 mM) with lidocaine (2%, 20 µL) and capsaicin (1 µg) significantly (P<0.001) increased the duration of the trigeminal nerve block in comparison to all groups (Table 2). No adverse effects were observed in rats receiving QX-314 and capsaicin alone or in combination with all doses used.

Table 2. The effect of Qx314 in combination with lidocaine and capsaicin on the duration of trigeminal nerve block

Groups	Duration of Anesthesia (Min)
Lid	46.6±13.3
Lid-QX3	273.3±17.63
Lid-QX3-CPZ	600±62.9

Abbreviations: Lid: Lidocaine; Lid+QX3: Lidocaine in combination with Qx314 (30 mM); Lid+QX3+CPZ: Lidocaine in combination with QX314 (30 mM) and capsaicin (1 µg). Values are presented as the Mean±SEM (n=5).

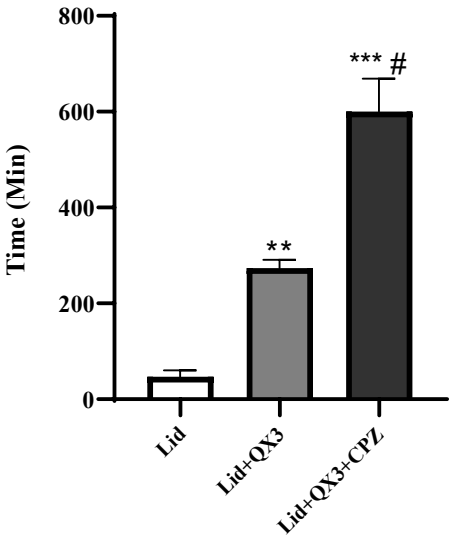

Figure 2. The effect of Qx314 on trigeminal nerve block in combination with lidocaine and capsaicin

Abbreviations: Lid: Lidocaine; Lid+QX3: Lidocaine in combination with Qx314 (30 mM); Lid+QX3+CPZ: Lidocaine in combination with QX314 (30 mM) and capsicine (1 µg). Values are presented as the Mean±SEM (n=5). Differences were considered statistically significant at P<0.05.

****P<0.01, ***P<0.001 vs lidocaine group and # P<0.001 vs Lid-QX3 group.**

Discussion

In the present study, we demonstrated that the combination of lidocaine, QX-314, and capsaicin produced much longer reversible local anesthesia compared to each drug alone or a combination of two in controlling trigeminal neuropathic pain in rats. The management of TN is often a challenge, and when medical treatment fails to control TN pain, it is necessary to consider alternative options, especially surgical treatment [16]. Surgical interventions for TN are either destructive (destruction of sensory function) or nondestructive (preservation of normal sensory function) and associated with risks of complications such as hearing loss, severe dysesthesia, subjective taste loss, tearing and visual disturbance, and so on [17].

Some surgical treatments are not recommended for the elderly or patients with associated comorbidities, and some patients prefer to experience less invasive alternatives before surgical intervention [18].

In patients with TN, peripheral nerve block with local anesthetics is a considered reversible and non-traumatic option without adverse effects [10, 11]. Peripheral nerve block requires minimal expertise to perform and is fast and safe without serious complications compared to invasive surgical procedures [19].

According to the studies of neuropathic pain pathogenesis, the expression of voltage-gated sodium channels plays a key role; therefore, local anesthetics by occupying intracellular sodium channels of the axon are potential therapeutic agents in TN [20].

Previous studies on the clinical application of local anesthetics for the treatment of TN reported successful blockage in infraorbital nerve to manage TN patients. Additionally, the combination of the local anesthetic has been used successfully in various treatment protocols for long-lasting pain relief.

Lidocaine is a commonly used local anesthetic in clinical practice with a short-acting effect, and QX-314 has been shown to have a longer anesthetic effect than lidocaine [21].

QX-314 is a quaternary derivate of lidocaine that is unable to cross the cell membrane if administered alone. QX-314 can be sent into the cell through TRPV channels, which inhibit sodium channels, resulting in anesthesia. One of the compounds that activate these channels is capsaicin. Studies have shown that the combination of qx314 and capsaicin facilitates qx314 entry into the cell membrane through the mentioned channels leading to the prolonged nerve block. The present study was designed to evaluate the effect of QX314 and capsaicin in the rats [22, 23]. Once QX-314 and lidocaine enter a neuron, they cannot be expelled from it easily. The long-acting effect might be related to its intracellular accumulation and slow leakage.

Capsaicin is an agonist of the transient receptor potential vanilloid receptor and inhibits neural transmission in sensory neurons. Currently, many studies have focused on topical capsaicin patches and reported successful results in relieving pain in various types of neuropathy, such as postherpetic neuralgia [24] and Human Immunodeficiency Virus (HIV)-associated neuropathy [25]. Administration of topical capsaicin for postherpetic neuralgia showed that a high concentration of capsaicin is more effective compared to a low concentration. Caution must be taken when applying a high concentration to prevent the initial burning sensation [26]. Forty-one percent of patients with chemotherapy-induced peripheral neuropathy reported toxicities using topical capsaicin in a prospective cohort study. Symptoms were mainly mild burning sensation [27]. In another study, treated-TN patients using oral capsaicin 0.25% were more effective in relieving pain than carbamazepine alone [28, 29].

Some limitations of the study should be mentioned. Only mechanical sensitivity was tested; however, infraorbital nerve injury may also produce thermal hypersensitivity, requiring additional assessments [27].

Conclusions

The combination of Qx314 with lidocaine and capsaicin completely relieved the TN pain for a long-lasting period. These findings increase the potential for the clinical use of QX-314.

Acknowledgments

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Ethical Permission

All experimental procedures were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz City, Iran (Ethical Approval Number, 2015014A).

Conflict of Interests

No conflicts of interest were reported for this study.

Authors' Contribution

Masoumeh ezzati givi and Narges ezzati givi and Hadi imani rastabi conceived of the presented idea and designed the project; Narges ezzati givi and Hadi imani rastabi and Farzin memari performed the experiments, Masoumeh ezzati givi performed the calculations, and Masoumeh ezzati givi and Narges ezzati givi wrote the manuscript.

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