Effects of Botulinum Toxin Landmark-Guided Intra-articular Injection in Subjects With Knee Osteoarthritis

Lin-Fen Hsieh, MD, Chia-Wei Wu, MD, Ching-Chieh Chou, PT, MS, Sai-Wei Yang, PhD, Shih-Hui Wu, MD, Yi-Jia Lin, MS, ATC, Wei-Chun Hsu, PhD, PT

Abstract

Background: Increasing evidence has suggested that botulinum toxin A (BoNT/A) can inhibit the release of selected neuropeptide transmitters from primary sensory neurons. Thus, intra-articular (IA) injection therapies with BoNT/A may reduce pain in patients with knee osteoarthritis (OA).

Objective: To investigate the effects of landmark-guided IA injection of BoNT/A on patients with knee OA.

Design: A prospective randomized controlled trial.

Setting: A rehabilitation clinic of a private teaching hospital.

Patients: A total of 46 patients with symptomatic knee OA (mostly Kellgren-Lawrence grade 2-3).

Methods: The patients were randomly assigned to 1 of the following groups: BoNT/A group (BoNT/A injection; n = 21) or control group (education only; n = 20). The patients in the BoNT/A group received an IA injection of 100 units of BoNT/A into the affected knee.

Main Outcome Measures: The short-term (1 week posttreatment) and long-term (6 months posttreatment) effects were evaluated using a pain visual analogue scale (VAS) and questionnaires concerning functional status, including the Lequesne and Western Ontario and McMaster Universities (WOMAC) indexes.

Results: The between-group comparison revealed significant differences with regard to the pain VAS score at 1 week (P < .001) and at 6 months (P = .001) posttreatment. Similar findings for the between-group comparison were observed for the WOMAC and Lequesne indexes at 6 months (P < .05) posttreatment. The pain VAS score in the BoNT/A group significantly decreased from 5.05 ± 1.12 (pretreatment) to 2.89 ± 1.04 at 1 week (P < .001) and 3.45 ± 1.70 at 6 months posttreatment (P < .001) but not in the control group (P = .476).

Conclusions: The IA injection of BoNT/A provided pain relief and improved functional abilities in patients with knee OA in both the short- and long-term follow-up.

Level of Evidence: I

Introduction

Osteoarthritis (OA) is the most common form of arthritis in humans, affecting approximately 15.8 million persons in the United States [1,2], and is a common type of arthropathy in older populations. The knee is the site most commonly associated with chronic pain and physical disability [1,3,4]. The prevalence of knee OA increases with age. In the United States, a symptomatic disease in the knee occurs in approximately 6% of adults aged 30 years or older [5]. Approximately 25% of persons aged 55 years or older experience knee pain in their daily life [6,7]. Patients with knee OA may have knee pain, range of motion limitation, and deformities that can affect their activities of daily living [8].

The primary goals of the clinical management of knee OA are minimizing pain and functional impairment as well as maintaining and improving joint mobility. The American College of Rheumatology has suggested an initial nonoperative and noninvasive treatment plan for knee OA that includes rest, weight loss, bracing and assistive devices, physical modalities, therapeutic exercises, and pharmacological interventions [8,9]. The pharmacological intervention may include topical and oral analgesics, nonsteroidal...
anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and opioids [8]. Moreover, if symptoms cannot be controlled by orally administered drugs, then the last nonoperative resort can be intra-articular (IA) injections.

