REFRACTORY TRIGEMINAL NEURALGIA: IS BOTULINUM THE ANSWER?

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Abstract:
Patient Case: The diagnosis of classical trigeminal neuralgia was made in a 58-year-old, otherwise healthy male patient who presented with sharp, electric shock like unilateral pains to his left cheek and eye. He continued to be symptomatic after titrated medical management with carbamazepine and baclofen, with candidacy for surgery uncertain.
Literature Review: A search in the PubMed databases found that botulinum toxin A may offer an alternative to medical management with carbamazepine or other first line agents. The side effect profile is mild and the efficacy has been found to be comparable and in some cases even supersede treatment with carbamazepine. However, due to limited research, botulinum toxin A is not currently recommended as first line therapy in classical or refractory trigeminal neuralgia.
Summary: Trigeminal neuralgia is a neuropathic pain condition that has been traditionally treated with medical management or surgery. Emerging evidence suggests that botulinum toxin A provides comparable results for pain relief, attack frequency and overall treatment response compared to carbamazepine. It should be considered as first line therapy for refractory and classic trigeminal neuralgia once the evidence becomes available.

Case Presentation:

A 58-year-old male presented to clinic in February 2016 with intermittent electrical pain on the left side of his cheek and below his left eye that had been ongoing for the past week, occurring at least five times a day. At that point, the pain could be elicited with light pressure but had not progressed. He was afebrile and his review of systems was unremarkable. He was started on CBZ 400mg daily and sent for a CT to rule out any possible secondary causes, which came back negative. The patient was sent for a neurological consult in March 2016 for further assessment and recommendation on treatment duration. His symptoms were well controlled on CBZ 400mg daily until June 2016, when he began experiencing increased pain and pain triggered with eating. At that point, his dose of CBZ was increased to 600mg daily and a starting dose of baclofen was added. In July 2016, the patient presented again with progressing symptoms and the neurologist increased his dose of CBZ to 400mg in the morning, 100mg at noon and 400mg in the evening, and baclofen was increased to 5mg TID. From July 2016 to December 2016, his symptoms appeared well controlled and the baclofen dose was reduced to 5mg BID. His symptoms continued to be well managed at the patient's follow up appointment in March 2017 and his dose of baclofen was reduced to 5mg once daily.

The patient presented to clinic on June 15th with abrupt progression of his symptoms that had become worse at night and were elicited with both eating and showering. His CBZ dose remained 400mg/100mg/400mg but the baclofen was increased from 5mg OD to 5mg both in the morning and at noon, and 10mg at night when his symptoms were at their worst. He returned two weeks later with even worse symptoms and attacks happening at least three times a day. He described a "Taser" sensation and while it no longer hurt when he showered or touched lightly, eating still caused him an unbearable amount of pain. In an attempt to better control his symptoms, his noon dose of CBZ was doubled (200mg compared to 100mg) and his CBZ levels were measured, which came back at 9.1 (within the therapeutic window). On July 12th he returned to clinic still experiencing the same "Taser" feeling with multiple episodes a day that were completely preventing him from eating, resulting in weight loss. The decision was made to increase his CBZ dose to 400mg TID, keep his baclofen at the same dose, and consult neurology for advise on how to proceed with management.

Literature Review:

Table 1. Search terms and number of results generated from *PubMed MeSH*

Search Number	Search Term	MeSH Term	Number of Results
1	Trigeminal Neuralgia	Trigeminal Neuralgia [Majr]	4,876
2	Treatment	Therapeutics [Mesh]	3,824,906
3	Carbamazepine	Carbamazepine [Mesh]	10,322
4	Baclofen	Baclofen [Mesh]	5,205
5	Botulinum toxin	Botulinum Toxins, Type A [Majr]	6,056

Table 2. Search results using *PubMed Advanced Search* and filters: "within 5 years", "full text", and "English".

Search[a]	Number of Results	Citations Used
1 + 2	284	Al-quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. *NeuroSciences*. 2015;20(2):107-114. doi:10.17712/nsj.2015.2.20140501.
		Burmeister J, Holle D, Bock E, Ose C, Diener H, Obermann M. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. *Trials*. 2015;16(550):1-10. doi:10.1186/s13063-015-1052-z.
1 + 2 + 3	19	Amanat D, Ebrahimi H, Lavaee F, Alipour A. The Adjunct Therapeutic Effect of Lasers with Medication in the Management of Orofacial Pain: Double Blind Randomized Controlled Trial. *Photomed Laser Surg*. 2013;31(10):474-479.
1 + 2+ 3+ 4	0	n/a
1 + 3 + 4	1	n/a
1 + 4	1	n/a
1 + 3	29	Cruccu G, Truini A. Refractory Trigeminal Neuralgia Non-Surgical Treatment Options. *CNS Drugs*. 2013;27(2):91-96. doi:10.1007/s40263-012-0023-0.
1 + 2 + 5	6	Yang KY, Kim MJ, Ju JS, et al. Antinociceptive Effects of Botulinum Toxin Type A on Trigeminal Neuropathic Pain. *J Dent Res*. 2016;95(10):1183-1190. doi:10.1177/0022034516659278.
		Li S, Ya-Jun L, Chen Y, et al. Therapeutic effect of Botulinum toxin-A in 88 patients with Trigeminal Neuralgia with 14-month follow-up. *J Headache Pain*. 2014;15(43):1-6.
		Xia J, He C, Zhang H, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. *Int J Neurosci*. 2016;126(4):348-353. doi:10.3109/00207454.2015.1019624.

