Contribution of Botulinum Toxin for the Treatment of Neuropathic Pain.

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ABSTRACT

Neuropathic pain is caused by an injury or a disease of the somatosensory system, including peripheral nerve fibres and central neurons. Botulinum toxin (BTX) is a neurotoxic protein produced by the bacterium Clostridium botulinum. BTX interferes with the release of the neurotransmitter acetylcholine from neuroaxon terminals at the neuromuscular synapse and thus causes flaccid paralysis. This literature review investigates the recent data regarding the efficacy of BTX in the treatment of various forms of neuropathic pain. A total of 18 original clinical trials published after 2010 were selected, 12 of which were randomized controlled studies, one was a non-randomized controlled study and the remaining 5 were case series. A total of 1,131 patients were enrolled. BTX represents an effective treatment for neuropathic pain. Further randomised controlled trials are needed to demonstrate treatment efficacy, provide guidelines in relation to its application protocols and establish possible treatment variations at different sub-groups of patients.

Key words: Neuralgia, Botulinum toxins, Therapeutics

Introduction

Neuropathic pain is mediated through the somatosensory system, including peripheral nerve fibers (Aβ, Aδ, and C) and central neurons, and affects 7–10% of the general population (1). Its frequency is more likely to increase due to population' aging, increased number of diabetes mellitus and post-chemotherapy cancer patients. There are several pathophysiologic mechanisms that are involved in the development of neuropathic pain, including imbalance between excitatory and inhibitory somatosensory signalling, changes in ion channels and variability pain signals' modulation in the central nervous system.

Patient burden due to chronic neuropathic pain appears to be related to the: (a) complexity of neuropathic symptoms, (b) poor outcome of applied therapeutic interventions, and (c) difficulty in choosing the optimal therapeutic method. Progress of understanding

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the pathophysiology of neuropathic pain prompts the development of new diagnostic methods and personalized therapeutic interventions, which highlight the need for a multi-level and multidisciplinary approach to the management of neuropathic pain (1).

Botulinum toxin (BTX) is a neurotoxic protein produced by the bacterium Clostridium botulinum. It prevents the release of the neurotransmitter acetylcholine from the axonal endings at the neuromuscular synapse and thus causes flaccid paralysis. BTX is one of the most poisonous biological agents known. Eight antigenically distinct exotoxins (A, B, C1, C2, D, E, F and G) are produced by C. botulinum. All serotypes interfere with nerve transmission by blocking the release of acetylcholine causing muscle paralysis. The muscle weakness caused by the BTX-A injection usually lasts for three months. BTX play an important role in the management of a wide variety of pathological conditions, such as strabismus and focal dystonias, hemifacial spasm and various spastic movement disorders, headaches, hyperalgesia, hyperhidrosis, and some chronic conditions that are only partially responsive in conventional medical treatment in fact, the list of potential new indications is expanding rapidly (2).

The aim of this review was to investigate the data of the recent literature in relation to the effectiveness of BTX in the treatment of the various forms of neuropathic pain. To achieve the above-mentioned aim of the present diploma thesis, the tool of the systematic literature review was chosen (3). The databases searched for relevant published clinical studies were PubMed/NCBI, Google Scholar and Cochrane Library of Systematic Reviews. The key words (mesh terms) entered into the search engines of the specific databases were Botulinum, Toxin, Neuropathic, Pain, Treatment, in various combinations and with the use of AND and OR disjunctive terms. For the study entry we used the following criteria: (i) randomized and non-randomized clinical studies with a control group as well as series studies, (ii) date of publication later than year 2010, (iii) publication language English and possibility to study the full text, or at least an extended summary of the study, (iv) clinical studies conducted on humans. On the other hand, the review did not include single case reports as well as reviews / systematic reviews / meta-analyses of the literature, animal studies as well as experimental – in vitro studies. Figure 3 shows the flow diagram of the review, according to the PRISMA principles (4).

Discussion

According to the above-mentioned method of collecting the scientific data, 18 original clinical studies were isolated and studied, of which 12 were randomized controlled studies, one was a non-randomized controlled study, and the remaining 5 were series studies. A total of 1,131 patients participated. Table 1 summarizes the findings of the specific studies. Their findings will then be presented in more detail, grouped according to the specific pathological condition to which the studies referred.

