Therapeutic Effects of Intra-articular Botulinum Neurotoxin in Advanced Knee Osteoarthritis

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Background: Osteoarthritis (OA) is a major cause of musculoskeletal pain that causes morbidity, physical limitation, and poor quality of life. The purpose of this study was to evaluate the therapeutic effects of intra-articular (IA) injection of botulinum neurotoxin A (BoNT/A) for advanced knee OA.

Methods: Twenty-four patients (38 knees) were enrolled, and the subjects were radiographically verified as having stage III or IV OA according to the Kellgren–Lawrence classification. We used the Western Ontario and McMaster Universities Osteoarthritis Index to evaluate the therapeutic effects monthly for 6 months. BoNT/A (100 U) was reconstituted with 4.0 mL saline and was injected into the symptomatic knee joints after baseline evaluation and 3 months later.

Results: The therapeutic effects of BoNT/A were clinically significant at 1 month after the first injection, but statistical significance was not noted until 3 months after the first IA injection. Pain and stiffness improved clinically; however, the effect of BoNT/A achieved statistical significance only for the pain subscale in stage III OA. There was no significant difference between the stage III and IV groups. There was no significant muscle atrophy or serious adverse effect in any group after treatment.

Conclusion: IA BoNT/A provides a new therapeutic option for refractory pain in patients with advanced knee OA. Although IA BoNT/A appears to be effective and safe for the management of advanced knee OA, these results cannot be generalized to patients with mild knee joint pain or nonspecific soft tissue pain in the knee joint region. [*J Chin Med Assoc* 2010;73(11):573–580]

Key Words: botulinum toxin type A, intra-articular injection, knee osteoarthritis

Introduction

Osteoarthritis (OA) is a major cause of musculoskeletal pain that causes morbidity, physical and functional limitation, and poor quality of life. OA of the knee is the most common form of arthritis in older adults and is an important community health care burden.[1–3] OA of the knee is characterized by pain, stiffness, decreased joint range of motion, and increasing disability. It can have an impact on several aspects of normal life, such as function and social activity, relationships, socioeconomic status, body image, and emotional well-being. Due to the aging of the population, the prevalence and impact of the disease is projected to greatly increase.[4,5]

The goals of symptomatic conservative therapies are to reduce pain and maintain or improve function.[6] Management options such as medication, local intra-articular (IA) injection, physical modalities, exercise, self-management programs, and surgery focus on providing symptom relief and maintaining function. Although oral analgesics can achieve moderate reduction of pain and slight functional improvement, they have substantial limitations because they might not provide sufficient joint pain relief, often produce intolerable side effects, and can adversely interact with other drugs.[7] Several clinical trials have demonstrated the effects of symptom-modifying drugs (such as glucosamine sulfate, chondroitin sulfate, doxycycline and diacerein) in OA patients, but further experimentation is

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required to confirm the effect of these dietary supplements.[8–10] There is also interest in the use of pulsed electrical stimulation and electromagnetic fields as potential OA disease-modifying treatments, but there have been a limited number of studies on their effects in humans.[11–13] IA injection of hyaluronic acid for OA knee pain is widely accepted, but the duration of its effect is variable and sometimes results in inadequate or unsatisfactory benefits.[7,14,15] There are surgical interventions with arthroscopic lavage and debridement for refractory joint pain when medical therapies fail, but the benefits of these procedures are still being debated.[16] Total joint arthroplasty for end-stage OA is the only treatment option, and is effective in improving physical function and reducing pain in >90% of patients.[17,18] However, surgery might be inappropriate when the individual is too young or when the patients experience too many comorbid conditions.[7] It is necessary to give these patients other treatments that relieve chronic joint pain, improve joint function, and avoid toxic effects caused by symptomatic therapy and surgical complications, and surgical mortality. Such treatment is especially beneficial for elderly patients. One of the options for these patients is to receive IA injections of botulinum neurotoxin type A (BoNT/A).

