

The Effect of Local Botulinum Toxin A Injections in Long-Term Management of Chronic Pain in Post-Herpetic Neuralgia: Systematic Review and Case Reports Treated With Incobotulinumtoxin A

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ABSTRACT

Back ground: Botulinum toxin A (BoNT A) may be helpful in modulating severe chronic neuropathic pain in Post-Herpetic Neuralgia (PHN).

Method: Clinical studies and case series were searched with term “neuropathic pain” and “botulinum” on PubMed to 28. Feb. 2019. Pain was measured with Visual Analogue Scale (VAS) at baseline and at follow-up after BoNT A therapy.

Results: As result 6 cases /case series and 8 studies including 199 patients with PHN, treated by BoNT A, were analyzed and presented. Additionally the effects of a long-term management of PHN with intra/subcutaneous incobotulinumtoxin A (Xeomin) injections in 3 patients with severe PHN is presented. Most of studies (5 cases/case series reports and 8 trials) suggested that BoNT A therapy result in significant pain reduction and impact on quality of life, i.e. improvement in sleep quality. The duration of effect (pain reduction) seems to be positively correlated with BoNT A doses injected per injection site (range per site 5-10 IU). Interval between BoNT injections were 10-14 weeks. No severe side effects were reported, even when BoNT A was given in 2 pregnancies, babies were normal. Our 3 cases with more than 4 intra/subcutaneous injections of Incobotulinumtoxin A (Xeomin) showed good effects in pain reduction (VAS) and secondary complains.

Conclusion: BoNT A injections in severe PHN can be helpful as an adjunctive therapy and result in significant pain reduction (up to 30-50% VAS reduction) for up to 14 weeks, which is difficult to gain from oral medications and/or local anesthetic therapies. Data analysis result in no significant difference of efficacy and safety of the different BoNT A products available and injections technique (intra- or subcutaneous). The better effect and the longer duration effect seems to be positively correlated with the dose of BoNT A injected at one injection site. Data suggested that adjunctive local BoNT A injections might be a good option for long-term management in severe PHN.

INTRODUCTION

Post-Herpetic Neuralgia (PHN) is a very painful neuropathic status, which occurs by nerve injuries (e.g. demyelination, loss of axon, small-fiber-degeneration, reorganization in dorsal horn, neuroplastic central changes) due to herpes-zoster-virus infection, and is defined by duration of local neuropathic pain for more than 3 months following initial acute zoster infection [1,2]. Frequently burning pain with shooting pain

points and often also with dynamic tactile allodynia are complained. Severe PHN reduce QOL (Quality of Life) and often induces disorder of sleep [3]. Even though the intensive pharmacological treatments with classic oral drugs including anticonvulsants, antidepressants, opioids and local therapy with lidocaine or capsaicin are mostly recommended, patients often show severe side effects from oral treatments, especially in over 50 years of age and are also not satisfied by the magnitude and duration of effects of current local treatment options. However, their continued use increases the risk of adverse events, as well as reductions in analgesic efficacy. Usually the aim of such chronic symptomatic systemic and local therapies for PHN is to reduce pain by about 30-50% [4-8].

After the first publication on effect of botulinum toxin type A (BoNT A) for pain in dystonia by Brin et al. 1987, many studies on positive effects on chronic pain including modulation and management of spasticity associated pain and neurogenic pain, have been published [9-13]. The evidence for the efficacy of BoNTA in neuropathic pain relief in humans was first presented by Klein in 2004 in relation to neuropathic pain linked to multiple sclerosis, neuralgia and peripheral neuropathy [14].

Several mechanisms of pain reduction by BoNT A injections have been discussed in the literature, mainly on the inhibitory effect of release of various inflammation-mediated substances (substance P, glutamate, calcitonin gene – related peptide) by blocking of exocytosis from BoNT A, acting via SNAP-25 [9-13]. The toxin also blocks conductivity in the autonomic system through sensory fibers and reduces the majority of substances acting on nociceptors [15].

