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The Role of Botulinum Toxin Type A in Neuropathic Pain: A Literature Review Based on Randomized Controlled Trial Studies

Chandra Wirawan[1], Shierly[2]

[1]General practitioner in Dumai General Hospital, Dumai, Riau Province, Indonesia
[2]Master Program of Biomedicine in Anti-Aging Majoring of Faculty of Medicine of Udayana University, Denpasar, Bali, Indonesia

Abstract–Neuropathic pain is caused by disorder of somatosensory nervous system. It affects mostly in women and older population. The causes of peripheral neuropathic pain are trigeminal neuralgia, diabetes peripheral neuropathy, postherpetic neuralgia and so on. The causes of central neuropathic pain are spinal cord injury, multiple sclerosis, brain tumors and so on. To date, managing neuropathic pain is still challenging to physicians. The available choice of drugs is limited to efficacy and adverse effects. In addition, neuropathic pain has poor response to current medications. Botulinum Toxin type A (BoTN-A), which is produced by *Clostridium botulinum*, is known as potential analgesia in neuropathic pain. This review aims to outline the efficacy of BoTN-A in some causes of both peripheral and central neuropathic pain. The conclusion of this review is BoTN-A is safe and effective in reducing pain intensity in neuropathic pain.

Keywords–neuropathic pain, botulinum toxin, pain, rct

1. Introduction

Neuropathic pain is resulted from a lesion or dysfunction of somatosensory nervous system, including central and/or peripheral nervous system. [1] Approximately 6-8% of adult population and 20-25% chronic pain patients are dealing with neuropathic pain worldwide. [2,3] Neuropathic pain is more likely in women and older patients (>50 years old). [4]

The etiologies of peripheral neuropathic pain are trigeminal neuralgia, diabetes peripheral neuropathy, postherpetic neuralgia and so on. [5] Nerve injury in peripheral nervous system results to ectopic hyperexcitability and spontaneous ectopic discharges. In addition, it also increases response to inflammatory cytokines and inflammatory mediators which are released by injury cells. These mechanisms can lead to pain hypersensitivity, including hyperalgesia and spontaneous pain. [5,6]

Central origin neuropathic pain can be caused by spinal cord injury, multiple sclerosis, brain tumors and so on. [5]Central neuropathic pain is carried by decreased inhibition and increased excitation of central nervous system. Moreover, sensitization of peripheral C fibers can cause central sensitization by increasing excitability of brain, brainstem and spinal cord. These mechanisms mediate the symptoms of central neuropathic pain, such as aftersensation, allodynia, increase temporal summation and hyperalgesia. [5,6]

Neuropathic pain is related with poor quality of life. [2] Most neuropathic pain patients are disabled due to moderate and severe pain. The symptoms of neuropathic pain differ between particular disease and people. [7]

To date, treating neuropathic pain is still challenging for physicians. The current available pharmacologic medications are limited to efficacy and side effects. Besides, topical pharmacologic medication as sole therapy is less effective in treating neuropathic pain. [8] Furthermore, neuropathic pain is poor respond to available medications. [2]

Botulinum toxin (BoTN) has been used widely for a long a time ago for treating various diseases, such as cosmetic treatments, seizure and dystonia.There are two kinds of BoTN, such as botulinum

toxin type A (BoTN-A) and botulinum toxin type B (BoTN-B). [9] BoTN is produced by *Clostridium botulinum*. [10]

BoTN-A is a potent neurotoxin which inhibits the release of acetylcholine from presynaptic nerve endings by interrupting the activity of soluble N-ethyl amide-sensitive-factor attachment protein receptors (SNARE) proteins. [11] It can also prevent the release of nociceptive neuropeptides, such as substance P, glutamate and calcitonin gene-related peptide. In addition, it can prohibit the expression of vanilloid receptor TRV1, which may play a role in inflammatory hyperalgesia, in the surface of peripheral nociceptors. [12] Furthermore, it has been noticed as a painkiller with significant result in neuropathic pain. [11] This review aims to outline the efficacy of BoTN-A in reducing pain intensity in some causes of neuropathic pain based on randomized controlled trial (RCT) studies.

2. The effect of botulinum toxin type A in neuropathic pain

2.1. The effect of botulinum toxin type A in trigeminal neuralgia

Trigeminal neuralgia is a chronic disease marked by sudden unilateral attack and electric shock-like pain, which can involve one or more branches of trigeminal nerve. The prevalence of trigeminal neuralgia is approximately 4-28.9/100.000 people globally. It is more likely in older population and among women. [13]

A systematic review of 4 RCT studies measured the frequency of trigeminal neuralgia attacks and VAS (visual analogue scale) score between BoTN-A and placebo group. Mean frequency of attack decreased by 85% and 15.9% in BoTN-A and placebo groups, respectively. In addition, mean VAS score after intervention was also decreased by 68% and 21.6% in BoTN-A and placebo group, consecutively. The adverse events reported in this study were headaches, facial asymmetry following injection and hematoma, which recovered in one week. [14]

A systematic review and meta-analyses of 4 RCT studies (178 patients) found that more than 50% of pain reduction was observed in BoTN-A group compared to placebo group ($p < 0.0001$). The VAS score was significantly decreased in BoTN-A group at the end of 1st month, 2nd month and 3rd month of follow up with $p = 0.001$, $p = 0.001$ and$p = 0.0002$ respectively. The adverse effects, which were observed in BoTN-A group, were facial asymmetry (14 patients) and edema/hematoma at the injection area (7 patients). Facial asymmetry resolved within 8-7 weeks, whereas edema/hematoma recovered within 5-7 days. [15]