BoNT/A is effective for treatment of painful movement disorders, spasticity, myofascial pain and conditions with increased muscle tone, abnormal posture, and pain.[7,19–21] BoNT/A was initially used to decrease muscle tone and improve abnormal posturing of the head or limbs. The above effects can also decrease pain. Later studies have demonstrated that the analgesic effect of BoNT/A occurs earlier and to a greater degree than decreased muscle tone. These findings have led to speculation that the neurotoxin might have effects on other systems beyond the neuromuscular junction.[19,22,23]

There have been only a few studies about the therapeutic effects of IA BoNT/A in patients with knee OA. In 1 preliminary joint pain study, patients with general OA were selected.[7] The purpose of our study was to evaluate the therapeutic effect and safety of BoNT/A in patients with advanced OA of the knees.

Methods

Patients

Only patients with advanced OA of the knee, radiographically verified as stage III or IV according to the Kellgren–Lawrence classification,[24] were selected for this study. The inclusion criteria were age >60 years with significant OA signs and symptoms in the knees, and contraindications for surgical treatment because of age or comorbidity, or both. Exclusion criteria were: (1) significant inflammation of the OA joint; (2) previous IA injection of a steroid or any other invasive procedure in the knee within the previous 6 months; (3) history of IA knee fracture; (4) any other condition that might have interfered with the efficiency assessment or trial completion (such as oral analgesic drug use or opioid injection, physical therapy for knee OA); (5) any medical condition that might have increased the risk to the subject of exposure to BoNT/A (such as disorders that might have interfered with neuromuscular function); and (6) known allergy or sensitivity to any component of the medication. All patients were notified regarding IA injection of BoNT/A because this is an off-label use that is not approved by the US Food and Drug Administration, and BoNT/A injection has known side effects.

Study design

One hundred units of BoNT/A (Allergen Inc., Irvine, CA, USA) were injected into the symptomatic OA knee joint. One vial of BoNT/A (100 U) was reconstituted with 4.0 mL normal saline to a concentration of 25 U/mL. All patients received 2 injections into the joint, with a 3-month interval between injections. The patients were evaluated before the first injection and were monitored monthly thereafter for a total of 6 months.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate the therapeutic effects at baseline (pre-injection) and each month thereafter.[25,26] The index included 3 dimensions, pain (5 questions), stiffness (2 questions), and physical function (17 questions), which were rated on an ordinal scale of 0 to 4. Lower scores indicated lower levels of symptoms or physical disability. The validation study reported internal consistency for the pain, stiffness and physical function subscales of 0.86, 0.86 and 0.95, respectively.[25] Reliability for the pain, stiffness and physical function subscales was 0.68, 0.48 and 0.68, respectively.[26] Thigh circumference at 5 cm above the midline of the patella, with the knee at 90° flexion, was measured to evaluate potential muscle atrophy after IA injection of BoNT/A.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used to evaluate the data. One-way analysis of variance was used to calculate the differences between baseline and the 6-month evaluations for pain, stiffness, physical function, and WOMAC scores. When significant differences were found, the Bonferroni *post hoc* test was

applied. To compare the differences between stages III and IV at baseline, 3 months, and 6 months, the Mann–Whitney *U* test was used to evaluate pain, stiffness, physical function, and WOMAC scores. The Wilcoxon signed rank test was used to evaluate the differences between the WOMAC scores at 3 and 4 months. To compare thigh circumferences at baseline, 3 months, and 6 months, analysis of covariance was used to evaluate the differences. Results were considered statistically significant when the p values were < 0.05.

The study protocol was approved by the institutional review board of the hospital, and all participants provided signed, written informed consent before participation. All patients were notified that IA injection of BoNT/A was an off-label use of the drug and not approved by the US Food and Drug Administration; patients were also informed of the known side effects of BoNT/A injection.

