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Case Report

Study of Side Effects Associated with: Botulinum Toxin at A Dose of 25 Iu in Head and Face Pathologies Refractory to Oral Treatment. On 283 Cases

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Abstract

Introduction: The use of Botulinum Toxin is increasingly expanding, in various doses, for the management of myofascial or neuropathic pain refractory to other treatments.

Objective: To assess the incidence of side effects in the treatment with Botulinum Toxin Type A for chronic migraine, trigeminal neuralgia (regardless of the affected branch), and temporomandibular joint disorders and/or bruxism in patients refractory to other pharmacological or interventional therapies, using doses not exceeding 25 IU.

Methods: A total of 283 patients of both sexes, aged between 43 and 85 years, were included. Patients were divided by gender and age: Group A - older than 80 years; Group B - between 65 and 79 years; and Group C - younger than 64 years.

A dose of 25 IU of Botulinum Toxin Type A was administered for trigeminal neuralgia, severe Temporomandibular Joint (TMJ) pain, migraine, and headache refractory to medical treatments for two years or more.

The following parameters were evaluated: allergic reactions, fever or flu-like symptoms, muscle weakness, and discomfort at the injection site.

Results: In all groups treated with 25 IU, the incidence of side effects was minimal, with only persistent pain at the injection site being noted (P>0.05), in all cases lasting less than 48 hours.

Conclusions: The use of Botulinum Toxin at doses of 25 IU produces a minimal incidence of side effects, with notable effectiveness in the treatment of the studied conditions.

Keywords: Temporomandibular joint; Trigeminal neuralgia; Headache; Migraine; Botulinum toxin; Side effects

Introduction

In 1949, the first study was published demonstrating how botulinum toxin inhibited the release of acetylcholine at the neuromuscular junctions of skeletal muscles and its potential application in spasticity. This discovery was made by Burgen, Dickens, and Zatman, and its first medical use was in the treatment of ocular deviation in strabismus [1].

The use of Botulinum Toxin (BTX-A) was first approved in 1989 by the U.S. Food and Drug Administration (FDA) for the treatment of strabismus and blepharospasm in patients over 12 years of age.

Today, when we hear about the use of Botulinum Toxin or "Botox," we almost always associate it with rejuvenation therapies in aesthetic medicine, mainly for the correction of facial wrinkles such as frontal, periorbital, nasal, and perioral lines, or the platysmal bands of the neck [2].

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Objectives

Primary objective: To determine the occurrence of side effects in treatment with Botulinum Toxin Type A for chronic migraine, trigeminal neuralgia (regardless of the affected branch), and temporomandibular joint disorders and/or bruxism, following sustained therapeutic failure after more than two years of prior pharmacological (oral or topical) therapies.

Secondary objectives: To evaluate the effectiveness of the dose used (25 IU) in improving pain and minimizing the incidence of side effects, and to confirm this response six months after treatment.

Methods

After approval by the Clinical Research Ethics Committee (CEIC 2894), the study was conducted from January 2020 to November 2024.

A total of 283 patients of both sexes, aged between 43 and 85 years, were included. The patients were stratified by sex and age: Group A - older than 80 years; Group B - aged 65 to 79 years; and Group C - younger than 64 years (Table 1).

The pathologies under study, also grouped into A, B, and C, included trigeminal neuralgia, severe Temporomandibular Joint

(TMJ) pain, migraine, and headache refractory to medical treatments for two years or more.

Exclusion criteria were:

- Age under 18 years
- Patient's refusal to participate in the study
- Previous infiltrations with corticosteroids or local anesthetics
- Associated psychiatric disorders

The dose of Botulinum Toxin Type A administered in all cases was 25 IU.

Patients completed a questionnaire at the beginning of treatment and at the end of the established six-month follow-up period.

Demographic data are shown in Table 1. These data were subsequently processed using the SPSS 29.0 statistical package for mean comparison and group analysis, considering a P<0.05 as statistically significant for the variables studied.

Table 1: Demographic data.

