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Review Article

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Transnasal Neuro-Prolozone for the Management of Trigeminal Neuralgia; Dramatic and Long-Term Relief of a Novel Technique

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Abstract

We report two cases of trigeminal neuralgia, dramatically relieved with transnasal neuro- prolozone infiltration of the sphenopalatine ganglion. To be mentioned, we are the first to describe this technique in the treatment of trigeminal neuralgia. The two cases had a history of trigeminal neuralgia for more than 2 years, refractory to pharmacological treatment. Case one is a 63 year-old female, with a 5-year history of trigeminal neuralgia. This patient reported a history of hypertension and atrial fibrillation. The second patient, a 33 year-old male, had a 2-year history of trigeminal neuralgia, and a reported history of type-1 diabetes and ischemic heart disease (IHD). No side effects were reported, along the 6-month follow- up period. 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 patients' satisfaction and pain intensity were assessed using the 11-point numeric rating scale (NRS) at the pre-defined time points. The two cases reported long-term improvement, regarding pain intensity and quality of life. In conclusion, transnasal neuro-prolozone infiltration is emerging as an effective, long-term and immediate-acting treatment modality for mitigating the burden of trigeminal neuralgia.

Background

Trigeminal neuralgia is a chronic orofacial neurological condition, characterised 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 inbetween 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.

Furthermore, trigeminal neuralgia may be associated with trigger zones, located along the course of the trigeminal nerve divisions. They are mostly distributed around the ala of the nose, mouth opening and the eye. Interestingly, trigeminal neuralgia episodes are 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. It is estimated that the prevalence of trigeminal neuralgia ranging from 0.1 to 0.7 %. Nevertheless, the prevalence of trigeminal neuralgia is believed to be underestimated, because of misdiagnosis. Indeed, trigeminal neuralgia is primarily a clinical diagnosis, depending on the clinical presentation and the course of the disease. The clinical characteristics of secondary trigeminal neuralgia differs 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 is recommended to exclude any mass-occupying lesion. Currently, multiple treatment modalities are present for the management of trigeminal neuralgia, including the pharmacotherapy, microvascular decompression, ablative procedures and radiosurgery. Indeed, pharmacological treatment remained the first line for the management of trigeminal neuralgia, but its use is limited by the suboptimal efficacy and the significant side effects. Carbamazepine and oxcarbazepine, anticonvulsant medications, are usually started in low doses, which increase gradually, to produce effecient pain control. High doses and long-term use of carbamazepine and oxcarbazepine expose the patients to side effects, including dizziness, drowsiness and double-vision. 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. In addition, microvascular 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, may be unsuitable for high risk patients. It has risks of hearing loss, cerebellar hemorrhage, infarction, meningitis, and CSF leakage. Consequently, there is an

urgent need for novel therapeutic approaches to provide optimal care to patients suffering from trigeminal neuralgia. Indeed, dextrose perineural injection therapy (PIT) was first developed by Dr. John Lyftogt as a potential therapy of musculoskeletal injuries and neurogenic inflammation. He reported subcutaneous injection of hypertonic dextrose in a series of 300 cases, suffering from Achilles tendinopathy, with promising results. This study aimed to present two trigeminal neuralgia case, successfully treated by transnasal neuro-prolozone infiltration of the sphenopalatine ganglion.

Case Presentation Case 1

A 63-year-old female attended to the Pain-Cure clinic, with a 5-year history of trigeminal neuralgia. The cheif complain was intermittent attacks of burning sensation on the right side of the face, distributed in the maxillary and ophthalmic regions. Inbetween the episodes, the patient reported a background of annoying burning sensation, not similar to the left healthy side. The burning pain is 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 were 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.

Physical Examination

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

Assessment

Penn Facial Pain Scale-Revised (Penn-FPS-R) is 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 0 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.

Procedure and Results

The patient was placed in the supine head-down tilt position to allow 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 was administered. This session was repeated three times with one week apart. The patient was monitored for 15 minutes after injection. She was instructed to follow up weekly for a month and after 6 months. Pain intensity, interference and satisfaction were assessed at every visit, and summarised in table 1. The patient reported over 50% reduction of the pain, 5 minutes after injection. Complete resolution of the symptoms was reported at the 6-month visit, without the need of any medications. No adverse effects were reported.

Table 1: Summary of pain intensity and interference along the study period in case 1.

