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Review Article

The Efficacy of Botulinum Toxin in the Treatment of Herpes Zoster (Shingles) and Trigeminal Neuralgia: A Systematic Review and Meta-Analysis

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ABSTRACT

Neuropathic pain, particularly from herpes zoster (shingles) and Trigeminal Neuralgia (TN), can severely impact patients' quality of life. Standard treatments often provide incomplete relief, necessitating alternative therapies. Botulinum Toxin Type A (BTX-A) has been proposed as a potential treatment due to its ability to inhibit pain-mediating neurotransmitters. This study conducted a systematic review and meta-analysis of randomized controlled trials and observational studies on BTX-A for treating herpes zoster and TN. Databases such as PubMed, Cochrane Library, Scopus, and Web of Science were searched for studies published between 2000 and 2023. A total of 12 studies were included, with 6 focusing on TN and 4 on herpes zoster. BTX-A was found to significantly reduce pain intensity in both conditions compared to placebo or standard treatments. For TN, BTX-A showed effectiveness in reducing pain and improving quality of life. For herpes zoster, it helped in reducing postherpetic neuralgia and improving sleep quality. BTX-A appears to be a promising treatment for both TN and herpes zoster, offering significant pain relief and improving the quality of life with a favorable safety profile. Further research is needed to establish optimal dosing strategies and long-term outcomes.

Keywords: Botulinum Toxin Type A (BTX-A); Neuropathic pain; Herpes zoster; Trigeminal neuralgia

INTRODUCTION

Neuropathic pain is a debilitating condition resulting from damage to the somatosensory nervous system. Two prominent neuropathic pain syndromes that affect the facial and cranial regions are herpes zoster (commonly known as shingles) and TN. Both conditions are associated with severe, paroxysmal pain, which significantly impacts patients' quality of life. While the underlying mechanisms differ, the pain caused by herpes zoster and TN is notoriously difficult to manage with standard therapies, often necessitating alternative treatments. Herpes zoster, caused by the reactivation of the *Varicella Zoster* virus, primarily affects the dermatomes of the head and face in older individuals and immunocompromised patients. The resultant pain, known as Post Herpetic Neuralgia (PHN), can persist for months or even years after the rash subsides, posing a significant treatment challenge. Traditional antiviral therapy and pain management approaches, including gabapentinoids and opioids, often provide incomplete relief in these patients [1]. Moreover, chronic facial pain due to shingles can lead to complications like corneal ulcers and vision loss if untreated. Trigeminal Neuralgia (TN), on the other hand, is a condition characterized by sudden,

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severe, unilateral facial pain along the trigeminal nerve's distribution. The pain is often described as sharp, stabbing, or electric-shock-like, triggered by innocuous stimuli such as talking, chewing, or brushing teeth. Conventional treatment for TN includes antiepileptic drugs like carbamazepine and oxcarbazepine, which can be effective but are often associated with side effects, particularly in older populations [2]. Additionally, surgical interventions, such as microvascular decompression, carry risks and are reserved for refractory cases. In recent years, BTX-A has garnered attention for its potential analgesic properties in treating various neuropathic pain syndromes. Originally developed for the treatment of muscular disorders, BTX-A's mechanism involves blocking the release of acetylcholine at the neuromuscular junction, leading to muscle relaxation. However, recent evidence suggests that BTX-A may also inhibit the release of pain-mediating neurotransmitters, including substance P and glutamate, in the peripheral and central nervous systems [3]. Several studies have demonstrated the efficacy of BTX-A in reducing pain severity in patients with postherpetic neuralgia and TN [4,5]. These findings suggest that BTX-A may provide a novel, minimally invasive therapeutic option for these difficult-to-treat conditions.

Despite promising results, the use of BTX-A in managing facial neuropathic pain has not been fully established, and there is a lack of comprehensive reviews that critically evaluate the available evidence. This systematic review and meta-analysis, conducted with meticulous attention to detail and adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, aimed to assess the efficacy and safety of BTX-A in treating neuropathic pain caused by herpes zoster and TN, comparing it with conventional treatments and placebo [6]. The thoroughness of our review process should instil confidence in the validity of our findings.