Gender	Total Patients	>80 years	79-65 years	<65 years
Male	102 - 36.05%	11 - 10,7%	72 - 70,82%	19 - 18,62%
Female	181 - 63,95%	19 - 10,49%	98 - 54,14%	64 - 35,35%

Introduction

During the 1980s, botulinum toxin began to be used for the treatment of strabismus, blepharospasm, hemifacial spasm, dystonia, and aesthetic applications. In the 1990s, it became firmly established as a recognized therapeutic alternative for spasticity and dystonia [3].

Subsequently, its use expanded to the treatment of autonomic disorders (such as sialorrhea and hyperhidrosis), facial asymmetry, tension-type headache, migraine, myofascial pain, chronic low back pain, and musculoskeletal disorders [4,5]. In recent years, its clear analgesic effect in neuropathic pain has been increasingly recognized [6].

Botulinum toxin represented a true revolution in the treatment of focal dystonias and has therefore been a routine therapy for decades in the practice of many specialists, including neurologists, pain physicians, and rehabilitation experts [7].

The chemical formula is C6760H10447N1743O2010S32, consisting of two chains: a heavy chain (H) and a light chain (L) [8].

The heavy chain binds to gangliosides and protein receptors located at presynaptic nerve terminals, while the light chain blocks the release of acetylcholine, resulting in paralysis. Seven different serotypes have been identified, classified from A to G, although only types A and B have clinical applications [9-10].

One of its most notable characteristics is the longevity of its action, attributed to the protease activity of the light chain, which prevents cellular degradation mechanisms and remains active in the cytoplasm for a long period of time [10].

The use of botulinum toxin continues to expand in conditions such as dystonias, hemifacial spasm [11], masseteric hypertrophy, temporomandibular joint disorders [12], masticatory myalgia, recurrent mandibular dislocation, bruxism, mandibular pain [13], and oral disorders [14], as well as Chronic Migraine (CM) refractory to other treatments [15].

The first publication describing the analgesic benefit of BTX-A in the treatment of trigeminal neuralgia was by Micheli et al. [16].

Currently, and with official approval in its product label, BTX-A is indicated for the treatment of blepharospasm, cervical and focal dystonias, hemifacial spasm, severe primary axillary hyperhidrosis, focal spasticity following stroke, focal spasticity in cerebral palsy, chronic migraine, and bladder dysfunction (overactive bladder, spinal cord injury). It is also used on a compassionate basis for myofascial trigger points, chronic low back pain, strabismus, bruxism, sialorrhea, and tension-type headache.

Studies have also explored its use in chronic pelvic pain, chronic anal fissure, morbid obesity, knee osteoarthritis, plantar fasciitis, complex regional pain syndrome, and Parkinson's disease.

The main clinical indications for its use are summarized in Table 2, and possible side effects are presented in Table 3.

Results

In all groups, with a 25 IU dose, there was no significant incidence of side effects, except for mild discomfort at the injection site, reported in approximately one-third of all cases. There were no significant occurrences of headache, flu-like symptoms, muscle weakness, or visual disturbances (only 10 cases in total, all resolving within less than 48 hours). There was only one case of allergic reaction-manifested as urticaria and redness-but no anaphylaxis.

In general, positive responses to treatment persisted for an average of over five months with the established 25 IU dose, particularly in cases of trigeminal neuralgia and bruxism and/or temporomandibular joint disorders. This effect was most evident in the younger groups, with no significant incidence of side effects, as already noted (Table 4, 5 and 6).

Discussion

The therapeutic use of botulinum toxin type A (BoNT-A) has expanded remarkably over the past two decades beyond its initial indications-primarily cosmetic and dystonia treatments-now encompassing fields such as pain management, neuromuscular rehabilitation, and headache medicine. Its mechanism of action, based on the inhibition of acetylcholine release at the presynaptic terminal, accounts for both its clinical benefits and its adverse-effect profile.

Although the safety of BoNT-A is well established, off-label applications-such as in trigeminal neuralgia, bruxism, or chronic migraine-require careful review of potential side effects and

Table 2: Indications for use of botulinum toxin.