IA corticosteroid (CS) and hyaluronic acid (HA) injections have been used in treating knee OA for several decades, and platelet-rich plasma (PRP) injections have recently demonstrated promising results [10,11]. IA CS injections are often used in treating acute and chronic inflammation, especially in the presence of joint effusion. These injections can provide short-term pain relief in patients with knee OA. However, the local and systemic side effects of CSs are of concern while IA CS injections are being administered. IA HA injections are believed to restore the lubricating and shock-absorbing properties of the synovial fluid and have exhibited effectiveness in treating mild knee OA for up to 24 weeks. However, the cost-effectiveness of IA HA injections is a concern. PRP is an autologous blood product with a platelet concentration that exceeds the normal level (usually 2-4 times). It can be injected into damaged areas to deliver various growth factors and to promote wound healing. Studies have reported that IA PRP injections are effective in treating knee OA and appear to be more effective than IA HA injections in younger patients with knee OA and low-grade arthritis. The effectiveness of PRP lasts for 6-9 months. However, PRP preparations are generally costly and variable, and additional high-quality randomized controlled trials are required to optimize PRP treatment methods and to define its role in the management of knee OA [8,12]. Operative management (mainly total knee replacement) has demonstrated effectiveness in managing knee OA [8]. However, surgical intervention can cause several complications such as deep vein thrombosis, pulmonary embolism, and cardiovascular morbidity and mortality, especially in some older patients and in those with various medical comorbidities. Under such circumstances, IA injections may be highly suitable for controlling pain and delaying surgery [8].

The mechanism of action of botulinum toxin (BoNT) A (BoNT/A) is the inhibition of the exocytotic release of acetylcholine from motor nerve terminals [13]. This makes it useful in the treatment of several pathological conditions involving excessive muscle contractions, such as painful movement disorders, spasticity, and other pain conditions [14-16]. However, increasing evidence has suggested that BoNT/A can relieve pain by inhibiting the release of selective neuropeptide transmitters (e.g., substance P, glutamate, and calcitonin gene-related peptide) from primary sensory neurons, thus directly reducing peripheral sensitization and indirectly reducing central sensitization [17,18]. IA BoNT/A injections may reduce pain; however, the long-term effects of these injections on pain and function of knee OA as well as the mechanism underlying its effects remain uncertain.

The first clinical study related to IA BoNT/A for pain was published by Mahowald et al in 2006 [19]. The investigators administered the IA BoNT/A injection for refractory joint pain caused by OA, rheumatoid arthritis, and psoriatic arthritis. They injected 50-100 units of BoNT/A into 15 joints, namely 3 knees, 3 ankles, and 9 shoulders. The 1-year follow-up examination revealed a significant decrease in pain in the injected joints without substantial side effects. Boon et al compared the effectiveness and safety among IA injections of low-dose BoNT/A (100 units), high-dose BoNT/A (200 units), and CS in 60 patients with symptomatic knee OA. The pain score in each treatment group decreased in the eighth week; however, changes in the pain score were significant only in the low-dose BoNT/A group. Nevertheless, no serious side effects were observed in any group [20]. In addition, several case reports have indicated significant pain reduction and functional improvement in individuals with OA-related chronic knee pain after the administration of IA BoNT injections at doses of 50-200 units with no substantial side effects [21]. This study investigated the short- and long-term effects of IA BoNT/A injections on patients with knee OA.

**Methods**

**Patients**

We recruited 46 patients with knee OA from the outpatient clinic of the Department of Physical Medicine & Rehabilitation of a private teaching hospital in Taiwan. The inclusion criteria for patients were as follows: fulfillment of the clinical criteria of the American College of Rheumatology for knee OA [22]; age >45 years; disease duration ≥3 months; willingness to receive the IA BoNT/A injection into the knee joint; a radiographic OA severity grade between 2 and 3 for the knee joint on the Kellgren-Lawrence (KL) scale [23]; pain visual analogue scale (VAS) score ≥4; and failure of previous conservative treatments (e.g., NSAIDs and physical therapy).

The exclusion criteria were as follows: receiving an IA injection into the affected knee within 3 months before the initial evaluation; moderate effusion in the affected knee; a fracture or history of surgical intervention in the lower limb on the same side as the affected knee; pregnancy or lactation; blood coagulation disorders or anticoagulant drug use; systemic neuromuscular disorders such as myasthenia gravis, Lambert-Eaton myasthenic syndrome, or amyotrophic lateral sclerosis; other arthropathies such as rheumatoid arthritis and gouty arthritis; allergy to BoNT; and lower extremity dysfunction caused by neurological or medical diseases such as cerebral vascular disease, traumatic
brain injury, diabetic foot problems, and knee joint infection.

