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# Functional Outcomes After Trans-nasal Prolozone for the Management of Classic Trigeminal Neuralgia; A Prospective Cohort Study of a Novel Technique

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**Abstract**

Multiple treatment modalities are present for the management of trigeminal neuralgia, including pharmacotherapy and micro vascular decompression. Nevertheless, the application is limited by the sub-optimal efficacy, side effects, and the invasive nature of the surgery. This study aimed to provide a more convenient technique for the management of classic trigeminal neuralgia. This prospective cohort study included 25 cases diagnosed with classic trigeminal neuralgia. The Penn Facial Pain Scale Revised (Penn-FPS-R) was conducted to assess pain interference with the quality of life in the included patients, 1-week before injection, 5 minutes, 15 minutes, one week, 4 weeks and 6 months after injection. The patient's satisfaction and pain intensity were assessed using the 11-point numeric rating scale (NRS) at the pre-defined time points. This study included 25 cases diagnosed with classic trigeminal neuralgia, and refractory to the standard treatment. Trans-nasal Prolozone revealed an immediate and long-term improvement, regarding pain intensity and quality of life (p value $< 0.001$). We are the first to describe trans-nasal prolozone infiltration of the sphenopalatine ganglion in the treatment of classic trigeminal neuralgia. Trans-nasal prolozone is simple, self-administered, and easily taughtable technique, which produced dramatic and long-term pain relief in trigeminal neuralgia.

**Keywords:** Regenerative medicine, prolotherapy, trigeminal neuralgia

**Full-length article** **Corresponding Author*, e-mail: *mohamedkhattab.g@gmail.com* Doi # https://doi.org/10.62877/77-IJCBS-24-25-19-77

## 1. Introduction

Trigeminal neuralgia is a chronic orofacial neurological condition, characterized by recurrent episodes of sharp, shock-like pain or burning sensation along the distribution of one or more branches of the trigeminal nerve. Trigeminal neuralgia may present by paroxysmal attacks of pain, with completely free intervals or with a remaining background of pain in between the attacks. Indeed, the majority of trigeminal neuralgia cases are idiopathic or classic type, in which there is no compressing tumor or mass along the course of the trigeminal nerve [1]. Furthermore, trigeminal neuralgia may be associated with trigger zones, located along the course of the trigeminal nerve divisions. They mostly distributed around the ala of the nose, mouth opening and the eye. Interestingly, trigeminal neuralgia episodes precipitated by routine manipulation of the trigger zones, including shaving, brushing teeth, and chewing. Importantly, the trigger zone is clinically pathognomonic for the diagnosis of trigeminal neuralgia [2]. It is estimated that the prevalence of trigeminal neuralgia ranging from 0.1 to 0.7 % [3]. Nevertheless, the prevalence of trigeminal neuralgia is believed to underestimated, because of misdiagnosis. Indeed, trigeminal neuralgia is primarily a clinical diagnosis, depending on the clinical presentation and the course of the disease [4]. The clinical characteristics of secondary trigeminal neuralgia differ from the idiopathic or the classic type, being more common to occur bilaterally in middle-aged patients. Moreover, sensory-neural defects are highly suggestive of secondary trigeminal neuralgia, so brain MRI recommended excluding any mass-occupying lesion [5]. Currently, multiple treatment modalities are present for the management of trigeminal neuralgia, including the pharmacotherapy, micro vascular decompression, ablative procedures and radiosurgery [6].

Indeed, pharmacological treatment remained the first line for the management of trigeminal neuralgia, but its use limited by the sub-optimal efficacy and the significant side effects. Carbamazepine and oxcarbazepine, anticonvulsant medications, usually started in low doses, which increase gradually, to produce adequate pain control. High doses and long-term use of carbamazepine and oxcarbazepine expose the patients to side effects, including

dizziness, drowsiness and double vision [7]. In the Asian population, carbamazepine/oxcarbazepine administration should be preceded by HLA genotyping, because HLA-B*15:02 is associated with the development of Stevens-Johnson syndrome [8].

