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Case Report

Effectiveness of Botulinum Toxin for Oncologic Pain

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Abstract

Introduction: The use of botulinum toxin for medical purposes has expanded nowadays through the extensive study of its complex structure and mechanism of action, highlighting its ability to inhibit the release of acetylcholine, and its impact on the chemical signaling cascade involved in different models of pain.

Objective: To evaluate the association of the use of botulinum toxin A with the reduction of pain in oncologic patients at Instituto Nacional de Cancerología, México.

Methodology: A retrospective, observational, descriptive, and cross-sectional study was performed. Data were obtained from patients attended during the period from January 1, 2022 to September 30, 2023 in whom botulinum toxin was applied as an adjuvant for pain management.

Results: Thirty-two patients who met the inclusion criteria were included. After the application of botulinum toxin there was a statistically significant reduction in pain, as measured by the Numeric Pain Rating Scale and Verbal Rating Scale. The degree of satisfaction after the application of botulinum toxin was measured by a Likert-type scale, and 68% satisfaction was found in the patients who underwent the onotoxin treatment.

Conclusions: The use of botulinum toxin proved to be an effective and safe therapy, complementary to the multimodal approach for the treatment of different pain patterns in oncologic patients. It can be considered as a pharmacological option for use in this group of patients.

Keywords: Oncologic pain, Pain management, Botulinum toxin

INTRODUCTION

The first known reference to botulinum toxin (BoNT) dates back to 1793 by the Dutch physician Justinus Kerner, who, at that time, discovered the deadly disease known as botulism. [1]

It was in 1920 that German researcher Otto Platter described it as a protein produced by the bacterium Clostridium Botulinum and it was not until 1949 that German microbiologist Werner Hamm isolated the toxin to treat extraocular strabismus. However, it was not until 1989 that the FDA approved its commercial use and since then, its use and applications have been studied worldwide. [2]

The study of the Clostridiaceae family has now expanded, and it is known that they are spore-producing gram-positive anaerobic bacteria, Clostridium botulinum, Clostridium butyrricum, Clostridium barati, and Clostridium argentinensis. [3]

There are 7 types of botulinum toxin produced by Clostridium botulinum ranging from A to G, classified serologically by their specific neutralizing antiserum, of which BoNT/A, BoNT/B, BoNT/E and BoNT/F can cause the clinical entity known as "botulism" in humans and animals. Likewise, all known subtypes except subtype C2 are neurotoxins and all inhibit acetylcholine release, although their intracellular target proteins, specific features of action and potencies vary substantially. [4]

All BoNT serotypes produced by the anaerobic bacterium Clostridium botulinum share a mechanism of action based on their intraneuronal endocytosis to block acetylcholine (ACh) release and inhibit muscle contraction; which is achieved through their chemical structure given by 2 peptide chains, light chain A (of 50 kDa) and heavy chain B (of 100 kDa) linked together by a disulfide bond.

Both chains present 3 domains in total, each with a specific function, with 1 domain in the light chain known as the "catalytic domain" and 2 in the heavy chain known as the "binding" and "translocation" domains, respectively.[5]

As a first step, the binding domain of the BoNT heavy chain binds to gangliosides located on the cell surface, to be internalized by a protein called synaptotagmin (SyT) for

BoNT/B, BoNT/C, BoNT/D, and BoNT/G subtypes, and in the case of BoNT/A and BoNT/E by the glycosylated synaptic vesicle protein (Sv2). Once internalized, the BoNT is harbored in synaptic vesicles to subsequently interfere with the fusion and release of ACh vesicles across the synaptic cleft.