**Study Design**

This was a prospective, randomized, controlled trial with a 6-month follow-up period to observe the effect of IA BoNT/A injections on patients with knee OA. The study protocol was approved by the institutional review board of the hospital, and all patients provided written informed consent. The patients were randomly assigned to either of 2 groups. The first group received a BoNT/A injection (BoNT/A group); the second group received only education (control group). Randomization was produced using a table of computer-generated numbers. After the baseline assessment, sequentially numbered, opaque, sealed envelopes were opened by a research assistant. All of the patients received education for arthritis care, and acetaminophen (Tinten) use was allowed for ethical reasons.

**Intervention**

The patients in the BoNT/A group underwent injection of 100 units of botulinum toxin type A (Botox, Allergan Inc, Parsippany, NJ) into the affected knee. One vial (100 units) of BoNT/A was diluted with 2 mL of preservative-free 0.9% saline solution. For the patients with bilateral involvement, injections were delivered into the more severely affected side. An experienced physician performed all of the injections using the same technique and in the same injection sites. The patients were in the supine position (lying face up) with the knee extended, and the physician fixed the patella and compressed the gap between the medial aspect of the patella and the femoral bone. The injection was administered using landmark or palpation guidance (without ultrasound guidance). The knee joint was injected by inserting a needle posterior to the lateral aspect of the patella at the junction of the upper one-third and lower two-thirds of the patella without ultrasound guidance. Physical examination (including bulge sign and patellar ballottement) and ultrasound were performed to detect possible joint effusion. If a mild joint effusion was noted (usually <5 mL), then the joint effusion was aspirated before the BoNT/A injection. Moreover, if moderate effusion (≥5 mL) was aspirated, then the patient was excluded.

**Outcome Measures**

The baseline information included age, gender, body weight, body height, body mass index (BMI), range of motion of the knee, muscle strength of lower extremities, and history of trauma. The KL grading scale was determined from the standing anteroposterior radiographs of the knee [23] (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BoNT/A Group (n = 21)</th>
<th>Control Group (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67.82 ± 9.06</td>
<td>68.06 ± 4.53</td>
<td>.92</td>
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<tr>
<td>Gender</td>
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<tr>
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<td>KL grade</td>
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<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.53 ± 7.84</td>
<td>68.12 ± 25.18</td>
<td>.57</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.24 ± 7.57</td>
<td>155.46 ± 21.67</td>
<td>.30</td>
</tr>
<tr>
<td>BMI</td>
<td>27.34 ± 3.59</td>
<td>27.42 ± 3.81</td>
<td>.63</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation or as absolute number.

Abbreviations: BoNT/A = botulinum toxin A; KL scale = Kellgren-Lawrence scale; BMI = body mass index.

* Group differences were analyzed by either $\chi^2$ test or Mann-Whitney $U$ test.

The degree of pain was assessed using the 10-cm pain VAS, where a higher score indicates a higher degree of pain. Functional ability was assessed using the Lequesne index and the Western Ontario and McMaster Universities (WOMAC) index. The patients were examined before the injection (pretreatment) and 1 week (1 week posttreatment) and 6 months (6 months posttreatment) after the injection. The plain radiographs of the knee were evaluated only before the injection, whereas the pain VAS as well as the Lequesne and WOMAC indexes were evaluated 3 times. The primary outcome measure was the change in the pain VAS score between 1 week posttreatment and pretreatment and between 6 months posttreatment and pretreatment. In patients with knee OA, the mean threshold of reporting "minimal clinically important improvement (MCII)" was determined to be 19.9 mm on the pain VAS [24].

The Lequesne index is a 10-question, interview-style survey administered to patients with knee OA. It comprises the measurement of pain (5 questions), walking distance (1 question), and activities of daily living (4 questions). The scores for each question are summed to provide a combined disease severity score. The total questionnaire is scored on a 0-24 scale. Scores of 1-4, 5-7, 8-10, 11-13, and ≥14 are classified as mild, moderate, severe, very severe, and extremely severe OA, respectively. The reliability of the Lequesne index was previously reported [25].

