Botulinumtoxin A for Post-herpetic neuralgia

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Post-herpetic neuralgia (PHN) is a very painful neuropathic condition, which occurs after nerve injury (e.g., demyelination, loss of axons, small-fiber-degeneration, reorganization in the dorsal horn of the spinal cord, and neuroplastic central changes) due to herpes-zoster-virus infection and is defined as a local neuropathic pain lasting for more than three months following the initial acute zoster infection. Adjunctive local BoNT A injection is a promising option for severe PHN, as a safe and effective therapy in long-term management for chronic neuropathic pain.

post-herpetic neuralgia botulinumtoxin neuropathic pain

1. Introduction

Post-herpetic neuralgia (PHN) is a very painful neuropathic condition. Frequently, the patient's complaints are burning pain with rushing pain points and dynamic tactile allodynia. Severe PHN reduces QOL (Quality of Life) and often induces sleep disturbance [1]. Despite even escalated pharmacological treatment regimens including anticonvulsants, antidepressants, opioids, and local therapy with lidocaine or capsaicin, patients frequently suffer from severe side effects (especially in patients older than 50 years of age) lacking relevant pain relief. A widely accepted therapy goal with oral medication and/or local therapy strategies for PHN is to reduce the pain by about 30–50% [2][3][4][5][6].

After the first publication on the effect of BoNT A injection against pain due to dystonia by Brin et al. (1987), many studies showed positive effects on chronic pain, including spasticity-associated pain and neurogenic pain [7][8][9][10][11]. The evidence for the efficacy of BoNT A in neuropathic pain relief in humans was firstly presented by Klein in 2004 [12].

2. Mechanisms and Action Sites of botulinumtoxin A (BoNT A)

Several mechanisms of pain reduction by BoNT A injections have been discussed in the literature, assuming an inhibitory effect on the release of various inflammation-mediated substances (e.g., substance P, glutamate, calcitonin gene-related peptide). This inhibitory effect is mediated by blocking exocytosis by BoNT A, acting via SNAP-25 cleaving [7][8][9][10][11]. The mechanisms mediating the toxin effects on sensory fibers and nociceptors and on the autonomic system are assumed to be mediated in the same way [13]. It was shown that BoNT A leads to a deactivation of sodium channel conductance in cell cultures of central and peripheral neurons [14]. In addition,

BoNT A inhibits afferents to muscle spindles, reduces sympathetic signal transmission, and, at least, leads to μreceptor-mediated pain relief at the spinal level [15][16][17]. In 2008, Antonucci et al. suggested that central effects of peripherally applied BoNT A might be due to retrograde transport of the toxin or, alternatively, due to transcytosis leading to an inhibition of neurotransmitters release onto dorsal horn neurons [18]. Moreover, two recent animal studies showed, that BoNT A diminishes the CCI (chronic constriction injury)-induced level of IL-1β (interleukin-1β) and IL-18 within the spinal cord and/or the dorsal root ganglia and, in parallel, enhances the levels of the anti-nociceptive factors IL-1RA (IL-1-receptor antagonist) and IL-10. However, it is still unclear whether those BoNT A actions are mediated locally or indirectly from distant sites. Another recent in-vitro study by Piotrowska (2017) showed new light on the analgesic effect of BoNT A as they suggested a toll-like receptor (TLR2) mediated inhibition of both intracellular signaling pathways and release of pro-inflammatory substance cultured rat neocortical microglial cells [19]. Inhibitory effects of BoNT A were also found on G-proteins and prostaglandin synthase COX-2 (cyclooxygenase-2), the latter known to activate the proinflammatory cytokine Interleukin-1 (IL-1) [20][21]. On that basis, Rojewska et al. (2018) suggested that BoNT A not only exerts its analgesic action directly neuronal but also indirectly via modulating microglial-astrocytic-neuronal crosstalk on the spinal level. In summary, non-neuronal cells are one of the targets of the pain-modulating BoNT A action and have to be taken into account in the context of neuropathic pain treatment [2]. However, the detailed and widely accepted mechanism of BoNT A's effects against neuropathic pain remains elusive and is still under debate. The positive effect of BoNT A on PHN at the clinical aspect is nevertheless clearly proven lacking data for long-term efficacy and safety. The local BoNT A treatment of PHN is still an "off-label" option without reimbursement of the drug, at least in Germany and other European countries.

3. BoNT A Management of Chronic Pain in Post-Herpetic Neuralgia

The safety of the therapy with BoNT A was shown even in two pregnant women, who delivered healthy babies after PHN management with BoNT A [22]. As we only found are case reports or case series with a small number of patients, the formal level of evidence for BoNT A therapy in PHN is still low. However, the beneficial effect of BoNT A therapy in PHN is supported by the publications, which reported more evidence for BoNT A treatment of neuropathic pain in other neuralgias, complex regional pain syndrome, traumatic nerve injury, and diabetic neuropathic pain [23][24].