Table 1. Basic patient data

Male/female	13/11
Mean age	73.38 ± 11.13 yr
Bilateral knee osteoarthritis	
Stage III	9
Stage IV	3
Stage III/IV	2 (bilateral but different stages)
Unilateral knee osteoarthritis	
Stage III	3
Stage IV	7

Results

Among the 24 study participants (Table 1), 38 knees were studied. Two patients had bilateral OA, but the knees were at different stages of OA; for the WOMAC evaluation, these 2 patients were placed into the stage IV group. The therapeutic effects of IA injection of BoNT/A were clinically significant (Figures 1–4), but statistical significance was not noted until 3 months after the first BoNT/A injection. The effect lasted for the entire month. The pain and stiffness subscales differed significantly from baseline (Table 2). In the subgroup evaluation of IA BoNT/A, only the pain subscale among stage III patients was statistically significant at 3 months (Tables 3 and 4). There was gross exacerbation of the therapeutic effect between 3 and 4 months (Figures 1–4). Thus, we compared the therapeutic effect between the 3rd and 4th months for all patients and stage III and IV groups; the therapeutic effect did not differ significantly among the groups (Tables 5 and 6). There was no significant quadriceps muscle atrophy during the study (Table 7). There was no serious systemic or local adverse effect in any group during the 6-month follow-up period. Transient injection site pain, mild joint swelling, or tenderness was reported by 3 patients.

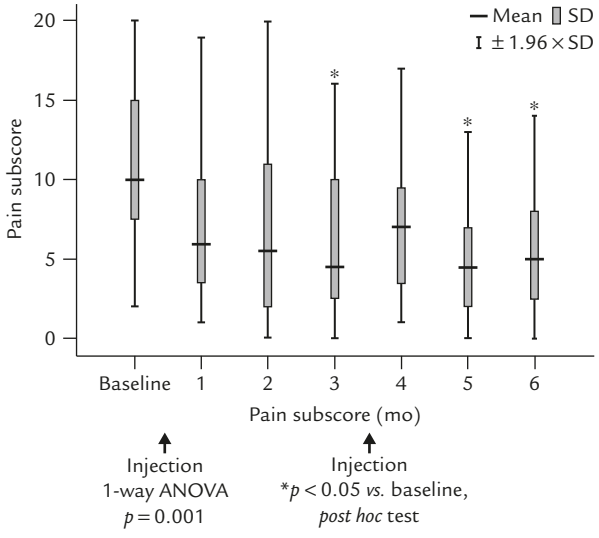

Figure 1. WOMAC pain subscore (total of 38 knees). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; ANOVA = analysis of variance.

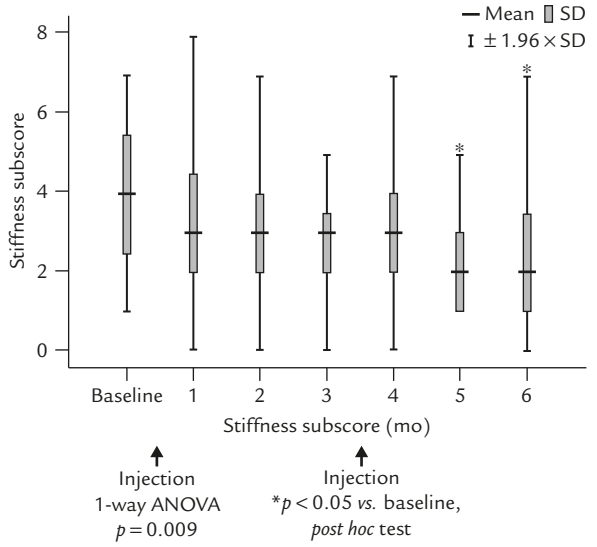

Figure 2. WOMAC stiffness subscore (total of 38 knees). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; ANOVA = analysis of variance.

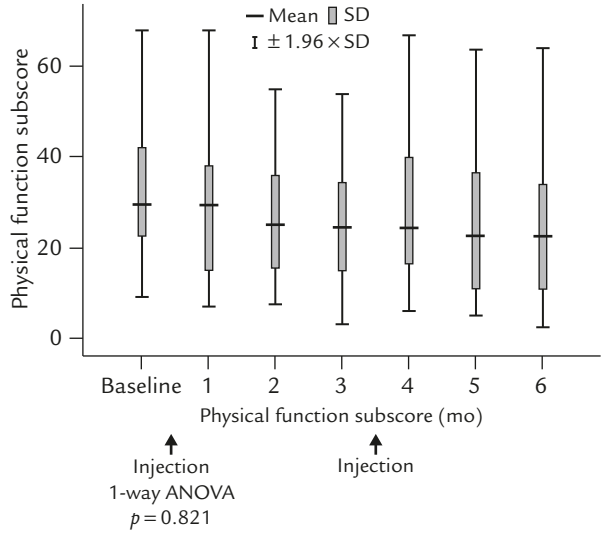

Figure 3. WOMAC physical function subscore (total of 38 knees). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; ANOVA = analysis of variance.

