Observational Study

The Effectiveness and Safety of Thermocoagulation Radiofrequency Treatment of the Ophthalmic Division (V1) and/or Maxillary (V2) and Mandibular (V3) Division in Idiopathic Trigeminal Neuralgia: An Observational Study

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Disclaimer: X.M.L and Q.D.H contributed equally to this work There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 12-31-2015
Revised manuscript received: 02-27-2016
Accepted for publication: 03-15-2016

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Background: Trigeminal neuralgia (TN) is a pain appearing in the ophthalmic (V1), maxillary (V2), and mandibular (V3) trigeminal branches. Pharmacologic treatment is the first line for TN; however, many patients prefer to receive minimally invasive treatment rather than medicine because of intolerable side effects. Thermocoagulation radiofrequency (TRF) is a minimally invasive treatment that has been shown to effectively treat the maxillary (V2) and mandibular (V3) divisions, but the safety of TRF treatment of the ophthalmic (V1) division has been controversial.

Objective: This study was to observe the effectiveness and safety of TRF treatment of the ophthalmic (V1) division of trigeminal branches in idiopathic TN patients.

Study Design: An observational study.

Setting: All of patients received temperature controlled TRF, the effectiveness and safety of TRF was assessed by VAS and complications.

Methods: Eighty patients with ophthalmic division (V1) or ophthalmic division (V1) combined with maxillary (V2) or mandibular (V3) divisions of idiopathic TN were treated with step-increased temperature TRF for 6 minutes. At a pulse width of 20 ms, the temperature was titrated up 2 degrees from 60 degrees to 66 degrees every 60 seconds, and then another 66 degrees or 68 degrees for 2 minutes. Meanwhile, the tip of the cannula was turned 180 degrees with each temperature titration. Patients were assessed for pain relief and corneal reflex, numbness, and masticatory muscle weakness at one week, one month, and 3 months after the procedure.

Results: Eighty patients were successfully treated with temperature controlled TRF for ophthalmic (V1) division. Excellent pain relief was achieved in 79 of 80 patients (98.75%) after one week, one month, and 3 months, and 78 of 80 patients (97.5%) patients experienced tolerable numbness. Only one patient lost the corneal reflex, 14 experienced a corneal reflex that was mildly decreased, and 2 patients felt a foreign body sensation in the ipsilateral eye after TRF, but there were no corneal ulcers, incidences of blindness, or other complications.

Limitations: This study is limited by being an observation study and a non-prospective trial with a short-term follow-up period.

Conclusion: Temperature controlled TRF to the ophthalmic division (V1) of the semilular ganglion is effectiveness and safe in TN.

Key words: Thermocoagulation radiofrequency, pulsed radiofrequency, trigeminal neuralgia, ophthalmic division, trigeminal ganglion, pain, numbness, corneal reflex

Pain Physician 2016; 19:E1041-E1047

Trigeminal neuralgia (TN) is a sudden, usually unilateral, severe, brief, stabbing pain that occurs in the distribution of the trigeminal nerve, primarily involving the maxillary (V2) and mandibular (V3) branches (1). Recurrent episodes are common in TN patients. Most of the pain happens in the maxillary or mandibular divisions of the nerve and only 5% of pain is in the ophthalmic (V1) division (2). Pharmacologic treatment is the first line therapy for TN, whether idiopathic or secondary to diseases such as tumors or multiple sclerosis. There are some patients, however, that do not achieve effective relief or who experience intolerable side effects. Even though surgical treatment has a higher success rate, relative to microvascular decompression or balloon micorvascular decompression, there are still many patients that prefer to receive minimally invasive treatment.

Thermocoagulation radiofrequency (TRF) has been extensively used in the treatment of TN and has quickly been developed as a pain treatment method in the last decade (3-5). TRF of the maxillary or mandibular divisions of the trigeminal nerve is relatively safe and has fewer complications, but TRF treatment of the ophthalmic division has been controversial and challenging. Due to the ophthalmic division fibers transmitting corneal sensations, once the V1 branch incurs injury, corneal sensation is lost and scardamyxis function is reduced, which can easily damage the cornea and induce inflammation, and can finally result in corneal ulcers.

In this study, we observed the postoperative therapeutic effects and safety of Digital Subtraction Angiography (DSA) guided TRF at the ophthalmic division (V1) and/or maxillary (V2) and mandibular (V3) divisions in idiopathic TN.