To achieve this, the translocation domain present in the heavy chain promotes the translocation of the light chain from the interior of the vesicle to the cytoplasm, where it remains inactive as long as it remains bound to the rest of the molecule. However, once the cleavage enzymes, heat shock protein 90 (hsp90) and the thioredoxin reductase-thioredoxin system (TrxR-Trx), interfere, the light chain is released and activated to cleave and inactivate vesicle-associated membrane protein (VAMP) and synaptosome-associated protein (SNAP25), which are essential for ACh release resulting in reversible chemical muscle paralysis. [5,6]

The cleaved target protein VAMP is specific for BoNT/B, BoNT/D, BoNT/F, BoNT/G and SNAP7 for BoNT/A and BoNT/E subtypes, as well as SNAP25 and syntaxin (Syx) for BoNT/C. [5,7]

It is important to mention that the inhibition of ACh release is not isolated, as other neurotransmitters and neuropeptides are also affected in this chemical signaling cascade, such as glutamate, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide 38 (PACAP38), substance P, as well as receptors and proteins such as transient receptor potential subfamily V (TRPV1) of subfamily A (TRPA1), and purinergic receptors linked to type 3 ion channels (P2x3) whose insertion into the cell membrane is critical for nociception. [8]

The neurotransmitters and neuropeptides involved in the chemical signaling cascade, such as glutamate, CGRP, PACAP38, substance P, as well as TRPV1, TRPA1 receptors and proteins, and P2x3 purinergic receptors are closely related to the genesis of neuropathic pain, present in pain models such as postmastectomy syndrome, postherpetic neuralgia, among others.[9]

The first clinical use of BoNT was for the treatment of strabismus in 1980, and its medical indications were modified over time to be used even for aesthetic purposes, however, its use is not limited only to the aesthetic area, there are multiple musculoskeletal pathological entities that result in pain and where the application of BoNT can be a favorable alternative. [10]

There are 4 variables of BoNT approved by the FDA that are currently commercial and are indicated to treat pain by a pharmacological mechanism that has not yet been fully discovered, however, some theories have been proposed in which, for example, BoNT/A, being the most potent subtype, acts at the level of type 1 vanilloid receptors (TRPV1) and at the purinergic receptor (P2X3), reducing its expression in the dorsal root ganglion and has been the most studied for therapeutic purposes. [11]

In addition, the spasmolytic activity of BoNT has been postulated as an effective method to treat muscle spasticity and as an analgesic in specific conditions.

Products such as Xeomin, Dysport and Botox can be found in the market in Mexico, each of them with different characteristics and potencies that are not comparable. Even in 2009, the FDA issued a statement mentioning that: "potency units are specific for each BoNT product and doses or units of biological activity cannot be compared or converted from one product to another", which was endorsed by the American Academy of Neurology in the clinical practice guidelines for the use of BoNT published in 2016. [12]

Said statement released by the FDA has a relevant argument: the biological nature of BoNT/A is totally dependent on the characteristics and conditions in its manufacture. For example, in the case of the production of OnabotulinumtoxinA, the production is carried out by crystallization to subsequently perform a dry stabilization process to be prepared in a sodium chloride vial which at an average temperature of 2-8°C can be stored for 36 months.

Unlike the more recent BoNTs, AbobotulinumtoxinA and IncobotulinumtoxinA are prepared in a vial of lactulose and sucrose respectively (Table 1). [11,12]

Table 1.

	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA
Date of approval	1989, United States	1991, United Kingdom	2005, Germany
Production process	Crystallization	Chromatography	Chromatography
Stabilization process	Vacuum drying	Freeze-drying	Freeze-drying
Molecular weight	900 kDa	400 kDa	150 kDa
Excipient	NaCl	Lactose	Sucrose
Units	100 U	500 U	100 U
Storage	36 months	24 months	48 months
Storage after reconstitution	24 hours	8 hours	24 hours
Storage temperature	2- 8ºC	2- 8ºC	2- 8ºC

Table taken and adapted from: Ferrari A, Manca M, Tugnoli V, Alberto L. Pharmacologic differences and clinical implications of various botulinum toxin preparations: a critical appraisal. Funct. Neurol. 2018; 33:7-18.

As mentioned above, pathologies involving pain and biomechanical dysfunction can delay clinical improvement by limiting the movement of the affected area, which is why BoNT has proven effective for the treatment of pain of musculoskeletal origin.

