Efficacy of Intra-Articular Injection of Botulinum Toxin Type A in Refractory Hemiplegic Shoulder Pain

Alberto Castiglione, MD, Sergio Bagnato, MD, PhD, Cristina Boccagni, MD, Marcello C. Romano, MD, Giuseppe Galardi, MD


Objective: To evaluate the efficacy of intra-articular injection of botulinum toxin type A (BTX-A) in relieving hemiplegic shoulder pain (HSP).

Design: Pilot study with assessments before and after BTX-A intra-articular injection.

Setting: Hospital rehabilitation department.

Participants: Patients (N=5) with HSP refractory to standard treatments and pain score at rest greater than 7 on a pain visual analog scale (VAS) of 0 to 10cm.

Intervention: Intra-articular BTX-A injection.

Main Outcome Measure: Variation in VAS score at rest and during 90° passive arm abduction 2 and 8 weeks after BTX-A intra-articular injection.

Results: Baseline VAS score was 8.7±1 at rest and 9.8±0.4 during passive arm abduction. It clearly decreased at 2 (1.5±1.1 at rest, P=.001; 3±1.2 during arm abduction, P<.001) and 8 weeks (1.5±1.2 at rest, P=.001; 2.3±1.1 during arm abduction, P<.001) after BTX-A intra-articular injection.

Conclusions: We found a strong correlation between intra-articular BTX-A injection and pain relief in patients with HSP. This result could provide the rationale for blind randomized controlled trials designed to better evaluate the safety and efficacy of intra-articular BTX-A injection in patients with refractory HSP.

Key Words: Botulinum toxin type A; Intra-articular injection; Refractory pain; Rehabilitation; Shoulder pain; Stroke.

© 2011 by the American Congress of Rehabilitation Medicine

Shoulder pain is one of the most common complications of stroke. It occurs in up to 70% of patients with stroke. Poststroke shoulder pain impacts negatively on daily activities. Moreover, it interferes with the rehabilitation process, is related to poor quality of life, and has been associated with worse outcome and prolonged hospitalization. The cause of poststroke hemiplegic shoulder pain (HSP) is uncertain, although it has been associated with various factors: joint disorders, capsulitis adhesiva, subluxation of the head of the humerus, rotator cuff tendon injuries and spasticity of surrounding muscles.

Clinicians use a wide variety of approaches to treat postsstroke HSP, although none has yet proved effective. Correct positioning and careful handling of the hemiplegic limb are believed to prevent HSP. Physiotherapy alone does not seem to be effective for this complication. Capsulitis adhesiva can be treated successfully by means of corticosteroid injections in the shoulder. However, despite many randomized controlled trials of corticosteroid injections for shoulder pain, their effects are controversial. The large number of interventions and lack of consensus about their effectiveness suggest that the cause is poorly understood and hence its treatment remains to be established.

Intramuscular injections of botulinum toxin type A (BTX-A) also have decreased HSP. The mechanism by which intramuscular BTX-A inoculation decreases pain may include a muscle relaxant effect and inhibition of the release of neurotransmitters by sensory neurons. Nevertheless, this approach has some limitations. It probably is more effective in muscular than articular pain and may be influenced by the muscles affected and site of injection.

Intra-articular BTX-A injection recently has been proved safe and effective in the treatment of refractory joint shoulder pain caused by chronic arthritis. The mechanisms by which it exerts this effect are not known, but could include inhibition of the release of pain peptides from nerve terminals and sensory ganglia and anti-inflammatory and anti-glutaminergic effects.

The aim of this pilot study was to evaluate the efficacy of intra-articular BTX-A injection in patients with severe HSP refractory to conventional treatments. Results of this study may help devise new therapeutic and rehabilitation strategies for patients affected by HSP.

METHODS

Participants

Patients (N=5; 4 men, 1 woman; mean ± SD age, 63.8±5.1y) with HSP were recruited in our rehabilitation department. All patients had severe shoulder pain after a stroke causing plegia or severe paraesis of the upper limb (see Table 1 for details). Inclusion criteria were HSP duration of at least 2 months, pain score greater than 7 on a pain visual analog scale (VAS) of 0 to 10cm (0 = no pain, 10 = worst possible pain) at rest, pain refractoriness to conventional treatment (common analgesics, such as paracetamol and nonsteroidal anti-inflammatory drugs; slings, strapping, and handling of the arm; functional electrical stimulation of shoulder muscles), and 1 session of intra-articular steroid injection. Exclusion criteria were no

<table>
<thead>
<tr>
<th>List of Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTX-A</td>
</tr>
<tr>
<td>HSP</td>
</tr>
<tr>
<td>VAS</td>
</tr>
</tbody>
</table>
significant spasticity in the upper shoulder joint, defined as a score of 1 or less on the Modified Ashworth Scale, and no history of shoulder pain or shoulder diseases, neurologic diseases, or botulinum toxin treatment.

All patients gave written informed consent to the procedure. The study was performed according to the Declaration of Helsinki and approved by the local ethics committee.

