Advances in botulinum toxin type A for the treatment of pain

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ABSTRACT: Clostridium botulinum (CB) is a Gram-positive anaerobic bacterium and a significant cause of food spoilage. Foodborne botulism occurs worldwide every year and even lead to death from respiratory distress in severe cases after eating botulism-contaminated food. The pathogenicity of CB lies in its ability to produce a potent neurotoxin, “botulinum toxin (BTX)”, for which eight different subtypes have already been isolated so far. Botulinum toxin type A (BTX-A) is widely used to treat critical clinical issues due to its good affinity and tolerability. Studies have shown that BTX-A injections effectively treat myofascial pain, inflammatory pain, and neuropathic pain. The current article mainly reviews the latest research progress using BTX-A in pain treatment during two years.

1. INTRODUCTION

Clostridium botulinum (CB) is a Gram-positive anaerobic bacterium widely distributed in nature, and spores are found in silt sediments, dust and animal faeces. Especially, spores in water and soil are the primary source of food contamination (Tiwari et al., 2021). The pathogenicity of CB lies in the neurotoxin botulinum toxin (BTX), a potent neurotoxin known to date (Dong et al., 2018). Clinically, botulism caused by BTX is a severe disease that can lead to respiratory distress and death, and cases of foodborne botulism are pretty frequent. The anaerobic growth and low-temperature growth of BTX for toxicity production give it a growth advantage in the increasingly popular vacuum-packed, frozen and canned foods, thus making it one of the significant causes of poisoning from such foods. A study evaluated foodborne botulism from 1955 to 2018 in Ukraine using the National Epidemiological Surveillance Data System. The metadata analyses revealed that during this period (1955-2018), Ukraine recorded 8,614 cases of botulism, resulting in 659 deaths, with self-canned meat and fish being the main contributors to botulism (Semenko et al., 2021). BTX is generally classified into eight (A, B, Cα, Cβ, D, E, F, G) subtypes according to their serotypes and antigenicity. Botulinum toxin type A (BTX-A) is widely used for its high affinity and good tolerability in clinical practice (Satriyasa, 2019). Studies have shown that BTX-A is sustainable and non-addictive in analgesia (Ostrowski et al., 2009) and has good efficacy in myofascial tension pain, neurogenic pain and inflammatory pain. Because of the discussion above, the current article was designed to review the latest research progress of BTX-A in pain treatment in the last two years.

2. MYOFASCIAL PAIN

Myofascial pain, affecting both muscles and fascia, is a painful neuromuscular disorder featuring limited muscle pressure. A randomized clinical trial assessed the therapeutic efficacy and safety of BTX-A in treating temporomandibular disorders resulting in persistent myofascial pain. It was found that three different doses of BTX-A (40U, 70U and 100U) had noticeable analgesic effects, but a side effect of reduced electromyographic activity was observed after one month of BTX-A injection, and only the low dose group of BTX-A recovered after three months and returned to baseline levels after six months. Therefore, when considering BTX-A injections for persistent myofascial pain, lower doses of BTX-A are the appropriate choice (La et al., 2020). A prospective randomized controlled trial assessed the benefit of BTX-A injections for chronic plantar fasciitis. Thirty-two patients with chronic plantar fasciitis were randomized to the BTX-A and placebo groups, and 70 U of BTX-A was administered into the medial head of the gastrocnemius muscle under ultrasound guidance. The outcome of the present study showed that local injection of BTX-A into the gastrocnemius muscle had a positive effect on improving pain and foot function in the patients, and the effect lasted for over a year (Abbasian et al., 2019).