In addition, micro vascular decompression is an invasive procedure, produces long-term pain relief through posterior fossa exploration and isolation of the fifth cranial nerve roots. Despite the proven long-term efficacy, it is a major surgery, and may be unsuitable for high-risk patients. It has risks of hearing loss, cerebellar hemorrhage, infarction, meningitis, and CSF leakage [9]. Consequently, there is an urgent need for novel therapeutic approaches to provide optimal care to patients suffering from trigeminal neuralgia. Indeed, Dr. John Lyftogt as a potential therapy of musculoskeletal injuries and neurogenic inflammation first developed dextrose perineural injection (PIT). He reported subcutaneous injection of hypertonic dextrose in a series of 300 achilles tendinopathy, with promising results [10]. This study aimed to present two trigeminal neuralgia cases, successfully treated by Tran's nasal neuro-prolozone infiltration of the sphenopalatine ganglion.

## 2. Materials and Methods

### *2.1. Methods*

This prospective cohort study conducted on 25 trigeminal neuralgia cases in Pain Cure Clinics, Cairo, Egypt. From March 2023 until September 2023. The departmental ethical committee of the Medical Military Academy approved the research procedure. Any unforeseen dangers that arise throughout the investigation should be clarified to the participants & to the ethical committee in time.

### *2.2. Eligibility criteria*

We included 25 patients of both sex with age > 18 years old, diagnosed with primary trigeminal neuralgia of more than 2 years, and intolerant to medical treatment for 6 months. Characteristics of trigeminal neuralgia included Unilateral, episodic, paroxysmal, electrical shock-like pain, along the distribution of one and/or more of the divisions of trigeminal nerve. Patients experienced post- herpetic neuralgia or multiple sclerosis excluded.

### *2.3. Procedure*

All patients received initial clinical assessment, through detailed history taking, physical examination and radiological investigation, to rule out any focal neurological deficit and neuro-vascular insufficiency. A detailed physical examination obtained for the eyes, ears, teeth, and temporomandibular joint, to rule out any similar condition. All patients placed in the supine, head-down tilt position to allow the spread of the prolozone to the sphenopalatine ganglion, located posterior to the middle turbinate in the pterygopalatine fossa. Dripping 10 ml of the prolozone solution (Dextrose 5%+ O3/O2 mixture 5 µg/mL) through the nostril on the affected side over 10 minutes administered. Subcutaneous perineural injection therapy (PIT) of prolozone at the mental, infra- and supraorbital nerves; terminal sensory branches of V3, V2, and V1 respectively. After skin preparation with 70% alcohol swab for 30 seconds, a 27-gauge 0.5 inch needle is used to subcutaneously infiltrate the prolozone solution near the mental, infra- and supraorbital foramina. All patients monitored for 15 minutes after the session. Then, all patients were taught to repeat the session, three times with one week apart. Those three sessions self-administered at home. The patients were instructed to follow-up weekly for a month and after 6 months. Pain intensity, interference and satisfaction assessed at every visit, using Penn Facial Pain Scale-Revised (Penn-FPS-R) and the 11-point numeric rating scale (11-NRS).

## 3. Results and discussion

### *3.1. Results*

This prospective cohort study included 25 patients diagnosed with primary trigeminal neuralgia. Most of the included patients were female, aged from 18 to 50 years old. Table 1 presented the demographic characteristics of the study patients. Table 2 represented a summary of the functional outcomes of the included cases. This study reported a statistically significant improvement of pain intensity and Penn-FPS-R at 5, 15 minutes after injection, 1 week, 4 week and 6 months follow up visits.

