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Prospective Study on the Use of Botiulin Toxin at A Dose of 25 UI in Head and Face Pathologies Refractory to Oral Treatment: Regarding 283 Cases

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Abstract

Introduction: The use of Botulinum Toxin is increasingly being extended in different conditions refractory to other treatments. Thus, it is being used in dystonias, trigeminal neuralgia, migraines, headaches and alterations of the temporomandibular joint,

Objectives: Primary: To assess the analgesic response in the pathologies under study: Chronic migraine. Trigeminal neuralgia (regardless of the affected branch) and involvement of the temporomandibular joint (Bruxism) after therapeutic failure maintained for more than two years of previous oral or topical pharmacological therapies.

Secondary: To verify the effectiveness of the treatment after six months.

Methods: 283 patients of both sexes were included, aged between 85 and 43 years. The patients studied were separated by sex. Group An over 80 years. Group B: between 65 and 79 years and Group C under 64 years. 25 IU of botulinum toxin type A were administered for trigeminal neuralgia, severe temporomandibular joint (TMJ) pain, migraines and headaches, refractory for two years or more to medical treatments.

Results: In all groups, with doses of 25 IU in a single dose, a significant improvement in pain occurred at 6 months.

Conclusions: In all groups the effectiveness was greater in trigeminal neuralgia at the established doses P<0.05 and more in the younger group (C) with more than 7 months of improvement in the condition. In the rest of the pathologies treated the results at the established doses are very similar to the referenced studies, although in our case, with significantly lower doses.

Keywords: Temporomandibular pain; Trigeminal neuralgia; Headache; Migraine; Botulinum toxin

Introduction

In 1949, the first work was published indicating how botulinum toxin inhibited the release of acetylcholine in the neuromuscular junctions of skeletal muscles, and its possible application in spasticity. This discovery was carried out by Burgen, Dickens and Zatman, and its first medical application was to treat ocular deviation in strabismus [1].

In 1989, the use of botulinum toxin type A (BTA) was authorized for the treatment of strabismus and blepharospasm. Since then, its use and applications have evolved and it is now a widely used treatment in different types of pathologies.

Its chemical formula is: C6760H10447N1743O2010S32 and it is made up of two chains; a heavy chain (H) and a light chain (L).

The H chain binds to ganglia and a protein receptor located in the presynaptic nerve endings, while the light chain blocks the release of acetylcholine, which causes paralysis. There are 7 different types, classified from A to G, although clinically only types A and B are useful [2,3].

For analgesic use, it is generally administered subcutaneously, at various points within the painful area, as well as intramuscularly in locations such as the neck and head (refractory migraines).

Another application option is intradermal, using this method when what is sought is a much more local effect [4] without invading neighboring spaces. It can also be used perineurally or in peripheral nerve blocks

The possible side effects of botulinum toxin are listed in **Table 1.**

Table 1: Most Common Side Effects of Botulinum Toxin.

Local muscle weakness
Discomfort or pain at the injection site.
Tiredness.
Headaches
Eye problems such as double vision, blurred vision, decreased vision, drooping eyelids, eyelid swelling and dry eyes.
Possible allergic reaction.
Cases of fever and flu-like symptoms have also been reported

Objectives

Primary: To assess the analgesic response in the pathologies under study: Chronic migraine. Trigeminal neuralgia (regardless of the affected branch) and involvement of the temporomandibular joint (Bruxism) after therapeutic failure maintained for more than two years of previous oral or topical pharmacological therapies and at doses of 25 IU.

Secondary: To verify the response after six months of treatment

Methods

After approval by the Clinical Research Committee CEIC 2894, the study was conducted from January 2020 to November 2024, 283 patients of both sexes were included, aged between 85 and 43 years. The patients studied were separated by sex. Group An over 80 years old. Group B: age between 65 and 79 years and Group C under 64 years. The pathologies studied, and also grouped into groups A, B and C, **(Table 2)** were: Trigeminal neuralgia, severe Temporomandibular Joint (TMJ) pain, migraines and headaches, refractory for two years or more to medical treatments.

Table 2: Demographic Data.

Gender	Total Patients	>80 years	79-65 years	< 65years
Male	102- 36.05%	1110,7%	72- 70,82%	19- 18,62%
Female	181-63,95%	19- 10,49%	98- 54,14%	64-35,35%

The exclusion criteria were:

Age under 18 years

Patient 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.