Variables	Before injection		Post injection (Transnasal Prolozone Infiltration)				
	1-week	Just before injection	5 minutes	15 minutes	1 week	4 weeks	6 months
NRS-intensity	7	8	3	3	5	2	0
Quality of pain	Burning pain		Mild burning sensation				No pain
NRS-satisfaction	1	NA	8	8	7	7	9
Daily activities	6	6	NA	NA	3	1	1

Mood	6	4	NA	NA	2	0	0
Relationships	4	4	NA	NA	1	1	0
Eating a meal	7	7	NA	NA	4	1	0
Biting or chewing	8	8	NA	NA	3	1	0
Touching your face	9	10	3	3	5	4	1
Self-care	7	7	NA	NA	3	3	1
Brushing teeth	9	9	NA	NA	2	3	0
Smiling or laughing	5	5	2	2	3	1	0
Talking	5	2	1	1	0	0	0
Opening mouth widely	6	5	2	1	0	0	0
Activities with temperature changes	9	9	NA	NA	5	2	1
Total Penn-FPS-R	81/120	76/120	8/40	7/40	31/120	17/120	4/120
Total Penn-FPS-R reduction rate	NA	NA	68%	72%	61.7%	79%	95.1%

Case 2

A 33-year-old male presented to the Pain-Cure clinic, with the chief complain of excruciating, sharp, shooting electric-like pain, along the distribution of the three divisions of the right trigeminal nerve. This condition was associated with hemifacial periorbital spasm. Over The Counter (OTC) pain medications were 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 lacinating episode. The patient reported a history of type-1 diabetes and 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 was immediately initiated. The patient was 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 the symptoms bout 50% after 5 minutes. This technique is supported by subcutaneous perineural injection therapy (PIT) of the 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

in injected along the axis of the 2nd premolar, halfway between the inferior border of the mandible and the alveolar crest.

The infraorbital foramen is found at the point in the lower border of the infraorbital ridge, intersecting the vertical line from the public 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 repeated three times with one week apart, but without PIT of the mental, infra- and supraorbital nerves. The results of pain intensity and interference at each time point are summarized in table 2.

Table 2: Summary of pain intensity and interference along the study period in case 2.

Variables	Before injection		Post injection (Transnasal Prolozone Infiltration+PIT)				
	1-week	Just before injection	5 minutes	15 minutes	1 week	4 weeks	6 months
NRS-intensity	7	10	3	3	5	2	0
Quality of pain	Stabbing pain		Cannot be identified				No pain
NRS-satisfaction	3	0	9	10	9	9	10
Daily activities	8	10	NA	NA	2	0	0
Mood	7	10	3	3	1	2	0
Relationships	4	8	NA	NA	1	1	0
Eating a meal	7	10	5	4	5	1	0
Biting or chewing	7	10	6	4	4	0	0
Touching your face	9	10	5	5	6	2	1
Self-care	7	7	NA	NA	3	3	1
Brushing teeth	9	9	NA	NA	2	3	0
Smiling or laughing	7	10	6	5	3	1	0
Talking	6	10	4	4	1	0	0
Opening mouth widely	6	9	3	1	0	0	0
Activities with temperature	4	4	NA	NA	1	0	0

changes							
Total Penn-FPS-R	81/120	107/120	32/70	26/70	29/120	13/120	2/120
Total Penn-FPS-R reduction rate	NA	NA	70.1%	75.7%	73%	88%	98%

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, then 10 cm of the prolozone is self-administered over 10 minutes through a nasal dropper. Indeed, self administration and easy taughtability of the technique are points of great concern, due to the episodic and chronic nature of trigeminal neuralgia. 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 is strongly implicated in the pathogenesis and progression of trigeminal neuralgia. The randomised controlled study, conducted by Kanai et al., included 25 cases with refractory trigeminal neuralgia. Intranasal lidocaine 8% spray was 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 transnasal injection of sphenopalatine ganglion in trigeminal neuralgia patients. It is continuously reported that the sphenopalatine ganglion has an important role in the pathophysiology of various pain syndromes, including trigeminal neuralgia.

We are the first to combine the transnasal sphenopalatine ganglion approach 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%. Supportingly, Itkin, 2016 reported a refractory trigeminal neuralgia case, treated by only one session of dextrose 5% PIT and reported a 5- month pain relief. Moreover, PIT has been reported in the management of other neurogenic pain syndromes, as carpal tunnel syndrome, complex regional pain syndrome and diabetic neuropathy.

The conceptual basis of neuro-prolotherapy depends on the control of neurogenic inflammation and restoration of homeostasis. Neurogenic inflammation is 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. 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. 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. Moreover, the successful role of dextrose PIT in the management of neuropathic pain can be postulated by the hydrodissection and relief of the chronic constriction injury points (CCIs) along the course of the nerve. Chronic tissue injury leads to the development of micro-adhesions which constrict the cutaneous nerves in certain points along the course. Cao et al., developed a sciatic CCI model in rats. The aim was to explore the epigenetic background of neuropathic pain. They found that CCI was associated with over-expression of circular RNAs (circRNAs) in the dorsal horn cells of the affected rats. CircRNAs are increasingly reported as biomarkers in different pathologies, including cancer, Alzheimer's disease, and the coronary artery disease. It is hypothized that circRNAs may be involved in the pathogenesis of chronic neuropathic pain [1-3].

Conclusion and future direction

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, cheap, not time-consuming, self-administerd, 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 is not fully elucidated, and epigenetic dysregulation may have a role. Prolozone administration is hypothized to restore the homeostatic function on cellular basis.

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