Approved in product specifications	Compassionate use	Under study
Blepharospasm	Trigger points (MPS)	Chronic pelvic pain
Cervical and focal dystonias	Chronic low back pain	Chronic anal fissure
Hemifacial spasm	Strabismus	Morbid obesity
Severe primary axillary hyperhidrosis	Bruxism	Knee osteoarthritis
Focal spasticity in stroke	Sialorrhea	Plantar fasciitis
Focal spasticity in infantile cerebral palsy	Tension headache	Complex regional pain syndrome
Chronic migraine		Parkinson's disease
Bladder pathology (overactive bladder).		
Spinal cord injuries		
Cosmetic use (temporary improvement of glabellar lines)		

appropriate patient counseling (Table 3).

In trigeminal neuralgia, multiple clinical series and meta-analyses have demonstrated that BoNT-A provides significant pain relief and reduces attack frequency without causing relevant systemic complications. Reported adverse effects are mostly mild, local, and transient, including transient facial weakness, hypoesthesia, or slight facial asymmetry following injections into facial branches-symptoms that usually resolve within a few weeks [17]. These effects are attributed to local diffusion of the toxin beyond the target muscle. Administration in low doses, with precise technique and multiple injection sites, minimizes this risk.

In our series, no relevant adverse events were observed in any group (see tables). Only transient discomfort lasting less than 48 hours was reported in approximately 50% of patients-occasionally higher-with no other side effects associated with the administered doses.

No systemic toxic reactions have been described with therapeutic doses [18]. Recent studies confirm these findings and show that BoNT-A maintains a high safety profile when applied following standardized protocols [19,20], In our series, only one mild case of erythema and transient dyspnea was documented in a 67-year-old woman with multiple allergies, which resolved spontaneously within 20 minutes. This low incidence may be attributed to the use of very low doses across all studied pathologies.

In bruxism, BoNT-A is injected into the masseter and temporalis muscles to reduce occlusal force and pain. Although its efficacy is supported by randomized controlled trials and systematic reviews, side effects are mainly related to excessive muscle relaxation. The most common are transient masticatory weakness, fatigue, local pain, and aesthetic changes due to masseter atrophy after repeated injections [21,22], In our series, post-injection pain was the most notable adverse effect, similar to that observed in trigeminal neuralgia (see percentages). Occasionally, mild facial asymmetry or speech alterations have been reported [23].

The degree of atrophy is dose-dependent and usually partially reversible; therefore, it is recommended to use the minimum effective dose and to maintain adequate intervals between sessions [24], a criterion strictly followed in our study, never exceeding 25 IU per point. Recent literature also confirms its safety in sleep bruxism, without serious complications [25,26].

In chronic migraine, BoNT-A is an approved therapy according to the PREEMPT protocol, which uses 155-195 IU distributed over 31-39 cranio-cervical injection sites. In our study, by contrast, much lower doses (25 IU in two sites) were used, yielding comparable efficacy and better tolerability.

The PREEMPT trials demonstrated a favorable safety profile compared to placebo, with mostly mild to moderate transient

Table 3: Adverse effects of botulinum toxin type A (BoNT-A) according to therapeutic indication.

Clinical Indication	Most Common Adverse Effects	Severity/ Reversibility	Probable Mechanism or Cause	Level of Evidence
Trigeminal Neuralgia	Transient facial weakness, mild hypoesthesia, facial asymmetry	Mild - Reversible within 2-4 weeks	Local diffusion of the toxin beyond the target muscle	High (meta-analyses and RCTs)
Bruxism/Temporomandibular Dysfunction	Transient masticatory weakness, chewing fatigue, local pain, masseter atrophy	Mild to moderate - Partially reversible	Excessive muscle relaxation; high doses or repeated sessions	Moderate-high (systematic reviews)
Sleep Bruxism	Aesthetic changes (mandibular contour), local discomfort	Mild - Reversible within weeks	Atrophy due to partial denervation	Moderate (observational series)
Chronic Migraine	Neck pain (≈ 9 %), post-injection headache (≈ 5 %), local stiffness or muscle weakness (3-4 %), ptosis (≤ 4 %)	Mild - Transient (1-3 weeks)	Diffusion or manipulation effect at injection sites	High (PREEMPT and COMPEL studies)
Various Off-Label Uses (neuropathies, refractory neuralgias)	Dysphonia, dysphagia, generalized weakness (very rare)	Potentially severe but exceptional	Systemic diffusion of the toxin at a distance	Low (isolated cases/FDA warnings)

Table 4: Side Effects.

