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Effects of Intraarticular Botulinum Toxin A in the Treatment of Ankle Osteoarthritis

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Background: Preliminary evidence suggests that Botulinum toxin type A (BoNT-A) injected intraarticularly into painful joints has a significant nociceptive effect. The purpose of this study is to investigate the effects of intraarticular BoNT-A on the pain and physical function for patients with ankle osteoarthritis (OA).

Method: A prospective study with 6 months follow-up done in a university-affiliated tertiary care medical center, patients with symptoms and radiographic evidence of ankle OA for at least 6 months were recruited. Patients received intraarticular injections of 100 units of BoNT-A in 2 cc of normal saline. The injections were performed by the same experienced doctor. The primary outcome were assessed with the Ankle Osteoarthritis Scale (AOS) score. Secondary outcomes were assessed with American Orthopaedic Foot and Ankle Society (AOFAS) ankle/hindfoot score, VAS, ankle sagittal range of motion (ROM), single leg stance test (SLS), Timed “Up-and-Go” test (TUG) and consumption of rescue analgesics. These tests were conducted pre-injection and at 2 weeks, 1 month, 3 months, and 6 months post injection. Patients’ global satisfaction was assessed at 2 weeks, 1 month, 3 months, and 6 months post injection. Adverse events during the study period were recorded also.

Results: Fifteen patients were recruited and 13 patients completed the study. All patients showed significant improvements in their AOS, AOFAS, VAS, SLS and TUG scores. These improvement persisted for at least 6 months. Acetaminophen consumption dropped significantly following treatment (p<0.001). Ankle sagittal ROM did not change significantly throughout the study period. Patients’ global satisfaction rate was high and no serious adverse events were reported.

Conclusions: Intraarticular BoNT-A injection to the ankle joint is well tolerated. It effectively reduces pain, disability as well as improves balance function in patients with ankle OA. These effects can last for 6 months. Future studies that include rigorously controlled designs and larger number of patients would be necessary to determine the efficacy for the treatment of ankle OA. (Tw J Phys Med Rehabil 2012; 40(3): 127 - 134)

Key Words: ankle osteoarthritis, botulinum toxin, intraarticular injection

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INTRODUCTION

Symptomatic osteoarthritis (OA) is a leading cause of pain and disability, with significant indirect costs to society. \[1,2\] Current treatment options for OA include simple analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), intraarticular corticosteroid injections, physiotherapy (including physical modalities, various stretching or strengthening exercises, shoe modifications or assistive devices such as canes or crutches, etc.), weight reduction, orthotics and surgical treatment. The goals of local and systemic therapy for OA are to reduce pain and maintain or improve function. Oral analgesics have substantial limitations because they may not provide sufficient joint pain relief and often produce intolerable drug side effects and adverse drug interactions. These limitations have prompted the use of localized intraarticular treatments with corticosteroids or viscosupplements. Intraarticular therapies may reduce pain, but the duration of effect is variable. All treatment options should be fully exploited before managing OA with surgery, which is expensive and risky. An option for patients may be the intraarticular application of Botulinum toxin type A (BoNT-A).

Recent pilot studies report that intraarticular injection of Botulinum toxin type A (BoNT-A) into painful joints of patients with various types of arthritis leads to significant and durable improvement in pain and function and is safe to use. \[3-6\] To date, there is rare published literature that evaluate the effects of intraarticular BoNT-A in the treatment of ankle OA. The purpose of this study is to investigate the effects of intraarticular BoNT-A on the pain and physical function of patients with ankle OA.

Participants:

Patients in this study were referred from our outpatient orthopedic department with a diagnosis of ankle OA. All patients met the following inclusion criteria: (1) an age of at least 20 years, ankle pain that had lasted for at least 6 months, with no significant benefit from conservative treatments (rest, physical therapy, orthoses or pain medications etc.) or with an inability to tolerate the side effects of medications; (2) ankle radiographs taken within 6 months equivalent to grade 2 or 3 on the Kellgren-Lawrence grading system (grade 2, definite osteophytes and possible narrowing of joint space; grade 3, moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour); \[7\] (3) a current total Ankle Osteoarthritis Scale (AOS) score of (described below) of \(>3\) and \(<9\) (possible range, 0-10); (4) a normal activity level—i.e., not bedridden or confined to a wheelchair, and are able to walk 30 meters without the aid of a walker, crutches or cane; and (5) no physical therapy, shoe changes or orthotic devices used during the study period.