Deactivation of Sodium-channels, inhibition, reduction of afferent into muscle spindle, reduction of sympathetic transmission and influence into spinal α -receptors by BoNT A have been discussed partially [16-18]. In 2008, Antonucci et al. suggested that the effects of BoNTA might be due to retrograde transport or to the effect of transcytosis and peripherally applied BoNTA gains access to Central Nerve System (CNS) and directly inhibits neurotransmitters release onto dorsal horn neurons [19]. In recent 2 animal studies, BoNT A diminished CCI (Chronic Constriction Injury)-induced level of IL-1 β (Interleukin-1 β) and IL-18 within the spinal cord and/or the dorsal root ganglia and

in parallel, it enhanced the levels of the anti-nociceptive factors IL-1RA (receptor antagonist) and IL-10. They suggested that BoNT A, in addition to altering neuronal function, can also influence spinal microglial cells, [20,21] however it is still unclear whether those BoNTA actions are mediated in a direct or indirect manner. The latest in vitro research by Piotrowska (2017) showed new light on the analgesic effect of BoNTA and suggested a possible direct impact of the BoNT A on microglia in the CNS [22]. The inhibition of important G-proteins and prostaglandin synthase COX-2 (cyclooxygenase-2), in activating of proinflammatory cytokines Interleukins-1 (IL-1) from BoNT A were also studied in animal models [23,24]. From these base data, Rojewska (2018) suggested that BoNT A, in addition having an impact on neuronal functions, can also influence the activation of microglia; therefore, the involvement of non-neuronal cells in the BoNTA mechanism of action should also be regarded as an important component of its analgesic effects. BoNTA might be a powerful modulator of neuron–glia interactions in the CNS in the context of neuropathic pain [4].

The general accepted mechanism of effects of BoNT A against neuropathic pain remains however uncertain and still stay under discussion. Although its mechanism is not completely understood, the positive effects of BoNT A in patients with severe PHN has been reported in previous studies, therefore we aim to support evidence for its effect in PHN throughout literature analysis and introduce a new case series from our clinic.

Although the effects of multifocal intra- and subcutaneously injected BoNT A for the treatment of PHN have been known by previous case/case series reports, clinical studies as over-mentioned, long term efficacy and safety data of this local therapy approach in PHN is lacking and however the treatment still is used as “off-label” option yet and no reimbursement is established, i. g. in Germany and other European countries.

METHODS

Relevant clinical studies and case/ case series reports on intra- and subcutaneous injections of BoNT A to treat PHN were searched with term “neuropathic pain” and “botulinum” on PubMed to 28. Feb. 2019. Our first analysis was performed with their titles and abstracts. Additionally we introduce 3 cases with severe PHN and with repeated intra- and

subcutaneous Incobotulinumtoxin A (product name: Xeomin®) the rapies which were applied to their color-marked painful areas with 2-2, 5 IU for case 1, 4-5 IU for case 2 and 7, 5-10 IU for case 3 (IU=international units, dilution in normal saline to 100 IU / 2 ml) per injection site with injection sites 2cm apart from each other (Figure 2). The doses of Xeomin injected per injection session ranged from 150 IU to 300 IU. We used small needles with 30 gauge and small tuberculin (1 ml volume) syringes for injection procedure without additional local anesthetics. Intensity of pain was evaluated by VAS before and every 10-14 weeks after BoNT A injections (or before next injections). Other treatments, e.g., oral medications and additional local anesthetic therapies, were documented and changes made by the patients were captured.

RESULTS

Of total 306 articles, which was searched with term “neuropathic pain and botulinum” on Pubmed, only 12 relevant publications were filtered by analyzing their titles and abstracts. These 6 case / case series reports and 8 prospective studies included totally included reports about 199 patients with PHN who were treated by BoNT A injections (Table 1). Follow-up of observation on effects of BoNT A injections were 1 to 6 months and maximum total doses for onabotulinumtoxin A (product name: Botox®) 300 IU and 5-20 IU (only for one case) per injection site . In 2 publications abobotulinumtoxin A (product name: Dysport®) was applied, no information on injection schema was available [25,26]. Jain (2017) reported about efficacy and safety in 2 pregnancies.25 Even though they applied different total- / single point doses and different technique with intra- and/or subcutaneous injections, the positive effect of BoNT A against PHN had been shown in all patients, despite of individually different effects. Except of case series report by Emad (2011) 25, others studies showed the significant effects of BoNT A against PHN. Injection’s technique reported were intracutaneously or subcutaneously application of BoNT A.

Case 1

The 56-years old male with severe pain due to PHN in the area of left shoulder and ventral thorax was introduced to us by an anesthesiologist and pain specialist for additional treatment in August 2013, following skin changes due to herpes

zoster in June 2011. He experienced at that time pimples within several hours in the painful area between the spinal processes of [3-11] and the medial line of left scapulae as well as on the body of sternum and some left skin areas of it (Figure 1). The constant severe pain niveau were judged by the patient with 7-8 of VAS, interrupted by severe shooting and electric-like pain episodes over seconds with levels up to [8-9] VAS even under regular oral drug treatments. Any accompanied diseases were unknown.



