Chapter 10
Botulinum Toxins for Treatment of Pain in Orthopedic Disorders

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Abstract A considerable number of orthopedic disorders are accompanied by pain which can be a clinical challenge for clinicians and a major problem for patients. Botulinum neurotoxins (BoNTs) have been recently shown to possess analgesic effects leading to their extensive use in various situations, including pain control for orthopedic issues. This chapter presents information on BoNT treatment of five orthopedic disorders with available placebo-controlled studies. The recommendations of the Assessment Subcommittee of the American Academy of Neurology are applied to establish an evidence-based level of efficacy for these disorders that include chronic lateral epicondylitis, refractory pain following total knee arthroplasty, painful local arthritis, anterior knee pain related to vastus lateralis imbalance, and orthopedic contracture and/or pain release (French and Gronseth, Neurology 71:1634–8, 2008; Gronseth and French, Neurology 71:1639–43, 2008).

According to the studies discussed in the following sections, an "A" level of evidence has been provided for chronic lateral epicondylitis, defining BoNT-A as being "effective" for this disorder. In painful local arthritis and issues related to orthopedic contracture and/or pain release including distraction osteogenesis and correction of scoliosis, the level of evidence is "B" demonstrating BoNT-A therapy to be "probably ineffective." For refractory pain after total knee arthroplasty, anterior knee pain related to vastus lateralis imbalance, and other problems related to orthopedic contracture and/or pain release, the level of evidence is determined as "C" or "possibly effective." Some of the studies providing these levels of evidence are of class III and IV types, and the number of class I studies in a few of these disorders is limited. Further class I/II studies are required to support a definitive analgesic role of BoNTs in orthopedic disorders.

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Introduction

Refractory pain associated with orthopedic disorders is a major problem for many individuals and has therefore led to the development of multiple studies attempting to provide accessible and simple management options for this issue. The efficacy of botulinum neurotoxin (BoNT) injection in relieving this type of pain has been a topic of interest in the past two decades. In this chapter, five such disorders with available blinded, placebo-controlled studies and case series will be discussed. These include chronic lateral epicondylitis, refractory pain following total knee arthroplasty, painful local arthritis, anterior knee pain related to vastus lateralis imbalance, and orthopedic contracture and/or pain release.

Chronic Lateral Epicondylitis (CLE)

Lateral epicondylitis (LE), also known as tennis elbow in athletes, is described as elbow pain resulting from overuse of the joint [1]. It is seen more often among heavy workers, and a prevalence of 4–7/1000 patients per year has been reported for this relatively common disorder [17, 43]. Degeneration of the extensor tendons is presently regarded as a responsible factor for the clinical symptoms of LE [30]; however, despite limited pathological evidence, the role of inflammation is still an ongoing discussion. The idea of tendinopathy and tendon degeneration is confirmed by studies using ultrasound for examination of the affected joints [11]. According to Smidt et al. [40], 83% of acute LE patients return to normal within 12 months. Nevertheless, a minor percentage of individuals develop the chronic form (CLE) and unfortunately do not respond to drugs. Management of these chronic types involves abstaining from applying heavy load to the damaged elbow, bracing, physical therapy, pharmacotherapy, and surgery. Cyclooxygenase inhibitors, nonsteroidal anti-inflammatory drugs, GABAergic analgesics (gabapentin and pregabalin), and, in more severe cases, opioids are commonly used medications in the management of CLE. Steroid and nonsteroid pharmaceutical substances are introduced into painful areas via injection.

A total of 141 randomized controlled trials (RCTs) were systematically reviewed by Krogh et al. [21] to compare the efficacy/safety of injection therapies in CLE patients. Seventeen RCTs using eight different treatments including corticosteroids, BoNTs, autologous blood, platelet-rich plasma (PRP), hyaluronic acid, prolother-

apy, polidocanol, and glycosaminoglycan polysulfate were selected. Despite the reported efficacy of injection therapy, most of the evaluated studies demonstrated issues related to blinding of the patient and/or health-care provider, allocation concealment, selective or attrition reporting, and company interest. These posed difficulties in accurate and definitive interpretation of the data.

The results of a more recent meta-analysis [24] comparing BoNT therapy with nonsurgical methods reported data on 321 LE patients participating in six randomized trials. The results indicated significant pain reduction in subjects treated with BoNT-A in comparison to those receiving placebo. This toxin was less effective in the short term (2–4 weeks) when compared to corticosteroids but showed identical effects after 8 weeks. Grip strength decreased in the first 2–4 weeks after BoNT-A injections, which lasted for 8–12 weeks and was more conspicuous compared to that produced by corticosteroid administration.

Botulinum Neurotoxin Studies in CLE

Of the eight reported RCTs in CLE, four were blinded, placebo-controlled trials, three were blinded comparator studies, and one was an experimental investigation on a series of patients.

Placebo-Controlled Studies

In a double-blind, placebo-controlled study on the efficacy of BoNT-A therapy in CLE, Wong et al. [46] showed significant analgesic effects of abobotulinumtoxinA (aboA) in 49 women and 11 men with this condition. The primary outcome of injection was reported as "pain reduction." A total of 60 U aboA diluted in 1 ml normal saline was used in this RCT. For both placebo (saline) and aboA, the injection point was directed toward the painful area, 1 cm from the lateral epicondyle, and the needle was inserted "deeply into the subcutaneous tissue and muscle." Measurements were based on 0–100 mm visual analog scale (VAS) scores and demonstrated pain reduction on the 4th and 12th weeks of the study period. The 40.2 mm VAS score reduction in the toxin group compared to the 15.7 mm decrease in the placebo group was statistically significant. These findings were also replicated at 12 weeks where significant differences in mean VAS scores were found between the aboA (23.5 mm) and saline subjects (43.5 mm), in favor of BoNT. Grip strength was measured as a secondary outcome, and despite a slight decrease in both groups, it was not significantly different between the test and control patients at any timepoint. The most common adverse effect was paralysis of finger extension, which occurred in four patients on week 4 of the study.

Hayton et al. [19], in another blinded and controlled trial, compared pain, quality of life, and hand grip, between aboA and placebo (saline), in 40 CLE patients unre-

sponsive to steroids. These outcomes were measured with VAS scale, short-form SF12, and Jamar dynamometer, respectively. Assessments were made at baseline and 3 months after injection of 50 U aboA or saline. All injections were intramuscularly administered, 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. No differences in neither of the outcomes were reported between aboA and saline at 3 months.