[a] numbers used refer to search numbers from table 1

Discussion:

DIAGNOSTIC PROCESS AND OUTCOMES

The diagnosis of TN is clinical. In the case of classical TN, it is sometimes referred to as "idiopathic" since most often the exact aetiology remains unknown.[1] This is because in order to determine the exact cause, invasive and expensive testing would need to be conducted and the results often do not dramatically change management.[1] TN is considered refractory when patients continue having multiple attacks per day despite therapeutic levels of medications.[1] First line therapy for TN is either with Carbamazepine (CBZ) or Oxcarbazepine (OXC).[2] Second line therapy most often includes either lamotrigine or baclofen.[2] Third line therapy options include gabapentin, pregablin, topirmate, and botinum toxin.[2] CBZ doses exceeding 600mg/day tend to cause intolerable side effects and may cause severe drug-drug interactions, limiting its use.[3] Other modalities must be considered when medical management has been exhausted and surgical treatment is not applicable.

RELEVANT LITERATURE

The American Academy of Neurology and the European Federation of Neurological Societies suggest that CBZ (400-1200mg/day) or OXC (900-1800mg/day) be used as first line therapy for treatment of TN.[4] They also suggest that surgery be pursued if therapeutic levels of these drugs cannot be reached due to limitations in dosing (such as intolerable side effects) or if patients experience refractory symptoms despite maximal therapy.[4] For those with refractory TN there are very few treatment options available other than surgery, and even fewer among them are proven to be effective.[4] Alternative therapy such as laser therapy was also found to be ineffective against TN orofacial pain.[5] Botulinum toxin A, previously considered a third line therapy option, is now being reviewed for its potential as a first line therapeutic. This is because of its favourable side effect profile and the efficacy, which is comparable or may even supersede that of CBZ.[4] Studies have shown that therapeutic doses of botulinum toxin A may be as low as 6-9IU and significant symptom relief can be achieved in patients with as little as one low-dose injection.[4,6] The need for research of other therapeutics for TN management is evident in the fact that only about 50% of patients being treated with CBZ or OXC actually remain responsive long-term.[3] Not only that, but often the therapy is limited as a result of intolerable side effects (ataxia, fatigue, vertigo, and drug interactions) when the dose of CBZ exceeds 600mg/day.[3]

A study was conducted in which 88 patients with classic TN were treated with 3 different doses of botulinum toxin A (0.1, 1 and 3U/kg) and followed up after 14 months to evaluate two primary end points: pain severity, using the visual analog score (VAS), and attack frequency per day.[7] The results found that all 88 patients showed symptom improvement in 2 weeks after treatment and that symptoms were entirely controlled within 3 months in 46 of the cases.[7] The effect of the toxin diminished after 3 months but 38.6% of subjects still experienced symptom relief and 25% had complete control of their TN beyond 14 months.[7] Of the 54 patients who experienced diminished efficacy, 40 of them chose re-injection over medical therapy or surgery.[7] Another study found that therapy with botulinum toxin A not only provided statistically significant improvement in TN pain, but that it also provided statistically significant improvement in reducing rates of depression, anxiety and sleep interference, and in many cases even cured them entirely.[8] There were very limited side effects experienced by patients including local swelling and muscle relaxation but all of them were transient and required little or no treatment.[8]

Conclusion:

Based on this literature review, botulinum toxin A may be an appropriate next step in management for this patient. The evidence thus far suggests that botulinum toxin A may be an equivalent or superior treatment for TN compared to CBZ, especially for patients with refractory TN. However, the mechanism of analgesia in TN is not well understood and long-term studies are lacking. More research is required in order to support the use of botulnium toxin A as a mainstream treatment modality and to better determine dose titration and maximize the therapeutic effect.

References:

1. Bajwa ZH, Ho CC, Khan SA. Trigeminal Neuralgia. In: Post T, ed. *Up To Date*. Waltham, MA: Wolters Kluwer; 2017. https://www-uptodate-com.uml.idm.oclc.org/contents/trigeminal-neuralgia?source=search_result&search=trigeminal neuralgia&selectedTitle=1~150.
2. Al-quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. *NeuroSciences*. 2015;20(2):107-114. doi:10.17712/nsj.2015.2.20140501.
3. Burmeister J, Holle D, Bock E, Ose C, Diener H, Obermann M. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. *Trials*. 2015;16(550):1-10. doi:10.1186/s13063-015-1052-z.
4. Cruccu G, Truini A. Refractory Trigeminal Neuralgia Non-Surgical Treatment Options. *CNS Drugs*. 2013;27(2):91-96. doi:10.1007/s40263-012-0023-0.
5. Amanat D, Ebrahimi H, Lavaee F, Alipour A. The Adjunct Therapeutic Effect of Lasers with Medication in the Management of Orofacial Pain: Double Blind Randomized Controlled Trial. *Photomed Laser Surg*. 2013;31(10):474-479.
6. Yang KY, Kim MJ, Ju JS, et al. Antinociceptive Effects of Botulinum Toxin Type A on Trigeminal Neuropathic Pain. *J Dent Res*. 2016;95(10):1183-1190. doi:10.1177/0022034516659278.
7. Li S, Ya-Jun L, Chen Y, et al. Therapeutic effect of Botulinum toxin-A in 88 patients with Trigeminal Neuralgia with 14-month follow-up. *J Headache Pain*. 2014;15(43):1-6.
8. Xia J, He C, Zhang H, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. *Int J Neurosci*. 2016;126(4):348-353. doi:10.3109/00207454.2015.1019624.