The efficacy of BTX-A injections in treating masticatory myofascial pain syndromes (MMPs) is not apparent yet. It is
found that minimally invasive strategies and BTX-A injections of the temporalis and occlusal muscles applied to temporomandibular disorder treatment have shown positive results on quality of life and masticatory myofascial pain (Miotto et al., 2021). In a study comprising a 6-month trial, 60 patients with MMPs were randomized into three groups and given saline, lidocaine, and BTX-A, respectively, and seen the effects on days 7, 14, 28, 60, 90, and 180. The results showed significant pain reduction and improved jaw movement in the BTX-A group compared with the saline and lidocaine treated groups. Moreover, no significant adversities were seen, suggesting that BTX-A may be an effective treatment option for patients with localized MMPs (Montes-Carmona et al., 2020). However, a larger patient sample and a more comprehensive follow-up study are recommended to determine the long-term benefits of masticatory muscle injections with botulinum toxin. The efficacy of BTX-A with the local anaesthetic mepivacaine (LA) and platelet-rich plasma showing that all groups successfully improved the symptoms of myofascial trigger points in the masseter muscle at 1 and 3 months, with BTX-A and LA being significantly more effective than platelet-rich plasma at three months, but only the BTX-A group remained effective at six months (Yilmaz et al., 2020).

A pioneering retrospective study demonstrated that long-term treatment of myofascial neck pain with BTX-A injections is effective and safe, with patients included in the study receiving BTX-A injections at least once a year for a mean duration of 8.3 ± 4.7 years (Diep et al., 2020). The efficacy of BTX-A combined with 0.2% local anaesthetic ropivacaine hydrochloride injection (BTX group) with ropivacaine hydrochloride injection alone (LA group) for the treatment of pelvic floor myofascial syndrome and chronic pelvic pain showing that neither group exhibited any significant differences on day 60. However, the two groups showed an overall improvement in pain, meaning that intramuscular injection with ropivacaine hydrochloride alone was justified (Gorimanipalli et al., 2019; Levesque et al., 2021). The randomized clinical trials of BTX-A for myofascial pain has also been elaborated (Table 1).

3. INFLAMMATORY PAIN

3.1. Knee osteoarthritis

The main objectives of knee osteoarthritis (KOA) treatment are to reduce pain, lower inflammatory response, restore function, and slow the progression of the disease. To date, the literature is conflicting as to whether intra-articular injections of BTX-A can treat KOA. In a clinical trial, 30 eligible older adults with KOA received a single injection of 100U of BTX-A solution. The analgesic effect of BTX-A was evaluated before and after treatment using the 100 mm visual analogue scale (VAS) and the knee injury and osteoarthritis outcome score (KOOS), respectively. The results showed that BTX-A reduced the subjective pain of KOA patients (Najafi et al., 2019). Another study compared the efficacy of physical therapy, hyaluronic acid intra-articular injections, intra-articular dextrose prolotherapy and BTX-A intra-articular injections for treating KOA in middle-aged and older adults. The outcomes of this study showed better performance in knee pain control in the BTX-A and glucose groups and better efficacy of BTX-A in symptom relief (Rezasoltani et al., 2020). In a meta-analysis comparing the efficacy and safety of intra-articular injections of BTX-A (100U/200U) and placebo in the short-term (≤4 weeks) and long-term (≥8 weeks) treatment of KOA in men, it was also shown that BTX-A is effective and safe in the treatment of KOA (Zhai et al., 2019), and the above results suggest that BTX-A may have the ability to treat KOA. However, a trial has the opposite conclusion. The researchers found no benefit with BTX-A intra-articular injections for primary KOA versus the use of corticosteroids (tretinoin) and saline. No benefit in improving range of motion, function, pain and quality of life with BTX-A in either the short term (4 weeks) or the medium term (12 weeks) (Mendes et al., 2019). It is unclear whether the dose and duration of treatment affect the efficacy or not. Some reports mention that placebo treatment such as intra-articular injection with saline is also efficacious. However, the articles also point out that the efficacy with saline may lead to opposite conclusions because of differences in study methods (Blanshan & Krug, 2020). Therefore, more high-quality trials and larger sample sizes are needed to confirm the efficacy of intra-articular injections of BTX-A for knee pain.

