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Toxina Botulínica no Tratamento da Dor*

Botulinum Toxin in Pain Treatment

Orlando Carlos Gomes Colhado[1], Marcelo Boeing[2], Luciano Bornia Ortega[3]

RESUMO:
Colhado OCG, Boeing M, Ortega LB - Toxina Botulínica no Tratamento da Dor.

JUSTIFICATIVA E OBJETIVOS: *A toxina botulínica (TxB), uma das mais potentes toxinas bacterianas conhecidas, tem reconhecidamente ação terapêutica eficaz no tratamento de algumas síndromes dolorosas. Entretanto, algumas de suas indicações ainda estão em fase de comprovação com relação a sua eficácia. O objetivo deste estudo foi revisar o histórico, propriedades farmacológicas e aplicações clinicas da TxB, quando empregada no tratamento de dores de diferentes origens.*

CONTEÚDO: *A TxB é o produto da fermentação do Clostridium Botulinum, uma bactéria anaeróbia Gram-positiva. Comercialmente, as TxB existem nas formas A e B, agentes biológicos obtidos laboratorialmente. A TxB, uma neurotoxina que possui alta afinidade pelas sinapses colinérgicas, ocasiona bloqueio na liberação de acetilcolina pelo terminal nervoso, sem alterar a condução neural de sinais elétricos ou síntese e armazenamento de acetilcolina. Comprovadamente, a TxB pode enfraquecer seletivamente a musculatura dolorosa, interrompendo o ciclo espasmo-dor. Com relação à dor, varias publicações têm demonstrado a eficácia e segurança da TxB-A no tratamento da cefaleia tipo tensão, migrânea, dor lombar crônica e dor miofascial.*

CONCLUSÕES: *A TxB-A é segura e bem tolerada em desordens dolorosas crônicas, onde regimes de farmacoterapia podem sabidamente provocar efeitos colaterais. Outra vantagem é a redução do uso de analgésicos e o tempo de ação de 3 a 4 meses por dose. Entretanto pesquisas futuras serão necessárias para se estabelecer a eficácia da TxB-A em desordens dolorosas crônicas e seu exato mecanismo no alivio da dor, bem como seu potencial em tratamentos multifatoriais.*

Unitermos: DOR, Crônica; DROGAS: toxina botulínica tipo A.

SUMMARY
Colhado OCG, Boeing M, Ortega LB – Botulinum toxin in Pain Treatment.

BACKGROOUND AND OBJECTIVES: *Botulinum toxin (BTX) is one of the most potent bacterial toxins known and its effectiveness in the treatment of some pain syndromes is well known. However, the efficacy of some of its indications is still in the process of being confirmed. The objective of this study was to review the history, pharmacological properties, and clinical applications of BTX in the treatment of pain of different origins.*

CONTENTS: *Botulinum toxin is produced by fermentation of Clostridium botulinum, a Gram-positive, anaerobic bacterium. Commercially, BTX comes in two presentations, types A and B. Botulinum toxin, a neurotoxin with high affinity for cholinergic synapses, blocks the release of acetylcholine by nerve endings without interfering with neuronal conduction of electrical signals or synthesis and storage of acetylcholine. It has been proven that BTX can selectively weaken painful muscles, interrupting the spasm-pain cycle. Several studies have demonstrated the efficacy and safety of BTX-A in the treatment of tension headaches, migraines, chronic lumbar pain, and myofascial pain.*

CONCLUSIONS: *Botulinum toxin type A is well tolerated in the treatment of chronic pain disorders in which pharmacotherapy regimens can cause side effects. The reduction in the consumption of analgesics and length of action of 3 to 4 months per dose represent other advantages of its use. However, further studies are necessary to establish the efficacy of BTX-A in chronic pain disorders and its exact mechanism of action, as well as its potential in multifactorial treatments.*

Keywords: DRUGS: Botulinum toxin type A; PAIN, chronic.

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Botulinum Toxin in Pain Treatment

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INTRODUCTION

The history of botulinum toxin (BTX) begins in 1817 when the first description of botulism (i.e., BTX poisoning) was published. The author, Justinus Kerner, associated deaths caused by intoxication with a poison found in smoked sausages (from the Latin, *botulus* means sausage). He concluded that poison interfered with the excitability of the motor and autonomous nervous system. This led to the publication of two studies describing the clinical characteristics of botulism [1]. Kerner proposed several potential medical uses of BTX at the time, especially in disorders of the central nervous system, which have been supported lately by new studies [2,3].

Only in 1895 the bacterial agent as well as the mechanism of action responsible for the toxicity of botulism were discovered; the discovery was attributed to Professor Emile Van Ermengen, who published a paper in 1897 [2].