Methods

Patients

A total of 80 patients with ophthalmic division (V1) or combined V1 with maxillary (V2) and/or mandibular division (V3) TN (26 men and 54 women, aged 27 – 88 years) were included in this study. The time of disease onset ranged between 0.5 years to 15 years, with a mean range of 4.98 ± 3.70 years. Patients had to fulfill certain inclusion criteria to be included in the study, which were aged over 45 and infirm patients not willing to receive microvascular decompression, patients with an ischemic cardiac disease and who were severely influenced by the pain, and patients on a high dose of carbamazepin but who were unable to achieve relief from the pain. Patients were excluded from the study if they fulfilled one of the following criteria: noncompliance with physician's advice, infection foci on the skin or the deep tissue at the puncture site, or the presence of bleeding tendencies or receiving anticoagulant therapy. In addition, patients in the unstable stage of severe cardiovascular or cerebrovascular disease, such as trigeminal neuralgia secondary to cranial tumors, were also excluded. All patients had a visual analog score (VAS) over 3, and there was no facial numbness, masticatory muscle weakness, or decrease in the corneal reflex.

Surgical Procedure

Our technique was that of Sengupta and Stunden (6) with some modifications. The availability of skilled anesthesiologists in pain management made the procedure simple and safe using intermittent intravenous anesthesia with propofol and sufentanyl. We found the following anesthesia regimen was satisfactory and patients were easily awakened. Our detailed operation was as follows: the patient was placed in a supine position with the head extended on the DSA bed and fixed by adhesive plaster. Blood pressure and blood oxygen saturation were continuously monitored and electrocardiograms were performed. The patient was pre-medicated with an intravenous (i.v.) injection of 0.5 mg atropine to keep the heart rate over 90, and then pre-emptive analgesia was achieved with sufentanyl 0.05 μg/kg i.v., and further increments of these were given later as required. Full disinfection was carried out with Anerdian and a sterile drape was spread. The C arm fluoroscopy bulb tube was adjusted to an incline of 15 – 25 degrees ipsilaterally and 30 – 35 degrees caudally to show the oval foramen, which was located at the upper third of the mandibular ramus and inside of the condyle (7) (Fig. 1). A metal marker was placed at a site on the lateral side of the labial angle; i.e., a site near the cheekbone above the second molars of the upper jaw. Local anesthesia was induced with 3 mL of mixed solution of 1% lidocaine with 0.5% ropivocaine, and a puncture was made by the radiofrequency trocar in the direction of the oval foramen, and the puncture direction was adjusted according to the fluoroscopic imaging until the radiofrequency trocar (naked tip was 0.2 cm for division 1, and 0.5 cm for divisions 2 or 3 pathologic lesion) was near the oval foramen. A total of 1 mg/kg propofol was administered intravenously before the trocar penetrated into the foramen oval to avoid severe pain, and the trocar continuously underwent fluoros-

