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

Chen-Liang Chou[1,2]*, Si-Huei Lee[1,2], Shin-Yo Lu[1], Ko-Lun Tsai[1], Chung-Yu Ho[1], Hsuan-Chu Lai[1]

[1]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, and [2]Department of Physical Medicine and Rehabilitation, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

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

*Correspondence to: Dr Chen-Liang Chou, Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: cl_chou@vghtpe.gov.tw • Received: June 4, 2010 • Accepted: July 30, 2010

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