Figure 1: The painful areas marked with blue lines (case 3)

At the second day of symptoms with pimples herpes virus infection was diagnosed and only treated with Zn-ointment, no other treatment was introduced by the dermatologist. The scabbing and crusting of the skin injuries needed several weeks, but the severe pain scares, pigments remained as post-herpetic neuralgia persisted. The severe PHN was treated at first by dermatologist and later by a pain specialist, an anesthetist. The patient had taken for PHN oral pregabalin up to 450mg per day, Morphine up to 80 mg per day, additionally local treatment was introduced with capsaicin ointment and lidocaine plasters were applied by the therapist.

He also took mirtazapine (NaSSA: Noradrenergic and Specific Serotonergic Antidepressant), and citalopram (SSRI), but all drugs applied had no positive effect for him. Serial lidocaine plasters also were applied locally on the affected skin, but had only a short time-relief of pain and therefore helped only a little. Additionally 6 acupuncture therapies for 3 weeks were introduced but had no reduction of pain intensity, but following acupuncture the very severe pain up to 8-9 VAS disappeared, but the constant pain level had been remained on levels of 7 - 8 of 10 VAS even under constant drug treatment with morphine 80 mg per day.

In August 2013 we introduced local intra/subcutaneous multi-point injections of BoNT A (Incobotulinumtoxin A, product name: Xeomin®) with dosage per treatment session of 150 IU (IU=international units, dilution in normal saline to 100 IU / 2 ml) to a total of up to 70-75 intra-/ subcutaneous injection points (one injection site within every 2cm) and a dosage per injection point of 2 - 2,5 IU every 3 months (Figure 2). We used very small needles with 30 gauge and small tuberculin (1 ml volume) syringes. Following the first and the following 20 injection cycles, usually for three weeks following intra- or subcutaneous BoNT A injections patient reported pain reduction from VAS 7 - 8 to pain levels VAS 4 - 5. Pain level reduction allows him to reduce Morphine to 40 mg per day (half of the initial dose) for the following years. During the first and following injection cycles the patient reported pain reduction for up to 11 weeks and then increasing pain levels up to the pre-injection levels before follow-up injections. Summing up the intra- or subcutaneous injections of BoNT A was effective in reducing the intensities of PHN pains and enabled to reduce oral administrations of morphine, so that the patient asked for continuation of BoNT A injections. Up to now we have performed 20 injection sessions. No side effects of BoNTA injections were found over the reported treatment regime of 3 years. When comparing the costs of drug including BoNT A injections with the costs before this additional local therapy regime with BoNT A we found an slight elevation in costs of 30%.



Figure 2: After injections of Incobotulinumtoxin A (case 3)

Case 2

The 77 years-old male was introduced to us by a neurologist for additional pain management with BoNT A. He complained severe PHN (7-8 of VAS) for more than 3 years, which could not be adequately managed with local and oral medications. Additionally he complained sleep disorder because of severe pain. Any other accompanied diseases were unknown. At time of first contact he was on amitriptyline 75 mg and local application of lidocaine cream (every 6 hours), occasionally he added opioids (tramadol) when necessary but his resumee was no sufficient effects from opioids and morphine. We applied intra- and subcutaneous incobotulinumtoxin A (product name: Xeomin) injections with a total dose of 160-200 IU, 4-5 IU x 40-45 in every 1,5 – 2 cm in the painful skin areas on the left front and lateral neck between chin and clavicae in dermatome C3 left side. We used the same material for injections as in case 1. Total 6 therapies with incobotulinumtoxin A every 3 months were applied and assessed with VAS. The relief of severe pain was observed

from 7-8 of VAS to 4-5 and his sleep disorder improved. Patient reported that effects of BoNT A lasted about 6 - 8 weeks and started about a week after injection. No side effects of local injection of BoNT A were reported for 6 therapy cycles.

Case 3

The 80-years-old male was introduced to us by an anesthesiologist / pain specialist for additional BoNT A in March 2017. She complained about severe PHN (6-7 of VAS), not controlled by oral or local medications. After diagnosed infection of herpes zoster in April 2015 he developed severe pain 3 months after acute herpes zoster infection. On the painful area in the right scapulae and in the right chest, incobotulinumtoxin A (product name: Xeomin) with total doses of 200–300 IU, 7,5 -10 IU per site at 30-40 sites on a grid with 1,5-2cm was applied intra- or subcutaneously every 3 months and total 4 injection sessions were performed since September 2017. Oral medications and local anesthetic therapy including Pregabalin, Amineurin, continued without any changes. Morphine as a treatment was not accepted by the patient, because of its side effects. By these intra- or subcutaneous BoNT A injections, the pain intensity was reduced to 3-4 of VAS from a starting level of 6-7 of VAS, but the positive effects of BoNT A therapy begun to decline 8-10 weeks after injections. There were no side-effects reported from BoNT A injections. The same injection materials for BoNT A therapy as in case 1 were applied. Polyarthrititis in fingers and regular oral administration of arhythmicants and Losartan were known.