Exclusion criteria included pregnancy or lactation in women, lower leg trauma other than ankle trauma, previous surgery involving the spine, hip or knee, the presence of an active joint infections of foot or ankle, previous surgery or arthroscopy on the ankle within 12 months, intraarticular steroid or hyaluronate injection in the treated ankle within the previous 6 months, treatment with anticoagulants or immunosuppressives, a history of rheumatoid arthritis, gout, or any other inflammatory arthropathy, the presence of other comorbidity (such as neoplasms, diabetes mellitus, paresis or recent trauma) or poor health status that would interfere with the clinical assessments during the study.

Intake of analgesics or NSAIDs was not permitted during the study period. Acetaminophen (500mg), limited to 4 g/day was allowed as rescue medication. If the treatment dose was above the stipulated limit (acetaminophen 4 g /day), the patient was regarded as a clinical failure. Patients taking analgesics or NSAIDs stopped them at least 7 days before the preinjection assessment. Administration of acetaminophen was stopped at least 8 hours before the follow-up assessments. The administration of all analgesic medication during the study period was recorded on a diary card by the patient.

The study was approved by the institutional review board for human investigation and all subjects provided signed informed consent before being enrolled in the study.

Botulinum Toxin and Injection Technique

One hundred units of BoNT-A (Allergan, Inc, Irvine CA) were reconstituted in 2 cc of normal saline. All patients received intraarticular BoNT-A injections by the
same experienced physician using aseptic procedures. The ankle joint (tibiotalar) was injected by inserting the needle 1 cm anterior to the distal medial malleolus and advancing the needle posteriorly and slightly superiorly toward the middle of the ankle joint above the talus. If an effusion was present, it was aspirated before injecting.

Outcome Assessments

The clinical assessment included the following items:

1. The AOS is a patient-rated, validated outcome measure that includes nine items on a pain subscale and nine items on a disability subscale. Using the AOS, a score of 0 represents no pain or disability and 10 represents the worst pain or disability imaginable.

2. AOFAS ankle/hindfoot score is a 100-point scale that devotes 40 points to pain, 50 points to function and 10 points to alignment. The maximum score of 100 points denotes no pain and normal function and alignment.

3. The patient rate the intensity of average ankle movement pain in the previous week using a 10-cm horizontal visual analog scale (VAS). The VAS is marked in 1-cm increments from ‘no pain’ to ‘worst pain’. Subsequent VAS recordings were completed on separate sheets of paper. This prevents participants from comparing the present VAS with the previous one.

4. Ankle sagittal ROM is measured with a hand-held goniometer. The axis of the goniometer is located at the intersection of the foot and the shank. It measures ankle dorsiflexion and plantar flexion range while the patient is supine with their knee flexed at 90 degrees.

5. Single-leg stance test (SLS) is done by raising one foot up without touching it to the supported lower extremity with ankle OA and maintain balance for as long as possible. Failure occurs if the stance foot shifts in any way or the nonstance foot touches the ground. In this study, each participant performed 3 trials, and the best result was recorded.

6. A Timed “Up-and-Go” test (TUG) measures functional mobility and the dynamic balance of an individual. A patient is asked to rise from an armchair, walk 3 meters at a safe and comfortable pace, turn around, walk back to the chair, and sit down again. The whole procedure is demonstrated first before the actual test. The score is the time in seconds it takes to complete these tasks.

7. Patients rated their global satisfaction level for ankle pain relief on weight bearing compared to their pre-injection condition at each follow-up visit. This rating is based on a 7-point categorical scale ranging from completely satisfied, satisfied, somewhat satisfied, no change, somewhat unsatisfied, unsatisfied to completely unsatisfied.

8. To monitor the safety of each injection, patients recorded any systemic and local adverse effects (defined as any unwanted effect whether it was thought to be related to the study or not) on a diary card.