Among these uses are the treatment of complex regional pain syndrome, plantar fasciitis, osteoarthritis, lateral epicondylitis and myofascial syndrome, headaches, different scenarios of neuropathic pain, among others. [13]

According to the Spanish Society of Neurology, the use of BoNT in the field of primary headaches such as chronic migraine, episodic migraine, trigeminal-autonomic headaches and nummular headache is recommended. [9]

Botulinum onotoxin has demonstrated effectiveness in the treatment of cervical myofascial syndrome, which is a disorder characterized by regional pain localized in a muscle or muscle group, referred at a distance and by the presence of a painful tension band of increased consistency, which is identified on palpation. It is diagnosed clinically by performing a directed interrogation, as well as the presence of trigger points in specific muscle groups. It is important to consider that a trigger point is that sensitive point within a tense muscle band, which is stimulated by acupressure, considering the upper trapezius and scalenes, the muscles most prone to present pain in patients with this syndrome. [14]

It is worth mentioning that trigger points not only cause local discomfort, but are also capable of causing referred pain and can present in two forms: latent and active trigger points. The clinical difference between a latent and an active trigger point lies in the fact that the presence of spontaneous pain is nil in latent trigger points and they can often become active under mechanical or chemical injury stimulus. [14,15]

The mechanism involved in the pathophysiology of trigger points, or the conversion of a latent trigger point to an active one, is ischemia which in turn generates a decrease in pH and consequently, the release of proinflammatory factors in the muscle tissue, producing muscle weakness, a reduced range of motion and probably the presence of symptoms related to the autonomic nervous system, such as excessive sweating and changes in skin temperature. [15]

The gold standard for the diagnosis of myofascial syndrome has not yet been described and the available evidence in the literature is controversial. However, in 2018 a systematic review was published where the reliability and its diagnostic criteria based on the presence of trigger points in 10 muscle groups were studied: the splenius of the head, sternocleidomastoid, upper trapezius, levator scapulae, infraspinatus, supraspinatus, anterior deltoid, latissimus dorsi, teres major and pectoralis major. [16]

In the case of trigeminal neuralgia, botulinum onotoxin is thought to modulate trigeminal neurons, inhibit peripheral sensitization and thus central sensitization, also acting indirectly by regulating the release of excitatory neurotransmitters such as glutamate and the activity of the endogenous opioid system, thus reducing pain perception.17 It is also thought to act by modifying the pathophysiology of neuralgia independently of the underlying cause, by desensitizing primary afferent Aα and Aβ fibers and nociceptive Aδ and C-fibers.[17]

Last but not least, glutamate release by SNAP-25 protein present in satellite glial cells in the trigeminal ganglion can also be inhibited by the action of BoNT. [17]

In 2014, Zhang et al published the largest trial so far, in which 84 non-oncology patients were randomized into 3 arms to receive: placebo, 25 IU dose and 75 IU dose; where the effectiveness rate was up to 86% at 8 weeks after the procedure in patients who received BoNT as opposed to the placebo group.[19]

Nowadays and according to the available evidence, the use of BoNT is recommended in trigeminal neuralgia, at a dose of 25-75 U, (2.5-5 IU) per point, with a separation of 15 mm between them, with the possibility of extending the infiltration map to trigger points of the oral mucosa. [18]

They also refer to the need to evaluate the possibility of infiltrating contralateral points, considering that there may be adverse effects such as facial asymmetry, weakness in mastication and palpebral ptosis, all of them mild and transitory so far. [19]

In addition to the above, the use of BoNT could have an additional beneficial effect in different painful syndromes present in oncological patients, since it has been suggested that the administration of this toxin causes a reduction in the growth and mitotic activity of neoplastic cells, promoting their apoptosis. [20]

MATERIAL AND METHODS

This retrospective, observational, descriptive, and cross-sectional study focuses on patients aged 18 years or older with a cancer diagnosis who attended the Pain Clinic at the Instituto Nacional de Cancerología, México, from January 1, 2022, to September 30, 2023. Inclusion criteria involved male or female patients with oncological diagnoses at any clinical stage, receiving botulinum toxin as an adjuvant for algologic treatment during the specified period. Exclusion criteria included patients without a complete clinical record. The sample size encompasses all eligible patients meeting the inclusion criteria within the aforementioned timeframe. Statistical analysis utilized Microsoft Excel for database creation and STATA 15® software, incorporating measures of central tendency, proportions, and measures of dispersion. Paired data on numerical scales underwent Student's t-test, while symmetry tests were applied to categorical scales.