Placzek et al. [33] conducted a double-blinded, placebo-controlled RCT in 16 centers to evaluate the effectiveness of BoNT treatment in chronic tennis elbow. A total of 130 CLE subjects were injected with either 60 units aboA diluted in 0.9% saline or the same volume placebo (saline). Half the solution was administered intramuscularly, 3–4 cm distal from the tender epicondyle, and the other half was injected after partially pulling the needle out and applying a horizontal rotation. This method provided different depths of infiltration. VAS was used to determine the level of pain before injections (baseline) and at 2, 6, 12, and 18 weeks. Satisfaction of both patients and blinded clinicians was measured at the same timepoints using a global assessment score of 0–4, which indicated "substantially worse" to "substantially better" outcomes, respectively. Furthermore, finger extension strength of all patients was assessed through a vigorimeter. The results demonstrated that aboA administration caused significant reduction of pain at all studied timepoints after injection (Table 10.1).

A randomized placebo-controlled study by Espandar et al. [14] aimed to assess BoNT efficacy in CLE patients using injection sites that were calculated by anatomical measurements. A total of 48 patients with chronic refractory LE received either 60 units of aboA or the same volume normal saline. Based on a cadaver study [25], 33% of the arm length inferior to the lateral epicondyle was selected for injection. This area forms the point where the posterior interosseous nerve innervates the extensor carpi ulnaris and extensor digitorum. Pain intensity at rest was considered as the primary outcome (0–100 mm, VAS score), which was measured postinjection at 4, 8, and 16 weeks. Secondary outcomes consisted of pain intensity during maximum pinch and maximum handgrip in addition to grip strength (kg). The primary outcome decreased significantly in the aboA group in comparison to

Table 10.1 Comparison of clinical pain scores between groups

	Score[a]		
Visit	Botulinum	Placebo	*p* value[b]
Injection	8.43 ± 0.24 (68)	8.55 ± 0.21 (62)	0.920
Week 2	5.24 ± 0.38 (68)	6.85 ± 0.35 (61)	0.003
Week 6	4.53 ± 0.37 (68)	5.69 ± 0.37 (61)	0.020
Week 12	3.76 ± 0.36 (68)	5.02 ± 0.41 (61)	0.023
Week 18	2.88 ± 0.35 (68)	4.29 ± 0.41 (57)	0.009

From Placzek et al. [33]. Printed with permission from the *Journal of Bone and Joint Surgery*

[a]The values are given as the mean clinical pain score and the standard error of the mean with the number of patients in parentheses

[b]The level of significance of the difference between the botulinum and placebo groups as assessed with the Mann–Whitney *U* test

the control group at 4, 8, and 16 weeks with VAS scores of 14.1 mm, 11.5 mm, and 12.6 mm, respectively ($p = 0.01$). Similarly, pain intensity during maximum pinch was significantly lower in patients injected with BoNT-A than those receiving saline ($p = 0.004$). Grip strength during follow-up diminished in the aboA group compared to the controls, but the difference was not significant in between-group comparisons. Weakness of finger extension interfering with functioning at work was reported in aboA patients at week 4 which resolved by the 8th week in one patient and the 16th week in the rest of the participants in the test group.

Ruiz et al. [36] studied the pain reduction and functional performance of 12 CLE patients after receiving injections of 10–30 U/muscle incobotulinumtoxinA (incoA). The toxin was diluted with 1 ml normal saline and administered into the extensor carpi ulnaris (20 U), extensor digiti minimi (10 U), extensor digitorum longus (30 U), and extensor carpi radialis brevis (20 U) muscles of all subjects. If more than one muscle was involved, injections were administered into each of the muscles, but none of the patients received the maximum allowed dose of 80 U. In order to locate the muscles for injection, the participant was asked to perform specific movements while the epicondyle was palpated. Ultrasound was used to confirm the correct selection of the insertion point. Pain intensity based on VAS scores (0, best, to 10, worst) was significantly diminished from 6.9 ± 1.8 at baseline to 4.3 ± 2.6, 4.0 ± 2.9, and 4.3 ± 3.9 after injections at the 1-, 3-, and 6-month timepoints, respectively. Likewise, hand functionality evaluated by the QuickDASH scale (0, best, to 100, worst) showed significant improvement from baseline (60.1 ± 20.9) to 1 month (47.6 ± 22.2), 3 months (44.5 ± 24.2), and 6 months (36.3 ± 32.3). Following injections, 87.5% of the patients were affected with third finger weakness, which disappeared after 45–90 days, but no adverse effects were reported at follow-up visits. Three patients required an additional dose of BoNT-A, and five subjects were required to undergo surgery due to insufficient recovery of normal functionality after toxin injection.

Comparator Studies

In a small double-blind study by Lin et al. [23], pain (VAS), handgrip (dynamometry), and quality of life (World Health Organization's brief questionnaire) were compared between patients receiving 50 units onabotulinumtoxinA (onaA) and those injected with 40 mg triamcinolone acetonide. The extensor carpi radialis brevis near the common origin of the wrist and finger extensors of the affected elbow was selected as the site of injection for both substances, and assessments were made at baseline and weeks 4, 8, and 12. In a total of 19 affected elbows in 16 subjects, pain reduction was observed at week 4 in both groups, but the reduction was significantly greater in patients injected with steroid ($p = 0.02$). The other two timepoints were also associated with pain improvement, but the difference between Botox and triamcinolone acetonide was not significant either at 8 or 12 weeks. Interestingly, the analgesic effect of BoNT-A increased with time, but the level of pain reduction decreased in the steroid group ($p > 0.05$). Grip strength showed mild decrease and

increase in the Botox and steroid groups, respectively, and demonstrated significant differences between the two groups at 4 and 8 weeks. There was no significant difference in quality of life between the groups, and no debilitating adverse effects were found in the participants.