A systematic review of RCT studies reported that BoTN-A injections were effective in reducing frequency of attack, pain intensity and the number of acute painkillers. The most reported side effects in this study were pain at the injection area, itching, transient edema, facial weakness at the injection area and facial asymmetry. The side effects were reported spontaneous recovery. [16]

A meta-analysis of RCT studies reported that there was a significantly decrease in VAS score in TN patients treated with BoTN-A compared to placebo group. However, no difference in adverse events was found between BoTN-A and placebo group. The reported adverse events were mild, transient and non-systemic. [12]

An RCT study in China, which was participated by 81 patients, compared the single-dose (70-100U) and repeated-dose (50-70U per time and a total dosage of 100-140U) of BoTN-A in treating trigeminal neuralgia. The injections were injected at the site of pain submucosally, intradermally, or both. Both dosages showed a significant decrease in VAS score. However, no difference was found in reducing pain intensity and safety assessment between two dosages ($p> 0.05$). The duration of efficacy was significantly longer in single-dose group ($p = 0.032$). [10]

2.2. The effect of botulinum toxin type A in diabetic peripheral neuropathy

Diabetic peripheral neuropathy, which is one of the chronic complications of type 2 diabetes mellitus, is the most frequent reason of neuropathy globally. [17] It affects 30% to 50% of type 2 diabetes mellitus patients. [18]

An RCT study in Italy (50 patients) measured the outcome of BoTN-A compared to placebo in management muscle cramps and pain intensity in diabetic peripheral neuropathy. The patients received two intramuscular injections into small flexor foot and gastrocnemius muscle, respectively. The BoTN-A dosages (100units diluted in 1ml saline) were 0.5ml and 0.15ml for each side in the gastrocnemius and small flexor foot muscle, consecutively. The placebo group obtained the same dosage of normal saline in the same muscle. 19 patients received repeated dose of BoTN-A after 20 weeks. The pain intensity and muscle cramp were significantly decreasing in BoTN-A group after 1 week and remained up to 14 weeks. The side effect observed in this study was pain in the injection area (4 patients) and it recovered within 2 to 3 days. [19]

A systematic review of RCT studies reported that the pain intensity in diabetic peripheral neuropathy was significantly decreasing in BoTN-A group compared to placebo group. The BoTN-A in this study was administered intradermally at the dorsal surface of the feet. [20] Another systematic review of RCT studies also found that BoTN-A could reduce pain effectively in diabetic peripheral neuropathy. [21]

2.3. The effect of botulinum toxin type A in postherpetic neuralgia

Postherpetic neuralgia, which is a neuropathic pain, occurs following an acute episode of herpes zoster infection. [22] About 10-20% herpes zoster patients suffer postherpetic neuralgia. The pain in postherpetic neuralgia is marked by hyperalgesia, dysesthesia, allodynia and paresthesia. [23]

A systematic review and meta-analysis based on RCT studies showed that BoTN-A group had a significant lower VAS score in postherpetic neuralgia compared to lidocaine group with $p< 0.00001$. Moreover, a significant lower VAS score was also observed in BoTN-A group compared to lidocaine and oral carbamazepine group ($p< 0.00001$) and lidocaine only group ($p = 0.0006$) at the 1st month follow-up. Consistently, VAS score was also lower in BoTN-A group compared to lidocaine group at the 2nd ($p< 0.00001$) and 3rd ($p = 0.0007$) month follow up. In addition, McGill pain questionnaire score in BoTN-A group was also lower than in lidocaine group. No significant difference of adverse effect was observed between BoTN-A and lidocaine group in this study. [24]

A systematic review of RCT studies demonstrated that BoTN-A was effective in reducing VAS score and number of patients taking opioids in postherpetic neuralgia patients. In addition, BoTN-A injection could improve duration of sleep. The effect of BoTN-A appeared at day 7 and remained for 3 months after intervention. The toxin was injected approximately 1-2cm radius over a painful site subcutaneously. [25]

2.4. The effect of botulinum toxin type A in spinal cord injury

Spinal cord injury is caused by the lesion in the neural part of spinal cord. [26] About 30-50% of spinal cord injury patients suffer neuropathic pain. [3] The pain in spinal cord injury is intractable to treatment, severe and steady for a long time. [27]

An RCT study, which was conducted in South Korea and participated by 40 patients, measured the outcome of BoTN-A in reducing pain intensity in spinal cord injury. The BoTN-A was administered subcutaneously at the most painful site. The dosage was 200U BoTN-A diluted in 4ml of normal saline solution. Each patient got 40 injections with a minimum distance of each injection was 1 cm. The vas score was reduced significantly in BoTN-A group compared to placebo in both 4 weeks ($p = 0.0027$) and 8 weeks ($p = 0.0053$) following intervention. Compared with baseline of BoTN-A group, there was also a significant decrease in VAS score in 4 weeks ($p< 0.0001$) and 8 weeks ($p = 0.0012$)

following intervention. The adverse effects, such as painful or triggered spasticity, were no difference in both groups. [28]

An RCT study in China, which recruited 44 patients, found that BoTN-A was able to lessen the refractory pain in spinal cord injury. The 200U of BoTN-A diluted in 4ml of normal saline solution was injected subcutaneously at the painful region. The pain intensity was decreasing significantly in BoTN-A group compared to placebo in both 4 weeks ($p < 0.01$) and 8 weeks ($p < 0.01$) following therapy. No life-threateningsideeffects were reported in this research. Only 4 patients and 3 patients in BoTN-A group and placebo group, respectively were reported painful as adverse event in this study. [27]

3. Conclusion

Based on the available literature, BoTN-A is safe and effective in reducing pain intensity in neuropathic pain, such as trigeminal neuralgia, diabetic peripheral neuropathy, postherpetic neuralgia and spinal cord injury. Pain at the injection site isthe most frequentnotifiedadverse effect.

4. References

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