Treatment of trigeminal neuralgia

Trigeminal neuralgia is a chronic painful pathological condition with repeated episodes of neuropathic pain in the distribution of the fifth cerebral conjugation (trigeminal nerve), which innervates the area of the forehead, cheek, and lower jaw. In most cases the condition occurs contralaterally and affects one or more of the three main branches of the trigeminal nerve (ophthalmic - V1, maxillary - V2 and mandibular - V3 nerve). Several pharmaceutical agents have been used in the attempt to treat trigeminal neuralgia, such as carbamazepine, oxcarbazepine, baclofen, gabapentin and valproic acid (5). The use of BTX has been proposed as a therapeutic intervention in specific groups of patients (especially middle-aged and older) who have failed drug therapy, or do not tolerate its adverse effects (6).

In 2013 Zuniga et al. (7), published the results of a double-blind randomized controlled trial to investigate the efficacy of BTX - A injection in 36 patients with trigeminal neuralgia. In a study group 20 patients 50 IU were administered subcutaneously in the affected area. The primary outcome measure was VAS pain scale. The results of the study showed the statistically significant superiority of the BTX group compared to the control group (infusion of 0.95 saline), at a period of 2 months (VAS 4.9 vs. 6.63, p = 0.07), and 3 months follow-up (VAS 4.75 vs. 6.94, p = 0.01). According to the authors, botulinum toxin is an effective, very well tolerated and without clinically significant side effects,

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treatment for trigeminal neuralgia.

One year later, the results of a new randomized double-blind controlled study (8) in 84 patients with trigeminal neuralgia were published. Two topical BTX-A regimens, 25 IU and 75 IU, were studied with control patients receiving placebo (saline). The results of the study showed, a statistically significant superiority of both treatment regimens compared to the control group8 weeks after the injections. On the other hand, no statistically significant difference was found between the two dosages of BTX-A, while at the same time, all side effects of the drug were rated by patients as “mild” or “moderate”. In 2016, Xia et al.(9), published the results of a prospective study of 87 patients with bilateral trigeminal neuralgia who received topical BTX-A. With a follow-up time of 8 weeks, a gradual improvement in pain was recorded (from 48.28% in the first week to 80.46% in the eighth week), while at the same time a reduction in anxiety and depression levels was found (90.32% and 96.77% respectively). At the same time, a series of parameters of patients’ quality of life improved significantly ($p < 0.01$) after the therapeutic intervention, while patients’ physical activity showed no impronement ($p = 0.317$). In 2017, Zhang et al. (10), in a pilot randomized controlled trial, investigated the efficacy of two different regimens in 87 patients with trigeminal neuralgia. Patients in the first group received one injection of BTX-A 70-100 IU in the affected area, while those in group B received two doses, 50-70 IU, over a period of two weeks. The results of the study showed a no significant remission of patients’ symptoms, between the two study groups, in terms of their effectiveness and safety, at the 6th month’s follow-up. Wu et al., (2019) (6), in a retrospective study investigated the efficacy of local infusion of 100 U BTX-A in 104 elderly patients (mean age 59.2 years) with persistent trigeminal neuralgia. The results of the study, with a total patient follow-up time of 12 months, showed that 1) 83.7% successful treatment. The age group > 50 years had the best results ($p = 0.033$) at the 12 mont’s follow-up. Crespi et al. (11) investigated the efficacy of 25 IU BTX-A injection into the sphenoid ganglion in 10 patients with persistent trigeminal neuralgia. Although the treatment proved to be safe and well tolerated by the patients, the main outcome criterion of the study (reduction of the frequency of seizures by at least 50% during the 5-8 week period after the intervention) did not prove the effectiveness. Conclusively, botulinum toxin for trigeminal neuralgia was found to be a safe and well-tolerated treatment with non-significant clinical side effects. The local injection of BTX-A in the affected area was particularly effective in reducing the frequency of seizures as well as the intensity of pain. The single-dose regimen appears to be non-inferior to re-dosing after two weeks. Patients of an older age group (> 50 years old) seem to have a better response to the therapeutic intervention.