STATISTICAL ANALYSIS

All statistical procedures were conducted with the Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, Illinois). The data were presented as the mean ± standard deviation or percentage as appropriate. Change of outcome measures in AOS, AOFAS, VAS, ankle sagittal ROM, TUG, and rescue analgesics consumption were assessed using paired t-test comparing baseline value with each follow-up score. Changes in SLS were analyzed using Wilcoxon signed rank test. P values of less than 0.05 were regarded as significant.

RESULTS

Fifteen patients were recruited for the study. Two patients withdrew from the study, one moving to another city and the other because of unrelated intercurrent illness. Thirteen patients with ankle OA, 10 men and 3 women, completed the study. Ankle OA was attributed to primary OA without history of trauma or purulent arthritis in 4 patients. Secondary OA because of ligamentous injury, malleolar fracture, plafond fracture, talar fracture, previous purulent arthritis or other causes was noted in 9 patients. Table 1 shows a summary of patient characteristics and Table 2 shows a summary of test outcomes before and after treatment.

Compared with baseline findings, results of AOS, AOFAS, VAS, SLS and TUG tests improved significantly in all patients (p<0.001) after completion of BoNT-A injections at each follow-up visit. The treatment effects lasted for at least 6 months. Ankle sagittal ROM
did not improve significantly (p>0.05). Acetaminophen consumption decreased from an average of 14 tablets per week at baseline to 5, 3, 3 and 4 tablets per week at 2 weeks, 1 month, 3 months and 6 months post injection (p<0.001 at each time point compared with baseline) (Table 2).

All patients tolerated the treatment well. Two patients reported local adverse effects with transient pain at the injection site that cleared in 2 days. No life-threatening or incapacitating adverse events were reported.

Most patients reported satisfaction at 2 weeks (92.3%), 1 month (92.3%), 3 months (84.6%) and 6 months (84.6%) follow-ups.

Table 1. Demographic data and disease characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=13)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.2±14.5</td>
<td>38-70</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/3</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.5±15.9</td>
<td>40-73</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.4±8.3</td>
<td>150-171</td>
</tr>
<tr>
<td>Etiology of osteoarthritis (primary/secondary)</td>
<td>4/9</td>
<td></td>
</tr>
<tr>
<td>Heavy worker/light worker</td>
<td>8/5</td>
<td></td>
</tr>
<tr>
<td>Side of ankle injected (Lt/Rt)</td>
<td>7/6</td>
<td></td>
</tr>
<tr>
<td>Radiographic stage (Kellgren-Lawrence stage)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.3±4.7</td>
<td>1-9</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation.

Table 2. Summary of outcomes before and after treatment (n=13)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>2 Weeks</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.1±1.9</td>
<td>3.2±2.1</td>
<td>2.5±2.0</td>
<td>2.6±1.7</td>
<td>2.4±1.9</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>Pain subscale&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.8±1.7</td>
<td>2.8±2.0</td>
<td>2.4±1.7</td>
<td>2.1±1.6</td>
<td>2.1±1.8</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>Disability subscale&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.5±2.4</td>
<td>3.7±2.3</td>
<td>2.9±2.3</td>
<td>3.3±2.1</td>
<td>2.8±2.1</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>AOFAS ankle/hindfoot score</td>
<td>64±17</td>
<td>75±15</td>
<td>78±16</td>
<td>79±15</td>
<td>78±14</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>VAS pain scale&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.8±1.7</td>
<td>2.1±1.7</td>
<td>2.1±1.6</td>
<td>2.1±1.8</td>
<td>2.1±1.5</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>SLS</td>
<td>6.27±21.47</td>
<td>13.4±23.9</td>
<td>12.4±23.9</td>
<td>15.5±24.9</td>
<td>14.5±26.1</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>TUG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.6±3.28</td>
<td>15.2±2.7</td>
<td>17.2±2.7</td>
<td>16.04±2.8</td>
<td>17.8±2.63</td>
<td>AB* AC* AD* AE*</td>
</tr>
<tr>
<td>Ankle sagittal ROM</td>
<td>36.9±14.6</td>
<td>37.7±15.0</td>
<td>37.8±14.4</td>
<td>36.1±14.3</td>
<td>37.7±13.6</td>
<td>AB=0.086, AC=0.255, AD=0.514, AE=0.158</td>
</tr>
</tbody>
</table>

Acetaminophen (tablets/week) 14.3±2.4 5.1±2.4 3.4±2.2 3.1±2.5 4.3±2.2 AB* AC* AD* AE*

NOTE: Values are the mean ±standard deviation; AOS =Ankle Osteoarthritis Scale; AOFAS=the American Orthopaedic Foot and Ankle Society; ROM= range of motion; SLS=single leg stance test; TUG=timed “Up-and-Go” test.
The possible range for the AOS score was 0-10; the possible range for the AOFAS score was 0-100.