Guo et al. [18] in a double-blind, randomized, active drug-controlled trial compared the effect of low-dose onabotulinumtoxinA (20 units, 1 ml) and the commonly used steroid injection of triamcinolone acetonide (40 mg, 1 ml) in 26 patients with CLE. Additionally, the antinociceptive impact of BoNT-A was compared between two different injection sites which included the most tender point of the common extensor muscles (Botox-Tend group) and 1 cm distal to the painful lateral epicondyle (Botox-Epic and Steroid groups). The primary outcome was intensity of pain measured by VAS before intervention and at 4, 8, 12, and 16 weeks after treatment. The only significant difference in pain improvement among the three groups was found at week 4, in favor of steroid administration. All interventions were similar in VAS score reduction after 8, 12, and 16 weeks of injection. Secondary outcomes including grip strength analyzed by dynamometry and functionality determined through the Patient-Rated Tennis Elbow Evaluation Questionnaire were significantly better for the steroid group at 4 weeks. However, no significant differences were observed at the other timepoints. Primary and secondary outcomes were worse when BoNT-A was administered to the tender points of the muscles (Botox-Tend group), compared to steroid injections at week 4 but not the other timepoints. These outcomes were not significantly different between Botox-Epic and steroid groups (4, 8, 12, and 16 weeks). No severe adverse events were reported, except that two patients in the Botox-Tend group had either extension lag or diminished strength of the middle finger, which were temporary. The authors concluded that low-dose BoNT-A and steroids injected into the lateral epicondyle both successfully decreased pain and improved upper limb function for at least 16 weeks.

In a double-blind randomized trial, Lee et al. [22] compared the analgesic impact of small and large doses of BoNT-A in CLE. Sixty patients with this condition were randomly assigned to receive a single dose of either a 10I U or 50I U BoNT-A (Meditox), diluted in 0.7 ml dextrose solution (30%) and 0.3 ml mepivacaine (2%). Injections were administered under ultrasound guidance in the common wrist extensor tendon, using the peppering technique (Fig. 10.1). Outcome measures were assessed at baseline and every month for 6 months and included pain intensity (numeric rating scale from 0 to 10), grip strength (kg, dynamometer), and questions about weakness in the wrist or fingers. The results indicated significant pain reduction in both groups at all timepoints, which was significantly higher in patients receiving the high-dose treatment at all timepoints except months 5 and 6. However, "successful pain treatment" did not differ between the groups. This parameter was defined as more than, or equal to, 50% decrease in pain intensity scores at 6 months [change in numeric rating scale (%) = (pretreatment score – six-month post-treatment score/pretreatment score × 100)]. Similar results were obtained for grip strength, except that between-group differences were absent only at month 5. Motor weakness was significantly more pronounced in the high-dose group but did not cause debilitation. In general, it was concluded that BoNT-A administered at high doses yields better results, compared to lower doses of this toxin.

BoNT studies in CLE are summarized in Table 10.2.

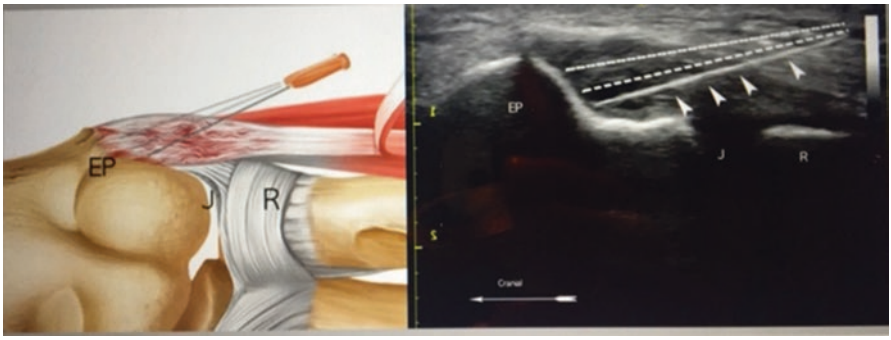

Fig. 10.1 Schematic (left) and ultrasound image (right) demonstrating injection of botulinum toxin A into the common wrist extensor tendon. Arrowheads, needle; EP, epicondyle; J, joint; R, radius. (From [22], with permission from Oxford University Press)

Comment

Table 10.2 categorizes BoNT studies in CLE, based on the level of evidence criteria described by the Assessment Subcommittee of the American Academy of Neurology [15, 16]. Accordingly, three class I and three class II studies using botulinumtoxinA and one class IV study utilizing incobotulinumtoxinA have all reported effectiveness of BoNT-A. However, there was one class III study with onaA [19] who contradicted these results and found BoNT to be ineffective against pain in CLE patients. Predicated on this information, it is safe to say that treatment of CLE with botulinumtoxinA meets level A evidence or in other words could be considered "effective" for treating CLE. The problem with the abovementioned class III study was the limited number of subjects selected for evaluation, and more importantly it only used one efficacy assessment at only one timepoint (3 months). Previous experience with the application of BoNT indicates that its effect is temporary and often disappears within 3 months. In the comparator study by Lin et al. [23], results were based on only 16 patients which is too small and may lead to type II statistical error. On the other hand, Gou et al. [18] evaluated the efficacy of BoNT with a larger number of subjects, reducing this type of error and leading to the conclusion that triamcinolone is as effective as botulinumtoxinA but without its side effects on finger function.

At present, favorable findings on BoNT injections used for the treatment of CLE exist in the literature, which are based on blinded studies. However, an important problem is that the favorable effects are accompanied by weakness in finger extension that develops after BoNT injection. To deal with this issue, larger blinded studies using different neurotoxins and methods are required so that patients can benefit from the positive outcomes of this toxin without enduring its negative effects.