### *3.2. Representative sample cases*

#### *3.2.1. Case 1*

A 63-year-old female attended to the Pain Cure clinic, with a 5-year history of trigeminal neuralgia. The chief complaint was intermittent attacks of burning sensation on the right side of the face, distributed in the maxillary and ophthalmic regions. In between the episodes, the patient reported a background of annoying burning sensation, not similar to the left healthy side. The burning pain was triggered by brushing tooth, touching the upper face or the scalp region, and getting out from a hot bath. The patient underwent cataract surgery, a week before the symptoms worsened. Cataract surgery was conducted bilaterally, but the patient reported excessive lacrimation and burning sensation in the right eye, not comparable to the left one. Carbamazepine 400 mg in two divided doses, combined with pregabalin 75 mg prescribed to control the condition. Response to the treatment was neither optimal in pain reduction, nor sufficient to gain the patient satisfaction, especially after the cataract surgery. Medical history revealed hypertension and atrial fibrillation, on olmesartan 40mg, carvedilol 25mg and warfarin 3mg once daily.

##### *3.2.1.1. Physical Examination*

General examination revealed that the patient is fully conscious, oriented and vitally stable. We ruled out any focal neurological deficit and neuro-vascular insufficiency. A detailed physical examination obtained for the eyes, ears, teeth, and temporomandibular joint, to rule out any similar condition. Dental and ophthalmological consultations requested and revealed that no abnormalities detected apart from the cataract operation. Based on the clinical presentation and physical examination, secondary trigeminal neuralgia is almost excluded. Consequently, brain MRI imaging was postponed until reassessment after the intervention.

##### *3.2.1.2. Assessment*

Penn Facial Pain Scale-Revised (Penn-FPS-R) was conducted to assess pain interference to the quality of life. It was assessed 1-week before injection, 5 minutes, 15 minutes, one week, 4 weeks and 6 months after injection. The Penn-FPS-R is a 12-item assessment scale, including daily activities, mood, relationships, eating, biting, touching face,

brushing teeth, self-care, smiling, talking, opening mouth widely and temperature changes activities. The scale is 0 to 10, where zero is no interference and 10 most interference. Pain intensity and satisfaction were assessed using the 11-point NRS, where (0) is no pain /fully unsatisfied, and (10) is most pain/fully satisfied.

#### *3.2.1.3. Procedure and results*

The patient placed in the supine, head-down tilt position to allow the spread of the prolozone to the sphenopalatine ganglion, located posterior to the middle turbinate in the pterygopalatine fossa. Dripping 10 ml of the prolozone solution (Dextrose 5%+ O3/O2 mixture 5 μg/mL) through the right nostril over 10 minutes administered. The patient monitored for 15 minutes after the session. This session self-administered three times with one week apart. She instructed to follow-up weekly for a month and after 6 months. The patient reported over 50% reduction of pain 5 minutes after injection. Complete resolution of the symptoms reported at the 6-month visit, without the need for any medications. No adverse effects reported.

### *3.2.2. Case 2*

A 33-year-old male presented to the Pain-Cure clinic, with the chief complaint of excruciating, sharp, shooting, electric-like pain, along the distribution of the three divisions of the right trigeminal nerve. This condition was associated with hemi facial per orbital spasm. Over The Counter (OTC), pain medications administered before seeking medical advice. Paracetamol 1000 mg orally and ketorolac 30mg IM were administered, but not sufficient to alleviate the condition. Indeed, the patient reported a 2-year history of trigeminal neuralgia, treated by carbamazepine 400mg administered in two divided doses. Carbamazepine was not enough to control trigeminal neuralgia or prevent the emergence of this lancinating episode. The patient reported a history of type-1 diabetes and ischemic heart disease (IHD) with preserved systolic function. Physical examination revealed no focal neurological deficits or neuro-vascular insufficiency.

Upon pain assessment and a thorough physical examination, the first treatment session immediately initiated. The patient placed in the supine head-down tilt position, followed by dripping 10 ml of the prolozone solution (Dextrose 5%+ O3/O2 mixture 5 μg/mL) through the right nostril over 10 minutes. It was enough to reduce the severity of symptoms about 50% after 5 minutes. This technique is supported by subcutaneous perineural injection therapy (PIT) of prolozone at the mental, infra- and supraorbital nerves: terminal sensory branches of V3, V2, and V1 respectively. After skin preparation with 70% alcohol swab for 30 seconds, a 27-gauge 0.5-inch needle was used to subcutaneously infiltrate the prolozone solution near the mental, infra- and supraorbital foramina.