Botulinum toxin, one of the most potent bacterial toxins known, is a result of the fermentation of *Clostridium botulinum*, a Gram-negative, spore-forming, anaerobic organism commonly found in the soil and oceans throughout the world [3]. Eight immunologically distinct serotypes have been identified. Of those, seven: A, B, C1, D, E, F, and G are neurotoxins (another BTX, C2, is also produced by *C. botulinum*, but it is not a neurotoxin) [4].

Although all serotypes inhibit the release of acetylcholine from nerve endings, their intracellular proteins, mechanisms of action, and potencies vary considerably. Type A is the most extensively studied serotype; however, the number of studies on the effects of the remaining serotypes has been increasing.
In 1978, Alan Scott conducted the first tests with BTX-A in humans for the treatment of strabismus[2]. Posteriorly, its indication was extended to segmental dystonias, tremors, and other abnormal movements.
Botulinum toxin was first used in the treatment of spasticity in 1989; the results of its use in muscles with severe spasm for six months in adults with hemiplegia secondary to stroke were published. Neurologists realized the potential of using BTX in neurologic disorders involving excessive muscle contraction or tonus [5].
The International Unit (IU) is used to define the biological potency of all preparations of BTX, in which one IU is the amount of BTX capable of killing (in the laboratory) half of a mice population (DL50) [6].

MECHANISMS OF ACTION

The active principle of BTX is a protein complex derived from *Clostridium botulinum*. This protein complex consists of a 150,000-Dalton neurotoxin linked non-covalently to non-toxic accessory proteins that stabilize and protect the pharmacologically active component, resulting in a final molecular weight that varies from 300,000 to 900,000 Daltons [1,3,4]. The composition and total molecular weight of the macromolecular complex depend on the serotype and species of *Clostridium botulinum* that produced it, as well as on purification and analysis methods. Commercially, BTX types A and B are biological agents obtained in laboratory, being stable, crystalline, lyophilized substances associated with human albumin, and used after dilution in normal saline (NS) [7].
In physiological conditions, it is expected that the complex will dissociate and release pure neurotoxin since those complexes are stable only in acid pH [4].
Botulinum toxin is composed of a light and a heavy protein chain linked by a disulfide bridge. The heavy chain is responsible for the internalization of BTX into pre-synaptic cholinergic terminals. On the other hand, the light chain is a zinc endopeptidase responsible for its toxic effects.
Ingenious and patient biochemical studies have shown that those toxins are highly specific proteases that cleave pre-synaptic SNARE proteins (*Soluble NSF Attachment* protein *Receptors*) involved with the exocytosis process of synaptic vesicles in nerve endings. Destruction of those pre-synaptic proteins is the basis of the action of those toxins on the release of neurotransmitters [8].

EFECTS ON THE RELEASE OF ACETYLCHOLINE

Botulinum toxin is a neurotoxin with high affinity for cholinergic synapses, blocking the release of acetylcholine from those nerve endings; however, it does not change neural conduction of electrical signals and/or the syntheses and storage of acetylcholine [7]. The intramuscular injection of BTX in appropriated doses and locations causes partial chemical denervation and reduction of muscular contraction without causing complete paralysis. In glandular tissue, it blocks the secretion.
After local intramuscular administration of a selected dilution of BTX, it deposits rapidly in the interstitial tissue and specifically in the motor neuron terminal of skeletal muscles (neuromuscular junction).
Inhibition of the release of acetylcholine by BTX involves several steps. First, BTX binds irreversibly to receptors in the pre-synaptic membrane of the motor nerve ending. This binding specificity guarantees the high selectivity of BTX for cholinergic synapses. Those pre-synaptic receptors are responsible for the endocytosis of the neurotoxin into the motor nerve ending [7].
After internalization the molecule is separated in two polypeptidic chains by proteases present in the motor nerve ending. Cleavage of BTX is considered the decisive step for its activation since as a single 150,000-Dalton chain it has little pharmacological activity. Cleaving results in two polypeptide fragments: a heavy chain with 100,000 Daltons and a light chain with 50,000 Daltons. The percentage of cleaving varies according to the serotype. Type A shows the higher percentage of cleaving, usually from 90 to 95%, while type B shows a smaller percentage (approximately 70%) [3,4].
The light chain is translocated through the membrane of the endocytic vesicle into the cytosol showing a high-specificity for SNARE protein complex. The protein target also varies according to the serotype. Playing the role of enzymes, the light chains of each serotype cleave a distinct peptidic bond in one or more sites of the SNARE proteins in such a way that none of the serotypes attacks the same location, and, therefore, their actions and potencies vary considerably, although all subtypes present the same final effect: inhibition of the release of acetylcholine from nerve endings [4].
Serotypes A and E cleave SNAP-25 (Synaptosomal-Associated Protein of 25 kDa), serotype C behaves as a protease on syntaxin; both are SNARE proteins of the pre-synaptic membrane. Botulinum toxin types B, D, F, and G cleave specifically VAMP (Vesicle-Associated Membrane Protein), better known as synaptobrevin II, a protein located in the synaptic vesicle [1,9].
Proteolytic cleavage of the SNARE complex by the light chain of BTX prevents the synaptic vesicle from anchoring on the internal surface of the cellular membrane, blocking, therefore, vesicular fusion and preventing the release of acetylcholine, leading to the development of flaccid paralysis on affected muscle fibers (chemical denervation).
This translates clinically in dose-dependent weakness or paralysis of the skeletal muscle. The initial effect on the muscle affects the function of the alpha motor neuron,