RESULTS

Forty-one electronic files of patients who were seen at the Pain Clinic of Instituto Nacional de Cancerología, México, in the period from January 01, 2022 to September 30, 2023 were reviewed, of which 32 patients (78%) met the inclusion criteria for this study.

Of the 32 patients, the female population represented 53.13% of the sample, compared to 46.88% of the male population (Table 2).

The patients in both groups had a mean age of 59.63 years, with a higher prevalence of the algologic diagnosis of pain associated with cancer treatment (neuropathy induced by chemotherapy, chronic postoperative pain and phantom limb syndrome) with 46.88% versus other diagnoses such as myofascial syndrome in 18.75%, neuralgia (trigeminal nerve neuralgia and post-herpetic neuralgia) in 25% and migraine in 9.38% of patients.

Table 2. General characteristics of the population

n= 32	M	SD
Age	59.63	12.99
Sex	n	%
Female	17	53.13
Male	15	46.88
Algologic diagnosis	n	%
Migraine	3	9.38
Neuralgia[1]	8	25
Myofascial syndrome	6	18.75
Pain associated with cancer treatment [2]	15	46.88

[1] Neuralgia: term referring to the affection of the somatosensory system, which for the purpose of this work were reported trigeminal neuralgia and postherpetic neuralgia.

[2] Pain associated with oncological treatment: catalogued as pain related to the application of chemotherapy, radiotherapy or surgical treatments (chemotherapy-induced neuropathy, post-surgical chronic pain, phantom limb syndrome, etc.).

In relation to the basic pharmacological treatment to treat pain in these patients, it was identified that most of them (87.55%) were being treated with opioid analgesics, only 12.5% of the patients included in the study were not prescribed them (Table 3).

Table 3. Baseline treatment with opioid analgesics

n= 32	n	%
No	4	12.5
Yes	28	87.5

We analyzed the number of infiltrated points as well as the total units of botulinum toxin administered, finding that after mapping the painful region (understood as the specific location of greatest pain on physical examination), the infiltrated points varied depending on the extension of the same, being more than 21 points in 43.75% of the patients and up to 300 IU the total dose administered in 50% of them. In the 9 patients in whom a total dose of more than 500 IU was administered (43.75%) the brand used was Dysport (Table 4 and 5).

Table 4. Number of points infiltrated with BoNT

n= 32	n	%
1-10	14	43.75
11-20	4	12.5
>21	14	43.75

Table 5. Total administered dose of BoNT

Total units (IU)	n	%
0-300	16	50
301-499	7	21.88
>500	9	28.12

A paired samples analysis (Table 6) of the pain score reported by patients before and after the application of BoNT, based on the Numeric Pain Rating Scale (NPRS) and the Verbal Rating Scale (VRS), showed that after the intervention the decrease in baseline pain, at the time of consultation (current) and incidental pain was statistically significant with p 0.001 for baseline pain and p <0.001 for incidental pain (Figure 2 and 3).

Table 6. Analysis of pre and post botulinum toxin pain score, n=32.

	Pre intervention		Post intervention		Difference	CI 95%	p
	M	SD	M	SD			
Actual NPRS	2.63	1.88	1.56	1.87	1.06	0.17-1.95	0.02
Basal NPRS	2.38	1.66	1.25	1.5	1.13	0.49-1.76	0.001
Incidental NPRS	7.19	1.84	4.84	2.69	2.34	1.33-3.36	<0.001