The mental foramen is injected along the axis of the second premolar, halfway between the inferior border of the mandible and the alveolar crest. The infraorbital foramen was found at the point in the lower border of the infraorbital ridge, intersecting the vertical line from the pupil to the mental foramen. The supraorbital nerve is infiltrated 0.5 cm below the supraorbital foramen in a cephalad direction. Injection of 1-2 cm of the prolozone at each point was enough to boost the results obtained from the transnasal infiltration of the sphenopalatine ganglion. The patient reported more than 70% reduction of his agonizing symptoms after 5 minutes of the session. This session was self-administered three times with one week apart, but without PIT of the mental, infra- and supraorbital nerves.

## *3.3. Discussion*

This is the first study to describe the transnasal infiltration of neuro-prolozone to the sphenopalatine ganglion. It is an easy, simple, self-administered technique, associated with dramatic and long-standing relief from the symptoms of trigeminal neuralgia. It also significantly improved the quality of life without any reported side effects. Regarding the technique, the patient only needs to lie in the supine position with head-down tilt, and then 10 cm of the prolozone self-administered over 10 minutes through a nasal dropper. Indeed, self-administration and easy taught ability of the technique are points of great concern, due to the episodic and chronic nature of trigeminal neuralgia [11]. In addition, there is no need for injection or introduction of cotton-tipped catheters to infiltrate the sphenopalatine ganglion and produce immediate pain relief. Indeed, the sphenopalatine ganglion strongly implicated in the pathogenesis and progression of trigeminal neuralgia [12].

The randomized controlled study, conducted by Kanai et al., included 25 cases with refractory trigeminal neuralgia [13]. Intranasal lidocaine 8% spray administered and compared to placebo and revealed a significant pain reduction for an average of four hours. The reported side effects included bitter taste, numbness of the nose and throat. Supportingly, the retrospective study conducted by Coven et al, performed fluoroscopic-guided trans nasal injection of the sphenopalatine ganglion in trigeminal neuralgia patients [14]. It continuously reported that the sphenopalatine ganglion has an important role in the pathophysiology of various pain syndromes, including trigeminal neuralgia [12]. We are the first to combine the transnasal sphenopalatine ganglion approaches with the perineural subcutaneous technique in the second case complaining of severe symptoms, resulting in instantaneous relief. Conaway, 2014 reported a case of V1 trigeminal neuralgia, successfully treated by PIT of dextrose 5% [15].

Supporting, Itkin, 2016 reported a refractory trigeminal neuralgia case, treated by only one session of dextrose 5% PIT and reported a 5-month pain relief [16]. The conceptual basis of neuro-prolotherapy depends on the control of neurogenic inflammation and restoration of homeostasis. Neurogenic inflammation elicited by stimulation of the Transient Receptor Potential Cation Channel V1 (TRPV1) receptors, located at the nerve endings, and mediated by the release of Calcitonin Gene-Related Peptide (CGRP) and substance P. Chronic stimulation of the TRPV1 receptors leads to sensitization and neuropathic pain [17]. Meng et al. reported that the release of the proinflammatory CGRP leads to central sensitization of the trigeminal sensory neurones through activation of CGRP1 receptors in the brainstem [18]. Dextrose prolotherapy blocks nociceptive sensation through inhibition of TRPV1 receptors. Unlike lidocaine, dextrose blocks only the mechano-insensitive nociceptors, whilst the mechano-sensitive receptors are intact, so numbness does not occur with dextrose [16].