responsible for the stimulation of muscle fibers, but BTX also can affect gamma motor neurons that innervate the muscle spindle. Their inhibition results on a reduction in muscle tonus due to the consequent reduction of the afferent feedback on alpha motor neuron from the muscle spindle [1,10,11] (Figure 1).

DURATION OF ACTION AND RESTORATION OF NORMAL PHYSIOLOGY

The onset of action of BTX on the skeletal muscle takes a few days (2 to 5 days), but occasionally it can take up to two weeks. Once instituted, the effects last for six weeks to six

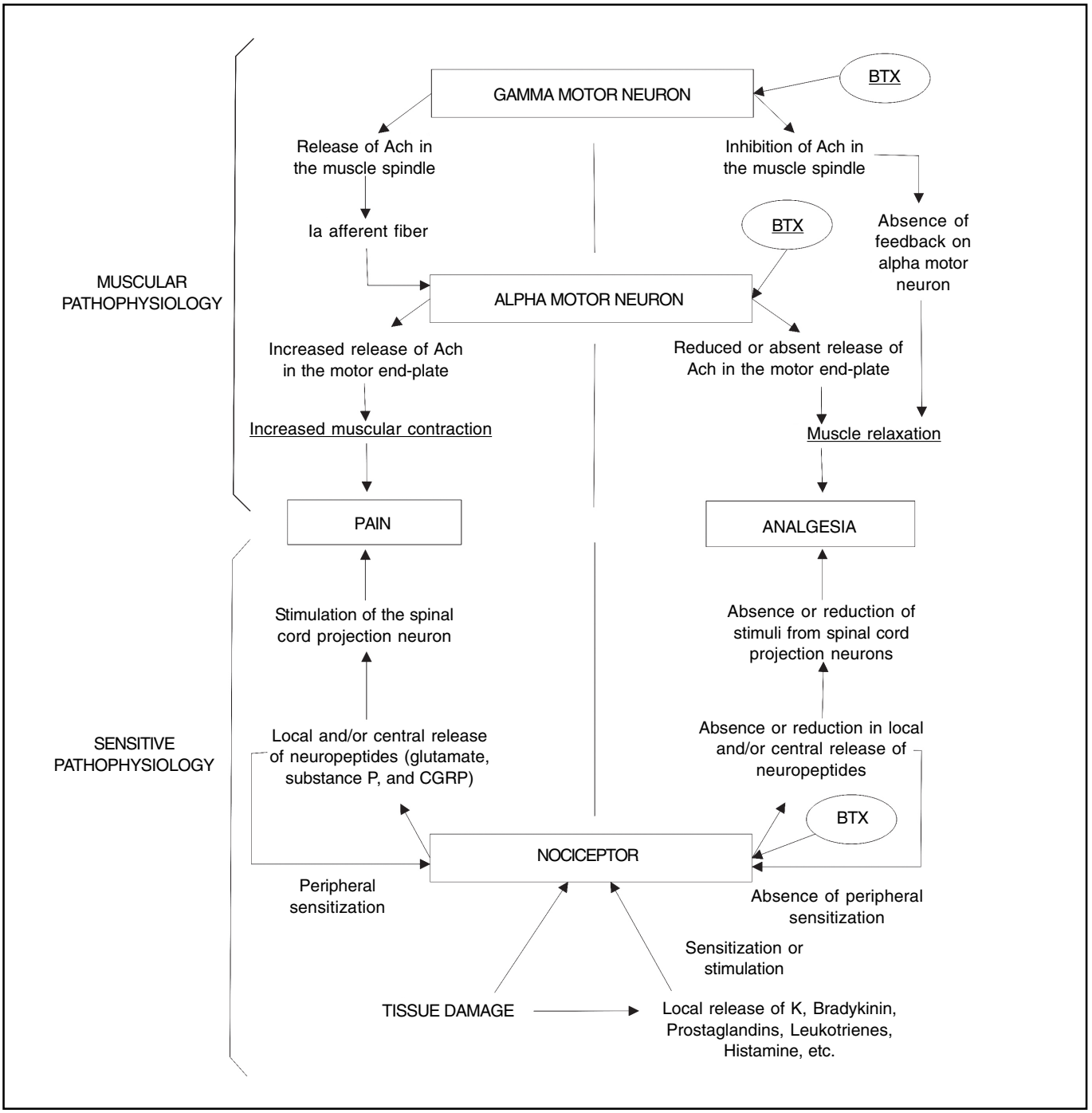

Figure 1 - Analgesic Actions of Botulinum Toxin. On the left, the muscular and sensorial pathophysiology that triggers pain. On the right, the analgesic effects of botulinum toxin on those pathophysiological mechanisms. Ach - acetylcholine; CGRP – calcitonin gene-related peptide; BTX – botulinum toxin.

months (a mean of three to four months). During the period when the effect is more intense, histological exam reveals muscular atrophy and changes of the fibers [7,12]. After two to three months, its action starts to decrease gradually.

Two mechanisms are responsible for the reversal of local paralysis: 1) "Neuronal budding", with the formation of axonal budding, reinnervation, and formation of new and smaller end-plates with temporary muscle reinnervation (extra-junctional acetylcholine receptors), and 2) Regeneration of acetylcholine coupling proteins in the vesicles (SNARE complex) [14], whose function is reestablished in one to four months [10].

The metabolic pathway of BTX is not properly documented, but it can be explained by the presence of proteases that cause degradation of the polypeptidic chains.

IMMUNOGENICITY OF BTX-A AND PARTICULARITIES OF THE B SEROTYPE

Since these are protein complexes alien to the human body, the main characteristic of the BTX complex is the activation of the patients' immune system.

Despite being used clinically for local administration, the presence of BTX in the blood stream has been demonstrated. The resulting antibody levels after the local injection of BTX demonstrated by ELISA (enzyme-linked immunoabsorbent assay) or RIA (radioimmunoassay) can be considered proof of its systemic absorption.

High doses, frequent applications (short intervals), and high protein load associated with BTX in commercially available presentations increase the risk of developing neutralizing antibodies.

It has been observed that the development of neutralizing antibodies against BTX in the treatment of dystonias has similar prevalence in children and adults, usually occurring between the first and fourth year after beginning the treatment, and this probability reduces after this period (with low immunogenecity after 18 years of treatment) [13].

