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DOI:10.26502/fjppr.097

Botulinum toxin has the potential to reduce the activity of a wide dynamic range neurons, hence preventing both central sensitization and local neurogenic inflammation [31]. K Roger Aoki stated in a 2003 paper that the current study assessed the in vivo mechanism of action for the antinociceptive activity of type A botulinum toxin. These investigations discovered that glutamate release is inhibited by botulinum toxin type A. Moreover, peripheral exposure to the toxin inhibited Fos, a product of the immediate early gene, c-fos, which is produced in response to neuronal inputs. According to these results, type A botulinum toxin inhibits peripheral sensitization and hence lessens central sensitization. The mechanism by which botulinum toxin type A reduces migraine pain by acting on these two routes may be explained by the current theory that migraine includes both peripheral and central sensitization [32]. Botulinum toxin has been used well to treat tension headaches, cervicogenic headaches, migraines, and chronic daily headaches in clinical settings. Neurotransmitter release into nerve terminals is facilitated by the cleavage and inactivation of SNARE (Soluble N-ethylmaleimide-sensitive factor activating protein receptor) proteins,[33] which is accomplished by these injections. The intense, shooting pain associated with neuralgias can be alleviated by a BoNT-A injection, but the dull, agonizing ache cannot be [33]. Table 1 summarizes the studies with Botulinum toxin.

In many situations, higher dosages of BT (Botulinum Toxin) proved to be more beneficial than 20 U for patients with prominent glabellar characteristics, and they were also shown to be safe. Nowadays, a lot of therapists begin with doses of 15 to 20 U and increase them based on the patient's sex, muscle mass, and/or other factors [34]. Zhang et al.'s investigation, however, did not find a difference between the BT-A doses of 25 U and 75 U. When Wu et al. (2012) used a BT-A (Botulinum Toxin A) dosage of 75 U, the VAS was much lower than in the study by Shehata et al., where the dose was 100 U [35].

Study	Study design	Case No.	Follow-up duration	Outcome measure method	Results
The treatment of Neuralgia with botulinum toxin injection					
Taylor et al. 2008	Retrospective	6	12 wk	VPAM	Sharp/shooting pain significantly improved;
					Dull aching pain not significantly improved,
Kapural et al. 2007	Case series	6	4 wk	VAS	VAS 8.5 → 1
				PDI	PDI 56 → 17.5
Volcy et al. 2006	A case report	1	N/A	N/A	Improved temporarily
The treatment of Neuralgia with PRF					
Huang et al. 2012	Retrospective, multicenter	102	At least 3 mon	≥ 50% pain relief for at least 3 mon	51% positive result
Vanelderen et al. 2010	Prospective	19	1, 2, and 6 mon	VAS	52.6% significant improvement at 6 mon
				Likert scale	
Choi et al. 2012	Retrospective	10	6-10 mon	VAS, TPI	All patients improved

Table 1: Summarising various studies on Botulinum toxin injections for treatment of neuralgias

VPAM, visual analog pain and medication use diary; VAS, visual analog scale; PDI, pain disability index; N/A, not available; PRF, pulsed radiofrequency; TPI, total pain index; NRS, Numerical rating scale.

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• Pulsed radiofrequency treatment

A non-invasive method called pulsed radiofrequency (PRF) of the larger greater occipital nerve (GON) and lesser occipital nerve (LON) is recommended for the treatment of chronic pain with a variety of causes, including headaches. [36,37] Because of its non-destructive characteristics, PRF has a recognized neuromodulative effect, with the active tip's ultimate temperature never rising over 42°C [38]. It works by creating a weak electric field that reduces the transmission of pain across the neural pathways. Rather than on myelinated C-fibers, its primary influence is felt on unmyelinated ones [39,40]. The procedure is applied in accordance with established guidelines and a prior positive diagnostic block of the nerves using a local anesthetic [41].