The WOMAC index is a disease-specific, self-administered instrument for patients with OA of the knee or hip. It has 3 separate dimensions (with 24 individual scenarios), measuring pain (5 scenarios), stiffness (2 scenarios), and physical function (17 scenarios). It may be administered using the 10-cm VAS (where 0 is none and 10 is extreme) or the Likert scale (0-4, where 0 is none and 4 is extreme). These results are then scored on a 0-20 scale for pain, 0-8 scale for
stiffness, and 0-68 scale for physical function. Higher scores for both scales indicate a higher degree of pain, stiffness, or physical dysfunction. In this study, a new version of the WOMAC index was used, and the data were represented on a metric scale (score of 0-100, where 0 is no difficulty and 100 is the most difficulty). The WOMAC index is a valid and reliable tool for determining the self-reported status of OA of the knee or hip in a double-blind, randomized, controlled trial [26].

Statistical Analysis

Group differences in demographic data were analyzed through the \( \chi^2 \) test for gender, tested knee, and the KL grade, and the independent \( t \) test for age, weight, height, and BMI. The Mann-Whitney U test was used to examine the group effect (groups: BoNT/A and control), whereas the Kruskal-Wallis H test was used to examine the time effect (evaluation time: pretreatment, 1 week posttreatment, and 6 months posttreatment) on the pain VAS, Lequesne index, and WOMAC index. In addition, the \( \chi^2 \) test was used to determine whether MCII in the pain VAS varied according to the treatment groups. By using mean differences and their variances in 2 independent-sample groups, namely the BoNT/A and control groups with \( \alpha = 0.05 \), powers were calculated using GPOWER [27]. The power of group comparison for the pain VAS, WOMAC index, and Lequesne index was 0.985, 0.621, and 0.583, respectively. The Pearson correlation was used to evaluate the relationship between changes in the pain VAS score and those in the baseline data including the pain VAS score, Lequesne index, and WOMAC index. A \( P \) value of <.05 indicated a significant difference. Data were analyzed using SPSS, version 19.0 for Windows (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

We recruited 46 patients with knee OA. Of these, 2 patients were excluded because they received other treatments, and 1 patient in the BoNT/A group and 2 patients in the control group were lost to follow-up. The patient in the BoNT/A group dropped out in the sixth month because of traveling abroad. In addition, in the control group, 1 patient dropped out in the first week because of a cerebral vascular accident, and another patient dropped out in the sixth month because of loss of interest in the study. In total, 21 patients in the BoNT/A group and 20 patients in the control group completed the study (Figure 1). The baseline characteristics such as age, gender, grading on the KL scale, weight, height, and BMI did not significantly differ between the 2 groups (Table 1). Two patients in the BoNT/A group and 1 patient in the control group presented with a positive bulge sign (indicating small

Figure 1. Flow chart of study patient inclusion.
effusion in the knee), and 2-4 mL of serous effusion was aspirated through the affected knee joint. The consumption of acetaminophen was 5.28 ± 2.19 and 10.67 ± 3.66 tablets per month in the BoNT/A and control groups, respectively, which significantly differed between the 2 groups (P < .001). No side effects were reported in the BoNT/A group.

**Pain VAS Score**

In the between-group comparison, the pain VAS score did not significantly differ at baseline; however, changes in the pain VAS score significantly differed at 1 week and 6 months posttreatment in the BoNT/A group (P < .001). The percentage decrease in the pain VAS score (compared with the baseline) was higher than the MCII value. Furthermore, this decrease in the BoNT/A and control groups was 52.4% (11/21) and 5.0% (1/20), respectively (P = .001), at 1 week posttreatment and 52.4% (11/21) and 0% (0/20), respectively (P = .001), at 6 months posttreatment (Table 2). In the within-group comparison, significant improvement in the pain VAS score was observed in the BoNT/A group (P < .001) but not in the control group (P = .377; Table 3). The average decrease in the pain VAS score in the BoNT/A group was 42.6% at 1 week posttreatment and 34.9% at 6 months posttreatment.