Table 10.2 Blinded studies of BoNT-A in chronic lateral epicondylitis

Study	Class	# of pts	Type	Toxin	Dose (u)	PO at week(s)	SO	Results
Wong et al. [46]	II	60	DBPC	AboA	60	VAS: 12	Handgrip	$p < 0.001$ (VAS)
Hayton et al. [19]	III	40	DBPC	AboA	50	VAS	SF12, handgrip	NS
Placzek et al. [33]	I	130	DBPC	AboA	60	VAS: 2, 6, 12, 16	PPS	$p < 0.05$ (VAS) all weeks, PPS $p < 0.05$
Espandar et al. [14]	II	48	DBPC	AboA	60	VAS: 4, 8, 16 MP, MG		$p = 0.01$ (VAS) $p = 0.04$ (MP)
Lin et al. [23]	II	16	Comp	OnaA and triamcinolone	50	VAS: 4, 8, 12		$p = 0.02$ (VAS) week 4 triamcinolone >onaA
Gou et al. (2017)	I	36	Comp	OnaA (two sites) and triamcinolone	20	VAS: 4, 8, 12, 16	handgrip, PTEE	$p = 0.01$ (VAS) and all SO at week 4 in favor of triamcinolone
Lee et al. [22]	I	60	Comp	Meditox small and large doses	10 and 50	NRS, grip strength, weakness in wrist/finger: 1, 2, 3, 4, 5, and 6 months		$p < 0.05$ (NRS) 1, 2, 3, 4 months; $p < 0.05$ grip strength (kg) all times except month 5 all in favor of 50 U; $p = 0.044$ motor weakness more prevalent in 50 U

Study class according to definition of the Assessment Subcommittee of AAN [15, 16]
DBPC double blind, placebo controlled, *AboA* abobotulinumtoxinA, *onaA* onabotulinumtoxinA, *PO* primary outcome, *SP* secondary outcome, *PPS* patient and physician satisfaction scale (0–4), *MP* maximum pinch, *MG* maximum grip, *ns* not significant, *PTEE* Patient-Rated Tennis Elbow Questionnaire, *NRS* numeric rating scale

Refractory Pain Following Total Knee Arthroplasty (TKA)

A significant source of chronic pain in adults is chronic, advanced osteoarthritis of the knee which responds poorly to medication. A successful modality for improving pain and quality of life in patients with this problem is total knee arthroplasty [29], which is very commonly performed in the USA, estimated as 500,000 cases annually. This number is proposed to have a sixfold increase by 2030, reaching 3.48 million/year [39].

Unfortunately, the procedure is not always satisfactory for the patients, and almost a quarter of them complain of various issues after treatment [2]. Furthermore, an additional 7–44% continue to have persistent pain following the procedure [4, 47]. The mechanism of TKA-related pain depends on the active contribution of known pain transmitters. In contrast to normal joints, elevated levels of substance P have been demonstrated in the joint fluid of patients with chronic osteoarthritis who have been subjected to TKA [35]. Considering that the chronic pain which develops after this treatment is resistant to drug therapy, novel treatment strategies are clearly welcome in this area of pain medicine.

Singh et al. [39] conducted a randomized, double-blind, placebo-controlled study to evaluate the efficiency of intra-articular (IA) injection of onaA, in relieving TKA-induced pain. The 54 patients enrolled in this study were mostly male (84%) with a mean age of 67 years and had undergone complete arthroplasty of the knee. Their mean TKA-related pain duration was 4.5 years, which exceeded 6 months and was moderate or severe (>6 on 0–10 VAS). For the BoNT injections, 100 units of onaA was reconstituted in 5 ml of 0.9% saline without preservative and injected IA. The primary outcome was the proportion of patients who experienced a reduction of two or more points of the numerical VAS scale (0–10), which was compared between the BoNT and placebo groups at 2 months. VAS and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index physical function were assessed at baseline and at 2, 3, and 4 months. The patient and physician's global impression of change were also determined at the same timepoints.

The proportion of patients who reported VAS-based pain reduction was significantly larger in the group who received onaA (71%) compared to the saline group (35%), at the 2-month timepoint ($p = 0.028$). A significant difference in duration of meaningful pain relief was found between the onaA and placebo groups recorded as 39.6 ± 50.4 days and 15.7 ± 22.6 days, respectively ($p = 0.045$). Similar significant differences in favor of onaA was reported in physician global assessment of change ($p = 0.003$), Short-Form 36 pain subscale score ($p = 0.049$), the physical function subscale ($p = 0.026$), stiffness subscale ($p = 0.004$), and total scores ($p = 0.024$) of WOMAC Osteoarthritis Index at all timepoints. There were no serious treatment-associated adverse events in the onaA group. Local pain due to injection and mild temporary weakness around the joint was observed in some of the participants, but they were not significantly different between the two groups.

One of the major challenges in the discipline of pain medicine is postsurgical pain. Due to its numerous attributes, BoNT therapy has emerged as a successful option for a heterogeneous group of conditions related to postsurgical pain such as that arising from mastectomy, hemorrhoidectomy, cholecystectomy, hernia repair, and post-adductor release surgery in children with cerebral palsy. Its mechanism of action is multifaceted, and elements like local accumulation of pain transmitters, damage to terminal nerve endings, local inflammation, etc., may be responsible for or play a role in its clinical effects.

Comment

The RCT by Singh et al. [39] can be categorized as a class II study with level C evidence, indicating that BoNT treatment for TKA-induced pain could be "possibly effective," based on the criteria and guidelines of the American Academy of Neurology's Subcommittee on Assessment of the efficacy of randomized clinical trials [15, 16]. Further high-quality (classes I and II) studies are suggested to confirm these encouraging results and help provide a better understanding of the role of BoNT treatment in the refractory pain associated with TKA.

Painful Local Arthritis

Arthritis is regarded as one of the most common debilitating health conditions worldwide. It can involve a variety of joints including the knee, which afflicts 46 million people in the USA.

In a recent review, Cheng et al. [10] reported data gathered from systematic reviews and clinical trials pertaining to the efficacy of IA administration of different agents for the treatment of arthritic knee pain. Accordingly, steroids and hyaluronate both effectively reduced pain, but the pain relief obtained from hyaluronate lasted longer. Among steroids, triamcinolone hexacetonide demonstrated superior results compared to triamcinolone acetonide and was suggested as a good option for IA use. Other effective substances included tropisetron, a 5-HT3 receptor antagonist, and tanezumab, a monoclonal antibody against nerve growth factor, which were given a 2B+ efficacy level, similar to BoNT-A. A variety of IA radioisotopes have also been reported to be partially effective, but there is uncertainty regarding their long-term safety and efficiency.