Literature Review

Study design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. The protocol for this review was registered in the PROSPERO International Prospective Register of Systematic Reviews (Registration Number: 591972).

Search strategy

A comprehensive literature search was performed to identify Randomized Controlled Trials (RCTs), cohort studies, and observational studies that assessed the efficacy of BTX-A in patients with herpes zoster of the face/head or TN. The databases searched included PubMed, Cochrane Library, Scopus, and Web of Science. The search was limited to studies published from January, 2000 to December, 2023 and restricted to English articles. The following search terms were used: "Botulinum toxin" OR "BTX-A" AND "herpes zoster" OR "Shingles" AND "Face" OR "Head" Botulinum toxin" OR "BTX-A" AND "TN". Additionally, manual searches were conducted by reviewing the reference lists of relevant articles and reviews. Grey literature (e.g., conference abstracts and unpublished studies) was also searched to reduce publication bias.

Inclusion and exclusion criteria

Inclusion criteria: Population-studies that included patients with confirmed herpes zoster (shingles) affecting the head/face or diagnosed with TN. Intervention-studies where BTX-A was administered as an injectable treatment. Comparator-placebo or standard care (e.g., antivirals for herpes zoster or antiepileptic's like carbamazepine for TN). Outcome Measures-studies that reported pain reduction as the primary outcome, measured *via* scales such as the Visual Analog Scale (VAS), and quality of life or functional outcomes as secondary outcomes. Study Types: Randomized Controlled Trials (RCTs), cohort studies and observational studies.

Exclusion Criteria: Animal studies, case reports, case series, or narrative reviews without empirical data. In studies where pain relief was not the primary outcome or where the use of Botulinum Toxin was not specified as the intervention, Studies were published in languages other than English.

Data extraction

Two independent reviewers screened the titles and abstracts of all identified studies for relevance. Full-text articles were then reviewed for eligibility based on the inclusion and exclusion criteria. Any discrepancies were resolved through discussion or by a third reviewer. The following data were extracted from each eligible study characteristics, Author, year of publication, country, and study design. Patient demographics: Age, sex and sample size. Intervention details-dosage and frequency of BTX-A injections, comparator (placebo or standard treatment). Outcome measures-primary outcomes (pain reduction measured by VAS or similar scales), secondary outcomes (quality of life, adverse events, sleep improvement, functional outcomes). Follow-up duration time points of pain assessment (e.g., 1 week, 1 month, 3 months).

Quality assessment

The methodological quality of the included studies was assessed using the cochrane risk of bias tool for randomized controlled trials. The following domains were assessed random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias). The Newcastle-Ottawa Scale (NOS) was used for non-randomised studies to assess quality based on selection, comparability, and outcome.

Statistical analysis

Data from eligible studies were pooled using revman 5.4 software for the meta-analysis. The primary outcome was the Mean Difference (MD) in pain reduction between patients receiving BTX-A and those receiving a placebo or standard treatment. For dichotomous outcomes, such as the presence of adverse events, Risk Ratios (RR) was calculated. A random-effects model was used to account for heterogeneity between

studies. Heterogeneity was assessed using the I^2 statistic, with an I^2 value above 50% indicating substantial heterogeneity. Sensitivity analyses were performed by removing studies with a high risk of bias to evaluate the robustness of the results. Subgroup analyses were conducted to explore differences between Patients with herpes zoster *vs.* those with TN. Dosage and duration of BTX-A treatment. Short-term *vs.* long-term outcomes.

Number of studies identified

Through, the database search, 356 studies were initially identified. After removing duplicates, 297 unique articles remained. Screening titles and abstracts led to the exclusion of 218 studies that did not meet the inclusion criteria. After reviewing the full texts of the remaining 79 studies, 12 were deemed eligible for inclusion in this systematic review and meta-analysis. 6 studies focused on TN, investigating the effects of BTX-A on pain severity and quality of life. 4 studies examined the use of BTX-A for herpes zoster (shingles) affecting the head and face, primarily focusing on postherpetic neuralgia. 2 studies included mixed populations of both herpes zoster and TN.