The pain-relieving effects of pulsed radiofrequency [PRF] therapy is attributed to the suppression of pain signals traveling along sensory nerves as a result of the induction of a low- intensity electrical field around these nerves. The descending noradrenergic and serotonergic pathway may be modulated by PRF, according to animal research, resulting in pain alleviation [42, 43, 44]. Only a small number of papers have been written about using PRF to treat craniofacial neuralgia so far [Table 2]. All studies were cohort studies reporting observations but not controls.

The parameters employed in these various neuralgia tests for short- to medium-term pain control were as follows: voltage output of 40-60 V, frequency of 2 Hz, pulse width of 20 ms at a rate of 120 Hz per second, impedance range of 150- 500 W, and plateau temperature of 42°C. Treatment outcomes may be enhanced by paying close attention to selection criteria and treatment parameters, as suggested by the authors [44]. When the identical parameters were applied for each patient's unique electrical resistance, a 2013 study also discovered that the PRF output voltage varied. Furthermore, high-voltage PRF has been shown to be a successful therapy choice for TN patients in our later single-center trials [74, 75]. Research by Luo F et al. (2013) found that there was a significant difference ($p<0.05$) in the PRF output voltage between the effective and ineffective groups [45].

After a nerve block, many patients experienced pain reduction within a day of the treatment. However, over 40% of patients who received PRF needed time to recover before they experienced adequate pain relief [46, 47]. The explanation for this delayed impact might be that gradual neuromodulation brought on by PRF therapy can result in plastic changes in pain transmission pathways, which could make it take longer for certain patients to experience adequate pain relief. Therefore, pain managers should be aware of patient variability in pain response during PRF treatment. This may include continuing to prescribe sufficient anti-epileptic medications before obtaining appropriate analgesic effectiveness [48, 49].

• Non-invasive neuromodulation

Transcranial magnetic stimulation, electrical stimulation of the supraorbital nerve, and transcutaneous electrical stimulation of the vagus nerve are all examples of non-invasive neuromodulation. Self- administered non-invasive neuromodulation eliminates the requirement for invasive surgical procedures and all the risks and expenses that come with them [50, 51]. Using a therapeutic laser is one of these non-invasive techniques that lowers pain by decreasing histamine, acetylcholine, bradykinin, and prostaglandins locally. This decrease also causes an increase in serotonin, acetylcholinesterase, ATP, beta endocrines, enkephalins, aerobic metabolism, lymphatic drainage, and pain threshold concentrations. Nevertheless, there aren't much research on how well lasers work to treat trigeminal neuralgia pain [52]. Trigeminal neuralgia can also be treated non-invasively using transcranial direct current stimulation (tDCS). This technique preserves the neuromodulation effect even after electrical stimulation by varying the motor cortex's cortical excitability according to the anodal or cathodal direction of the electric current. Thus, N- methyl-D-aspartate (NMDA-R) receptors mediate a modulation membrane potential in neurons of the activated cortical region [53]. For more than 40 years, prolonged transcutaneous electrical nerve stimulation, or TENS, has been extensively utilized to reduce pain and cause hypoalgesia [54]. According to medical literature, it is useful in reducing both acute and chronic pain, including in neurological conditions like causalgia, carpal tunnel syndrome, peripheral neuropathy, and other miscellaneous disorders, as well as in muscle and connective tissue disorders like arthritis, backache, cervical pain, and bursitis [55, 56].

TENS creates electro-analgesia most likely via one or more of the following mechanisms: endogenous pain control (through endorphins, enkephalins, and dynorphins), direct inhibition of an abnormally excited nerve, and restoration of afferent input. Presynaptic inhibition occurs in the dorsal horn of the spinal cord. TENS is also affordable, non-invasive, safe, and has little adverse effects. Patients only need to follow basic instructions to self- administer the Treatment [57, 58]. In order to find out how transcutaneous electrical nerve stimulation (TENS) affected acupuncture sites and neck exercises in people with persistent neck discomfort, Thomas T. W. Chiu performed a research in 2005. He discovered that during the six-week course of therapy, patients in the exercise and TENS group showed greater and clinically meaningful improvements in pain, isometric neck muscular strength, and impairment. At the six-month follow-up, every improvement in the intervention groups had persisted [59].