DISCUSSION

Most of publications included in our systematic review showed significant reduction of pain in PHN as well as other secondary complications from PHN such as sleep disorder and improvement of QOL (Quality of Life) was documented [14,25-37]. Reduction of pain intensity to a significant degree and no side effects of intra- or subcutaneous BoNT A therapy were found in our 3 cases and all previous publications included in our systematic review. Even in 2 pregnancies and the healthy babies delivered after PHN management with BoNT A, the safety of BoNT A injections was evident in long-term follow-up [25]. Because of small study size, there has been no strong evidence for this therapy in PHN, but there are more

publications and more evidences for neuropathic pain treatment with BoNT A including other neuralgia, complex regional pain syndrome, traumatic nerve injury, diabetic neuropathic pain [38,39].

The direct comparison of therapeutic effects was performed between subcutaneous injected BoNT A 5 IU and 0.5% Lidocaine. While the effect of BoNT A started 3-7 days after injections and lasted for about 3 months, Lidocaine helped only for 1 day. As like this subcutaneous lidocaine injections, local anesthetic therapy has a short-time effect by applying injections as well as creams or pads [31]. Oral medications showed much more side effects with also risk of increasing to necessary doses and frequently these management could not manage pain adequately to levels of below 5 VAS [4,5]. Therefore, recent more focused additional therapies like local BoNT A injections have been often inquired by patients with severe PHN.

Applied Botulinum Toxin A

Most of reports applied onabotulinumtoxin A (Botox) (100IU/2ml 0.9% NaCl). In 174 patients with PHN onabotulinumtoxin was injected. Only in two case series by Emad (2011) and Jain (2017), with a total of 17 patients abobotulinumtoxin A (Dysport) was used. In those two different dilution rates of the toxin were applied, respectively 500IU/4ml 2% Lidocaine or 500IU/5ml 0.9% NaCl. 2 case reports by Ruiz (2008) and Liu (2015) and one study by Eitner (2017) did not identify the product used for treatment. One study with abobotulinumtoxin A by Emad (2011) showed no significant reduction of pain, but this is not strong evidence for differentiating the effects by BoNT A subtypes in PHN (Table 1). It might be resulted from other factors such as doses and injection technique.

Actually the specific effect of BoNT A on voluntary muscle contraction or muscle tone reduction in other indication including spasticity and cervical dystonia, showed dose depended responses, e.g. higher dose more pronounced muscle force / tone reduction, therefore a dose depended effect per muscle injected could be shown. Up to now incobotulinumtoxin A never caused a development of secondary non-responsiveness to BoNT A due to antibodies against BoNT A therefore it could be argued that long-term repetitive BoNT A therapies with higher

cumulative doses might be better with this compound [40]. There were however no reports with incobotulinumtoxin A in our literature research. In our 3 cases we introduced BoNT A therapy with incobotulinumtoxin A (product name: Xeomin) against severe PHN.

Doses and injection technique

The single dose for one injection site was different in different studies and case series from 2, 5 IU [27,29,31,32,35,37] for onabotulinumtoxin A (injection grid every 1,5-2cm one injection site) and 15 IU for abobotulinumtoxinA26 injection grid every 10cm² per injection site). But the effect of pain reduction with single dose of 15 IU (Dysport) per injection site (one site every 10cm²) was not significant. Higher doses per square cm² were significantly effective. 5 IU per site seemed to have longer effect than with 2, 5 IU per injection site, but could not be compared and were only with small study sizes.

The total doses per injection session were in most cases under 300 IU for onabotulinumtoxinA and 500IU abobotulinumtoxinA (Table 1). Our first case had single dose of 2-2,5 IU per injection site with incobotulinumtoxinA in a grid of every 1,5-2cm, in second case 4-5 IU per injection site, and in third case 7,5-10 IU per injection site. Total doses of incobotulinumtoxinA were 150-300 IU per injection session. In our experience single dose per injection site was important because the duration of effects depended on doses in our small case series, i. e. duration of maximal effects with 3 weeks for 2-2,5 IU (Case 1), for 6-8 weeks for 4-5 IU (Case 2) and for 8-10 weeks for 7,5-10IU (case 3). Perhaps 15 IU in every 10cm² for abobotulinumtoxinA was probably too low dose or so wide in distance to develop significant effect on pain reduction.