When antibodies against BTX are formed, the duration of action and maximal duration of the therapeutic effects are usually decreased after a few administrations (partial therapeutic failure).

Despite the data on BTX-A shows loss of response (secondary non-responders) in 10% or more of the patients treated with repeated injections [16], studies on the use of BTX-A in the treatment of cervical dystonia demonstrated that conventional preparations can induce the development of antibodies in up to 5% of the patients [1]. Other studies on the use of BTX-A in dystonias measured the levels of neutralizing antibodies in approximately 1% of the patients (0 to 2%) [15,16].

Studies have demonstrated that antibodies against BTX-A do not have any effects on BTX-B and that the BTX-B protein binds to a different site of the protein of a carrier chain than BTX-A, indicating a strategy for the management of immunologically reactive patients, i.e., treating them with other serotypes of BTX [12].

It should be emphasized that further, well-based, clinical studies are necessary to observe the use of BTX-B since it is less potent than BTX-A (because its cleavage and consequent activation occur at a lower proportion), requiring higher doses (in IU), i.e., higher protein load and greater immunogenic potential. Studies indicate that a dose between 7,500 and 10,000 IU of BTX-B is necessary in patients with cervical dystonia to produce a reasonable therapeutic effect. Similar therapeutic effects are achieved with doses of 150 to 200 IU of BTX-A (BOTOX™) or 500 to 700 IU of BTX-A (DYSPORT™). This indicates a conversion factor from BOTOX™ to BTX-B in the order of 40 to 70, and for DYSPORT™ and BTX-B of 10 to 20 times. Without exact conversion data it is difficult to compare the effectivity, adverse effects, and costs of BTX-A and BTX-B [12].

Patients with cervical dystonia treated with BTX-B presented a substantially greater incidence of dryness of the mouth and visual disturbances (incidence of 30%) than those treated with BTX-A. These are undesirable side effects, but it is also an interesting phenomenon that demonstrates greater affinity of these serotypes for autonomic fibers [14].

THE NEW THERAPEUTIC HORIZON OF BTX: PAIN

It has been proved that BTX can cause selective weakness of painful muscles and disrupt the spasm-pain cycle, providing sustained pain relief, allowing patients to perform physical exercises that are fundamental for long-term recovery [17].