Prior to the infiltration, the patient was asked to assess their pain according to the Visual Analogue Scale (VAS) (grading from 0 to 10). 0 no pain. 10 maximum imaginable pain and after 6 months the patient was contacted again for evaluation after this time

This was subsequently processed by the statistical package to process means and comparison of the study groups SPSS 29.0 - a value of $P<0.05$ being significant, in the different variables studied.

Results

In all groups, with a single dose of 25 IU, there was a significant improvement in pain at 6 months with a mean VAS score of +- 3 points.

This was more significant in cases of trigeminal neuralgia in all groups ($P<0.05$), with a longer duration in the younger groups (around 7 months).

In cases of migraines and headaches, we also obtained significant values with mean durations of the effect of around 8 months in groups B and C, but less in group A of older patients.

In general, positive responses to the treatments established exceeded 6 months on average, with the dose established at 25 IU **(Table 3-5).**

Table 3: Results I.

CONDITION >80 Years	Middle Ages 11 19	NMNF	Pretreatment. oral	Previous VAE (averages)	Average dose of botulinum toxin. IU	VAE post infiltration
Trigeminal neuralgia	88.3	4 10	Yes	7+-1	25	3+-1
TMJ	86.4	3 6	Yes	6+-2	25	3+-1
Bruxism	88.7	2 1	Yes		5	
Migraine	85.2	11 1	Yes	7+-2	25	2+-1
Headaches	87.7	11	Yes	7+-1	25	1+-1

VAE: Visual Analógic Escale

N: Number of patients

M: Male

F: Female

UI: International Units

TMJ: Temporomandibular Joint

Table 4: Results II.

CONDITION 79-65 Years	Edad	NMNF 72 98	Pretreatment.	Previous VAE (averages)	Average dose of botulinum toxin	VAE post infiltratión
Trigeminal neuralgia	68 +- 3	21 37	Yes	7+-2	25	4+-1
TMJ	70+-2	20 26	Yes	6-+1	25	2+-2
Bruxism	67+-2	9 7	Yes		5	

Migraine	66+-1	21 25	Yes	8+-2	25	3+-2
Headaches	70+-3	- 3	Yes	7-+2	25	2+-1

VAE: Visual Analógic Escale

N.: Number of patients

M: Male

F: Female

UI: International units

Table 5: Results III.

CONDITION< 64 Years	Age	NMNF 72 98	Pretreatment.	Previous VAE (averages)	Average dose of botulinum toxin	VAE post infiltratión
Trigeminal neuralgia	54+-3	7 21	Yes	7+-2	25	5+-2
TMJ	32+-2	5 19	Yes	7+-2	25	4+-1
Bruxism	28+-4	3 5	Yes		5	
Migraine	36+-4	2 14	Yes	8+-1	25	3+-2
Headaches	30-+5	2 5	Yes	6+-2	25	3+-2

VAE: Visual Analógic Escale

N: Number of patients

M: Male

F: Female

UI: International units

Discussion

In all the study groups, the effectiveness was greater in Trigeminal Neuralgia (TN) at the established doses (25 IU), although it is true that this improvement was more significant P<0.5 in the younger group (C) with more than 7 months of improvement in the condition [5-21]. The works of Cheng, Zahan and Rubis also show a reduction in pain by 68% after therapy [22-24]. Maximum efficacy was observed between 6 weeks and 3 months after the procedure, in our case these periods were longer; reaching 8 months in some cases. Our study agrees with the results of Serrera-Figallo [25] although with more than 50 IU of mean IU (higher than ours). Our data also approach the works of Zhang [26]

(152 patients), Ostrowski H [27] (87 patients); and, most of them stated that their pain was completely controlled at 3-4 months (in our case it even reached 7-8 months, as we have mentioned). The authors indicated that their study suggests that the success of the treatment was greater in patients aged 50 years or older (OR = 3.66, 95% CI: 1.231-10.885, which partially agrees with our data.

The review by Muñoz Lora [28] indicates that it is effective for the treatment of trigeminal neuralgia (category A), on the other hand Moore [29] concluded that BTX-A is effective in this type of conditions by infiltration in trigger points, as reported by Sridharan K Meng and Castilo and Sandrini although in all cases, as can be seen in **Table 6**, the doses range between 50-100 IU [30-33].