Figure 2. Mean NPRS scores Pre and Post Intervention

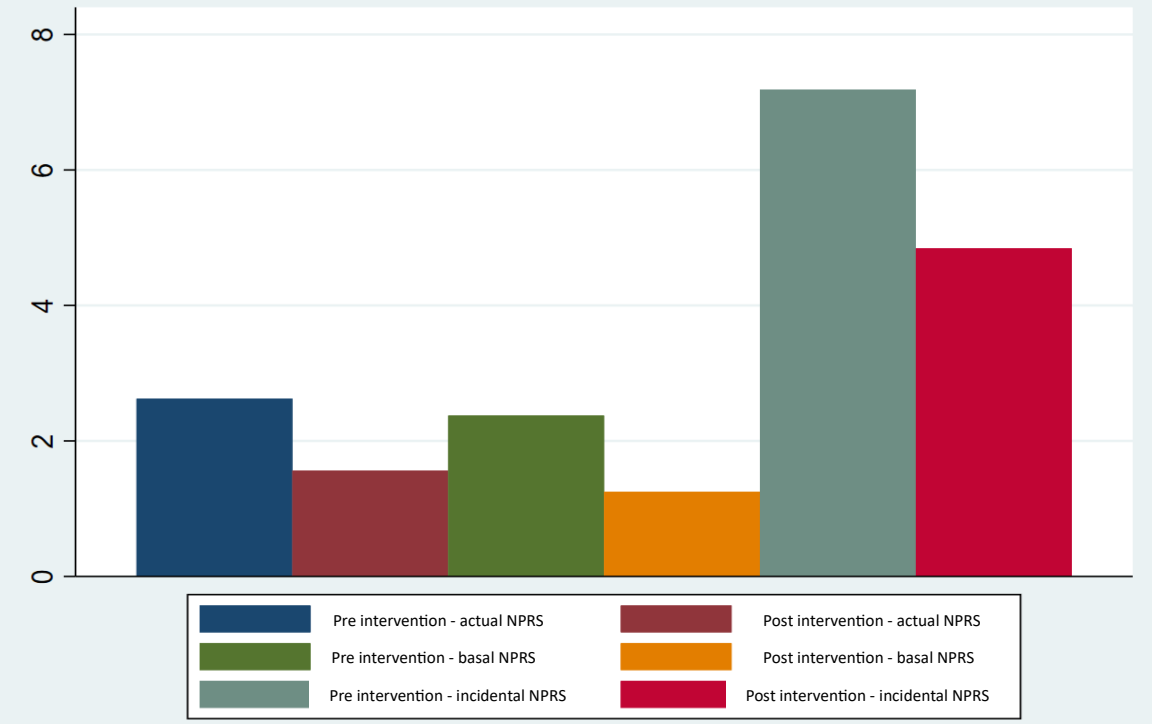


Figure 3. VRS Pre-intervention

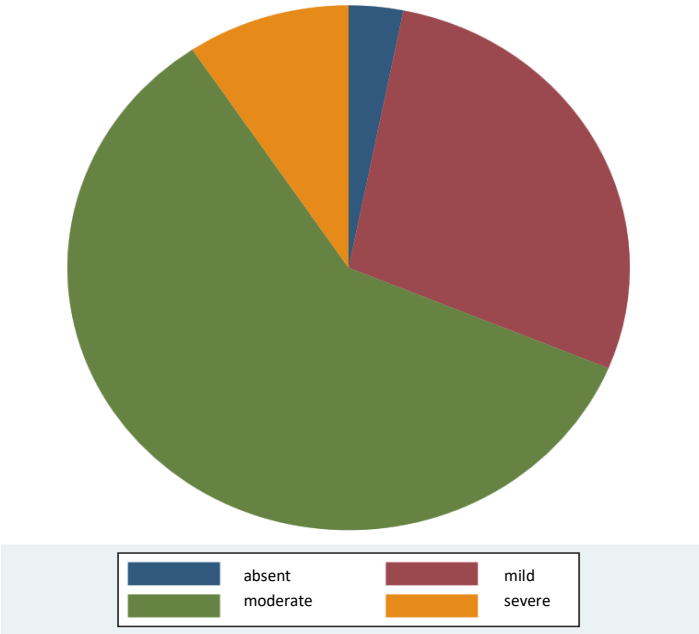
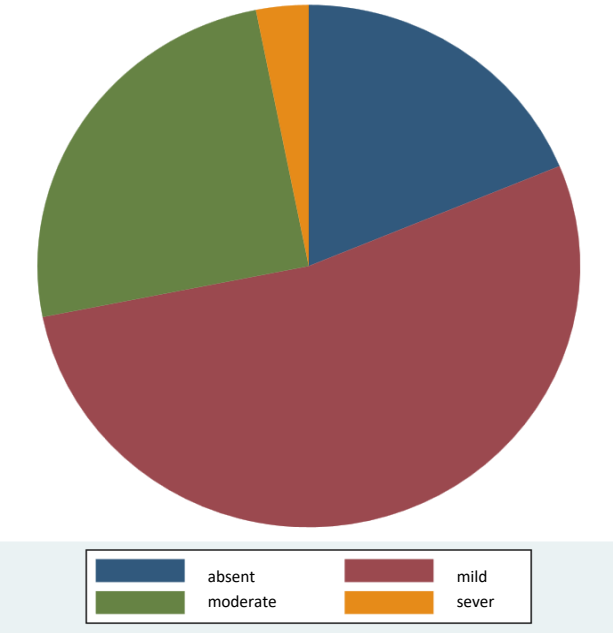