As mentioned before, BTX was initially used in the treatment of motor disorders, such as dystonias, and further studies demonstrated significant benefits regarding pain which frequently exceeded the improvement of the muscle spasm and did not correspond strictly to the area of neuromuscular effects. This suggested that this drug could have a direct effect on pain mechanisms independently of its neuromuscular actions.

In humans, the analgesics effects of BTX-A were first demonstrated after observing significant pain relief in cervical dystonia. Although the antidystonic and anti-spasmodic effects of BTX-A are frequently attributed to the blockade of acetylcholine release from synaptic vesicles, recent animal studies suggest other analgesic mechanisms for this neurotoxin.

At the moment, evidence suggest that the analgesic properties observed are part of a more complex mechanism of analgesia that goes beyond simple muscle relaxation. Studies raise the possibility of a complex interaction of BTX with peripheral tissues and occasional indirect influences on central pain mechanisms [10,11].

POSSIBLE ROLES OF BTX ON PAIN REDUCTION

As mentioned before, the apparent specificity of BTX for cholinergic nerves *in vivo* is due to the presence of specific

receptors or acceptors in the membrane of the motor nerve ending. Alternatively, it has been observed in experimental models that internalization of BTX by the nerve ending inhibits immediately the exocytosis of other neurotransmitters, such as norepinephrine, and the mechanism of action is identical to that observed in cholinergic synapses, i.e., cleavage of the SNARE complex. However, *in vivo* many nerve cells do not have the extracellular receptors/acceptors responsible for internalization of BTX, making it not very effective since the only alternated entry into the nerve terminal is the non-specific pinocytotic pathway. In this context, it is possible to state that the high affinity of BTX for cholinergic synapses is part of what makes it so useful in neuromuscular disorders.

On the other hand, several exceptions to this specificity have been observed in the laboratory. Botulinum toxin type A was associated with the release of substance P in culture of neurons from the dorsal root ganglion of mice embryos, as well as the reduction of the stimulated release (but not the basal release) of calcitonin gene-related peptide (CGRP) in cultures of neurons from the trigeminal ganglion. Additionally, prior administration (subcutaneous) of BTX-A in mice paws attenuated significantly the inflammatory response induced by the subcutaneous administration of formalin, a pain-evoking agent, besides reducing glutamate release by the peripheral axon of the nociceptor. Reduced activity of dorsal horn neurons in the spinal cord has also been demonstrated. Those results analyzed together point to a direct inhibitory action of BTX-A on the nociceptor promoted by inhibiting the release of neuropeptides (glutamate, CGRP, and substance P) responsible for neurotransmission and/or peripheral and central sensitization of pain pathways (Figure 1). Thus, besides being a potent inhibitor of the release of acetylcholine, BTX would have an inhibitory effect in other neurotransmitters and neuropeptides, explaining its anti-inflammatory and analgesic actions [9,18,19].

Further studies are necessary to elucidate the mechanisms involved in this inhibitory action of BTX on the nociceptor, but it is believed that there are four possible ways by which BTX can interrupt painful signals:

1) Normalization of muscular hyperactivity;
2) Normalization of excessive muscle spindle activity;
3) Retrograde neuronal flow to the CNS; and
4) Inhibition of the release of neuropeptides by the nociceptor, both in peripheral tissues and central nervous system [9,20].

CLINICAL APPLICATIONS

In 1990, the NIH (National Institutes of Health) issued a consensus on the clinical use of BTX:

- Botulinum toxin is safe and effective in the treatment of strabismus* and symptomatic treatment of essential blepharospasm*, hemifacial spasm, adductor spasmodic dysphonia, bruxism, teeth grinding, mandibular dystonia, and cervical dystonia* (*current indications approved by the Food and Drug Administration); all others are used without regulation by the FDA.
- Botulinum toxin is promising in the treatment of other conditions; however, further studies are necessary for the following disorders: focal and segmental dystonia, including dystonia of the hands and limbs, hypercontractility of the internal anal sphincter, detrusor dyssynergy (usually as a consequence of spinal cord injury), spasticities, adductor spasmodic dysphonia, vocal tremor, and stuttering.
- Additional clinical studies are encouraged to elucidate several unanswered questions on BTX and its therapeutic uses [2].

Studies with BTX-A were the basis for this reference. Immediately after, BTX-B was introduced in clinical studies of cervical dystonia, and its effectivity and safety was demonstrated. The use of BTX for focal dystonia became widespread. This was followed by reports on its efficacy in spasticity and other neurological conditions. The safety of the treatment with BTX has allowed its use in aesthetics, hyperhidrosis, sialorrhea, and tension pain, among others. The efficacy in each one of those applications can be readily explained by the effects of BTX on cholinergic neurotransmission [21].

The clinical use of serotype F has been evaluated, demonstrating the short duration of its effects. Currently, therapeutic benefits with serotype C have been reported only in three patients: one with blepharospasm and two with idiopathic facial hemispasm [11].