Injection technique was different in different studies and not observed the difference between intracutaneous and/or subcutaneous injections. We reported our injections in the case series as intra- or subcutaneous injections. Theoretically intracutaneous injections make small pale in the skin, so that will be evidence, however there is no absolute confirmation that

toxin will be also partially in subcutaneous tissues and in intracutaneous injected toxin it can be spreaded at least to the subcutaneous tissues. The effect of BoNT A injections in studies on BoNT A treatment in hyperhidrosis showed no differences to reduction of hyperhidrosis with respect to the two injection techniques. There has been no direct comparison between effects by intracutaneous and subcutaneous injections of BoNT A, but intracutaneous injection is more painful than subcutaneous and additionally volume-limited [41]. For instance, in our case 3 we needed more volume per injection points for 10 IU (0,2ml) and was impossible only to inject into intracutaneous tissue. The histological difference of skin in different areas is one reason to be difficult to distinguish the effect of intracutaneous or subcutaneous BoNT A injections.

CONCLUSION

Add on of BoNTA injected intracutaneously and/or subcutaneously can be helpful in pain reduction in severe PHN. In the published literature most studies were performed with onabotulinumtoxinA but up to now there is no evidence of differences in efficacy of different BoNT A products and injections techniques. For the better effect and the longer duration in pain reduction by BoNT A injections, more doses of BoNT A can be recommended, therefore on a- and incobotulinumtoxinA products 5 to 10 IU of toxin at one injection site will be a good choice. Injection interval can be suggested 10-14 weeks. Botulinum toxin A seems to be a good option for long-term repeated therapy in severe PHN.

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CONFLICTS OF INTEREST

Songjin Rideclares no conflict of interest. Jörg Wissel was a speaker and advisory board member with honorarium for Allergan, Ipsen, Merz, Sintetica and Medtronic.

Table 1: Case/ case series reports and studies on management of PHN with BoNT A

Publications	Study type	N	I. T.	BoNT A	Doses	Follow up	Results
Klein 2004[14]	Case report	1	i.c.	Ona A	20 IU	4 months	Completely pain reduction
Liu 2006[27]	Case report	1	s.c.	Ona A	20 X 5 IU	52 Days	VAS reduction from 10 to 1
Ruiz H. 2008[28]	Case report	1	i.c.	unknown	unknown	2 Months	Dramatically pain reduction
Ranoux 2008[29]	RCT (total n=29)	4	i.c.	Ona A	Up to 40× 5 IU	14 weeks	NNT, 50% pain reduction at 12 weeks
Sotiriou 2009[30]	Case series	3	s.c.	Ona A	20×5 IU	12 weeks	VAS reduction from 8,3 to 2
Xiao 2010[31]	RCT	60	s.c.	Ona A	Up to 40× 5 IU	3 months	Significant pain reduction (mean decreased 4,5 in VAS), improvement of sleep disorder, decreased opioid use
Emad 2011[26]	Case series	15	i.c.	Abo A	15 U/10 cm ² (4ml 2% lidocain)	30 days	pain reduction, but not significant
Apalla 2013[32]	RCT	30	s.c.	Ona A	40×5 IU	20 weeks	greater than 50% pain reduction in VAS, improvement of sleep disorder
Ponce 2013[33]	Case series	12	i.c./s.c.	Ona A	8–10×2,5 IU	3 months	Significant pain reduction
Li 2015[34]	Case report	1	s.c.	unknown	100 IU	6 months	Significant improvement in pain relief
Attal 2016[35]	RCT (total n=66)	5	s.c.	Ona A	Up to 60×5 IU, Repeated after 12 weeks	24 weeks	Significant pain reduction
Eitner 2017[36]	RCT, placebo (total n=66)	6	s.c.	No information in Publication	Every 1,5 - 2 cm, 100-300 IU (4ml 0,9%NaCl)	24 weeks after 2 injections	Significant pain reduction (VAS)
Ding 2017[37]	Cohort study	58	s.c.	Ona A (Chinese-Botox)	10-20 x 5 IU	6 months	Significant pain reduction (VAS)
Jain 2017[25]	Case series (in pregnancy)	2	s.c.	Abo	500 IU (5ml 0.9% NaCl)	16 weeks and until now under control	VAS from 9 and 10 to 1

I. T. Injection technique; N number of patients included; aboA Abobotulinum toxin A; i.c. intracutaneous; Ona A Onabotulinumtoxin A, RCT randomized control trial; sc. subcutaneous; VAS visual Analog Scale; NNT number needed to treat

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