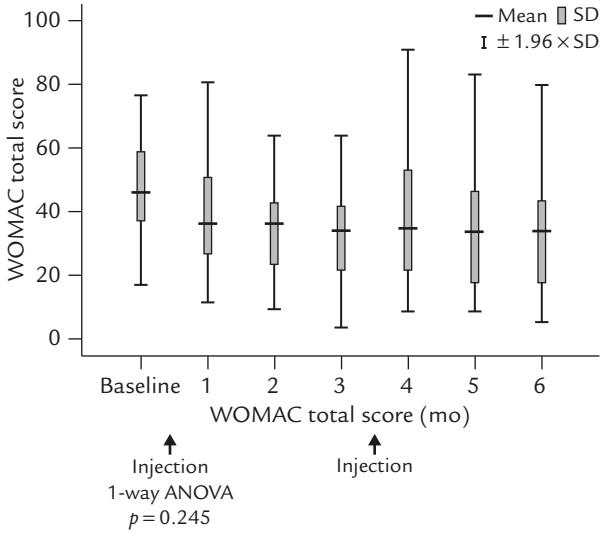

Figure 4. WOMAC total score (total of 38 knees). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; ANOVA = analysis of variance.

Table 2. Therapeutic effect after intra-articular injection of botulinum neurotoxin A in all patients*

	Baseline	1st mo	2nd mo	3rd mo	4th mo	5th mo	6th mo	p†
Pain	10.96 ± 5.21	7.38 ± 5.40	6.88 ± 5.68	6.29 ± 4.61‡	7.12 ± 4.43	5.17 ± 3.96‡	5.21 ± 3.71‡	0.000
Stiffness	4.17 ± 1.55	3.42 ± 1.89	2.88 ± 1.65	2.88 ± 1.68	2.88 ± 1.70	2.50 ± 1.50‡	2.46 ± 1.84‡	0.001
Physical function	32.25 ± 15.21	28.50 ± 15.74	27.08 ± 15.96	26.33 ± 16.48	28.21 ± 16.67	26.46 ± 16.37	25.25 ± 15.99	0.019
Total WOMAC score	47.38 ± 18.72	39.29 ± 21.00	36.83 ± 21.14	35.50 ± 20.27	38.21 ± 20.88	34.12 ± 20.06	32.92 ± 20.02	0.000

**Data are presented as mean ± standard deviation; †analysis of covariance; ‡significant difference compared with baseline ($p < 0.05$) by post hoc (Tukey's honestly significant difference) test. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.*

Table 3. Therapeutic effect after intra-articular injection of botulinum neurotoxin A in patients with stage III knee osteoarthritis*

	Baseline	1st mo	2nd mo	3rd mo	4th mo	5th mo	6th mo	p†
Pain	10.50 ± 4.01	7.67 ± 5.19	6.92 ± 5.53	6.08 ± 4.29	7.17 ± 4.45	4.67 ± 3.39‡	4.92 ± 2.64‡	0.045
Stiffness	4.17 ± 1.47	3.58 ± 1.78	3.08 ± 1.51	3.25 ± 1.76	2.92 ± 1.73	2.67 ± 1.67	2.50 ± 1.83	0.062
Physical function	33.25 ± 17.53	29.33 ± 16.77	27.33 ± 17.35	27.92 ± 17.62	28.58 ± 17.38	27.08 ± 18.61	26.25 ± 17.99	0.247
Total WOMAC score	47.92 ± 21.77	40.58 ± 22.42	37.33 ± 22.20	37.25 ± 21.30	38.67 ± 21.87	34.42 ± 22.28	33.67 ± 20.83	0.064