Only two serotypes are commercially available. The first formulation of BTX-A was introduced in the USA in 1989 by Allergan as Botulinum Toxin (Botox™). In 1991, a different formulation was introduced outside the USA by Ipsen as Botulinum Toxin (Dysport™). Botulinum toxin-B was approved by the FDA in 2000 and commercialized by Élan Pharmaceuticals in the USA as Botulinum Toxin (Myoblock™) (in Europe it is known as Neurobloc™). In 2002, BTX-A was commercialized as Botulinum Toxin (Botox Cosmetic™) by Allergan for aesthetic use (Botox™ and Botox Cosmetic™ have the same formulation).

In the Brazilian market, the laboratory Cristália recently introduced Botulinum Toxin (Prosigne™) as 50 IU and 100 IU formulations.

Currently, BTX-A has been used to treat more than one million patients around the world and its clinical use has been approved in 73 countries. Those approvals include the treatment of juvenile cerebral palsy in 52 countries and adult spasticity in 36 countries, although those indications are nor regulated in the USA. Other uses of BTX-A unregulated in the USA include primary headaches like migraines, myofascial pain, achalasia, excessive sweating disorders, and sialorrhea associated with conditions such as cerebral palsy and Parkinson's disease [2].

Botulinum toxin-A has been used for 20 years in the treatment of a variety of disorders characterized by the pathological increase in muscle contraction (tonus). Experimental studies have tried to focus on new areas for the use of BTX in specific pain treatments especially primary headaches and cervical,

scapular girdle, and dorsal myofascial pain syndromes resistant to currently available treatments.

Adjuvant treatment with physical therapy is important to maximize the benefits of BTX. Passive stretching is particularly beneficial immediately after the injections of BTX as well as deep massages for muscular relaxation and increase in the amplitude of movements of muscles, tendons, and ligaments. When pain becomes tolerable, active stretching exercises can be instituted. Neuromuscular reeducation, interrupting the spasm-pain cycle amplified by central sensitization, is the objective of those exercises. Therefore, posture and joint mechanics should improve and normal deep tendon reflexes could be reestablished [9].

The first clinical studies with BTX-A published were on myofascial pain (Aquadro and Borodic, 1994; Cheshire et al., 1994), disorders of the temporomandibular joint (Moore and Wood, 1994), facial pain (Girdler, 1994), and tension headache (Zwart et al., 1994). The number of cases was small and the results contradictory. Its efficacy became recently more evident with placebo-controlled, double-blind, randomized studies with large numbers of patients.

Based on its muscle relaxing properties, BTX-A has been used to treat a variety of muscular conditions, including disorders of the upper digestive tract, aesthetics, genitourinary disorders, spasticity, cervical dystonia, and blepharospasm [22]. Regarding pain more specifically, several publications have demonstrated the efficacy and safety of BTX-A in the treatment of tension headache, migraines, chronic lumbar pain, and myofascial pain [23].

BTX-A IN THE TREATMENT OF MYOFASCIAL PAIN SYNDROME

Conventional treatments of myofascial pain syndrome are frequently unsatisfactory, with episodes persisting for at least one year; analgesics used for relief of chronic pain are expensive and can cause a significant increase in nephropathies. On the other hand, a simple injection of BTX can be beneficial for one to three months when associated with adequate physical therapy without disrupting the kidney function [24].

In a comparative study of dry needling, injection of a local anesthetic (lidocaine), and low doses of BTX in trigger points in myofascial pain syndrome, an increase in the amplitude of movements of the cervical musculature was observed in all three groups. But parameters like pain, fatigue, and incapacity to work measured by the visual analogue scale (VAS) showed an important reduction in the lidocaine and BTX groups, but not in the dry needling group. However, lidocaine proved to be more effective than BTX when compared to dry needling.

Patients might complain of fatigue, muscle pain, and headache after the injection of BTX-A. However, those side effects only last a few days [25].

Botulinum toxin-A is also indicated in the treatment of temporomandibular dysfunction (TMD) caused by chronic myofascial pain. In this condition, myofascial pain is frequently the result of hyperactivity of the masticatory musculature (grinding of teeth and bruxism) and hypermobility of the condyle, and can irradiate to the area of the affected muscle during sleep or after intense use of the masticatory musculature.

As a rule, the muscles that close the jaw (masseter, temporal, and medial pterygoid) and those that retract it (lateral pterygoid) are affected.