<sup>a</sup>Higher scores represent worse pain or function.

*P<0.001 versus baseline.

AB is the comparison before and 2 weeks after the injections; AC is the comparison before and 1 month after the injections; and AD is the comparison before and 3 months after the injections; AE is the comparison before and 6 months after the injections.
### DISCUSSION

This study is the first clinical trial that examines the effects of intraarticular injection of BoNT-A in patients with ankle OA. The results show that injecting BoNT-A into the ankle joints can effectively reduce pain and disability and improves balance function in patients with ankle OA. These effects last for at least 6 months.

BoNT-A has been extensively studied and used clinically for its muscle paralyzing effects, but there is increasing evidence to support using it in pain modulation. Preliminary evidence suggests that BoNT-A has a significant anti-nociceptive effect, when injected intraarticularly, into painful joints. In several small open label studies, initial effects for BoNT-A were encouraging because two thirds of the patients had more than 50% reduction in joint pain severity that was associated with a significant improvement in function. Joint pain decreased within 2-14 days. Time to maximal pain relief varied from 4 to 12 weeks, and the effects lasted between 3 to 13 months.

Clinical presentation of OA is dominated by pain and disability during activity and often at rest. There is an increasing requirement for novel treatments of osteoarthritic joint pain as the aging population is expanding with many patients who are unable to undergo joint surgery. Effective therapy has been a key therapeutic challenge. The results of this study using BoNT-A for pain relief in the ankle are consistent with those of previously studies using BoNT-A in the joints. We demonstrated that BoNT-A may be an excellent treatment option for ankle OA, especially when surgery is contraindicated or deferred due to age, comorbidities, or patient preference. The clinical success of intraarticular BoNT-A in patients with ankle OA suggests that it is a promising and useful approach worthy of serious clinical investigation.

OA represents a complexity of pain conditions, including manifestations of both nociceptive and neuropathic mechanisms driven by joint pathophysiology and abnormal excitability in peripheral and central pain pathways. In cases of joint inflammation, articular primary afferent neurons become more reactive to mechanical, thermal, and chemical stimuli (peripheral sensitization) producing articular allodynia (joint pain with normal movement) and hyperalgesia (exaggerated pain and tenderness with joint palpation). Spinal cord neurons become increasingly sensitized to afferent input with sustained nociceptive afferent input from the painful joint (i.e., central sensitization). The peripheral and central sensitization thereby amplify the joint pain. Persistent afferent nociceptive input from a painful arthritic joint may actually produce neurogenic inflammation and amplify the joint pain. The mechanism of BoNT-A action is related to inhibiting transmitter release from nerve fibers. BoNT-A binds to nociceptor C-fibers, undergoes endocytosis and blocks the vesicle release of agents involved in joint pain generation and transmission to the spinal cord. These agents also sensitize the nociceptor by neurogenic inflammation. More recent studies have also indicated a potential for inhibiting the release of other mediators involved in nociception such as substance P, calcitonin gene related peptide and glutamate.

To our knowledge, this is the first study to examine the effect of intraarticular BoNT-A injections for ankle OA on balance. Sun et al previously reported significant improvements in pain, physical function, and balance after hyaluront injections in patients with knee or ankle OA, which provides additional support for the use of BoNT-A in ankle OA.
OA. Balance is an important component of performance for transfer, ambulatory tasks and many daily activities. The presence of OA may accelerate the deterioration of balance control systems. Reduced muscle strength and deficits in lower limb proprioception associated with OA could compromise effective and timely motor responses for maintaining balance. Pain in OA may result in reduced loading of the affected joint, potentially jeopardizing an individual’s ability to maintain balance. Several potential mechanisms may be responsible for the balance deficits observed in patients with OA. However, no study to date has assessed whether balance function would change after BoNT-A injections. Besides, previous studies utilized force platforms to evaluate balance and these expensive apparatus are not readily available to the majority of clinicians in the clinical settings. This study uses simple, economical, easy to administer clinical tests to assess both static and dynamic balance. We demonstrated that injecting BoNT-A into the ankle joints can not only reduce pain and disability, but also can improves balance function. Although the mechanism by which BoNT-A results in a clinical improvement in balance remains unknown, pain reduction might be a major contributing factors.