**Lequesne Index Score**

In the between-group comparison, the Lequesne index score did not significantly differ at the baseline; however, the Lequesne index score significantly differed at 1 week (P < .001) and 6 months posttreatment (P = .012) (Table 2). Furthermore, because no MCII value has been reported for the Lequesne index, we adopted 20% improvement as significant clinical improvement, similar to ACR20 and ASAS20 [27,28]. According to this criterion, the percentage of significant clinical improvement in the Lequesne index score in the BoNT and control groups was 52.38% (11/21) and 10.0% (2/20), respectively, at 1 week posttreatment and 47.62% (10/21) and 20.0% (4/20), respectively, at 6 months posttreatment. In the within-group comparison, a significant decrease was observed in the Lequesne index score in the BoNT/A group (P < .001) but not in the control group (P = .316) (Table 3).

**WOMAC Index Score**

In the between-group comparison, the WOMAC index score significantly differed at 1 week (P = .005) and 6 months posttreatment (P = .003) (Table 2). In the within-group comparison, a significant improvement in the WOMAC index score was observed in both the BoNT/A (P < .001) and control groups (P = .010) (Table 3).

**Correlation Among Pain VAS, Lequesne Index, and WOMAC Index Scores**

The correlation among the pain VAS score, changes in the pain VAS score, WOMAC index score, and Lequesne index score is shown in Table 4. The changes in the pain VAS score between the baseline and at 1 week posttreatment moderately correlated with the baseline pain VAS score but did not correlate with the baseline Lequesne index and WOMAC index scores. The results regarding the changes in the pain VAS score between the baseline and at 6 months posttreatment were similar except for a slightly lower significance level. In addition, a strong correlation was observed between the baseline Lequesne index and WOMAC index scores (r = 0.855, P < .001) and between the baseline pain VAS score and Lequesne index scores (r = 0.616, P = .008).

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group effect at 3 different evaluation times (pretreatment and at 1 week and 6 months posttreatment) performed according to scores obtained from the pain VAS, Lequesne, and WOMAC indexes for the BoNT/A group (n = 21) and control group (n = 20), respectively.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BoNT/A</th>
<th>Control</th>
<th>95% CI on Mean Difference</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain VAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>5.071 ± 1.1221</td>
<td>5.080 ± 1.1597</td>
<td>0.930–1.000</td>
<td>.99</td>
</tr>
<tr>
<td>1 wk posttreatment</td>
<td>2.905 ± 0.935</td>
<td>5.350 ± 1.263</td>
<td>0.000–0.070</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>6 mo posttreatment</td>
<td>3.295 ± 1.577</td>
<td>5.083 ± 0.975</td>
<td>0.000–0.070</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td><strong>Lequesne</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>12.950 ± 2.450</td>
<td>13.185 ± 2.880</td>
<td>0.745–0.962</td>
<td>.774</td>
</tr>
<tr>
<td>1 wk posttreatment</td>
<td>9.842 ± 3.074</td>
<td>13.539 ± 3.639</td>
<td>0.000–0.070</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>6 mo posttreatment</td>
<td>9.658 ± 4.925</td>
<td>13.400 ± 3.201</td>
<td>0.000–0.072</td>
<td>.012*</td>
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<tr>
<td><strong>WOMAC</strong></td>
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</tr>
<tr>
<td>Pretreatment</td>
<td>37.05 ± 5.661</td>
<td>37.15 ± 7.721</td>
<td>0.684–0.926</td>
<td>.814</td>
</tr>
<tr>
<td>1 wk posttreatment</td>
<td>25.947 ± 7.625</td>
<td>34.333 ± 8.163</td>
<td>0.000–0.070</td>
<td>.005*</td>
</tr>
<tr>
<td>6 mo posttreatment</td>
<td>24.526 ± 13.822</td>
<td>35.833 ± 8.324</td>
<td>0.000–0.070</td>
<td>.003*</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation.