There are very few published studies that expressly utilize or suggest TENS for the treatment of trigeminal neuralgia. Cheing et al's study investigated the clinical effectiveness of

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high-frequency transcutaneous electrical nerve stimulation (TENS) in reducing hand hypersensitivity. Nineteen patients with this condition were randomly assigned to either a treatment group or a placebo group. The tactile tolerance of the hand was measured using a visual analogue scale and the Downey Hand Centre Hand Sensitivity Test, while grip strength was assessed with a grip dynamometer. Over a period of two weeks, patients received daily applications of electrical stimulation. By Day 7 and Day 11, the treatment group showed significantly lower pain scores compared to the placebo group. Additionally, the treatment group had significantly higher rankings in the Downey Hand Centre Hand Sensitivity Test by the same days. However, there was no significant difference between the groups in terms of grip strength.[59] Similae study was conducted in 1994 by Bourke et al with similar results [60].

Neuromodulation technique	Disorder and treatment strategy		Level of evidence	Grade of recommendation
Transcutaneous stimulation	Migraine	Symptomatic	2	B
of the supraorbital		treatment		
nerve		Prevention	2	B
Single-pulse transcranial magnetic stimulation	Migraine	Symptomatic treatment	2	B
		Prevention	3	B
Non-invasive vagus nerve	Migraine	Symptomatic	2	A
stimulation		treatment		
		Prevention	2	B
	Cluster headache	Symptomatic	1	B
		treatment		
		Prevention	2	A
Invasive neuromodulation of terminal branches of the trigeminal nerve	Prevention in trigeminal neuralgia, painful trigeminal neuropathy, persistent idiopathic facial pain		4	C
Invasive stimulation of the trigeminal tract	Prevention in trigeminal neuralgia, painful trigeminal neuropathy, persistent idiopathic facial pain		4	C
Invasive stimulation of the	Cluster headache	Symptomatic	2	A
sphenopalatine ganglion		treatment		
		Prevention	3	B
Invasive stimulation of the	Occipital neuralgia	Prevention	3	B
occipital nerves	Cluster headache	Prevention	3	B
	Other TAC	Prevention	4	C
Cervical spinal cord stimulation	Prevention in cluster headache, migraine, trigeminal neuralgia, painful trigeminal neuropathy, persistent idiopathic facial pain		4	C
Transcortical brain stimulation	Prevention in trigeminal neuralgia, painful trigeminal neuropathy, persistent idiopathic facial pain		4	C
Deep brain stimulation of	Cluster headache	Prevention	2	B
the hypothalamus	Other TAC	Prevention	4	C
Deep brain stimulation of the thalamus	Prevention in trigeminal neuralgia, painful trigeminal neuropathy, persistent idiopathic facial pain		4	C

Table 2: Summarizing various neuromodulation techniques and their level of incidence and recommendation grade.

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Conclusion

In conclusion, neuropathic pain affecting millions globally presents a significant public health concern, particularly in the maxillofacial region where the mastication process plays a crucial role. Psychological stress is implicated in the onset and progression of chronic pain conditions, emphasizing the complex nature of pain experiences. Despite being a primary indicator of oral and dental issues, pain in this region often presents alongside various other symptoms, complicating diagnosis. Neuralgia, characterized by unilateral pain and recurrent attacks, poses diagnostic challenges, especially when overlapping with other conditions like temporomandibular disorders. Non-invasive treatments, including physiotherapy, pharmacological management, local anesthetic injections, botulinum toxin infiltrations, pulsed radiofrequency treatment, and non-invasive neuromodulation techniques, offer diverse options for managing head and neck neuralgia. These treatments target different aspects of pain pathways, providing relief and improving quality of life for patients. However, accurate diagnosis and individualized treatment plans remain paramount, considering the complexity of orofacial pain disorders and the need for comprehensive clinical assessment. Continued research and clinical evaluation are necessary to advance understanding and improve the efficacy of non-invasive treatments for head and neck neuralgia. Collaborative efforts between clinicians, researchers, and patients are essential for developing tailored approaches that address the multifaceted nature of neuropathic pain and ultimately enhance patient outcomes and well-being.