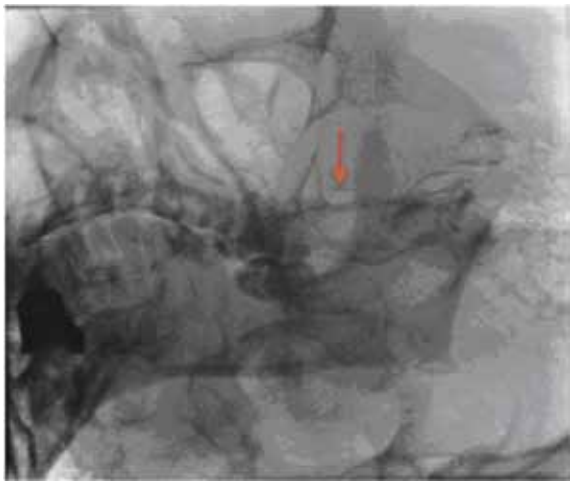

Fig. 1. *Oval foramen image under the C arm fluoroscopy bulb tube (arrow).*

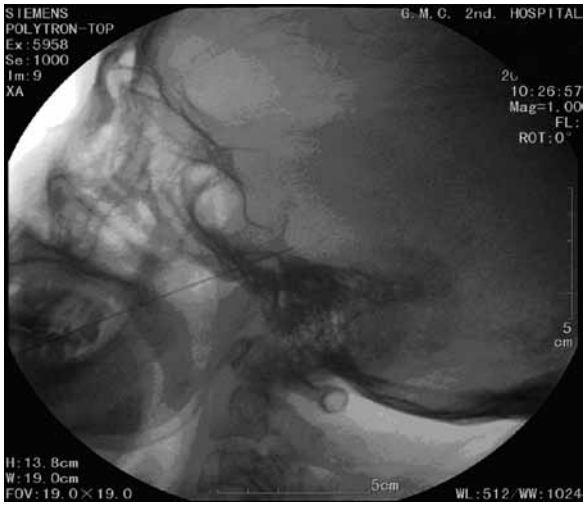

Fig. 2. *The trocar tip was over the slope 3 mm (V1).*

copy until the tip was over the slope 3 mm (less than 5 mm) (Fig. 2) . The patient was allowed to awaken and motor stimulation was given to test whether there were abnormal muscle restrictions, and then sensory stimulation was given to induce pain of the original area of the ophthalmic division. After successful induction of pain in division I of the trigeminal ganglion, the stepped TRF was administered with a radiofrequency generator (COSMAN Radiofrequency Therapy Apparatus, USA). At a pulse width of 20 ms, the temperature was titrated up 2 degrees from 60 degrees to 66 degrees every 60 seconds. Meanwhile, the tip of the cannula was turned 180 degrees with each temperature titration. At each episode of thermocoagulation, propofol was given intravenously 0.5 – 1 mg/kg. This small dose was adequate to produce unconsciousness and immobility. Keeping the airway unobstructed to avoid apnea was important, which included lifting the mandible bone. On waking, the patient's face was tested for loss of pinprick sensation to determine whether numbness was present. The corneal reflex sensation was also tested. If the pain sensation was only mildly decreased, the corneal reflex was normal, and the skin had weak numbness, then another 68 degrees TRF was given for 2 minutes until analgesia was obtained in the division 1 territory. Then the skin sensation and corneal reflex was assessed again to insure saving the corneal reflex. After TRF of division 1 and withdrawal of the tracor to division 2 and/or 3, the same testing methods and TRF with a higher stepped temperature from 70 degrees to 85 degrees with thermocoagulation was given to division 2 and 3. In the procedure, if the patient's blood pressure was higher than 160/95 mmHg, then 0.01 mg/kg Urapidil was injected intravenously at each event.

Table 1. *Follow-up period and VAS scores.*

VAS	Pre-surgery	Follow-up period		
		1 week	1 month	3 months
0 – 3	2	80*	79	79
≥ 4	78	0*	1	1

*$P < 0.001$, pre-TRF surgery compared to follow-up period for one week, one month, and 3 months

Observations and Follow-up

VAS: The effect of TRF was recorded by VAS before surgery and immediately after the procedure and the long-term effects at one week, one month, and 3 months after the surgery. Scores ranging from 0 to 3 meant mild pain and scores ranging from 4 to 6 meant moderate pain. Scores ranging from 7 to 10 indicated the worst possible pain (Tables 1).

Facial numbness before and after the operation were scored as: "0" no numbness, "1" mild numbness (tolerable, without significant impact on life or work), "2" moderate numbness (with some impact on life), and "3" severe numbness (intolerable) (Table 2).

Masticatory muscle weakness prior to and after the procedure were scored as: "0" no impact, "1" tolerable masticatory muscle weakness without significant

impact on life or work, "2" moderate masticatory muscle weakness with significant impact on life, and "3" severe masticatory muscle weakness.

Corneal sensations and reflex changes were observed prior to and after the procedure, and were recorded as normal, foreign body sensation, decreased corneal reflex, and disappeared corneal reflex.

Statistics

Statistical analyses were performed using Prism 5.0 software. The effects of postoperative VAS and numbness were analyzed by the generalized-estimated equation, and the pain relief and changes in postoperative corneal reflexes were analyzed with a chi-squared test.

Results

The morbidity of 1 branch (V1), 2 branches (V1+V2), and 3 branches (V1+V2+V3) of TN was 10%, 63.7%, and 26.3%, respectively (Table 3). The right and left side cases were 48 and 32, respectively.

Table 2. *The case of facial numbness and masticatory muscle weakness.*

	0	1	2	3
V1	2 (2.5%)	4 (5%)	2 (2.5%)	0
V1+V2	2 (2.5%)	34 (42.5%)	15 (18.8%)	0
V1+V2+V3	1 (1.25%)	18 (22.5%)	1 (1.25%)	1 (1.25%)

Table 3. *The morbidity of the divisions of TN.*

	V1	V1+V2	V1+V2+V3
Case	8	51	21
%	10	63.7	26.3

Table 4. *Immediate pain relief after TRF.*

VAS	Pre-RFT	Post-RFT
0 – 2	0	79
≥ 3	80	1*

*$P < 0.001$, pre-TRF compared to post-TRF.