Treatment of postherpetic neuralgia and atypical dental pain

Post-herpetic neuralgia (PHN) is the common complication, causing long-term and excruciating neuropathic pain. In addition, over 50% of patients with PHN report significant profound sleep disturbances, limitations in their daily activity and significant burden of their social life (12). Apalla et al. (2013) (13), in a randomized, double-blind, controlled study, investigated the efficacy of a 100 IU dose of BTX-A subcutaneously, in the affected area, in 30 patients suffering from PHN. The study outcome criteria were patients’ pain level (VAS scale), sleep quality and clinical improvement > 50%. The results showed that 13 patients in the intervention group experienced at least a 50% reduction in the VAS scale, compared to none in the control group ($p < 0.001$), an improvement that was maintained for a mean time of 16 weeks. According to the authors, this is a particularly effective therapeutic option in the treatment of PHN. Hu et al., (2020) (14), published the results of a randomized control trial in 33 patients with persistent PHN. The 13 patients received a subcutaneous injection of BTX-A (50-100 IU) in the affected area while the remaining 20 were treated with 0.3 g gabapentin orally, three times a day. The primary outcome measure was pain (VAS scale) at 1, 2, 4-, 8-, 12- and 16-weeks post-intervention. The main findings of the study were that patients in the intervention group had a statistically significant improvement in pain level as early as week 2, both compared to their status before BTX-A infusion and compared to patients in gabapentin group. In one of the most recently published randomized controlled trials, Chen et al. (2022)

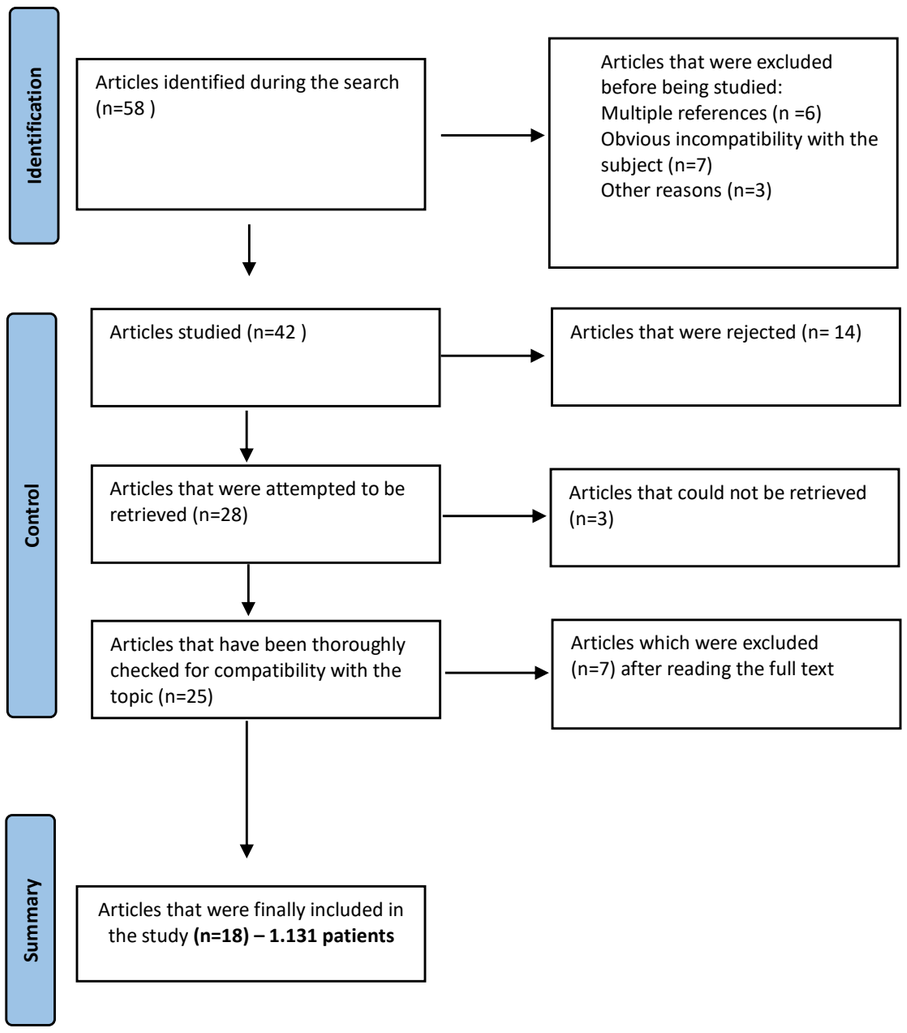

table 1: The flow chart of the systematic literature review.