3.2. Lateral epicondylitis

Lateral epicondylitis is common extensor tendinopathy that presents with tenderness at the common extensor tendon origin and pain with resisted wrist extension area. BTX-A has been suggested for recalcitrant lateral epicondylitis that has failed to respond to conservative treatment. In a recent, 60 patients with chronic lateral epicondylitis received BTX-A injections in the common extensor tendon. The results displayed a significant decrease in numeric rating scale (NRS) scores after treatment in both groups and no significant difference in pain relief success between the two groups. However, a more significant decrease in NRS scores and a tremendous increase in grip strength in the high-dose group, suggesting that BTX-A administration to the common extensor tendon is a workable therapeutic choice for chronic lateral epicondylitis and that high-dose BTX-A is more efficacious (S.H. Lee et al., 2020). This study showed the short-term effects of BTX-A in lateral epicondylitis, but the long-term benefits are unknown. One study evaluated the one-year treatment efficacy, adverse effects and recurrence rate of BTX-A injections for chronic lateral epicondylitis. Fifty patients were followed up on day 0 (G0), 90 days (G1), 180-270 days (G2), and 365 days (G3) after 40U of BTX-A injected with 40 U of BTX-A. The results showed that patients in the G1, G2, and G3 groups had a significantly better quality of life, reduced pain, and maximum grip strength than the G0 group, with significantly less impact on daily and business activities. Therefore, 1 to 2 injections of 40 U BTX-A were more effective in treating chronic lateral epicondylitis (Cogné et al., 2019). In addition, other studies have also analyzed the effect of different site injections of BTX-A on the efficacy of treatment of lateral
Table 1
A randomized clinical trial of BTX-A in treating myofascial pain

<table>
<thead>
<tr>
<th>Pain Conditions</th>
<th>Participants</th>
<th>BTX-A application</th>
<th>Primary outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>persistent myofascial pain</td>
<td>100</td>
<td>L: temporal(10U), masseter (30U) M: temporal(20U), masseter (50U) H: temporal(25U), masseter (70U)</td>
<td>Reduced VAS in the BTX-A group</td>
<td>La et al. (2020)</td>
</tr>
<tr>
<td>chronic plantar fasciitis</td>
<td>32</td>
<td>gastrocnemius(70U)</td>
<td>VAS score and AOFAS (American Orthopaedic Foot &amp; Ankle Society) score improvements were significantly better in the BTX-A group than in the placebo group over 12 months</td>
<td>Abbasiyan et al. (2019)</td>
</tr>
<tr>
<td>chronic myofascial pain</td>
<td>40</td>
<td>temporal(25U), masseter (50U)</td>
<td>Both the BTX-A group and the positive control group showed improvement at 30 days of treatment</td>
<td>Miotto et al. (2021)</td>
</tr>
<tr>
<td>masticatory myofascial pain</td>
<td>60</td>
<td>temporal(24U), maseter (24-30U), lateral pterygoid(8U), medial pterygoid(8U)</td>
<td>Compared to the SS and LD groups, the BTX-A group showed a significant decrease in VAS scores (P&lt;0.001) and a significant improvement in the values obtained in the 100-point questionnaire (P&lt;0.017) between day 0 and day 180</td>
<td>Montes-Carmona et al. (2020)</td>
</tr>
<tr>
<td>pelvic floor myofascial pain</td>
<td>80</td>
<td>Obturator internus muscle(100U), levator ani muscle(50U)</td>
<td>On day 60, the BTX-A combined with the LA group did not show any significant difference in PGI-I from the LA injection alone group, but both groups showed an overall improvement in pain.</td>
<td>Levesque et al. (2021)</td>
</tr>
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</table>

epicondylitis, suggesting the location of injection as a potential source of outcome heterogeneity (Song et al., 2020).