Mahowald et al. [26] presented their 1-year clinical experience on onaA injection for the treatment of arthritis and arthritic pain in nine shoulders, three knees, and three ankles in 11 patients. All participants had a history of failed treatments involving intra-articular administration of steroids and/or viscosupplement agents. Shoulder and limb joints were injected with 50–100 units and 25–50 units of onaA, respectively. Comparing pain at baseline and time of maximum relief, a significant ($p = 0.02$) mean maximum reduction of 55% was found in limb joints. The decrease was even greater in shoulder joints reaching 72% ($p < 0.001$). Similarly, significant improvements in lower extremity function (36%) and shoulders (67% in flexion, 42% in abduction) were reported at follow-up ($p = 0.044$, $p = 0.001$, and $p = 0.01$, respectively). Limb improvements occurred between 4 and 10 weeks postinjection. No significant adverse events were observed.

Castiglione et al. [8] conducted a prospective, open-label study of five patients with post-hemiplegic shoulder pain. OnaA (100 units), aboA (500 units), and incoA (100 units) were used to inject the glenohumeral painful joints in two, one, and two patients, respectively. At 2 and 8 weeks, VAS was used to determine the level of pain

at rest and pain during passive arm abduction. All subjects at both timepoints reported significant improvement of shoulder pain at rest ($p = 0.001$) and at arm abduction ($p < 0.001$). No difference in the level of pain relief was observed at 2 and 8 weeks.

McAlindon et al. [28] conducted a phase 2, multicenter, double-blind, randomized, placebo-controlled parallel-group study on 158 patients with knee osteoarthritis. Those with nociceptive pain, assessed through a painDETECT questionnaire ($\leq$12), were enrolled. All subjects received IA injections under ultrasound guidance after aspiration of synovial fluid effusion (if present). The injections included onaA with doses of 400 U or 200 U or normal saline which were administered in a total volume of 2 ml to patients allocated in a 1:1:2 ratio. The duration of follow-up was 24 weeks. On week 8, the "daily average numeric rating scale pain score," measured over a 7-day period, was recorded for the study knee. The results showed a two-point decrease for all treatments which was maintained during the entire follow-up. However, there were no significant between-group differences for any of the injected substances. These findings were repeated for all secondary outcome measures including WOMAC physical function scores and the patient global impression of change (PGIC).

In a double-blind, randomized, placebo-controlled, 12-week study by Arendt-Nielsen et al. [3], efficacy of BoNT therapy was evaluated in painful osteoarthritis of the knee. A total of 121 patients with this condition were randomly injected with botulinumtoxinA (200 U, 2 ml) or placebo (2 ml, 0.9% saline) and followed for 12 weeks. Injections were performed under ultrasound guidance. The test and control groups consisted of 61 and 60 subjects, respectively, and were further divided into nociceptive ($n = 68$) and non-nociceptive ($n = 53$) subgroups based on the painDETECT questionnaire. Outcomes were measured using quantitative sensory testing, WOMAC, average daily pain, and PGIC. No significant between-group differences were demonstrated for mechanistic pain biomarkers. However, the nociceptive subgroup demonstrated significant improvements in the above parameters.

Comparator Studies

In a study by Boon et al. [7], 60 knee osteoarthritis patients, unresponsive to conventional treatments and physical therapy, were recruited to compare different doses of onaA with steroids. All participants had a minimum VAS score of 6/10 and functional impairment of the knee. Injections of onaA were administered with either low (100 units) or high (200 units) doses, and its efficacy was compared with 40 units of methylprednisolone acetate. Evaluations were made at 8 and 26 weeks, and of the 60 participants, all competed the 8 weeks, while only 32 patients went through the entire study period. VAS-based pain reduction was considered as the primary outcome, which despite showing effectiveness for all three substances at week 8 reached significant levels only in the low-dose onaA group ($p = 0.01$). Secondary outcomes included quality of life determined via Short-Form 36,

WOMAC Arthritis Index, patient global assessment using a three-question format, and a 40-meter timed walk. Statistically significant decreases in pain and stiffness subsets of the WOMAC Arthritis Index scores were found in all groups. Side effects consist of local swelling and pain at the site of injection, dry mouth, and balance problems which were mild and did not differ among the groups. However, local swelling and pain at the site of injection along with balance problems were more common in the high-dose onaA group ($p > 0.05$).

In a single (assessor) blind, prospective study, Sun et al. [42] recruited 75 patients with symptomatic ankle osteoarthritis to compare the safety/effectiveness of IA "onaA" and "hyaluronate plus rehabilitation exercise." Single doses of BoNT-A (100 units) were administered to 38 subjects, while the rest received IA injections of hyaluronate along with physiotherapy for 30 min per session, three times a week for 1 month. The total score of the Ankle Osteoarthritis Scale (AOS) was regarded as the primary outcome of the study, and its endpoint assessment was 6 months. This patient-rated measure is based on two nine-item pain and disability subscales resulting in a final score of 0–10, denoting "none" to "worst" pain or disability. Several secondary outcomes were considered, and those related purely to pain included VAS and global patient satisfaction, which were determined before injection (baseline) and at 2 weeks and 1, 3, and 6 months. A minimum decrease of 30% in pain score was defined as significant. For ankle joint injections, the needle was inserted 1 cm anterior to the distal medial malleolus and advanced posteriorly and slightly upward toward the middle of the ankle joint above the talus to deliver 100 units of onaA or 2 ml sodium hyaluronate. In cases accompanied by effusion, aspirations were performed before injections. According to the measured pain subset of AOS and VAS scores, all patients reported a significant reduction of ≥50%. In onaA subjects, VAS scores decreased from 4 at baseline to 1.8 on week 2, which continued to decline to 1.7 on the third month of the study. Pain alleviation was similar between the two groups with no significant differences. Similarly considerable improvement in the disability scores was observed in both groups, which even lasted for 6 months in a number of participants. None of the patients experienced any serious side effects.

Bao et al. [5] in a single-center, placebo-controlled, single-blinded study randomized 60 patients with knee osteoarthritis into three injection groups including saline (placebo), onaA, and hyaluronate. The articular cavity of the knee was located using color Doppler ultrasound, which positioned the injection point at the level of the suprapatellar bursa. A dose of 100 U onaA in 2.5 ml saline and the same volume placebo were used, while the hyaluronate group received injections once a week for 5 weeks. Exercise therapy was administered in all groups, and outcomes were recorded at baseline and 4 and 8 weeks. WOMAC Index questionnaire score, VAS, and Medical Outcomes Study 36-Item Health Survey (SF-36) constituted the outcome measures. In the group receiving onaA, WOMAC, VAS, and both physical and mental components of SF-36 improved significantly compared to both placebo and hyaluronate groups at 4 and 8 weeks.