Acknowledgement: XXXXXX

Fundings: N/A

Conflicts of Interest: None

References

1. Sanders, Anne E and Gary D. Slade. "Gender modifies effect of perceived stress on o orofacial pain symptoms: National Survey of Adult Oral Health." Journal of orofacial p aim 25 (2011): 4.
2. Okeson, Jeffrey P., and Welden E. Bell. "Bell's orofacial pains" 1 (1995): 15-25
3. Kreisberg, Michael K, et al. "The scope of TMD/ orofacial pain (head and neck pain m management) in contemporary dental practice." Journal of Oral & Facial Pain and Headache 11 (1997): 78-83
4. Khan, Mohammad, et al. "Trigeminal neuralgia, glossopharyngeal neuralgia, and myofascial pain dysfunction syndrome: an update." Pain Research and Management (2017).
5. Tesseroli De Siqueira JT, Ching LH, Nasri C, et al. "Clinical study of patients with persistent orofacial pain," Arquivos de Neuro-Psiquiatria 62 (2004): 988–996,
6. Garven A, S. Brady S, Wood, et al, "The impact of enrollment in a specialized interdisciplinary neuropathic pain clinic," Pain Research and Management 16 (2011): 159–168.
7. I Gilron, SL Booher, JS Rowan, B Smoller and MB Max, "A randomized, controlled trial of high-dose dextromethorphan in facial neuralgias," Neurology 55 (2000): 964–971.
8. Headache Classification Subcommittee of the International Headache Society. "The international classification of headache disorders." cephalalgia 24 (2004): 9-160.
9. Minor, Marian A, Marilyn, K Sanford. "The role of physical therapy and physical modalities in pain management." Rheumatic Disease Clinics of North America 25 (1999): 233- 248.
10. Nadler, Scott F. "Nonpharmacologic management of pain." Journal of Osteopathic Medicine 104 (2004): 6-12.
11. De Leeuw, Reny and Gary D. Klasser, eds. Orofacial pain: guidelines for assessment, diagnosis, and management. Hanover Park, IL, USA: Quintessence Publishing Company, Incorporated (2018).
12. Danzig WN, Van Dyke AR. Physical therapy as an adjunct to temporomandibular join t therapy. J Prosthet Dent 49 (1983): 96–99.
13. McNeill C. "Epidemiology. Temporomandibular Disorders: Guidelines For Classification, Assessment, and Management" (1993): 19-22.
14. Rodrigues, Delaine, Anamaria Oliveira Siriani and Fausto Bérzin. "Effect of conventional TENS on pain and electromyographic activity of masticatory muscles in TMD patients." Brazilian oral research 18 (2004): 290-295.
15. Yeng, Lin Tchia, et al. "Medicina física e reabilitação em doentes com dor crônica." Revista de Medicina 80 (2001): 245-255
16. Lietz-Kijak, Danuta, et al. "Assessment of the short-term effectiveness of kinesiotapin g and trigger points release used in functional disorders of the masticatory muscles." Pain research and management (2018).
17. Kopacz, Łukasz, et al. "Comparative analysis of the influence of selected physical factors on the level of pain in the course of temporomandibular joint disorders." Pain Rese arch and Management (2020).
18. Bovim G, Sjaastad O. Cervicogenic headache: responses

to sic and therapeutic aspects of botulinum and tetanus toxins, nitroglycerin, oxygen, ergotamine and morphine. Headache Hannover, Germany. Naunyn Schmiedebergs Arch Pharmacol 33 (1993): 249-52

