Joint Bone Spine 83 (2016) 149–154

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Review

Usefulness of intra-articular botulinum toxin injections. A systematic review

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ARTICLE INFO

Article history:
Accepted 24 June 2015
Available online 29 November 2015

Keywords:
Botulinum toxin
Intra articular injection
Osteoarthritis
Adhesive capsulitis of shoulder
Rheumatology

ABSTRACT

Botulinum toxin is a proven and widely used treatment for numerous conditions characterized by excessive muscular contractions. Recent studies have assessed the analgesic effect of botulinum toxin in joint pain and started to unravel its mechanisms.

Literature-search-methodology: We searched the international literature via the Medline database using the term "intraarticular botulinum toxin injection" combined with any of the following terms: "knee", "ankle", "shoulder", "osteoarthritis", "adhesive capsulitis of the shoulder".

Results: Of 16 selected articles about intraarticular botulinum toxin injections, 7 were randomized controlled trials done in patients with osteoarthritis, adhesive capsulitis of the shoulder, or chronic pain after joint replacement surgery. Proof of anti-nociceptive effects was obtained in some of these indications and the safety and tolerance profile was satisfactory. The studies are heterogeneous. The comparator was usually a glucocorticoid or a placebo; a single study used hyaluronic acid. Pain intensity was the primary outcome measure.

Discussion-conclusion: The number of randomized trials and sample sizes are too small to provide a satisfactory level of scientific evidence or statistical power. Unanswered issues include the effective dosage and the optimal dilution and injection modalities of botulinum toxin.

1. Introduction

Botulinum toxin (BTX) is a neurotoxin produced by *Clostridium botulinum*. BTX blocks the neuromuscular junction by inhibiting the release of acetylcholine into the synaptic cleft, causing chemical denervation responsible for flaccid paralysis. The block is permanent, although peripheral axon regrowth contributes to explain that the paralysis is transient. The clinical effect develops between the 2nd and 5th days, peaks after 15 to 21 days, and lasts 3 to 9 months on average depending on the injection site.

When injected into a muscle, BTX diffuses locally, up to 45 mm from the injection site. BTX may also be found at a greater distance, due either to retrograde axonal diffusion or to more diffuse hematogenous diffusion, which may explain the occurrence in some patients of botulism-like effects [1]. Seven neurotoxin types classified from A to G have been identified. These neurotoxins combine with proteins to form BTX, which is the compound administered to patients [2].

The first description of BTX used as an analgesic was a 1994 report by Cheshire et al. of effects in patients with myofascial pain [3].

Recent data suggest that BTX may specifically inhibit mechanical nociceptor sensitivity in humans [4]. The underlying mechanisms have not been identified but may involve inhibition of mechanosensitive ion-channel expression on the nociceptor membrane. When administered peripherally, BTX seems to diffuse in the retrograde direction, thus exerting effects on the central nerve endings, most notably at the spine [5].

An update and a systematic literature review on the use of BTX in rheumatology have been published [6,7]. The primary

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http://dx.doi.org/10.1016/j.jbspin.2015.10.001
1297-319X/

objective of our work was to conduct a literature review focused on intraarticular BTX injections, with special attention to indications and suggested mechanisms of action.

1.1. Role for neuropeptides in joint pain

Sensory neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and neurokinin A contribute to joint pain sensation [8–10]. Spinal ganglion levels of these sensory neuropeptides were elevated in a rat model of acute or chronic unilateral arthritis [10] and proven to play a pivotal role in neurogenic inflammation [11–13], a well-documented process in inflammatory or degenerative arthritis [14,15].

1.2. Mechanisms by which a neurotoxin might induce pain relief

1.2.1. Formalin model

In a rat model of inflammatory pain induced by formalin injection into the paw, subcutaneous toxin A administration diminished c-fos expression in the spinal cord. Other effects included local glutamate release inhibition and decreased paw edema [16].

1.2.2. Capsaicin model

Capsaicin injection induces inflammatory pain by stimulating the sensory vanilloid receptors (TRPV1) found in the endings of unmyelinated group C fibers [17]. The stimulation causes severe pain by triggering the release of neuropeptides such as substance P and CGRP. In a rat model, pretreatment for 6 days with BTX type A (BTX-A) significantly decreased the enhanced sensitivity to mechanical and thermal stimuli induced by a capsaicin injection into the paw [18].