Table 6: Trigeminal Neuralgia.

AUTHOR-YEAR	METHODOLOGY	NUMBER OF PATIENSTS	SYNDROME/ DISEASE	DOSIS UI. International Units	RESULTS	EVIDENCE
Chen WJ 2021	Prospective study	rats	Trigeminal neuralgia induced	50 UI	Significant	yes
Zhang H 2020	Clinical trial	45	Trigeminal neuralgia	50-UI	Significant	yes
Rubis 2020	Systematic review	4 randomized trials	Trigeminal neuralgia	50-75 UI	Significant	yes
Serrera Figallo 2020	Systematic review	3 randomized trials	Trigeminal neuralgia	50-100 UI	Significant	yes
Zang H 2019	Prospective study	152	Trigeminal neuralgia	50-75 UI	Significant	yes
Ostrrows Ki 2019	Systematic review	7 randomized trials	Trigeminal neuralgia	50-100 UI	Significant	yes
Muñoz Lora 2019	Systematic review	35 randomized trials	Trigeminal neuralgia	.	Significant	yes
Moore 2019	Systematic review	17 randomized trials	Trigeminal neuralgia	50-100 UI	Significant	yes
Sridharan K 2018	Databases	250	Trigeminal neuralgia	-	Significant	yes
Meng F 2018	Databases	12 randomized	Trigeminal neuralgia	50-100 UI	Significant	yes

		trials				
Castillo-Álvarez F 2017	Systematic review	Not available	Trigeminal neuralgia	50-100 UI	Significant	yes
Sandrini G 2017	Systematic review	178	Trigeminal neuralgia	50-100 UI	Significant	yes

Moor **[34-36]** (n = 178), Oh HM, Hu Response was achieved in approximately 70-100% of patients, and mean pain intensity and frequency were reduced by approximately 60-100% at 4 weeks after treatment in most studies. No major adverse events were reported at 25 IU **(Table 7).**

Table 7: Temporomandibular Joint Pain.

AUTHOR -YEAR	METHODOLOGY	NUMBER OF PATIENSTS	SYNDROME/ DISEASE	DOSIS UI. International Units	RESULTS	EVIDENCE
Türk Börü Ü 2017	Clinical trial	27	Trigeminal neuralgia	100 UI	Significant	yes
Morra ME 2016	Systematic review	178	Trigeminal neuralgia	50-100 UI	Significant	yes
Oh HM 2015	Systematic review	Not Available	Trigeminal neuralgia	75-100 UI	Significant	yes
Hu Y 2013	Systematic review	5 randomized trials 1 double-blind study	Trigeminal neuralgia	50-100 UI	Significant	yes
Kaya DI 2021	Clinical trial	40	Bruxism	50-75 UI	Effective compared to occlusive splint	yes
Shandilya S 2020	Clinical trial	20	Temporomandibular joint. after surgery	50-100 UI	Significant improvement	yes
Thambar S 2020	database review	7 studies with evidence	Temporomandibular joint	50-100 UI	Inconclusive data	No
Machado D 2020	database review	12 studies with evidence	Temporomandibular joint	50-75 UI	Not significant	No
Awan KH 2019	database review	7 studies with evidence	Temporomandibular joint	50-100 UI	Not significant	No
Ghavimi MA 2019	Clinical trial	61	Temporomandibular joint	50 UI	Significant improvement	yes
De la Torre Canales 2017	database review	904	Bruxism	50-100UI	Significant improvement	yes
Thomas	Clinical trial	52	Temporoma	50-75	Significant	yes

NJ 2017			ndibular joint	UI	improvement	

A study with 40 patients with bruxism was conducted in 2021 by Kaya [37] at doses between 25 and 100 IU. Shandilya [38]. They conducted a study that included 20 patients with Temporomandibular Joint (TMJ) ankylosis. The BTX-A group showed better results with respect to pain during mouth opening exercises and improvements in mouth opening, similar to our results. This is also reflected in the work of Thambar - Machado and his group Awan, and Ghavimi De la Torre and his group and Thomas **(Table 8) [39-44].**

Table 8: Migraines.