The pain was completely relieved in 79 patients at one month and 3 months, one patient had moderate pain and continued to take medicine to control the pain (Table 4). Seventy-five of 80 patients (93.8%) experienced numbness of the skin in the forehead area.

Although we selected a temperature controlled method of TRF for TN and awakened the patient each time and tested the corneal reflex, pain sensation, and numbness at each temperature during TRF, there was still one patient that showed a disappeared corneal reflex and 10 patients with a decreased corneal reflex (Table 5). Eye drops were given to these patients to prevent a dry and foreign body sensation, and they wore spectacles with a protective eye shield to protect the eyes.

Discussion

Using temperature controlled TRF of the ophthalmic division in TN, and checking the corneal reflex repeatedly and carefully after each temperature change during TRF, we found that TRF of the first division of the semilular ganglion at 60 – 66°C can relieve TN immediately and can maintain the corneal reflex in most patients with a low complication rate. Our study demonstrated that TRF of trigeminal ganglion is safe and effective in the treatment of the ophthalmic division in TN.

TRF has been used to treat TN for several decades. White and Sweet (8) reported the long-term therapeutic effects of TRF for TN in 1969. Since then, more patients have received TRF for chronic pain, such as cervical radicular pain, facial pain including TN, sacroiliac joint pain, facet arthropathy, shoulder pain, postsurgical pain, radicular pain, groin pain, and myofascial pain conditions. From clinical practice and research studies, TRF for TN has been shown to be safe and effective with lower complications. There has been a systematic review of ablative neurosurgical techniques for the treatment of TN that was evaluated in 166 studies. These studies reported on TRF, glycerol rhizolysis, balloon compression of the gasserian ganglion, and stereotactic

Table 5. *Corneal sensation and reflex changes after minimal invasion treatment of TRF (cases).*

	Normal	Foreign body sensation	Decrease	Disappear
V1	5	0	0	0
V1+V2	41	3	8	0
V1+V2+V3	19	1	2	1
Total (%)	81.2	5	12.5	1.2

radiosurgery. The results showed that TRF offered the highest rates of complete pain relief (9). Erdine et al (10) also reported significant pain reductions in all of the patients suffering from idiopathic TN treated with a conventional RF procedure. In our study, the immediate pain relief after the procedure was 97.5% (Table 6). The underlying mechanism of TRF for effectively relieving the neuropathic pain by higher temperatures was due to damaging the nerve's pain signal transmission, as well as nonmyelinated fibers that conduct epicritic stimuli and block the transmission of electric activity (10). However, the safety of TRF for division 1 of the trigeminal nerve has been controversial due to the high temperature being potentially harmful to the ophthalmic division because of the potential to influence the corneal reflex, which could result in damage to corneal sensation and/or nutritional functions and the development of corneal ulcers, which could lead to blindness.

The ophthalmic division of the trigeminal nerve is a sensation nerve, except for corneal sensation, which is handled by the sense fibers of the ophthalmic division of the trigeminal nerve, which also exerts a cell nutritional function (11-14). Protecting corneal sensation is essential for maintaining normal corneal anatomy and function. Studies have shown that when corneal paralysis has appeared with ablation of the ophthalmic division of the trigeminal nerve, histamine release was not controlled, which resulted in epithelial edema and reflective vasodilation responses of inflammation (12). A report showed that a temperature of RF over 45 degrees resulted in irreversible nerve damage. This phenomenon has also been confirmed in an animal experiment with continuous RF at 67 degrees applied adjacently to the rabbit dorsal root ganglia (DRG). The mitochondria degenerated and nuclear membrane integrity was lost with the continuous RF, but pulsed RF (PRF) did not influence the mitochondrial and nuclear membrane integrity (11,15). PRF treatment is a delivery of short pulses of RF via a needle tip, which does not result in actual thermal lesions. This implies that the neurons may keep the normal function in PRF. There are contrasting views regarding the use of PRF for TN (10,11,15,16), some views deny PRF had a role in TN. Although Chua et al (17) reported that PRF for TN had an excellent pain relief of over 80% for 12 months in 36 consecutive patients, it still needed further evaluation as an alternative treatment method for TN. In an earlier TRF procedure for TN, it was reported that only one patient lost the corneal reflex with TRF at 60 °C (6), which suggested a lower temperature for TRF of the trigeminal ganglion is relatively safe for division 1 patients. Therefore, we used the lower temperature to block division 1 of the trigeminal nerve to explore the effect of TRF and side effects. In our study, at 66°C, there were 14 patients that showed a decreased corneal reflex immediately after TRF of the division 1 nerve, and drying and foreign body sensation of the ipsilateral eye occurred after day 1, but no corneal ulcers occurred, which suggested that temperature controlled TRF for division 1 of the trigeminal nerve was safe and the dry eye related to a high temperature destroyed the nerve's nutritional transfer to the corneal and there was decreased lacrimal gland secretion after innervation of the nerve.