In a prospective, placebo-controlled study, 90 patients with TMD underwent conservative treatment (myorelaxing plate and physical therapy with relaxing techniques and massage) for at least three months and a maximum of 34 months. In sixty of those patients 35 IU of BTX-A were injected via the intra-oral approach in the masseter, temporal, and lateral pterygoid muscles and 30 patients received NS in the same muscles by the intra-oral approach (77%); for some muscles like the masseter and temporal the extra-oral approach was used (23%). The injections were administered in the most painful areas of the muscle. Botulinum toxin-A was diluted with 0.7 mL of NS. Both NS (placebo) and BTX-A solution were injected bilaterally. Patients were asked to stop any other pain treatment seven days before the first injection.

Fifty-five patients (91%) in the BTX-A group showed improvement with a 3.2 reduction in the visual analogue scale (VAS). In the placebo group pain improved only 0.4 in the VAS. Patients with severe pain (VAS greater than 6.5) showed significant improvement [26].

BTX-A IN THE TREATMENT OF CHRONIC LUMBAR PAIN

In chronic lumbar pain the main inclusion criteria to use botulinum toxin are: 1) Pain for at least six months; 2) 18 years or older; and 3) Failure of pharmacological or surgical treatment. Exclusion criteria are: 1) Abnormal lumbosacral MRI with indication of urgent surgical or medical attention; 2) Pregnancy or planning on becoming pregnant; 3) Disorders of neuromuscular transmission; 4) Known allergy or toxicity to botulinum toxin-A; and 5) Current litigation. Box I shows those criteria.

In lumbar pain, administration can be uni- or bilateral based on the predominant pattern of pain distribution. The first site selected is at the level of most painful vertebra (defined by the patient and physician through deep digital palpation of the musculature). Subsequent injections are applied at least one and frequently two levels above or below the site of pain. Besides, patients can receive injections in five sites of the paraspinal musculature between L_1 and S_1. When pain extends laterally, the same dose is injected more laterally at the level of the paraspinal muscle. In underweight patients 40 IU are used for each injection (each site) while for normal weigh or overweight patients 50 IU are used per injection. The total dose in each session can vary from 200 to 500 units depending on whether pain is uni- or bilateral [27].

Box I – Main Inclusion and Exclusion Criteria for the Use of Botulinum Toxin in Lumbar Pain

Inclusion
- Pain for at least six months
- At least 18 years old
- Failure of pharmacological or surgical treatment
Exclusion
- Abnormal lumbosacral MRI requiring urgent surgery
- Pregnancy or planning a pregnancy
- Neuromuscular transmission disorders
- Allergy or toxicity to BTX-A
- Current litigation

Local anesthetics can be used as a vehicle for BTX-A without changing its clinical effects[28].
Analgesia after the use of BTX-A in lumbar pain lasts three to four months.

BTX-A IN THE TREATMENT OF HEADACHES

Until 2000, only five studies had been published on the use of BTX-A in the treatment of migraines. It is interesting that all studies showed evidence of good and consistent efficacy of BTX-A. Among those studies we should mention those by Brin et al. (2000) and Silberstein et al. (2000). Both were double-blind, placebo-controlled studies and the injection sites were standardized. In those studies, a significant reduction in the severity and frequency of migraines, tension headache, and other types of headaches was observed. A relatively low dose of BTX-A was used especially in the study by Silberstein et al. in which 25 IU of BTX-A were used. Variations on the results of clinical studies with BTX-A could have several causes, such as patient selection, injection protocol and variation of the doses, and concomitant prophylactic treatment of headaches. Muscular weakness, cervical rigidity, and cervical pain, which affect 3% of the individuals, are the most common side effects. Positive results of the treatment of headaches can only be fully seen 90 days after the injection [29].
Botulinum toxin-A is effective in the prophylaxis of several types of headaches, including migraines. Headaches with muscular disorders, including cervicogenic headache and chronic headache associated with whiplash-type cervical injury, show good response to treatment with BTX-A.
It is believed that the mechanism of action of BTX-A in migraines, although it has not been proven, includes relaxation of the musculature infiltrated with this toxin and the consequent reduction of the pressure on trigeminal nerve roots. This theory is supported by the fact that patients with migraine have considerable hypertrophy of the corrugator muscle, causing compression of branches of the trigeminal nerve and also of the temporal regions [30].
Box II shows the inclusion and exclusion criteria to select patients for headache treatment with BTX-A.