**Table 1.** Demographic characteristics of the included patients.

| Parameters | N (%) |
|---|---|
| **Age (Years)** | 13 (52) |
| (18-50) | |
| 50-65 | 9 (36) |
| > 65 | 3 (12) |
| **Gender** | |
| Female | 18 (72) |
| Male | 7 (28) |
| **Comorbidities** | |
| Diabetes | 9 (36) |
| Hypertension | 7 (28) |
| IHD | 2 (8) |
| **Side** | |
| Right | 17 (68) |
| Left | 8 (32) |
| **Distribution** | |
| V1 & V2 | 10 (40) |
| V2 & V3 | 13 (52) |
| V1, V2 & V3 | 2 (8) |

*IHD, ischemic heart disease*

**Table 2.** Summary of pain intensity and interference along the study period.

| Variable | Before injection | | Post injection | | | | |
|---|---|---|---|---|---|---|---|
| | **1-week** | **Just before injection** | **5 min** | **15 min** | **1 week** | **4 weeks** | **6 months** |
| **NRS-intensity** | 7 (7-9) | 8 (7-10) | 3 (2-4) | 3 (1-4) | 5 (3-6) | 2 (1-3) | 1 (1-3) |
| P value | - | - | 0.001 | 0.001 | 0.001 | 0.0001 | 0.0001 |
| **NRS-satisfaction** | 1 (1-3) | NA | 8 (6-9) | 8 (6-10) | 7 (7-9) | 7 (6-8) | 9 (7-10) |
| P value | - | - | 0.001 | 0.001 | 0.015 | 0.022 | 0.001 |
| **Interference with** | | | | | | | |
| **Daily activities** | 6 (6-8) | 6 (5-7) | NA | NA | 3 (2-5) | 1 (1-3) | 1 (1-2) |
| P value | | | | | 0.521 | 0.001 | |
| **Mood** | 6 (5-8) | 4 (3-7) | NA | NA | 2 (1-4) | 1 (1-3) | 0 |
| P value | - | - | - | - | 0.001 | 0.001 | - |
| **Relationships** | 4 (4-6) | 4 (3-7) | NA | NA | 1 (1-3) | 1 (1-2) | 0 |
| P value | - | - | - | - | 0.001 | 0.001 | - |
| **Eating a meal** | 7 (6-8) | 7 (5-8) | NA | NA | 4 (2-6) | 1 (1-0) | 0 |
| P value | - | - | - | - | 0.712 | 0.001 | - |
| **Biting or chewing** | 8 (7-9) | 8 (7-10) | NA | NA | 3 (1-4) | 1 (1-2) | 0 |
| P value | - | - | - | - | 0.001 | 0.001 | - |
| **Touching face** | 9 (8-10) | 10 (9-10) | 3 (2-4) | 3 (1-5) | 5 (3-6) | 4 (2-5) | 1 (1-3) |
| P value | - | - | 0.0001 | 0.0001 | 0.592 | 0.001 | 0.001 |
| **Total Penn-FPS-R** | 81 (77-105) | 76 (70-109) | 8 (5-22) | 7 (4-14) | 31 (19-33) | 17 (13-27) | 4 (2-9) |
| P value | - | - | 0.0001 | 0.0001 | 0.001 | 0.001 | 0.001 |

*Using: Wilcoxon test*

Moreover, the successful role of dextrose PIT in the management of neuropathic pain can postulated by the hydrodissection and relief of the chronic constriction injury points (CCIs) along the course of the nerve [16]. Chronic tissue injury leads to the development of micro-adhesions, which constrict the cutaneous nerves in certain points along the nerve course. Cao et al. developed a sciatic CCI model in rats [19]. The aim was to explore the epigenetic background of neuropathic pain. They found that CCI was associated with overexpression of circular RNAs (circRNAs) in the dorsal horn cells of the affected rats. It is hypothized that circRNAs may be involved in the pathogenesis of chronic neuropathic pain [20].

## 4. Conclusions

Transnasal prolozone infiltration of the sphenopalatine ganglion produced a dramatic, long-term pain relief, and improved the quality of life in trigeminal neuralgia. The technique is simple, self-administered, and easily taughtable. In severe cases, we propose to combine the transnasal approach with the subcutaneous perineural injection therapy along the course of the affected nerve. The molecular mechanism of neuropathic pain not fully elucidated, and epigenetic dysregulation may have a role. Prolozone administration proposed to restore the homeostatic function on cellular basis.