1.2.3. Retrograde effect

Another study in rats assessed the effect on formalin-induced facial pain of low-dose BTX-A injected into either the whisker pad (3.5 U/kg) or the sensory trigeminal ganglion (1 U/kg) [5]. Identification of the site of action of BTX-A transported along the axons was achieved via immunohistochemical labeling of synaptosomal-associated protein 25 (SNAP-25), which is cleaved by BTX-A in the dorsal horn of the spinal cord (spinal nucleus of the trigeminal nerve). Peripheral or intraganglionic BTX-A injection alleviated the pain induced by formalin. The BTX-A-truncated form of SNAP-25 was identified in the trigeminal nucleus 3 days after the whisker-pad injection, despite the low dose used. These findings constitute the first evidence of retrograde axonal BTX transport to sensory nuclei in the central nervous system (CNS), where it can induce analgesic effects.

1.3. Botulinum toxin and joint pain in experimental studies

Among experimental animal studies [19–22], one was conducted in a mouse model of chronic osteoarthritis induced by a collagenase injection into the left knee [20]. Blinded assessors measured spontaneous pain, evoked pain, and pain during gait, as well as joint stiffness. Four weeks later, BTX type B (BTX-B, Myobloc® 0.02 IU/0.005 mL) was then injected into the knee in 17 animals, whereas 7 animals received normal saline injections and 8 received sham injections. The gait analysis demonstrated significant impairments related to knee osteoarthritis, all of which decreased significantly after the BTX-B injection. No improvements were documented in the placebo or sham groups.

2. Literature review methodology

We searched Medline® using the term "intraarticular botulinum toxin injection" combined with the terms "knee", "ankle", "shoulder", "osteoarthritis", and "adhesive capsulitis of the shoulder". The date limits were 1970 to April 30, 2014. We confined our analysis to controlled clinical trials in humans, excluding case reports [23–25].

For each article retrieved by our search, we collected the following: reason for BTX therapy, study design, number of included patients, BTX dose, concomitant treatments, primary outcome measure, patient follow-up duration, time to peak effect, statistical significance of between-group differences in comparative studies, and number and type of adverse effects in each group.

3. Results

The results are reported joint by joint, independently from the reason for BTX therapy (Table 1).

3.1. Knee pain

A clinical double-blind RCT compared BTX to glucocorticoids in 60 patients with a mean age of 62 years, 35 females and 25 males, with knee osteoarthritis grade II or III according to Kellgren-Lawrence [26]. The patients were allocated at random in a 1:1:1 ratio to a single methylprednisolone acetate injection (40 mg), a single low-dose BTX-A injection (100 U), or a single high-dose BTX-A injection (200 U). Follow-up was 6 months. The primary outcome measure was pain intensity evaluated on a visual analog scale (VAS) at 8 weeks. Secondary outcome measures were the Western Ontario McMaster Arthritis Index (WOMAC), 40-m timed walk, and Short Form-36 (SF-36) scores. After 4 weeks, the VAS pain score was significantly decreased only in the low-dose BTX-A group ($P = 0.01$), and this difference was also significant after 8 weeks ($P = 0.01$). The WOMAC total score and subscores improved significantly in all three groups ($P < 0.05$). At follow-up completion after 6 months, 29 patients had been lost to follow-up. The only significant difference at this time point was a lower VAS pain score in the low-dose BTX-A group ($P = 0.02$). The main limitation of this study is the fairly small initial sample size with substantial attrition during the study (29 of 60 patients after 6 months). Although trends toward improvements were seen in all three groups, none of the primary or secondary outcome measures showed significant between-group differences.

An open-label study reported in 2010 included 24 patients, 13 males and 11 females with a mean age of 73.4 ± 11.1 years, who had stage III/IV knee osteoarthritis [27]. The knee osteoarthritis was unilateral in 10 patients and bilateral in 14, so that 38 knees were treated. Each knee received two intraarticular injections of 100 U of BTX-A reconstituted with 4 mL of normal saline, at an interval of 3 months. The primary outcome measure was the WOMAC, in all its dimensions, and the secondary outcome measure was quadriceps bulk. After 3 months, the only significant effect was a decrease in the WOMAC pain score in the subgroup with stage III disease ($P < 0.001$). This subscore was still significantly diminished versus baseline after 5 and 6 months ($P < 0.05$). Weaknesses of this study include the nonrandomized design, small sample size, and apparently heterogeneous patient population with a selection bias. The absence of BTX-A effects in stage IV disease is probably ascribable to the presence of advanced cartilage damage, which, in our view, indicates a need for knee replacement surgery.

In a clinical phase 1b double-blind RCT, BTX-A (200 U) was compared to a placebo in 121 patients, 62 females and 59 males with a mean age of 62.3 years, who had Kellgren-Lawrence grade I, II, or III knee osteoarthritis [28]. Safety and efficacy were evaluated over a 16-week period. The primary outcome measure was mean daily pain intensity after 2, 4, 8, and 12 weeks. The secondary outcome measures were the WOMAC, patient's and physician's