Comment

Two blinded class I studies [3, 28], one small blinded class II trial [26], three blinded comparator studies, and a small open-label study showed conflicting results regarding the efficacy of intra-articular injection of BonT-A in the treatment of arthritic joint pain. Two class I studies did not confirm the positive impact of BoNT, whereas one contradicted this finding and reported positive effects for this toxin [5]. Among the three comparator studies, one [7] had a considerable number of dropouts (30%) and reported a superior response to low dose compared to high doses of onaA, without adequate justification. On account of the high amount of subject dropout, this study can best be defined as class III. Of the two other comparator studies, both were single-blinded. One showed similar effects between BoNT-A and the other intervention [42], while the other study [5] reported favorable effects of BoNT therapy.

Therefore, the level of evidence for BoNT efficacy in the treatment of painful arthritis (AAN guidelines [15, 16]) is B (probably ineffective) based on the availability of two class I studies. Further controlled studies are required to substantiate these negative claims – especially considering one positive class I study.

Anterior Knee Pain Related to Vastus Lateralis Imbalance

A common complaint among the general population is anterior knee pain with a suggested incidence of 22/1000 individuals/year [6]. One of its major causes is patellofemoral syndrome, which is known as anterior knee pain that occurs mostly in young women, without any significant relevant pathology [32]. A probable source of anterior knee pain and the patellofemoral syndrome can be an imbalance of the vastus lateralis muscles [34].

Based on this probable source, a double-blind, placebo-controlled trial on 24 patients with anterior knee pain was conducted by Singer et al. [38] to study the effectiveness of BoNT in pain relief. The vastus lateralis muscles randomly received 4 ml aboA (500 units) or placebo (saline) in eight sites (0.5 ml/site) under electromyographic guidance (Fig. 10.2). The primary outcomes were measured at 3 months using Anterior Knee Pain Scale and VAS to assess improvements in “knee pain-related disability” and “activity-induced knee pain,” respectively. Significant improvement of the former was only found in patients injected with aboA. Similarly, “activity-induced knee pain” in the BoNT group showed clinically significant decreases in mean VAS for kneeling, stair walking, squatting, and level walking. In the placebo subjects, there was only a decline in stair walking, which was not statistically significant. The authors concluded that aboA had a significant favorable impact on chronic anterior knee pain due to vastus lateralis imbalance.

Chen et al. [9] conducted an unblind, prospective, case-control study on the efficacy of BoNT-A for the treatment of knee pain due to patellofemoral pain syn-

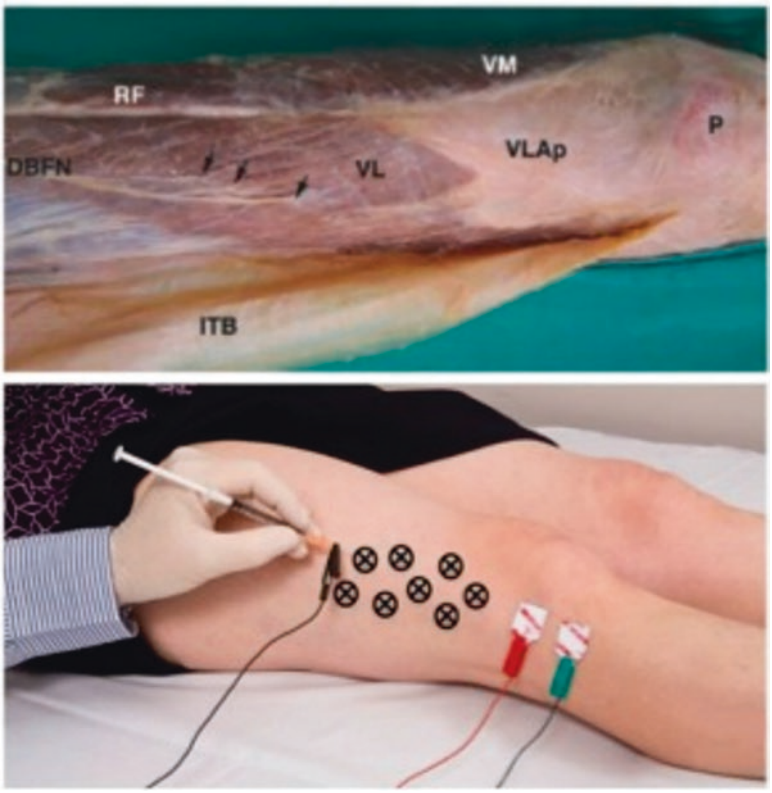

Fig. 10.2 Dissection showing the distal branch of the femoral nerve to vastus lateralis (small arrows), with the iliotibial band (ITB) reflected posteriorly (upper panel). As illustrated in the lower panel, multiple injection sites, using EMG guidance, were employed to ensure spread of injectate within the distal VL muscle. VLA p, vastus lateralis aponeurosis of the knee joint capsule; RF, rectus femoris muscle; VM, vastus medialis; p, patella. (Original figure is reprinted from Singer et al. [48], which has been made available under Creative Commons Attribution License)

drome. Case selection consisted of patients affected with this syndrome in both knees, so that the contralateral knee could be used as control. OnaA (10 U/0.1 ml diluted in saline) was injected into the vastus lateralis muscle of the knee in 12 subjects. The knee with the worse pain received BoNT-A under electromyographic guidance, and the control knee was left untreated. The dose was administered at one injection site, where the needle was inserted about 3–5 cm above the patella, on an oblique angle just lateral to the midline. Assessment involved changes in WOMAC score, which was evaluated at baseline and after 4, 8, and 12 weeks of onaA administrations to record pain, stiffness, and functional status of the knees. Additionally, muscle force was determined by an isokinetic dynamometer at the same timepoints. According to the WOMAC results obtained at 12 weeks, the BoNT-A-injected knees demonstrated a clinically significant reduction in mean pain (-1.8, $p = 0.014$) and function scores (-6.6, $p = 0.029$). Despite the decrease in stiffness scores, the

difference on week 12 was not significant. The isokinetic test demonstrated a significant reduction in flexion moment (12.1 Nm, $p = 0.041$) but not in extension moment, after BoNT-A treatment. The control knee did not achieve significant changes in WOMAC scores but demonstrated an increased flexion moment as in the treated knee. The authors concluded that injection of onaA could improve anterior knee pain, function, and isokinetic torque caused by vastus lateralis imbalance.