AUTHOR-YEAR	METHODOLOGY	NUMBER OF PATIENSTS	SYNDROME/ DISEASE	DOSIS UI: International Units	RESULTS	EVIDENCE
Torres Ferrus M 2020	Prospective study	395	Chronic Migraine	100 UI	Significant	yes
Bellon G 2019	Systematic review	4190	Chronic Migraine	100-200 UI	Significant	yes
Agostini 2019	Database review	-	Chronic Migraine	100 UI	Significant	yes
Herd 2019	Cochrane Database	4190	Chronic Migraine	100-200 UI	Significant	yes
Freund 2019	Systematic review	300	Chronic Migraine	100-200 UJ	Significant	yes
Barad 2019	Clinical trial	402	Chronic Migraine	100-200 UI	Significant	yes
Mimeh 2019	Databases	260	Chronic Migraine	100-200 UI	Significant	yes
Alpuente 2019	Clinical trial	578	Chronic Migraine	100-200 UI	Significant	yes
Winner 2019	Clinical trial	373	Chronic Migraine	100 -200 UI	Significant	yes
Blumenfeld AM 2018	Clinical trial	716	Chronic Migraine	100-200 UI	Significant	yes
Wieckiewicz M 2017	Prospective study	288 studies	Chronic Migraine	100 -200 UI	Significant	yes
Ashkenazi A 2013	Systematic review	210 studies	Chronic Migraine	100-200 UI	Significant	yes
Jackson JL 2012	Databases Cochrane	1115	Chronic Migraine	100-200 UI	Significant	yes

Our results on headache and migraine are similar to those obtained by Torres [45] on 395 patients. After 6 months, 49.1% of patients responded with improvement in headache. Similar data to ours.

Bellón [46] in 28 trials (N:4190 A can reduce the number of migraine days per month by 2 days compared to placebo treatment.

Agostini [47] based on the PREEMPT clinical trial, in administration of BTX-A reported the different routes of administration: At least 31 different injection sites have been determined in 7 muscles of the head and neck, and it is recommended as a second-line option for patients who have not responded adequately or who do not tolerate the oral administration commonly prescribed in the treatment of

migraine [48]. The treatment should be repeated every 3 months to ensure its effectiveness.

Barad [49] reported that after 120 days of treatment, 62% of patients noticed a reduction in the frequency of headaches. In our case it was similar since the decrease in the AVE scale was an average of 3 points.

Mimeh [50] and Alpuente [51], pointed out the effectiveness of the use of BTX-A at 6 months and remained stable during follow-up and became significant after 1 year of treatment. Our group did not follow up for such a long time

- Blumenfeld [52] reported that the reduction in headache day was significant at 108 weeks, very similar to our data
- Wieckiewicz M [53] performed a systematic review of 288 studies from January 2007 to August 2017. Among the studies analyzed in this study, it is worth highlighting those of De Ru who performed a study in a group of 10 patients (mostly women) suffering from localized frontal headache; using one session of BTX-A injections and reported that all patients had less pain for approximately two months after the injection. Our data point to a greater reduction, of almost 5 points on the VAE.

In this regard, we have already indicated that our work did not last so long **(Table 2-4).**

Ashkenazi [54] carried out a review in 2013 in which the authors indicate or point out the most common patterns of use of BTX-A in the prophylactic treatment of chronic migraine, the most serious and debilitating type of migraine, in adults.

It was not found to be effective for episodic migraine or tension headache. Uncontrolled studies suggested the efficacy of the toxin for headache associated with craniocervical dystonia. This aspect was not evaluated by us, as we did not initially determine the origin of the pain for tabulation of the data. The recommended injection method combines a fixed site/fixed dose and follows the pain approaches, with the toxin injected into multiple sites of the head and neck, in a total dose of 150 IU or 200 IU. This is clearly much higher than the ones we use and we obtain practically similar results.

Conclusions

Pain improvement was more significant in the groups of younger patients, although there is no significant difference between them. In all groups, effectiveness was greater in trigeminal neuralgia $P<0.5$, increasing its effectiveness in the younger group (C) with more than 7 months of improvement in the condition. It was also effective in cases of headaches and migraines. There are no differences in the temporomandibular joint in relation to studies with higher doses.

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