19. Castien, René, and Willem De Hertogh. "A neuroscience perspective of physical treatment of headache and neck pain." Frontiers in neurology 10 (2019): 276.
20. Mu, Alex, et al. "Pharmacologic management of chronic neuropathic pain: Review of the Canadian Pain Society consensus statement." Canadian Family Physician 63 (2017): 844- 852.
21. Côté, Pierre, et al. "Non- pharmacological management of persistent headaches associated with neck pain: A clinical practice guideline from the Ontario protocol for traffic injury management [OPTIMa] collaboration." European journal of pain 23 (2019): 1051-1070.
22. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain 152 (2011): 1018-23
23. Tfelt-Hansen, P., et al. "Ergotamine in the acute treatment of migraine: a review and European consensus." Brain 123 (2000): 9-18.
24. Ashkenazi A and M Levin. "How to manage trigeminal, occipital, and postherpetic pain." POSTGRADUATE MEDICINE 116 (2004): 16-36.
25. Dubrovsky, Alexander Sasha. "Nerve blocks in pediatric and adolescent headachedisorders."Current Pain and Headache Reports 21 (2017): 1-6.
26. Schiffer CA, Sanel FT, Young VB, Aisner J. Reversal of granulocyte adherence to nyl on fibers using local anesthetic agents: possible application to filtration leukapheresis. Blood 50 (1977): 213-25
27. Tsuda Y, Mashimo T, Yoshiya I, Kaseda K, Harada Y, Yanagida T. Direct inhibition of the actomyosin motility by local anesthetics in vitro. Biophys J 71 (1996): 33-41.
28. Wilkinson HA: Trigeminal nerve peripheral branch phenol/glycerol injections for tic douloureux. J Neurosurg 90 (1999): 828-832.
29. Shim, Jae Hang, et al. "Ultrasound-guided greater occipital nerve block for patients with occipital headache and short term follow up." Korean Journal of Anesthesiology 61 (2011): 50-54.
30. GoÈbel, Hartmut, et al. "Botulinum toxin A in the treatment of headache syndromes and pericranial pain syndromes." Pain 91 (2001): 195-199.
31. Aoki, K. Roger. "Evidence for antinociceptive activity of botulinum toxin type A in pain management." Headache: The Journal of Head and Face Pain, Volume 43 (2003): 9-15.
32. Li, Cuiping, et al. "Substance p is essential for maintaining gut muscle contractility: a novel role for neurotransmission revealed by botulinum toxin". American Journal of Physiology-Gastrointestinal and Liver Physiology 306 (2014): G839-G848
33. Harden, R. Norman, et al. "Botulinum toxin A in the treatment of chronic tension- typ e headache with cervical myofascial trigger points: a randomized, double- blind, placebo- controlled pilot study." Headache: The Journal of Head and Face Pain 49 (2009): 732-743.
34. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effectfrom a randomized, double-blind, placebo-controlled trial. J Headache Pain 27 (2014): 65
35. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, et al. Botulinum toxintype A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia 32 (2012): 443-50
36. Shehata HS, El-Tamawy MS, Shalaby NM, Ramzy G. Botulinum toxin-type A: could it be an effective treatment option in intractable trigeminal neuralgia? J Headache Pain 19 (2013): 92.
37. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien) 153 (2011): 763–71.
38. Bogduk N. Pulsed radiofrequency. Pain Med 7 (2006): 396–407.
39. Abejon D, Reig E. Is pulsed radiofrequency a neuromodulation technique? Neuromodulation 6 (2003): 1–3
40. Brasil LJ, Marroni N, Schemitt E, Colares J. Effects of pulsed radiofrequency on a sta ndard model of muscle injury in rats. Anesth Pain Med 10 (2020): e97-372.
41. Vanneste T, Van Lantschoot A, Van Boxem K, Van Zundert J. Pulsed radiofrequency in chronic pain. Curr Opin Anaesthesiol 30 (2017): 577-82.
42. Gooriah R, Nimeri R, Ahmed F. Evidence-based treatments for adults with migraine. Pain Res Treat (2015): 629382
43. Byrd D, Mackey S. Pulsed radiofrequency for chronic pain. Curr Pain Headache Rep 12 (2008): 37-41.
44. Luo F, Meng L, Wang T, Yu X, Shen Y, Ji N. Pulsed