Comment

The abovementioned class II and III studies define a C level of evidence (possibly effective) for anterior knee pain with vastus lateralis imbalance (AAN assessment of evidence, [15, 16]).

Orthopedic Contracture and/or Pain Release

Intramuscular injections of botulinum toxins are well-known options for the treatment of spasticity. Spasticity is a complex issue and a common symptom observed in a variety of neurologic conditions like stroke, multiple sclerosis, brain/spinal cord injury, and cerebral palsy. Despite the fact that spasticity responds well to drug therapy, it can cause unwanted adverse events and has a short response period. One of the FDA-approved applications of BoNT is its intramuscular injections to treat spasticity. However, the efficacy of BoNT therapy in pain related to this issue is less determined, and evidence level is more unclear [20]. The practice of intramuscular injection using BoNT has led to the development of new areas and additional options for treatment of other orthopedic-related issues. Scientific studies are beginning to evaluate the role of BoNT in treating these problems which include orthopedic contracture and/or pain release.

Smith et al. [41] investigated the efficacy of a single injection of onabotulinumtoxinA for improving flexion contracture after total knee arthroplasty in a prospective, randomized, double-blinded, placebo-controlled trial. Patients with flexion contracture after total knee arthroplasty were randomized to receive either 100 units of onabotulinumtoxinA diluted in 2 ml saline (nine knees) or the same volume of 0.9% saline (six knees). Injections were administered into the hamstrings, and all subjects were assessed at 1, 6, and 12 months. Extension significantly improved at all timepoints in both BoNT and control groups. Significant difference in extension between the two groups was noted 1 month postinjection in favor of BoNT-A. After a mixed model regression analysis, onaA also showed significant improvement compared to placebo on month 12 of the study period. Due to the fact that improvements were encountered in both groups, the authors concluded that the significant difference between the BoNT and placebo groups was of limited clinical significance.

Eibach et al. [12] presented a case report of a 47-year-old male with tetraplegia due to cerebral palsy. The patient required a total hip joint arthroplasty because of hip arthrosis. OnaA guided by CT fluoroscopy was injected preoperatively into hip flexor and adductor muscles (200 U in iliopsoas and 50 U bilateral in adductor magnus). This was performed in order to minimize the risk of postoperative luxation. Seven days after treatment, the patient had a reduction in spasticity, I think preoperatively is correct flexion and adduction contracture and was pain-free. Santamato et al. [37] reported the application of BoNT-A in a 34-year-old woman with persistent painful contracture in the adductor magnus muscle after total hip arthroplasty. OnaA (150 UM) was injected preoperatively into adductor magnus muscles of the hip under electromyographic guide. Seven days after treatment, the patient had a reduction in pain evaluated by VAS, and on day 20 Harris hip score and external rotation of the hip showed considerable improvement. The clinical effects were maintained at the 2-month follow-up. Both the abovementioned case studies reported no adverse events.

Eleopra et al. [13] conducted a prospective, randomized double-blind multicenter study to evaluate the effectiveness of intramuscular botulinumtoxinA injections in 46 patients with hip osteoarthritis. The rationale was to relieve pressure in the arthritic hip joint to improve pain and range of motion. AboA or saline was injected randomly into the adductor muscles of the affected arthritic hip joint. The total dose of abobotulinumtoxinA was 400 U in 2 ml of saline, with 250 U being injected in the adductor longus muscle and 150 U in the adductor magnus muscle under electromyographic guidance. The control group received the same volume of saline without the aboA. Evaluation was performed before injection and after 2, 4, and 12 weeks. After the fourth week, the BoNT-A group showed significant differences in pain level (VAS) and Harris hip scores compared to the controls and also in all timepoints compared to baseline (Fig. 10.3). Otherwise, there were no significant differences during follow-up neither in primary nor secondary outcome parameters such as Medical Research Council scale for muscle strength and Short Form scale (SF-36) scores. No adverse events were detected in either treatment groups. A pilot study by Marchini et al. [27] was conducted prior to the RCT by the same group [13], which included a series of 39 patients with the same treatment regime and scientific design, except for the fact that it was a longitudinal prospective series without a control group. Their results demonstrated a significant improvement in pain level evaluated by VAS and in Harris hip score after 2, 4, and 12 weeks and also in SF-36 scores after 4 and 12 weeks.

In a prospective randomized triple-blind, single-center study, Wong et al. [45] used intramuscular botulinumtoxinA injections for correction of neuromuscular scoliosis in 10 severely handicapped, tetraplegic children with cerebral palsy (gross motor function classification system 3–5). The randomization was based on a crossover design with two consecutive 6-month study periods. Radiologic examinations were performed before and 6 weeks after BoNT-A injections. OnaA (10 U/0, 1 ml) was administered in the iliopsoas, quadratus lumborum, and erector spinae muscles under ultrasound guidance using 100 U, 50 U, and 30 U, respectively. In the "control period," the participants received the same volume of saline without the onaA