3.3. Shoulder pain

A meta-analysis showed similar outcomes of BTX-A injection compared to the corticosteroid group or saline placebo group in relieving chronic shoulder pain at one month, but its efficacy was better than the other two groups at 1 to 3 months (Hsu et al., 2020). Another Meta-analysis showed that shoulder BTX-A injections in patients with hemiplegic shoulder pain had better analgesia and improved shoulder abduction and external rotation mobility than steroid or placebo injections in treating hemiplegic shoulder pain disease (Xie et al., 2021). A study comparing the efficacy of BTX-A administration to the pectoralis major and teres major muscles (BTX-A group) with suprascapular nerve blocks (SNB group) in treating hemiplegic shoulder pain. The results showed that the BTX-A group were as effective as the SNB group in improving pain, range of motion, and function in the short term at two weeks but were more effective in the mid-term at six weeks (Kasapoglu-Aksoy et al., 2020). A 38-year-old man with intractable acromioclavicular joint pain due to distal clavicle osteolysis received an intra-articular injection of BTX-A, experienced a significant reduction in pain, and did not experience pain by avoiding excessive shoulder activity during daily activities (B.J. Lee & Park, 2020). The above results indicate that BTX-A injection is a safe and effective alternative therapy for treating patients with shoulder pain. A list of the randomized clinical trials of BTX-A for inflammatory pain has also been tabulated (Table 2).

4. NEUROPATHIC PAIN

4.1. Spinal cord injury pain

A trial investigated the effect of subcutaneous injections of BTX-A for treating at-level spinal cord injury pain. Although the trial had a tiny sample size, patients were observed to have varying degrees of improvement in pain, activity, mood and sleep (Chun et al., 2019). A descriptive retrospective study article showed improvement in spasticity (pain, tone and articular limitations) in patients with spinal cord injury given with BTX-A, and no adverse effects linked with post-BTX-A injection were recorded (Palazón-García et al., 2018). There are hardly any studies that comprehensively analyze the efficacy and safety of BTX-A in treating neuropathic pain after spinal cord injury.

4.2. Postherpetic neuralgia

In a meta-analysis comparing the safety and efficacy of local administration of BTX-A vs lidocaine in the treatment of postherpetic neuralgia, the outcomes were assessed in terms of VAS, effective rate, McGill pain questionnaire and adverse events rate. The results showed that patients treated with BTX-A for postherpetic neuralgia had significantly lower VAS pain scores and lower McGill pain questionnaire than those treated with lidocaine at the first month, second month and third-month follow-ups. Furthermore, the effective rate of BTX-A treatment was significantly higher than that of patients receiving lidocaine,
Table 2
A randomized clinical trial of BTX-A for treating inflammatory pain

<table>
<thead>
<tr>
<th>Pain Conditions</th>
<th>Participants</th>
<th>BTX-A application</th>
<th>Primary outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>knee osteoarthritis</td>
<td>30</td>
<td>joint space (100U)</td>
<td>After four weeks of BTX-A treatment, the VAS scores decreased significantly (P&lt;0.001)</td>
<td>Najafi et al. (2019)</td>
</tr>
<tr>
<td>knee osteoarthritis</td>
<td>120</td>
<td>joint space(100U)</td>
<td>At month 3, VAS pain scores were significantly lower in the BTX-A and dextrose prolotherapy groups</td>
<td>Rezasoltani et al. (2020)</td>
</tr>
<tr>
<td>knee osteoarthritis</td>
<td>105</td>
<td>joint space(100U)</td>
<td>In the 12-week longitudinal analysis, the triamcinolone hexacetonide group performed best in terms of pain during movement. There was no difference between the three groups in the evolution of the VAS for pain at rest</td>
<td>Mendes et al. (2019)</td>
</tr>
<tr>
<td>lateral epicondylitis</td>
<td>60</td>
<td>common extensor tendon: SD (small-dose) 10U, LD (large-dose) 50U</td>
<td>At 0-6 months, there was a significant decrease in NRS scores in both the SD and LD groups. At 1-4 months, the LD group performed better in terms of NRS scores. There was no significant difference in the success rate of pain relief between the two groups</td>
<td>S.H. Lee et al. (2020)</td>
</tr>
<tr>
<td>hemiplegic shoulder pain</td>
<td>60</td>
<td>pectoralis major(100-150U), teres major(40-60U)</td>
<td>The BTX-A group displayed a significantly lower VAS score at week two and week 6</td>
<td>Kasapoglu-Aksoy et al. (2020)</td>
</tr>
</tbody>
</table>