radiofrequency treatment for idiopathic trigeminal neuralgia: a retrospective analysis of the causes for ineffective pain relief. Eur J Pain 17 (2013): 1189-1192.

45. Luo F, Wang T, Shen Y, Meng L, Lu J, Ji N. High voltage pulsed Radiofrequency for the treatment of refractory neuralgia of the Infraorbital nerve: a prospective double-blinded randomized controlled study. Pain Physician 20 (2017): 271-279

46. Shrestha N, Wang X, Wang T, Luo F. The long-term outcome of CT-Guided pulsed Radiofrequency in the treatment of idiopathic glossopharyngeal neuralgia: a retrospective Multi Centre Case Series J pain Res 13 (2020): 2093-2102

47. Zipu J, Hao R, Chunmei Z, Lan M, Ying S, Fang L. Long-term follow-up of pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier analysis in a Consecutive Series of 149 patients. Pain Physician 24 (2021): E1263-e1271

48. Tanaka N, Yamaga M, Tateyama S, Uno T, Tsuneyoshi I, Takasaki M. The effect of pulsed radiofrequency current on mechanical allodynia induced with resiniferatoxin in rats. Anesth Analg 111 (2010): 784–790.

49. Jones RC, Lawson E, Backonja M. Managing neuropathic pain. Med. Clin. Nort h Am 100 (2016): 151–167

50. Weber K. Neuromodulation and devices in trigeminal neuralgia. Headache 57 (2017): 1648-1653.

51. Antony AB, Mazzola AJ, Dhaliwal GS, Hunter CW. Neurostimulation for the treatment of chronic head and facial pain: A literature review. Pain Physician 22 (2019): 447–477.

52. Choi, Hyuk Jai, et al. "Clinical outcomes of pulsed radiofrequency neuromodulation for the treatment of occipital neuralgia." Journal of Korean Neurosurgical Society 51 (2012): 281-285

53. Yameen F, Shahbaz NN, Hasan Y, Fauz R, Abdullah M. Efficacy of transcutaneous electrical nerve stimulation and its different modes in patients with trigeminal neuralgia. J Pak Med Assoc 61 (2011): 437–439.

54. Emedicine Medscape Overview: Transcutaneous Electrical Nerve Stimulation.

55. MANNHEIMER C, CARLSON C-A. The analgesic effects of transcutaneous electrical nerve stimulation (TNS) in patients with rheumatoid arthritis. A comparative study of different pulse patterns. Pain 6 (1979): 329-34.

56. Rutgers MJ, Van Romunde LKJ, Osman PO. A small randomized comparative trial of acupuncture versus transcutaneous electrical neuro- stimulation in postherpetic neuralgia. Pain Clinic 2 (1988): 87-9.

57. Sweet WH and Wepsic JG. Treatment of chronic pain by stimulation: of fibers of primary afferent neuron, Trans. Amer. neurol. Ass 93 (1968): 103-105.

58. Chiu TT, Hui-Chan CW, Chein G. A randomized clinical trial of TENS and exercise for patients with chronic neck pain. Clin Rehabil 19 (2005): 850-60.

59. Cheing GLY, Luk MLM. Transcutaneous electrical nerve stimulation for neuropathic pain. Journal of Hand Surgery, European 30 (2005): 50-5.

60. Bourke D. TENS vs placebo. Pain 56 (1994): 122