(15) compared the efficacy of a 100 IU m BTX-A infusion and a pulsed radiofrequency treatment session in 100 patients with postherpetic neuralgia. With the primary outcome measure of pain and a follow-up duration of 24 weeks, it was found that patients in both study groups had a statistically significant reduction of pain ($p < 0.05$) compared to the state before the intervention. In addition, botulinum toxin injection was an easy and a less expensive treatment, compared to pulsed radiofrequency therapy.

Atypical ododalgia (AO) is a subcategory of persistent idiopathic facial pain, defined as persistent dental pain for which thorough examination does not reveal any dental pathology. It is a pain of neuropathic etiology, for the treatment of which a series of local and systemic pharmaceutical treatments have been used, with unsatisfactory results in most cases (16). Cuadrado et al. (2016) (17) showed that local injections of Onabotulinum toxin A (5-30 IU, from two to five infusion cycles), resulted in almost complete elimination of the pain, with the analgesic effect of the method appearing as early as the 3rd-14th day of the intervention and lasting for a period of 2-6 months.

Table 2: The IASP guidelines for the pharmacological management of neuropathic pain. Source: Finnerup et al., (2015) (10).	
Drug guideline	Medical drugs
First-line SNRI*	duloxetine, venlafaxine Tricyclic antidepressants Gabapentin, pregabalin
Second Line	Capsaicin Patches 8% Lidocaine (lignocaine) patches Tramadol
Third-line	Strong opioid pain relievers

*SNRI: Serotonin noradrenaline reuptake inhibitors.

Treatment of neuropathic pain after spinal cord injury

Pain is one of the most common complications following spinal cord injury (SCI), it has the characteristics of classic neuropathic pain and causes a significant burden on patient's quality of life, affecting his physical, cognitive, and emotional functions (18). Its incidence in patients with SCI is estimated to be 75%-81% of the cases (19). Han et al. (2016) (20) investigated the efficacy of subcutaneously injecting 200 IU of BTX-A into the affected area. The results showed a statistically significant reduction in pain at both 4th and 8th week post-injection, with simultaneous maintenance of patient's motor and sensory function peripheral to the level of neurological damage.

One year later, Li et al., (2017) (21) showed that local subcutaneous injection of 200 IU BTX-A resulted in statistically significant improvement in patients' pain, at both 4 and 8 weeks post-intervention. At the same time, statistically significant improvements were also recorded in patients 'quality of life, according WHO Quality of Life questionnaire (WHOQOL-BREF). Finally, Chun et al., (2019) (22) showed that local subcutaneous injection of 400 IU BTX-A had no significant improvement in the level of pain, compared to patients in the control group. According to the authors, this method may prove to be effective in the control of neuropathic pain following SCI and should be further studied with high-quality clinical studies that include many participating patients.

Treatment of various forms of neuropathic pain

Diabetic polyneuropathy is a serious complication that affects more than 25% of patients with type II diabetes, relapsing their sleep and quality of life (23). Chen et al., (2013) (24) showed that treatment with a local injection of BTX-A 50 IU in each leg (two injections with an interval 12 weeks), led to a statistically significant reduction in both tactile and mechanical pain of patients in the intervention group, up to the 24th week of follow-up.

The sciatic muscle syndrome is a neuromuscular disorder caused by the pressure of the sciatic nerve by the sciatic muscle as it exits the sciatic foramen. Its etiology is not yet fully understood, its diagnosis is difficult and even more difficult may prove to

TABLE 3:

The Summary Findings Of The Clinical Studies Which Were Isolated.