with no significant difference in the adverse events rate (Li et al., 2009). Another study also demonstrated that injectable BTX-A was more effective in treating postherpetic neuralgia than oral analgesic gabapentin capsules (Hu et al., 2019), thus indicating that BTX-A may be a very promising drug for the clinical treatment of postherpetic neuralgia.

4.3. Diabetic neuropathy pain

In a clinical trial, 32 patients with type 2 diabetes were randomized to the BTX-A and saline groups, and they were injected with 100U BTX-A (BTX-A group) or an equivalent amount of sodium chloride (SA group) in the foot. The results showed that BTX-A reduced neuropathic pain and improved the quality of life and sleep in patients with diabetic neuropathy (Salehi et al., 2019). Another prospective trial looked at the efficacy of BTX-A for diabetic polyneuropathy, which randomized 141 patients aged 40 to 70 years into three groups: the first group was injected with 150U BTX-A on one side of the foot and 0.9% saline on the other side; the second group was injected with 150U BTX-A in both feet; the third group was injected with 0.9% physiological saline, using VAS and NPS for comparison. The results showed a significant improvement in VAS and NPS (except dull and cold sensation) scores in the BTX-A group compared with the saline group, indicating that intradermal injection of BTX-A was effective in treating good diabetic polyneuropathy (Taheri et al., 2020). All of the above results demonstrate that BTX-A effectively improves neuropathic pain in diabetic patients, although different results were shown on NPS, which may be related to sample size and BTX-A dose.

4.4. Trigeminal neuralgia

Current studies have shown that BTX-A is an effective and safe treatment for trigeminal neuralgia (Ostrowski et al., 2009; Rubis & Juodzbalys, 2020). A recent study examining factors influencing the efficacy on BTX-A found that a higher success rate of BTX-A treatment was observed in patients aged 50 years or older, but the age factor did not make a significant difference in the time to recurrence of pain, the onset of effect, or peak-time after BTX-A treatment (Wu et al., 2019). Another study indicated that while various doses of BTX-A did not affect the short-term treatment effect, higher levels of BTX-A helped to control trigeminal nerve-induced pain more consistently over time. In addition, the study found that female patients under 70 years of age were more sensitive to BTX-A treatment and concluded that the duration of disease mainly affected the rate of adverse reactions in female patients. However, there was no significant correlation between the duration of disease and the change in side effects in male patients. Therefore, female patients with trigeminal neuralgia with a disease duration of 1-10 months should be more conservative in applying BTX-A, while higher doses of BTX-A injections would have a higher success rate in treating trigeminal neuralgia in male patients (Zhang et al., 2009). A study investigated the safety and efficacy of repeated botulinum toxin injections in the treatment of trigeminal neuralgia. The outcomes of this study
Table 3
A randomized clinical trial of BTX-A in treating neuropathic pain

<table>
<thead>
<tr>
<th>Pain Conditions</th>
<th>Participants</th>
<th>BTX-A application</th>
<th>Primary outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>spinal cord injury pain</td>
<td>8</td>
<td>subcutaneous injection</td>
<td>There was some reduction in pain in the BTX-A group compared to the placebo group</td>
<td>Chun et al. (2019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5-400U)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>postherpetic neuralgia</td>
<td>13</td>
<td>subcutaneous injection</td>
<td>The VAS scores showed different degrees of improvement two weeks after the treatment in the BTX-A group versus the oral analgesic gabapentin group, with statistical differences between the two groups at weeks 2, 4, 8, 12, and 16 (p&lt;0.5)</td>
<td>Hu et al. (2019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(50-100U)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetic sensorimotor polyneuropathy</td>
<td>32</td>
<td>feet (100U)</td>
<td>There was a significant difference in the mean VAS over time (12 weeks) (P &lt; 0.001), and the decrease in pain intensity was significantly higher in the intervention group than in the placebo group during the follow-up period (0-12 weeks)</td>
<td>Salehi et al. (2019)</td>
</tr>
<tr>
<td>diabetic polyneuropathy</td>
<td>141</td>
<td>Group 1: one foot (150U), another foot (saline) Group 2: both feet (150U)</td>
<td>There was a significant improvement in VAS in the BTX-A group versus the placebo group, while VAS scores did not differ significantly between the BTX-A groups</td>
<td>Taheri et al. (2020)</td>
</tr>
</tbody>
</table>