Patient satisfaction is a fundamental goal in the treatment of OA. Satisfaction reflects the summation of all factors relating to successful clinical treatment. Results of patients’ global satisfaction were shown in Table 3. Treatment of the ankles in this series resulted in high patients’ satisfaction. At the 2-week follow-up, 3 patients reported completely satisfied, 5 reported satisfied and 4 reported somewhat satisfied. The overall satisfaction rate was 92.3%. At 6 months post the injection. The reported satisfaction diminished as 2 patients reported completely satisfied, 6 satisfied and 3 somewhat satisfied. Two patients reported no change compared to their preinjection condition. The overall satisfaction rate was 84.6%. No patients reported dissatisfaction or aggravated ankle symptoms compared to their preinjection condition.

The study was limited by the relatively small number of patients, which might possibly decrease the statistical power. The study did not include a control group, thus the results should be interpreted with caution, because some improvements might be the result of the placebo effect. Future studies, which include larger number of patients with more rigorous study controls are necessary to determine the efficacy of BoNT-A injections for ankle OA and to predict good response factors. Further studies should also focus on determining the optimal injection doses and intervals. The efficacy of BoNT-A compared to hyaluronic acid (the only currently available injectable alternative to cortisone) should be studied also.

**CONCLUSION**

This study concludes that patients tolerate intraarticular BoNT-A ankle joint injections well. The injections effectively reduce pain and disability and improve balance function in patients with ankle OA. These effects lasted for at least 6 months. Future studies that include randomized controlled design and more patients are necessary to determine the efficacy of BoNT-A injections for the treatment of ankle OA.

**ACKNOWLEDGMENT**

We wish to express our sincere gratitude to all the investigators who participated in the trial. The study was supported by a grant of VGHKS100-061 (an academic research fund from the hospital’s medical research council).

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肉毒桿菌毒素用在踝退化性關節炎之療效研究

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背景：目前已有初步的證據顯示關節內注射肉毒桿菌毒素能有效改善疼痛。本研究目的將探討關節內注射肉毒桿菌毒素用在踝關節退化性關節炎，在疼痛及功能改善方面的療效。

方法：本研究採前瞻性方法，在醫學中心進行，收錄臨床症狀及X光顯示為踝退化性關節炎且至少六個月之病人，進入研究後所有病人接受踝關節內注射肉毒桿菌毒素(100單位於2cc生理食鹽水)。所有注射由同一經驗豐富的醫師施行。主要評估項目為踝退化性關節炎指數(AOS)，次要評估項目包括美國足踝醫學會踝-後腳分數(AOFAS)、疼痛度(VAS)、踝關節活動角度(ROM)、單腳站立測試(SLS)、計時的“起立向前走”測試(TUG)及止痛藥使用量，以上測量將在注射前、注射後二星期、第一、三及六個月時做各項評估。病患滿意度則在注射後二星期、第一、三及六個月時做評估；局部或全身性不良反應，也將予以記錄。

結果：15位病患加入此研究，有13位病患完成研究。所有病患在評估項目AOS、AOFAS、VAS、SLS、TUG皆有明顯的改善，且效果持續至少六個月。止痛藥使用量在研究期間也有明顯的下降。踝關節活動角度則無明顯的改變。病患的整體滿意度高，而且沒有任何嚴重的不良反應。

結論：關節注射肉毒桿菌毒素用在踝退化性關節炎耐受性佳，且能有效減輕疼痛、失能及改善平衡功能。療效至少持續六個月。未來的研究需要更嚴謹控制及更多的參與者加入來證實療效。（台灣復健醫誌 2012；40(3): 127 - 134）

關鍵詞：踝退化性關節炎(ankle osteoarthritis)，肉毒桿菌毒素(botulinum toxin)，關節內注射(intraarticular injection)