Loss of neurotrophic signaling negatively impacts corneal nerve function. If this process cannot be blocked and if recovery does not occur quickly, a corneal ulcer will develop. Due to small nerve fibers being more readily inactivated by heat than larger fibers, A-delta and C fibers carrying pain sensation are destroyed before the larger fibers that carry light touch sensations. Therefore, the pain sensations can be selectively ablated while leaving that of light touch sensation intact, as well as the corneal reflex (14). Studies have found damage to the first division of the TN and decreased lacrimal gland secretion led to corneal drying and lost protection for corneal and epithelial activity. Thereafter peeling neurotrophic obstructive lesions and nerve paralystic corneal ulcers were finally formed (18,19). Allowing the patient to awaken and testing the corneal reflex repeatedly can avoid too much thermocoagulation and can keep a relatively activated corneal reflex.

Table 6. *Follow-up period and VAS scores in the TN divisions.*

	Pre-surgery	Follow-up period (VAS)		
		1 week	1 month	3 months
V1	5.000 ± 0.655	0.800 ± 0.374***	1.143 ± 0.404	1.143 ± 0.404
V1+V2	7.091 ± 0.162	0.705 ± 0.120***	0.886 ± 0.143	0.886 ± 0.143
V1+V2+V3	6.667 ± 0.380	0.905 ± 0.168***	0.952 ± 0.162	0.952 ± 0.162

***$P < 0.001$, pre-TRF surgery compared to follow-up period for one week, one month, and 3 months

Fortunately, although there are 10% of patients that suffer from a decreased corneal reflex, only one patient had a corneal ulcer. This may be due to the protection from corneal ulcers that can be attributed to eye drops and wearing of spectacles, and prohibiting the patient from wiping the eye. The neurotrophic factors may also play a role in corneal damage recovery, and some neurochemical markers also serve as neurotrophic factors, such as substance P (SP) and calcitonin gene-related peptide (CGRP), both of which are involved in neurogenic inflammation and also synergism with epidermal growth factor (EGF) to stimulate epithelial proliferation and promote wound healing. This may be one of the reasons why there is a lower rate of corneal ulcers, although the corneal reflexes are decreased.

From our study and other reports, TRF of trigeminal ganglions in patients with TN is safe and well tolerated. TRF can be used for patients aged over 45 and even with other illnesses. The patient has a short time of hospitalization. Even with recurrence of TN, the patient can receive TRF of gasserian ganglions again. The TRF technique is easily mastered and repeatable, so it can be widespread and continuously used for TN at the present time. In our study, the incidence of corneal ulcers was zero, even though all of the patients received V1 TRF. Paraesthesia and masticatory muscle weakness are the principle adverse side effects of trigeminal thermocoagulation and most patients can readily tolerate these feelings and they diminish with time, which achieves high satisfaction with this minimally invasive treatment.

Regarding our TRF procedure for TN, there are several key points that need to be noted: 1) The relatively lower temperature exerted a protective role in TRF of the first division. To avoid a high temperature induced corneal reflex reduction, we started the TRF temperature lower than the temperature for TRF maxillary and mandibular divisions of the trigeminal nerve; i.e., from 60 degrees to 66 degrees, or 68 degrees titrated up 2 degrees at a time and then tested the patient's facial sensation and corneal reflex after each temperature change. 2) Once the pain sensation was decreased according to needle tingling or the corneal reflex was reduced mildly, the thermocoagulation ceased to destroy the nerve. 3) If the patient shows a decreased corneal reflex or drying and itching of the eye, the eye drops (e.g., artificial tears) and spectacles need to be used to protect the eye. From these methods, the rate of keratitis and corneal ulcers will be controlled to be at the lowest level. The controlled temperature of the TRF procedure can keep the nerve function intact and not significantly influence face sensations and masticatory functions. It results in a higher success rate and should be considered for application in TN management and pain medicine in general.