revealed that after single and continuous injections of BTX-A, the severity of pain in patients was significantly reduced, the efficiency of pain relief was 100% in both cases, and there was no significant difference in the mean duration of pain relief. No significant adverse effects were seen in either case, suggesting that repeated injections of BTX-A are safe and effective (Gorimanipalli et al., 2019). In addition, some cases have reported that BTX-A is equally effective in trigeminal neuralgia caused by multiple sclerosis, suggesting that BTX-A can also treat atypical trigeminal neuralgia (Calejo et al., 2019). Cases of intraoral botulinum toxin injections for trigeminal neuralgia have also been reported, with relief and no facial asymmetry and no adverse effects with repeated intraoral botulinum toxin injections (Dinan et al., 2020; Ostrowski et al., 2009). The list of the randomized clinical trials of BTX-A for neuropathic pain is detailed below (Table 3).

5. CONCLUSION AND PROSPECTS

In conclusion, BTX-A, as a new analgesic drug, has definite efficacy in clinical pain management, especially for musculoskeletal, muscle and neuropathic pain. Its advantages include ease of administration, sustainability of efficacy, and no toxic side effects or addiction even after multiple doses within a safe range. However, the application of BTX-A in pain treatment is still in the preliminary stage, and most of the treatments are mainly experience-based. Furthermore, the reports on BTX-A for pain treatment at home and abroad have problems such as a small number of cases and lack of observation of long-term effects, and further research is needed on injection sites and operation techniques. In addition, the effectiveness and side effects of the clinical application of BTX-A in the treatment of pain also need to be confirmed by clinical trials. The solution to these problems requires the accumulation of clinical experience and an accurate grasp of the mechanism of action. Current studies on the analgesic mechanism of BTX-A have focused on two directions: the peripheral nervous system and the central nervous system (Figure 1).

Figure 1. Outline of the mechanism of BTX-A in treating pain

Most studies suggest that BTX-A exerts its analgesic effects by releasing certain transmitters in the peripheral nervous system (such as calcitonin gene-related peptides, substance P and glutamate), anti-inflammatory and other modulation the peripheral nervous system (W.C. Lee et al., 2018; Muñoz-Lora et al., 2020; She et al., 2020). On the other hand, BTX-A exerts its therapeutic effect on pain by activating glial cells such as microglia and astrocytes and regulating the central nervous system-related pathways such as the upstream pain transmission pathway (Shi et al., 2019; Valois et al., 2020). However, to date, the specific targets of BTX-A action are not known, and the most likely targets are specific unknown receptors on the cell. When these targets are activated by binding to BTX-A through a specific pathway, they can produce a sustained effect over a while. BTX-A is well tolerated, with essentially no side effects reported after botulinum toxin injections in the studies included here or only minor adverse effects, such as the appearance of...
local erythema and facial asymmetry exhibited by injections in the face, and these minor adverse effects disappear within a short period. However, in different clinical trials and in vivo studies, BTX-A injections produced more serious adverse effects, such as reduced masticatory performance and muscle thickness in the occlusal muscles. These adverse events may hinder the benefits of this botulinum toxin. All these questions deserve further exploration in the future.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in the submission and publication of this research.

REFERENCES