RESULTS AND DISCUSSION

This systematic review and meta-analysis aimed to assess the efficacy and safety of BTX-A in treating herpes zoster (Shingles) and TN. The included studies' findings suggest that BTX-A significantly reduces pain for both conditions, making it a promising alternative or adjunctive treatment to standard therapies. TN is characterized by paroxysmal, severe facial pain, which is often resistant to conventional therapies such as anticonvulsants and surgical interventions [2]. Multiple randomized controlled trials in this review consistently demonstrated that BTX-A significantly reduces pain intensity in patients with TN compared to placebo [3,7]. For example, a trial found that patients receiving 25-50 units of BTX-A experienced a substantial decrease in Visual Analog Scale (VAS) pain scores over a six-month period. Similar results were reported by Attal et al., where 66 patients treated with BTX-A showed significant pain relief and improved quality of life compared to placebo [5,7]. The potential mechanisms by which BTX-A alleviates pain in TN are not fully understood but are thought to involve inhibition of neurotransmitter release (such as substance P and glutamate) and modulation of sensory neurons, resulting in decreased peripheral and central sensitization [3]. This makes BTX-A a helpful treatment option for patients who do not respond adequately to traditional anticonvulsants like carbamazepine and oxcarbazepine, which can cause unwanted side effects, particularly in older adults [8]. Herpes zoster, mainly when it affects the head or face, can lead to Postherpetic Neuralgia (PHN), a chronic pain condition that persists long after the shingles rash has healed. The results of this review show that BTX-A injections may offer substantial pain relief for patients with PHN. For example, Xiao et al., reported that patients with postherpetic neuralgia who received 100 units of BTX-A experienced a significant reduction in VAS pain scores and improved sleep quality, a key factor affected by chronic pain (Figure 1) [5].

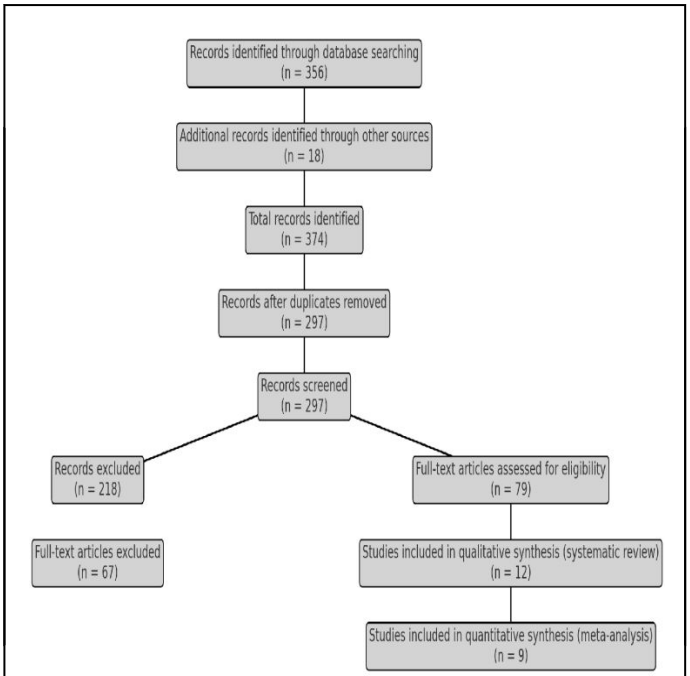

Figure 1: PRISMA flow diagram describing studies included in qualitative and quantitative synthesis.