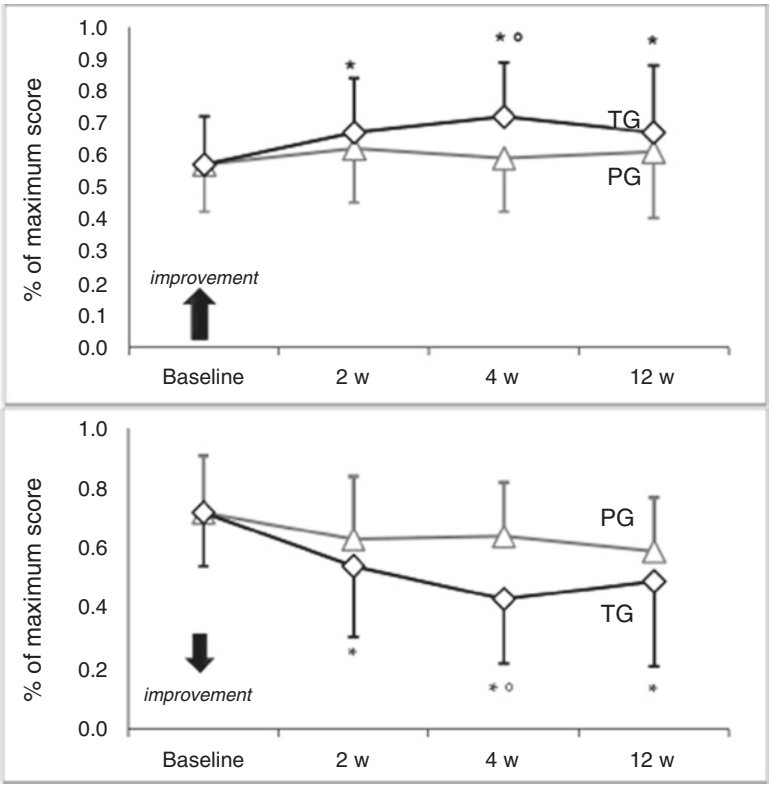

Fig. 10.3 Harris hip score (upper) and visual analog scale (lower) before injection and 2, 4, and 12 weeks after. Values are given as mean ± standard deviation and represent percentage of maximum score (100). PG, placebo group (n = 15); TG, treated group (n = 31); (*), significant difference with baseline; (0), significant difference with placebo group. (Original figure is reprinted from Eleopra et al. [13], which has been made available under Creative Commons Attribution License)

in the target muscles. Primary outcome parameter consisted of change in the radiological parameter for scoliotic curve severity of Cobb's angle, and no significant improvement was detected. Similarly, no clinical improvements were reported. The study was terminated at an interim analysis after the death of one patient. This occurred after two hand surgical procedures and several months after BoNT-A injection therapy termination. No other severe adverse events were detected. A follow-up study was conducted by Wong et al. [44] on a consecutive series of nine adolescent patients with idiopathic scoliosis to investigate the possible role of spinal muscular forces/pulls in the induction of spinal deformity. A single ultrasound-guided injection of onaA (10 U/0, 1 ml) with a maximum dose of 100 U was administered to the psoas part of the iliopsoas muscle on the concave side of the lumbar spine. Radiological examination (Fig. 10.4) evaluating curve severity and rotation as a primary outcome parameter was carried out before and 6 weeks after injections.

Significant, but not clinically meaningful, improvement was detected for curve severity of Cobb's angle. However, no significant improvement was found for radiological derotation evaluated ad modem Nash and Moe. Adverse events were not detected, except for temporary soreness at the injection site in two cases.

Park et al. [31] in a single-center, double-blind, randomized, placebo-controlled study examined the effects of botulinumtoxinA on clinical outcomes of femoral lengthening. Bilateral femoral distraction osteogenesis was performed on 44 patients with familial short stature. OnabotulinumtoxinA (200 U) was administered intraoperatively into seven points of the quadriceps muscle, and an equal volume of sterile normal saline was injected in the other thigh. The patients were evaluated at 4, 8, 12, 24, and 48 weeks. No improvement in range of motion of the hip or knee and also no difference in maximal thigh circumference or distraction-induced pain levels were observed.

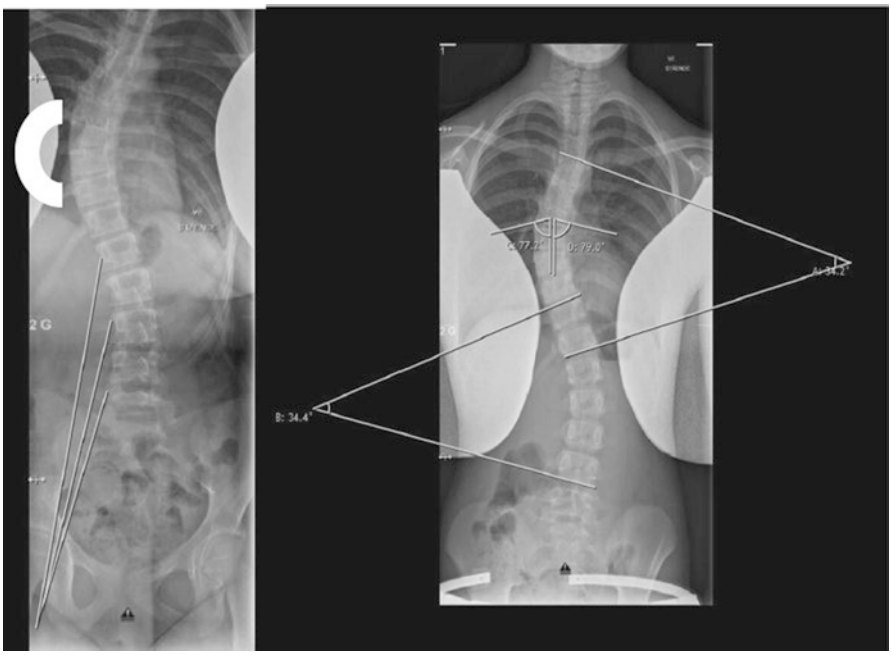

Fig. 10.4 Radiographic image of scoliosis depicting the psoas major on the concave side of a thoracic scoliosis; the stronger thoracic muscles are marked with C and are located in the convex side of the scoliosis (left). Measurements of thoracic and lumbar Cobb's angle and concave and convex rib vertebra angle (right). (Original figure is reprinted from Wong et al. [44], which has been made available under Creative Commons Attribution http://creativecommons.org/licenses/by/4.0/, http://creativecommons.org/publicdomain/zero/1.0/)

Comment

Intramuscular injection therapy using BoNT for orthopedic contracture and/or pain release in relation to arthroplasty and joint arthritis has been evaluated in one class I [13] and four class IV studies. This defines a C level of evidence (possibly effective) for this indication (AAN assessment of evidence, [15, 16]). One class I study for femoral distraction osteogenesis and one class I and one class III study for scoliosis correction define a level B evidence considered as probably ineffective.

Conclusion

The favorable findings of RCTs using BoNT therapy for orthopedic disorders discussed in the preceding chapter have set the stage for conducting additional controlled studies in this essential area of orthopedic surgery. Most likely, with the advent of improved methods and administration of optimum dosage, BoNT injection has the potential to become a valuable option for treatment of refractory pain in orthopedic disorders.

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