Conclusion

Temperature controlled TRF for the first division of the trigeminal ganglion provides thorough, safe, and acceptable pain relief, even though it can induce some weak complications, such as reduction in the corneal reflex. However, it can be relieved by careful follow-up and therapeutic actions. Our study suggested that temperature controlled TRF for division 1 in TN is a good candidate for invention treatment for idiopathic TN.

References

1. IASP. *Classification of Chronic Pain: Descriptors of Chronic Pain Syndromes and Definitions of Pain Terms.* 2nd edition. IASP, Seattle, 1994.
2. Son BC, Kim HS, Kim IS, Yang SH, Lee SW. Percutaneous radiofrequency thermocoagulation under fluoroscopic image-guidance for idiopathic trigeminal neuralgia. *J Korean Neurosurg Soc* 2011; 50:446-452.
3. Broggi G, Franzini A, Lasio G, Giorgi C, Servello D. Long-term results of percutaneous retrogasserian thermocoagulation for "essential" trigeminal neuralgia: Considerations in 1000 consecutive patients. *Neurosurgery* 1990; 26:783-786; discussion 786-787.
4. Siegfried J. 500 percutaneous thermocoagulations of the Gasserian ganglion for trigeminal pain. *Surg Neurol* 1977; 8:126-131.
5. Weng Z, Zhou X, Liu X, Wei J, Xu Q, Yao S. Perioperative pain in patient with trigeminal neuralgia undergoing radiofrequency thermocoagulation of the Gasserian ganglion. *J Craniofac Surg* 2013; 24:1298-1302.
6. Sengupta RP, Stunden RJ. Radiofrequency thermocoagulation of gasserian ganglion and its rootlets for trigeminal neuralgia. *Br Med J* 1977; 1:142-143.
7. Song WG, Zhen YJ, Lu ZZ. Radiofrequency pain management for semilular ganglion. In: Lu ZZ, Gao CR, Song WG (eds). *Radiofrequency Pain Management.* 1st edition. He Nan Science & Technique, Zhen Zhou, 2008, pp 26-33.
8. White JC, Sweet WH. *Pain and the Neurosurgeon: A Forty-year Experience.* Charles C Thomas, Springfield, Illinois, 1969, pp 594-621.
9. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. *Neurosurgery* 2004; 54:973-982; discussion 982-983.

10. Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional thermocoagulation in the treatment of iopathic trigeminal neuralgia. *Eur J Pain* 2007; 11:309-313.
11. Zhao WX, Wang Q, He MW, Yang LQ, Wu BS and Ni JX. Radiofrequency thermocoagulation combined with pulsed radiofrequency helps relieve postoperative complications of trigeminal neuralgia. *Gene Mol Res* 2015; 14:7616-7623.
12. Nakamura M, Nishida T, Ofuji K, Reid TW, Mannis MJ, Murphy CJ. Synergistic effect of substance P with epidermal growth factor on epithelial migration in rabbit cornea. *Exp Eye Res* 1997; 65:321-329.
13. Beuerman RW, Schimmelpfennig B. Sensory denervation of the rabbit cornea affects epithelial properties. *Exp Neurol* 1980; 69:196-201.
14. Belmonte C, Acosta MC, Gallar J. Neural basis of sensation in intact and injured corneas. *Exp Eye Res* 2004; 78:513-525.
15. Erdine S, Yucel A, Cimen A, Aydin S, Sav A, Bilir A. Effects of pulsed versus conventional radiofrequency current on rabbit dorsal root ganglion morphology. *Eur J Pain* 2005; 9:251-256.
16. van Kleef M, van Genderen WE, Narouze S, Nurmikko TJ, van Zundert J, Geurts JW, Mekhail N. Trigeminal neuralgia. *Pain Pract* 2009; 9:52-259.
17. Chua NHL, Halim W, Beems T, Vissers KC. Pulsed radiofrequency treatment for trigeminal neuralgia. *Anesth & Pain Med* 2012; 1:57-261.
18. Darwish T, Brahma A, Efron N, O'Donnell C. Subbasal nerve regeneration after penetrating keratoplasty. *Cornea* 2007; 26:35-940.
19. Shaheen B, Bakir M, and Jain S. Corneal nerves in health and disease. *Surv Ophthalmol* 2014; 59:263-285.