CONDITION >80 Years	Middle Ages	NM 21	NF 19	Fever or flu symptoms	Muscle weakness	Injection site discomfort	Headaches	Vision disorders
Trigeminal neuralgia	88.3	4	10	11	1	37	11	1
TMJ	86.4	3	6		1 1	25	1	
Bruxism	88.7	2	1	1		11		
Migraine	85.2	11	1			81		
Headaches	87.7	1	1		1	11		

Allergic reaction: 0

Table 5: Side Effects.

CONDITION 79-65	Middle Ages	NM 72	NF 98	Fever or flu symptoms	Muscle weakness	Injection site discomfort	Headaches	Vision disorders
Trigeminal neuralgia	68 +- 3	21	37	21	6 10	16 25	6	1 2
TMJ	70+-2	20 26	26		1 3	16 15	1	
Bruxism	67+-2	9 7	7		3 1	7 4		
Migraine	66+-1	21 25	25	2	1 3	17 16	1 4	2 3
Headaches	70+-3	-	3			2		

Allergic reaction: 1

Table 6: Side Effects.

CONDITION< 64	Middle Ages	NM 72	NF 98	Fever or flu symptoms	Muscle weakness		Injection site discomfort		Headaches		Vision disorders
Trigeminal neuralgia	54+-3	7	21		2	3	4	13	2	4	
TMJ	32+-2	5	19		1		2	11			
Bruxism	28+-4	3	5	1	2	1	2	3			
Migraine	36+-4	2	14		2		2	10	1		1
Headaches	30-+5	2	5								

Allergic reaction: 1

events: neck pain (≈ 9 %), post-injection headache (≈ 5 %), and mild muscle stiffness or weakness (3% - 4 %). [27,28], Ptosis occurred in approximately 4% of patients, resolving within a few weeks [29], Long-term follow-up confirmed a decrease in the frequency and intensity of adverse events with repeated cycles [30], in our study, using smaller doses, none of these complications occurred.

Across all groups, we recorded 9 cases of discomfort in series A, 33 in series B, and 12 in series C, without severe headaches, ptosis, or other serious events-supporting the safety of reduced, fractionated doses.

In all indications, systemic effects due to toxin diffusion are extremely rare. The FDA has issued a general warning about possible distant spread of toxin activity-with theoretical risks of dysphagia, dysphonia, or generalized weakness-but such complications are exceptional and usually associated with high doses or patients with pre-existing neuromuscular disorders [20]. In our series, only the aforementioned mild allergic reaction was observed.

From a risk-benefit perspective, BoNT-A remains one of the safest neuromodulators available. Its adverse effects are predictable, dose-dependent, and manageable. Key preventive strategies include individualized dosing, anatomical precision in injection technique, proper patient selection, and thorough patient education on potential risks.

In off-label indications such as trigeminal neuralgia or bruxism, informed consent should emphasize the non-approved nature of the treatment and possible reversible aesthetic or functional effects. In chronic migraine, where the indication is official, regular follow-up and reassessment ensure long-term safety.

Ongoing research aims to refine injection patterns and identify predictive biomarkers of efficacy and tolerability, to further minimize risks. Overall, accumulated evidence supports that, when administered by trained professionals, botulinum toxin therapy provides clinically significant pain relief with a very low incidence of serious adverse events.

Conclusion

The incidence of side effects was only significant regarding pain at the injection sites (observed in all study groups), which resolved spontaneously within 24-48 hours without recurrence.

No significant adverse manifestations were observed during the six-month follow-up period.

We consider that the use of doses below 25 IU ensures adequate analgesia with a very low incidence of secondary reactions.

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