Box II – Inclusion and Exclusion Criteria to Select Patients for Headache Treatment with BTX-A

Inclusion
- Patients with headache for six months with stable frequency and stability from the onset until the evaluation period
- Patients who experienced headaches with a frequency of 15 days or more per month for 6 months, including the evaluation period, confirmed by history and the headache journal
Exclusion
- Any clinical condition or the use of any agent that might make exposure to BTX-A dangerous to the patient (neuromuscular disorders, antibiotics, amynoglycosides, curare-type agents, or any other agent that can interfere with the neuromuscular function)
- Pregnancy or planning to become pregnant during the treatment, or a woman who is incapable or reluctant to use reliable contraceptive methods during treatment

BTX-A IN THE TREATMENT OF NEUROPATHIC PAIN

Nociception can be increased by the release of proinflammatory agents, such as cytokines, adenosine, bradykinin, serotonin, and prostaglandins that can alter or sensitize neuronal transmission and create a temporary state of neuropathic pain. On the other hand, chronic neuropathic pain results from injury of the peripheral or central nervous system, representing an abnormality in nerve transmission secondary to the injury.
Patients with complex regional pain syndrome type I (CRPS I) frequently have myofascial pain in muscles near the affected limb demonstrating that different types of pain can coexist in the same patient [31].
Patients with myofascial pain syndrome can have feelings characteristic of neuropathic pain, such as hyperesthesia, paresthesia, burning, pinching, and allodynia. Autonomic dysfunction has also been observed in trigger points and distal to them.
The importance of using BTX-A in muscles on the same side of the injury, such as in paracervical, suboccipital, and periscapular regions has been demonstrated in patients with complex regional pain syndrome type I who present concomitantly myofascial pain syndrome. Doses of 300 IU of BTX-A are injected in the sternocleidomastoid, trapezius, splenius capitis, splenius cervicis, supra- and infraspinal, and rhomboid muscles. Selection of the muscles to inject BTX-A is based on the patient's report about the maximal pain and identification of trigger points on physical exam. A total of 25 to 50 IU of BTX-A can be injected in each muscle, depending on its size [32].
In 2002, in a study on the effectivity of BTX-A in the treatment of segmental burning pain originating in the spinal cord, two patients with spinal cord injury at the cervical level who developed allodynia, hyperesthesia, and spontaneous burning

pain with segmental distribution were treated with multiple (16 to 20) subcutaneous injections of 5 IU of BTX-A (total dose of 100 U) every three months for 3 years. The author concluded that subcutaneous injections of BTX-A can reduce symptoms of neuropathic pain by changing peripheral mechanisms of pain transmission with the consequent reduction in central sensitization [33].

CONCLUSION

Botulinum toxin-A is safe and well tolerated and can be used in the treatment of chronic pain disorders in which pharmacological regimens are known to cause side effects. Treatment with BTX-A, which is initially expensive, should be considered due to the low incidence of side effects and, if necessary, hospitalization is short. Reduction in the use of adjuvant drugs and the length of action, three to four months per dose, opposed to the continuous use of other drugs, represent further advantages of BTX-A.

Further studies are necessary to establish the efficacy of BTX-A in chronic pain disorders and exact mechanism of action, as well as its role in multifactorial treatments [34].

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RESUMEN:
Colhado OCG, Boeing M, Ortega LB - Toxina Botulínica en el Tratamiento del dolor.

JUSTIFICATIVA Y OBJETIVOS*: La toxina botulínica (TxB), una de las más potentes toxinas bacterianas de que se tiene conocimiento, posee una reconocida acción terapéutica eficaz en el tratamiento de algunos síndromes dolorosos. Sin embargo, algunas de sus indicaciones, todavía están en fase de comprobación con relación a su eficacia. El objetivo de este estudio fue revisar el historial, las propiedades farmacológicas y las aplicaciones clinicas de la TxB, cuando se usa en el tratamiento de dolores de diferentes etiologías.*

CONTENIDO*: La TxB es el producto de la fermentación del Clostridium Botulinum, una bacteria anaerobia Gram-positiva. Comercialmente, las TxB existen bajo las formas A y B, agentes biológicos obtenidos laboratorialmente. La TxB, una neurotoxina que posee una alta afinidad por las sinapsis colinérgicas, ocasiona un bloqueo en la liberación de acetilcolina por el terminal nervioso, sin alterar la conducción neural de las señales eléctricas o la síntesis y el almacenaje de acetilcolina. Se ha comprobado que la TxB puede debilitar selectivamente la musculatura dolorosa, interrumpiendo el ciclo espasmo-dolor. Con relación a él, varias publicaciones han demostrado la eficacia y la seguridad de la TxB-A en el tratamiento de la cefalea tipo tensión, migraña, dolor lumbar crónico y dolor miofacial.*

CONCLUSIONES*: La TxB-A es segura y se tolera muy bien en los desórdenes dolorosos crónicos, donde los regímenes de farmacoterapia pueden de hecho provocar efectos colaterales. Otra ventaja es la reducción del uso de analgésicos y el tiempo de acción de 3 a 4 meses por dosis. Sin embargo, investigaciones futuras serán necesarias para establecer la eficacia de la TxB-A en los desórdenes dolorosos crónicos y su exacto mecanismo en el alivio del dolor, como también su potencial en tratamientos multifactoriales.*