Comparing subcutaneous BoNT A (Onabotulinumtoxin A) injections (5 IU per every site) with 0.5% Lidocaine, it has to be pointed out that the BoNT effect starts 3–7 days after injections and lasts for about three months, while lidocaine works for one day only. Similarly, subcutaneous lidocaine injections and local anesthetic therapy (creams, pads) have only a short-time effect on PHN [25]. Oral medication is associated with many more side effects and the risk of subsequent dosage increase, while it often lacks to adequately manage the pain to levels below 5 VAS [2][3]. Therefore, the medical needs and the patient's wants congruently focus on local highly effective therapies for severe PHN, which can be provided by intra-/subcutaneous BoNT A injections.

3.1. Applied Botulinumtoxin A

The majority of reports on PHN treatment with BoNT A applied onabotulinumtoxin A (Botox®) (100 IU/2 mL 0.9% NaCl). In a total of 174 patients suffering from PHN, onabotulinumtoxin was injected [12][26][27][28][29][30][25][31][32][33]. Only in two case series within a total of 17 patients published by Emad (2011) [34] and Jain (2017) [22] and one cohort study with 13 patients by Jain 2018 [35], abobotulinumtoxin A (Dysport®) was used with different dilution rates of the toxin: 500 IU/4 mL 2% Lidocaine or 500 IU/5 mL 0.9% NaCl. Two case reports by Ruiz (2008) [36] and Li (2015) [37] and one study by Eitner (2017) [38] did not disclose the toxin preparation used for the BoNT A treatment. The study by Emad et al. (2011) [34] using abobotulinumtoxin A found no significant reduction of pain which, however, does not allow for the derivation of the subtype-specific effectivity of BoNT A in PHN, but rather might result from other dosages and different injection techniques.

In principle, the specific effect of BoNT A on voluntary muscle contraction or muscle tone in spasticity and cervical dystonia shows dose-depended responses, e.g., higher dosage leads to a more pronounced effect on muscle force/tone reduction. Up to now incobotulinumtoxin A never induced a detectable development of antibody-mediated secondary non-responsiveness to BoNT A. Therefore, it could be argued that long-term repetitive BoNT A therapies with higher cumulative dosages might be more stable with this compound [39].

3.2. Doses and Injection Technique

The respective single doses for one injection site were different in the different studies and case series ranging from 2.5 IU [29] up to 5 IU [26][27][28][30][25][32][33] for onabotulinumtoxin A (injection grid every 1–2 cm one injection site) and 15–20 IU for abobotulinumtoxin A [34][35] (injection grid every 1–3 cm per injection site). As mentioned above, the effect of pain reduction with a single dose of 15 IU abobotulinumtoxin A per injection site (one site every 10 cm^2) was not significant [34], even though 20 IU of abobotulinumtoxin A per site with an injection interval of 1 cm showed the significant effect in pain reduction on VAS [35]. Perhaps 15 IU in every 10 cm^2 for abobotulinumtoxin A was probably too low dose or so wide in distance to develop a significant effect on pain reduction. Higher doses per square cm^2 were significantly more effective although the maximal volume for injections per site is limited therefore the ratio of dilatation is sometimes considered.

In terms of a valid assessment ability of the BoNT A effects on PHN over the studies evaluated, the different injection techniques have to be taken into account, in that most of the studies did not differentiate between intracutaneous and/or subcutaneous injections. However, it is conceivable, that the properties of different tissues might impact the diffusive ability of applied substances and thereby the local toxin concentration. We denoted if the injections of our cases were intra-or subcutaneous. Theoretically, pure intracutaneous injections make a small pallor in the skin, but it lacks an absolute confirmation that the toxin will not be also partially in subcutaneous tissue (or even beyond that). The effects of BoNT A injections in hyperhidrosis were different with respect to these two injection techniques. A direct comparison between the effects of intracutaneous vs. subcutaneous injections of BoNT A does not exist, but clinically the intracutaneous injection is more painful than the subcutaneous treatment and-thereby volume-limited [40].

4. Conclusions

Botulinumtoxin A seems to be a good option for long-term management in severe PHN, inducing significant pain reduction (up to 30–50% VAS reduction) for up to 3–4 months per injection cycle. It is difficult to reach such distinct effects by classical oral medication and/or local anesthetic therapies.

Adding intra-/subcutaneous BoNT A injections to standard oral medication is more helpful for pain reduction in severe PHN, especially in cases with non-response or non-tolerance of oral medication. There are no differences in both efficacy and safety of the different available BoNT A products and injection techniques (intra- or subcutaneous), respectively. It seems that a longer duration of pain reduction will be achieved by more injection points per session. In the case of ona- and incobotulinumtoxin A, the doses of 5–10 IU per injection point are recommended. The injection interval can be decided individually however, as in the proven range of BoNT A efficacy between 10 and 14 weeks.

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