Authors, Country	Type of study	Participants	Method	Outcome criteria	Results
Zuniga et al., (2013), Argentina (24)	Randomized, double-blind, control-group study	36 patients with trigeminal neuralgia	Control group: saline infusion. Intervention group: 50 IU BTX infusion	VAS pain scale. 3 months follow up.	Statistically significant superiority in favor of the BTX group
Zhang et al., (2014), China (25)	Randomized, double-blind, control-group study	84 patients with trigeminal neuralgia	Group A: placebo Group B: BTX-A 25 IU Group C: BTX-A 75 IU	VAS pain scale. 2 months follow up.	Statistically significant superiority in favor of the BTX group – no difference was found between the two dosage regimens.
Xia et al., (2016), China (26)	Prospective series study	87 patients with trigeminal neuralgia	Local injection BTX-A	VAS pain scale, Hamilton Anxiety Scale, Hamilton Depression Scale. 2 months follow up.	Significant improvement of all studied outcome criteria, without substantial adverse effects
Zhang et al., (2017), China (27)	Randomized, pilot study with a control group	81 patients with trigeminal neuralgia	Group A: 1 infusion BTX-A 70 – 100 IU Group B: Initial dose of BTX 50 – 70 IU and repeated 2 weeks later.	VAS scale, incidence of symptoms, side effects. 6 months follow up.	Both regimens were effective in treating symptoms, with no statistically significant difference between them.
Wu et al., (2019), Κινα (23)	Retrospective series study	104 elderly patients (mean age 59.2 years) with persistent trigeminal neuralgia	Local injection 100 IU BTX-A	VAS scale, frequency of symptoms, side effects.	87 patients (rate 83.7%) reported success of the intervention. Statistically significant difference in favor of the age group of > 50 years.
Crespi et al., (2019), Norway (28)	Prospective pilot series study	10 patients with persistent trigeminal neuralgia	Infusion 25 IU BTX-A into the sphenoid ganglion	Side effects, seizure frequency, patient functional level. 3 months follow up. 6 months follow up.	The efficacy of the method was not confirmed in the primary outcome criterion (reduction in seizure frequency during the 5-8 week period)
Apalla et al., (2013), Greece (30)	Randomized, double-blind, control-group study	30 patients with chronic postherpetic neuralgia	Infusion 100 IU BTX-A into the affected area	Pain (VAS scale), sleep quality. 24-week follow-up	Statistically significant reduction in pain and improvement in sleep quality, lasting at least 16 weeks
Hu et al., (2020), China (31)	Randomized control group study	33 patients with chronic postherpetic neuralgia	Group A: Infusion 50 – 100 IU BTX-A Group B: 0,3 g gabapentin, 3 times daily	Pain (VAS scale). 16-week follow-up	Statistically significant reduction in the pain level of patients in the intervention group both in relation to their previous condition and in relation to patients in the control group (gabapentin)
Chen et al., (2022), China (32)	Randomized control group study	100 patients with chronic postherpetic neuralgia	Group A: Infusion 100 IU BTX-A Group B: One session of pulsed radio frequencies	Pain (VAS scale). 24-week follow-up.	Statistically significant improvement of patients in both study groups – No difference was found between the two groups. Injecting BTX-A is easier and less expensive.
Cuadrado et al., (2016), Spain (34)	Prospective series study	4 patients with atypical ododalgia	Local injection BTX-A 15 – 30 IU, 2 -5 therapy sessions	Pain levels. Follow-up range 6 -20 months.	Almost complete or even complete remission of symptoms in all patients.
Han et al., (2016), N. Korea (37)	Randomized, double-blind, control-group study	40 patients with SCI	One injection of 200 IU BTX-A s.c	VAS scale, 8-week follow-up	Statistically significant reduction in pain at 4th and 8th weeks.
Li et al., (2017), China (38)	Randomized control group study	44 patients with SCI	One injection of 200 IU BTX-A s.c	VAS, SF-MPQ and WHOQOL-BREF scales, 8-week follow-up	Statistically significant improvement in all outcome criteria at 4th and 8th weeks post-intervention.
Chan et al., (2019) US (39)	Randomized, double-blind, control-group study	8 patients with complete SCI	One injection of 400 IU BTX-A s.c	VAS scale, 12-week follow-up	Reduction in pain level in the intervention group, with values that were not statistically significant.
Chen et al., (2013), Taiwan (41)	Randomized control group study	18 patients with painful diabetic polyneuropathy	Two infusions of BTX-A 50 IU in each leg, 12 weeks apart	Level of pain (mechanical and tactile). 24-week follow-up	Statistically significant improvement in pain levels during follow-up