**Abbreviations:** VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities; BoNT/A = botulinum toxin A; CI = confidence interval.

* P < .05 by Mann-Whitney U test for between-group comparisons at pretreatment and at 1 wk and 6 mo posttreatment.
Botulinum Toxin Injection in Knee Osteoarthritis

Table 3
<table>
<thead>
<tr>
<th>Score on Questionnaires</th>
<th>Group</th>
<th>Evaluation Time</th>
<th>Time Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pretreatment</td>
<td>1 wk Posttreatment</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>BoNT/A</td>
<td>5.071 ± 1.1211</td>
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<td>Lequesne</td>
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<td>Control</td>
<td>13.185 ± 2.880</td>
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</tr>
<tr>
<td>WOMAC</td>
<td>BoNT/A</td>
<td>37.05 ± 5.661</td>
<td>25.947 ± 7.625</td>
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<tr>
<td></td>
<td>Control</td>
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</tbody>
</table>

Values expressed as mean ± standard deviation unless otherwise indicated.

Abbreviations: VAS = Visual analogue scale; WOMAC = Western Ontario and McMaster Universities; BoNT/A = botulinum toxin A; CI = confidence interval.

* P < 0.05 by Kruskal-Wallis H test values for within-group comparisons at pretreatment and at 1 wk and 6 mo posttreatment.

Discussion

In our study, compared with the control group, the IA BoNT/A injection for knee OA considerably reduced the knee pain and improved the knee function in the BoNT/A group. The average decrease in the knee pain after a single-dose injection (100 units) of BoNT/A was 42.6% at 1 week posttreatment and 34.9% at 6 months posttreatment. In the BoNT/A group, the percentage of patients with a decrease in the pain VAS score higher than the MCII value was 52.4% at both 1 week and 6 months posttreatment. The improvement in the knee pain lasted for at least 6 months, and the decrease in pain was clinically significant. The decrease in pain was more significant among patients with a higher baseline pain VAS score. In addition, similar findings were observed for the Lequesne and WOMAC indexes.

The literature on the use of IA BoNT/A injections for treating arthritis is scant. Animal studies have suggested that BoNT injections can reduce chronic arthritis pain; however, these injections are not effective for relieving acute pain [29,30]. In an open-label study of patients with severe chronic arthritis pain who were unresponsive to IA CS injections, Mahowald et al observed that IA BoNT/A injections reduced pain in the joints of the lower extremities (knee and ankle) by 55% and in the shoulder by 71%. Moreover, improvements of 36%, 67%, and 42% were observed in the lower limb function, active shoulder flexion, and active shoulder abduction, respectively [19]. Our results are consistent with those of Mahowald et al.

Clinically, BoNT was initially used in patients requiring the blockade of neurotransmitter release, including strabismus, blepharospasm, hemifacial muscle spasms, cervical dystonia, hyperhydrosis, and management of spasticity. Later studies have demonstrated the analgesic effects of BoNT on painful movement disorders. According to recent studies, BoNT/A can inhibit the release of other mediators involved in nociception, such as substance P, calcitonin gene-related peptide, and glutamate, in the joints by peripheral nociceptors. A decrease in pain-mediating neurotransmitters directly blocks peripheral sensitization and indirectly blocks central sensitization [31]. In addition, BoNT inhibits Rho GTPase by the ADP-ribosylation of amino acid ASn-41, and Rho GTPase is necessary for activating interleukin-1. Because of the inhibition of interleukin-1 activation, cartilage degradation may be decreased in persons with OA [32]. On the basis of this