## Disclosure

All authors have declared that there no conflict of interest that could influence the submitted work.

## References


[1] G. Cruccu, N.B. Finnerup, T.S. Jensen, J. Scholz, M. Sindou, P. Svensson, R.-D. Treede, J.M. Zakrzewska, T. Nurmikko. (2016). Trigeminal neuralgia: new classification and diagnostic grading for practice and research. Neurology. 87(2): 220-228.

[2] G. Di Stefano, S. Maarbjerg, T. Nurmikko, A. Truini, G. Cruccu. (2018). Triggering trigeminal neuralgia. Cephalalgia. 38(6): 1049-1056.

[3] J.M. Zakrzewska, M.E. Linskey. (2014). Trigeminal neuralgia. Bmj. 348.

[4] M.H. Majeed, S. Arooj, M.A. Khokhar, T. Mirza, A.A. Ali, Z.H. Bajwa. (2018). Trigeminal neuralgia: a clinical review for the general physician. Cureus. 10(12).

[5] E.I. Araya, R.F. Claudino, E.J. Piovesan, J.G. Chichorro. (2020). Trigeminal neuralgia: basic and clinical aspects. Current neuropharmacology. 18(2): 109-119.

[6] N. Montano, G. Conforti, R. Di Bonaventura, M. Meglio, E. Fernandez, F. Papacci. (2015). Advances in diagnosis and treatment of trigeminal neuralgia. Therapeutics and clinical risk management. 289-299.

[7] K.W. Al-Quliti. (2015). Update on neuropathic pain treatment for trigeminal neuralgia: The pharmacological and surgical options. Neurosciences Journal. 20(2): 107-114.

[8] S.-H. Kim, K.W. Lee, W.-J. Song, S.-H. Kim, Y.-K. Jee, S.-M. Lee, H.-R. Kang, H.-W. Park, S.-H. Cho, S.-H. Park. (2011). Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy research. 97(1-2): 190-197.

[9] J. Shi, Y. Qian, W. Han, B. Dong, Y. Mao, J. Cao, W. Guan, Q. Zhou. (2020). Risk factors for outcomes after microvascular decompression for trigeminal neuralgia. World Neurosurgery. 136: e559-e566.

[10] J. Lyftogt. (2007). Subcutaneous prolotherapy for achilles tendinopathy: the best solution? Australasian Musculoskeletal Medicine. 12(2).

[11] A.-P. Gobeil-Lavoie, M.-C. Chouinard, A. Danish, C. Hudon. (2019). Characteristics of self-management among patients with complex health needs: a thematic analysis review. BMJ open. 9(5): e028344.

[12] M. Piagkou, T. Demesticha, T. Troupis, K. Vlasis, P. Skandalakis, A. Makri, A. Mazarakis, D. Lappas, G. Piagkos, E.O. Johnson. (2012). The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. Pain Practice. 12(5): 399-412.

[13] A. Kanai, A. Suzuki, M. Kobayashi, S. Hoka. (2006). Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. BJA: British Journal of Anaesthesia. 97(4): 559-563.

[14] I. Coven, E.H. Dayısoylu. (2016). Evaluation of sphenopalatine ganglion blockade via intra oral route for the management of atypical trigeminal neuralgia. Springerplus. 5: 1-5.

[15] E. Conaway, B. Browning. (2014). Neural prolotherapy for neuralgia. J Prolotherapy. 6: e928-e931.

[16] A. Itkin. (2016). Treatment of trigeminal neuralgia utilizing neural prolotherapy: a case report. J Prolotherapy. 8: e961-5.

[17] P. Geppetti, R. Nassini, S. Materazzi, S. Benemei. (2008). The concept of neurogenic inflammation. BJU international. 101: 2-6.

[18] J. Meng, S.V. Ovsepian, J. Wang, M. Pickering, A. Sasse, K.R. Aoki, G.W. Lawrence, J.O. Dolly. (2009). Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential. Journal of Neuroscience. 29(15): 4981-4992.