**Data are presented as mean ± standard deviation; †analysis of covariance; ‡significant difference compared with baseline ($p < 0.05$) by post hoc (Tukey's honestly significant difference) test. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.*

Discussion

BoNT/A has been widely used to treat neurological diseases of spasticity and other forms of muscle activity.[27–33] Recently, it has been used to treat the chronic pain of plantar fasciitis, myofascial pain syndrome, tennis elbow, various types of headaches, and neuropathic pain.[34–39] The mechanism of pain reduction by BoNT/A might include muscular relaxation (but dissociation between pain relief and muscle relaxation has been observed) and inhibition of neurotransmitter release by sensory neurons.[40–47]

Table 4. Therapeutic effect after intra-articular injection of botulinum neurotoxin A in patients with stage IV knee osteoarthritis*

	Baseline	1st mo	2nd mo	3rd mo	4th mo	5th mo	6th mo	p†
Pain	11.42±6.35	7.08±5.82	6.83±6.06	6.50±5.09	7.08±4.60	5.67±4.56	5.50±4.64	0.117
Stiffness	4.17±1.70	3.25±2.05	2.67±1.83	2.50±1.57	2.83±1.75	2.33±1.37	2.41±1.93	0.113
Physical function	31.25±13.20	27.67±15.34	26.83±15.22	24.75±15.86	27.83±16.68	25.83±14.61	24.25±15.60	0.105
Total WOMAC score	46.83±16.07	38.00±20.39	36.33±21.00	33.75±19.97	37.75±20.80	33.83±18.57	32.17±20.08	0.186

**Data are presented as mean±standard deviation; †analysis of covariance. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.*

Table 5. Comparison of WOMAC score at 3 and 4 months after botulinum neurotoxin A therapy

	p*			
	Pain	Stiffness	Physical function	Total score
Total	0.144	1.000	0.418	0.210
Stage III	0.077	0.157	0.437	0.128
Stage IV	0.681	0.206	0.645	0.655

**Wilcoxon signed rank test. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.*

Table 6. Comparison of WOMAC score at baseline, and at 3 and 6 months after botulinum neurotoxin A therapy in patients with stages III and IV knee osteoarthritis*

	Stage III	Stage IV	p†
Pain subscore			
Baseline	10.0 (7.3–13.0)	12.5 (4.3–17.0)	0.443
3rd mo	5.0 (2.3–10.0)	4.5 (2.3–10.8)	0.932
6th mo	4.5 (3.25–6.5)	5.0 (1.0–9.0)	0.977
Stiffness subscore			
Baseline	4.0 (3.0–5.5)	4.0 (3.0–5.8)	0.977
3rd mo	3.0 (3.0–3.8)	2.0 (1.3–3.8)	0.291
6th mo	2.0 (1.0–3.0)	2.0 (1.0–4.8)	0.843
Physical function subscore			
Baseline	33.5 (19.3–45.5)	29.5 (20.8–41.0)	0.887
3rd mo	25.0 (15.5–35.30	21.0 (13.5–39.5)	0.630
6th mo	23.0 (10.0–35.3)	22.0 (8.5–34.3)	0.713
Total WOMAC score			
Baseline	49.0 (30.0–58.8)	44.0 (37.0–59.3)	0.932
3rd mo	34.0 (22.8–41.8)	33.0 (19.8–46.5)	0.755
6th mo	28.5 (16.8–44.0)	31.5 (14.0–47.3)	0.977

**Data are presented as median (25th–75th percentiles); †Mann–Whitney U test. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.*

Table 7. Comparison of thigh circumference in all patients ($n=38$ knees)*

	Baseline	3rd mo	6th mo	p†
Thigh circumference	42.06±6.53	42.31±6.21	42.13±6.76	0.984