Figure 4. VRS Post-intervention



The degree of patient satisfaction was evaluated after the intervention, which was measured by a Likert-type scale, in which 68% of the patients reported being satisfied with the results of the intervention (Table 7).

Table 7. Degree of satisfaction measured by LIKERT-type scale		
	n=32	%
1.Very dissatisfied	1	3.12
2. Dissatisfied	3	9.37
3.Indifferent	5	15.62
4.Satisfied	10	31.25
5.Very satisfied	13	40.62

With regard to the presentation of adverse events associated with the application of onotoxin, none were described in the patients included in this study.

DISCUSSION

The application of botulinum toxin in different fields of medicine has expanded over time to be used in oncologic patients in order to control chronic pain in different pain syndromes.

The relationship between botulinum toxin and the regulation of the chemical signaling cascade associated with different pain models, including neurotransmitters and neuropeptides, has been highlighted, demonstrating its therapeutic potential beyond acetylcholine inhibition.

The results of this work represent a population in which pain associated with oncologic treatment stands out as the main condition, observing a high percentage of patients treated with opioid analgesics, which is in line with what is described in the medical literature as a baseline treatment. This opioid prescription was associated with baseline and incidental pain in the patients included in the study.

According to the statistical analysis, pain control was statistically significant both in baseline pain and in the pain referred by the patient at the time of consultation (current) and significantly in the incidental pain described by this group of patients, mainly in those with pain associated with cancer treatments (chemotherapy-induced neuropathy, chronic postoperative pain [postmastectomy pain] and phantom limb pain in 1 patient) and in patients with neuralgia (trigeminal neuralgia and post-herpetic neuralgia).

When contrasting our results with those described in the world literature, we identified that there are few reports indicating the therapeutic benefit of onotoxin in the oncologic population; however, if we transpose these findings with reports of botulinum toxin for the treatment of neuralgias, our results are similar to randomized clinical trials in which a significant decrease in pain has been reported in at least 50% of the intervened population. [21]

The degree of patient satisfaction was classified as "satisfied" in more than 50% of the total sample, which leads us to infer an adequate therapeutic response with the use of this therapy.

With regard to adverse events associated with the application of botulinum toxin, none were described in our population, although in the publications of clinical trials in which their occurrence was recorded, facial asymmetry in cases of trigeminal neuralgia, as well as pain and edema at the injection site, stand out. [22]

On the other hand, the main limitation of our study is that it was retrospective, so it will serve as a basis for developing a prospective, controlled protocol that considers the heterogeneity of oncological patients as well as their co-morbidities.

Within the research perspectives in this area, the central challenge in the treatment of pain in oncologic patients involves a state of vulnerability that favors the use of minimally invasive treatments, so the application of BoNT represents a dynamic and promising field of research.

This study provides a basis for future research to further investigate the efficacy and safety of the use of botulinum toxin in different models of pain in oncology patients.

CONCLUSIONS

This study highlights the effectiveness of botulinum toxin in the management of oncologic pain associated with various pathologies, such as myofascial syndrome, neuralgia and pain related to oncologic treatment.

The integral evaluation of the studied population reveals benefits that go beyond the reduction of pain, considering the complexity and vulnerability of the medical conditions implicit in this population group, proving to be a safe and well tolerated procedure, with a marked improvement in pain control in this group of patients.

The use of botulinum toxin proved to be a versatile tool and an effective complement in the multimodal approach for the treatment of oncologic pain, responding to the need to opt for minimally invasive and safe outpatient therapeutic options.

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