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Mitchel et al., (2013), Γαλλία (43)	Non-randomized study with control group	280 patients with piriformis syndrome	Infusions (1-5) of BTX-A 50-100 IU into the apioid muscle	77% of patients reported very good remission of symptoms
Attal et al., (2016), France (44)	Randomized, double-blind, control-group study	66 patients with peripheral neuropathic pain from nerve injury	2 infusions of BTX-A up to 300 IU 12 weeks apart	Statistically significant improvement in the symptomatology of patients in the intervention group
Eitner et al., (2017) (45), Germany	Randomized control group study	46 patients with peripheral neuropathic pain from nerve injury	Subcutaneous injection of BTX-A (100 - 300 IU).	Statistically significant reduction in patient symptoms
Meyer-Friebem et al., (2019), Germany (46)	Prospective series study	60 patients with peripheral neuropathic pain from nerve injury	Perineural infusion, under ultrasound guidance of 25 – 100 IU BTX-A	Reduction of pain levels by 24.8%, without disturbing the sensibility of the area. Further clinical studies need at least 84 participants in order to have statistical power.

be its definitive treatment (25). Mitchel et al., (2013) (26) in a non-randomized study with a local injections of 50-100 IU BTX-A in the opioid muscle, found that 77% of patients reported very good symptom relief, 7.4% moderate and the remaining 15.6% poor. In 2016 Attal et al., (27) in a double-blind randomized controlled trial in 66 patients with peripheral neuropathic pain due to a peripheral nerve injury, showed that local injection of BTX-A resulted in a statistically significant reduction of pain in the intervention group. The dose of BTX-A was not higher than 300 IU, and the beneficial effect lasted for at least for 24 weeks. Eitner et al., (28) in a randomized controlled trial, showed a statistically significant improvement in neuropathic pain symptomatology in 46 patients with peripheral nerve injury following subcutaneous injection of BTX-A. This improvement was maintained for period of at least 24 weeks. Finally, in 2019 Meyer-Friebem et al., (29) published the results of a prospective series study in 60 patients with painful peripheral nerve injury, who were treated with perineural injection, under ultrasound guidance, with 25-100 IU BTX-A, to treat single peripheral nerve damage. The results of the study showed that the rate of pain reduction was 24.8% ($p<0.0001$). As the specific findings are promising, the authors of the study suggested that in the future, randomized controlled trials with at least 84 patients will be conducted to draw clearer conclusions regarding the effectiveness of the method.

With the present systematic review of the literature, recent research data were investigated in relation to the effectiveness of the action of botulinum toxin in the treatment of neuropathic pain. The main conclusions drawn from this review can be summarized as follows:

Statistically significant efficacy versus placebo was found in the treatment of neuropathic pain for trigeminal neuralgia (6), postherpetic neuralgia (13)), atypical ododalgia (17), neuropathic pain after spinal cord injury (20), diabetic neuropathy (24), piriformis syndrome (26) and peripheral nerve injury (27-29).

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Even though there is no specific protocol for the administration of the botulinum toxin (both in administration dose and repetitions) in the various cases of the above-mentioned pathological conditions, all researchers agree that t side / adverse effects are minimal and clinically insignificant.

Further research is needed with high-quality randomized control group studies as well as their meta-analyses, to accurately establish the effectiveness, indications, and protocols of use of the method.

Conclusion

This literature review reached the conclusion that the use of botulinum toxin is an effective treatment for neuropathic pain arising from a range of pathological conditions. Complications and side effects of the method are not clinically significant. Additional randomized controlled clinical studies with many patients are needed to further demonstrate the effectiveness of the method, to provide guidelines regarding its application protocols, and to identify possible differences in the effectiveness of the method in the various subgroups of patients.

Conflict of interest:

The authors declared no conflicts of interest.

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