Table 4

<table>
<thead>
<tr>
<th>VAS diff1</th>
<th>VAS diff2</th>
<th>VAST0</th>
<th>LequesneT0</th>
<th>WOMACT0</th>
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<tbody>
<tr>
<td>VAS diff1</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
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<tr>
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<tr>
<td>VAST0</td>
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<td>LequesneT0</td>
<td>0.361</td>
<td>.155</td>
<td>0.339</td>
<td>0.616*</td>
</tr>
<tr>
<td>WOMACT0</td>
<td>0.299</td>
<td>.244</td>
<td>0.063</td>
<td>0.811†</td>
</tr>
</tbody>
</table>

Abbreviations: VAS = visual analogue scale for pain; VAST0 = visual analogue scale for pain at the baseline; VAS diff1 = change in VAS pain score between baseline and 1 week after injection; VAS diff2 = change in VAS pain score between baseline and 6 months after injection; LequesneT0 = Lequesne index at the baseline; WOMAC = Western Ontario and McMaster Universities; WOMACT0 = WOMAC index at the baseline.

* Correlation significant at 0.01 level (2-tailed).
† Correlation was significant at 0.05 level (2-tailed).
The present study demonstrated that a 100-unit injection of IA BoNT/A provided long-term pain relief and reduced physical disability in patients with knee OA. IA BoNT/A injections may provide an opportunity for treating OA that is increasing in magnitude with the aging of the population. Although total joint replacement and several conservative treatments are cost-effective for relieving pain and improving quality of life, complications and side effects exist, including some that may be life threatening. Furthermore, some patients may be unwilling to undergo or are unsuitable for joint replacement or drug treatment. The IA BoNT/A injection provides a new therapeutic method for treating patients with knee OA. Because of high costs, few clinical experiences, and scarce animal and clinical studies, IA BoNT/A injections have not been considered as a first-line treatment for osteoarthritic pain. This study and previous studies suggest that IA BoNT/A injections should be added to the algorithm for treatment of refractory cases.

This study has several limitations. First, it was a single-blinded study, and patients in the control group did not receive any injection; therefore, a placebo effect because of the injection was possible in the BoNT/A group. Second, because of a limited budget, we recruited only 46 patients and analyzed 21 patients in the BoNT/A group and 20 in the control group. The small number of participants may limit the reliability. However, the power analysis indicated that the power for group comparison of the pain VAS score was >0.8. Third, 3 patients (6.8%) failed to return for follow-up visits, which may have resulted in a bias. Fourth, administering an IA injection to the osteoarthritic knee requires a physician to be highly skilled. Thus, outcomes may depend on the level of experience of the physician administering the injection. In addition, an IA injection was administered into the knee by using landmark guidance throughout this study. However, if the injection had been administered with ultrasound guidance, then the results may have been different. The current study described the short- and long-term effects of the IA BoNT/A injection on patients with knee OA having both KL 2 and 3 grades. However, because the degree of OA may affect the results, additional studies with a larger sample size are required to examine the effects of the OA severity on the results.

Conclusions

The present study demonstrated that a 100-unit injection of IA BoNT/A provided long-term pain relief and reduced physical disability in patients with knee OA. IA BoNT/A injections may provide an opportunity for improvement in refractory cases of knee OA. Future studies with double blinding and an injection placebo arm are required to distinguish the true effect from the placebo effect. Moreover, studies comparing the effect...
of IA BoNT/A injections with that of CS, HA, or PRP may be warranted, to provide clinical guidance in the management of patients with knee OA.

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References

38. Hawker GA. Who, when, and why total joint replacement is aapmr.org. This activity is FREE to AAPM&R members and available to nonmembers for a nominal fee. For assistance with claiming CME for this activity, please contact (847) 737-6000.
Disclosure

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CME Question

Intra-articular injection of botulinum toxin has demonstrated effectiveness in reducing pain associated with knee osteoarthritis. The proposed mechanism of action of pain relief is:

a. Quadriceps muscle relaxation via cholinergic inhibition at the neuromuscular junction.
b. Systemic toxin absorption and direct effect on central sensitization.
c. Decrease in peripheral nociceptive neurotransmitters.
d. Activation of chondrification, resulting increased mature cartilage.

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