**Data are presented as mean±standard deviation; †1-way analysis of variance.*

OA pain can come from many sites. The C-fiber nociceptors form a diffuse lattice throughout the articular capsule, and A-δ fiber-free nerve endings are found in IA and peri-articular ligaments.[48,49] Substance P and calcitonin gene-related peptide are found in nerve fibers of the synovium.[50] Increased neuropeptide synthesis (substance P, calcitonin gene-related peptide, dynorphin and enkephalin) is found in the dorsal ganglia and the spinal cord when joints are inflamed, which causes joint pain.[49,50] Peripheral sensitization such as mechanical, thermal and chemical stimuli can cause articular allodynia and hyperalgesia of sensitized articular primary afferent neurons. The spinal cord neurons can be sensitized by sustained nociceptive afferent input from a painful joint (central sensitization). The peripheral and central sensitization amplifies nociceptive processing.[51–53] The direct analgesic effect of BoNT/A on formalin-induced pain in mice was based on the action of neurotransmitters other than acetylcholine; thus, it was independent of neuromuscular junction blocking in cholinergic α motor neurons.[54] BoNT/A suppresses OA pain.[54–56] Nonetheless, in a study of local inflammatory leg pain (not OA pain), no anti-inflammatory or antinociceptive effect of BoNT/A in human inflammatory pain was found, despite highly promising data from animal research.[40] In our study, IA BoNT/A treatment for advanced OA knee pain significantly improved clinical pain and stiffness, although the WOMAC scores for physical function and total score were not significantly different from baseline.

Several studies of the WOMAC have shown that it is difficult for some patients to make distinctions between questions about pain (5 questions) and physical function for activities of daily living (17 question).[57,58] Additionally, the term "difficult", as it is translated from English to Chinese, might not have been clear to some of our participants. For the subgroup evaluation, only stage III OA knees had statistically significant improvement in the pain subscale. This could have been due to the small sample size in each group. In future studies, sample size should be increased. The therapeutic effect of BoNT/A did not differ between the stage IV and/or III OA groups. Although total knee arthroplasty has been suggested traditionally for stage III and IV OA patients, IA BoNT/A could provide a new therapeutic option for patients in whom such surgery is contraindicated.

Among our patients, therapeutic effect persisted after a booster injection 3 months after the initial injection. BoNT/A was injected intra-articularly for advanced knee OA every 3 months to maintain the therapeutic effect from month 3 till the end of the study. Hence, it is implied that the therapeutic effect of BoNT/A is transient rather than long-term.

There was a wide variation in the degree to which knee pain was related to radiographic knee OA and vice versa. OA severity (Kellgren–Lawrence classification, stages III and IV) is a strong predictor of pain; the greater the OA severity, the greater the knee pain.[59] For evaluation of the therapeutic effect of IA BoNT/A injection on knee OA pain, we selected only patients with high-grade OA of the knee, and the therapeutic effects of BoNT/A treatment did not differ between stages III and IV OA. As mentioned before, there was no significant change in the X-ray appearance of the knee after BoNT/A injection. Additionally, thigh circumference did not significantly change during the study. No significant muscle atrophy occurred with the use of IA BoNT/A. Finally, because our patients were all Taiwanese, we avoided potential racial and/or ethnic bias in self-reporting disability data for OA of the knee.[2]

There were some limitations in our study. This was an open-label clinical trial with non-randomized treatment allocation, which favors patient and observer bias. Our subgroup sample size (stages III and IV) was small, so the therapeutic effect was statistically significant only for the WOMAC pain subscale in the stage III OA group. We did not resolve the dose, dose-duration and dilution effects for BoNT/A IA use. Most OA patients describe experiencing notable fatigue and indicate that this side effect has a substantial impact on their lives.[3] We did not evaluate the relationship between pain, fatigue and quality of life. We did not determine the baseline level of cartilage oligomeric matrix protein, which is predictive of subsequent magnetic resonance imaging-determined cartilage loss in knee OA.[60] Future studies should include the measurement of this biomarker. IA injection of BoNT/A provides a new therapeutic option for refractory pain among patients with advanced knee OA. Although IA BoNT/A is effective and safe for the management of chronic advanced knee OA, our results cannot be generalized to patients with mild knee joint pain or nonspecific soft tissue pain in the knee joint region.

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