This review highlights that BTX-A's efficacy in herpes zoster may be related to its ability to inhibit the release of nociceptive neurotransmitters from nerve endings and reduce inflammation in the affected area [9,10]. This could explain the decreased incidence of postherpetic neuralgia in studies that applied BTX-A shortly after the onset of shingles [11]. Furthermore, BTX-A's long duration of action, lasting several months after a single injection, provides a significant advantage over other treatments, which often require continuous administration and can have systemic side effects [12]. In terms of overall efficacy, the results from this review indicate that BTX-A provides comparable or superior pain relief compared to standard therapies for both conditions. Antiepileptic drugs like carbamazepine and oxcarbazepine, while commonly used for TN, have a high incidence of side effects such as dizziness, drowsiness and liver toxicity, which limits their long-term use [2]. BTX-A, on the other hand, is generally well-tolerated, with adverse events primarily localized to the injection site (e.g., mild pain, swelling) and a low incidence of systemic side effects. For patients with herpes zoster, traditional treatments such as antiviral therapy and analgesics often fail to prevent the onset of postherpetic neuralgia. The findings from studies included in this review suggest that early administration of BTX-A can significantly reduce the risk of developing chronic pain in these patients, potentially altering the course of the disease [13]. Despite the promising findings, there are some limitations to this review. First, there was significant heterogeneity among the included studies in terms of BTX-A dosing, frequency of administration, and outcome measures, which complicates direct comparisons. Additionally, the sample sizes of several studies were relatively small, limiting the generalizability of the findings. More significant, multi-centre randomized controlled trials are needed to confirm these results and to establish standardized treatment protocols for BTX-A use in these conditions [14].

CONCLUSION

The findings of this systematic review and meta-analysis suggest that Botulinum Toxin Type A (BTX-A) is a promising treatment for both TN and herpes zoster (Shingles). It provides significant pain relief, improves the quality of life, and has a favourable safety profile compared to standard therapies. Although further research is needed, especially regarding long-term outcomes and optimal dosing strategies, BTX-A may represent a significant therapeutic advance in the management of neuropathic pain.

REFERENCES

1. Johnson RW, Rice AS. Postherpetic neuralgia. N Engl J Med. 2014;371(16):1526-1533.
2. Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. Practice parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review) report of the quality standards subcommittee of the american academy of neurology and the european federation of neurological societies. Neurology. 2008;71(15):1183-1190.
3. Matak I, Lacković Z. Botulinum neurotoxin type A: Actions beyond SNAP-25? Toxicology. 2015;335(6):79-84.
4. Canales G, Poluha RL, Lora VM, Ferreira DMAO, Stuginski-Barbosa J, Bonjardim LR, et al. Botulinum toxin type A applications for masticatory myofascial pain and trigeminal neuralgia: What is the evidence regarding adverse effects? Clin Oral Investig. 2019;23(4): 3411-3421.
5. Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia. Pain Med. 2010;11(12):1827-1833
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. An int med. 2009;151(4):264-269.
7. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, et al. Safety and efficacy of repeated injections of Botulinum Toxin A in Peripheral Neuropathic Pain (BOTNEP): A randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2016;15(6):555-565.
8. Korczeniewska OA, France K, Khan J, Greenberg MS, Benoliel R, Eli E. Neuropathic orofacial pain. Oral Med. 2021;2(3):419-452.
9. Ri S, Kivi A, Wissel J. The safety and effect of local Botulinumtoxin A injections for long-term management of chronic pain in post-herpetic neuralgia: Literature review and cases report treated with incobotulinumtoxin A. J Pers Med. 2021;11(8):758.
10. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes-an evidence based review. Toxicon. 2018;147(6):120-128.
11. Meng F, Peng K, Yang JP, Ji FH, Xia F, Meng XW. Botulinum toxin-A for the treatment of neuralgia: A systematic review and meta-analysis. J Pain Res. 2018;7(8):2343-2351.
12. Datta Gupta A, Edwards S, Smith J, Snow J, Visvanathan R, Tucker G, et al. A systematic review and meta-analysis of efficacy of botulinum toxin A for neuropathic pain. Toxins. 2022;14(1):36.
13. Oliveira KM, Barreto ES, Alencar VB, Lins-Kusterer LE, Azi LM, Kraychete DC. The efficacy of botulinum toxin in neuropathic pain: A systematic review. Br J Pain. 2024; 18(5):388-402.
14. Oh HM, Chung ME. Botulinum toxin for neuropathic pain: A review of the literature. Toxins. 2015;7(8):3127-3154.