Assessments and BTX-A Injection

Before being enrolled in the study, all patients underwent a thorough neurologic examination. Pain scores at rest and during passive arm abduction up to 90° were evaluated by using a 0- to 10-cm VAS. The clinical examination and pain VAS were repeated 2 and 8 weeks after intra-articular BTX-A injection. BTX-A treatment was carried out arbitrarily using a vial of BTX-A (500 U of Dysport in 1 patient; 100 U of Botox in 2 patients; 100 U of Xeomin in 2 patients; see table 1). BTX-A was reconstituted with 2.0 mL of saline solution in all cases. BTX-A was injected in the glenohumeral joint by using a standard posterior approach under echographic guidance in all patients (fig 1). All patients continued their standard rehabilitation treatment after the BTX-A injection.

Statistical Analysis

Changes in pain VAS scores at rest and during passive 90° arm abduction after 2 and 8 weeks were compared with baseline values by using paired Student t test. \( P < .05 \) was considered significant.

RESULTS

As shown in figure 2, mean VAS scores before intra-articular BTX-A injection were 8.7 ± 1 and 9.8 ± 0.4 at rest and during passive arm abduction, respectively. VAS scores were much lower 2 weeks after BTX-A injection, both at rest (1.5 ± 1.1; \( P = .001 \)) and during passive arm abduction (3 ± 1.2; \( P < .001 \)). The beneficial effect persisted 8 weeks after BTX-A injection (VAS score at rest, 1.5 ± 1.2; \( P = .001 \); VAS score during passive arm abduction, 2.3 ± 1.1; \( P < .001 \)). There were no significant differences between VAS scores 2 and 8 weeks after BTX-A injection at rest (\( P = 1 \)) or during passive arm abduction (\( P = 0.1 \)). There were no differences in results of the posttreatment neurologic examination versus baseline. Similarly, no collateral effects were reported after BTX-A treatment.

DISCUSSION

In this pilot study, we found a strong correlation between intra-articular BTX-A injection and pain relief in patients with HSP after stroke. All recruited patients had severe HSP, witnessed by a pain VAS score at rest of 8 to 10, lasting for at least 2 months. In all cases, HSP drastically decreased 2 and 8 weeks after intra-articular BTX-A injection.

BTX-A has been used widely to treat spasticity and, through intramuscular injection, other forms of muscle overactivity, as well as chronic pain. A recent randomized controlled study showed that intramuscular BTX-A injections into selected muscles of the shoulder girdle provided more pain relief and motion improvement than intra-articular injection of steroids in patients with HSP. It is conceivable that BTX-A decreases pain by inducing muscle relaxation, although a direct nociceptive effect cannot be excluded. Intramuscular BTX-A injections may be considered in patients with HSP if the pain is associated with some overactivity of the related muscles. However, HSP is more common in the early poststroke phase, associated with flaccidity of the upper limb with or without glenohumeral laxation. In this condition, intramuscular BTX-A injections should be avoided to prevent further muscle weak-

Table 1: Features of 5 Patients Affected by Severe Shoulder Pain After Stroke

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (y)</th>
<th>Cause of Stroke</th>
<th>Time Between Stroke and BTX-A Injection (mo)</th>
<th>Neurologic Examination at Time of BTX-A Injection</th>
<th>VAS Score Before BTX-A Injection</th>
<th>BTX-A Injected and Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/59</td>
<td>Right ICA dissection</td>
<td>4</td>
<td>Slight neglect, left homonymous hemianopia, left facial droop, left hemiparesis (arm more affected than leg), impaired pinprick and light touch sensation</td>
<td>9.5 at rest, 10 during arm abduction</td>
<td>Dysport, 500 U</td>
</tr>
<tr>
<td>2</td>
<td>M/63</td>
<td>Left ICA thrombosis</td>
<td>3</td>
<td>Motor aphasia, ideomotor apraxia, right facial droop, right hemiplegia</td>
<td>8 at rest, 10 during arm abduction</td>
<td>Botox, 100 U</td>
</tr>
<tr>
<td>3</td>
<td>M/70</td>
<td>Left MCA infarction</td>
<td>3</td>
<td>Motor aphasia, right facial droop, plegia of upper right limb, severe paresis of lower right limb</td>
<td>8 at rest, 10 during arm abduction</td>
<td>Botox, 100 U</td>
</tr>
<tr>
<td>4</td>
<td>F/68</td>
<td>Left MCA infarction</td>
<td>5</td>
<td>Slight motor aphasia, right hemiparesis (arm more affected than leg)</td>
<td>10 at rest, 10 during arm abduction</td>
<td>Xeomin, 100 U</td>
</tr>
<tr>
<td>5</td>
<td>M/59</td>
<td>Right ICA thrombosis</td>
<td>4</td>
<td>Slight neglect, left homonymous hemianopia, left hemiparesis (arm more affected than leg), impaired pinprick and light touch sensation</td>
<td>8 at rest, 10 during arm abduction</td>
<td>Xeomin, 100 U</td>
</tr>
</tbody>
</table>

Abbreviations: BTX-A, botulinum toxin type A; F, female; ICA, internal carotid artery; M, male; MCA, middle cerebral artery.
ness. None of our patients experienced relevant spasticity of the upper-limb muscles.

A major cause of shoulder pain is the development of adhesive capsulitis, characterized by inflammation of the ligaments attaching the shoulder bones. In such cases, the analgesic potential of BTX-A would not be caused by its muscle relaxant effect consequent to inhibition of acetylcholine release. Rather, BTX-A might inhibit the release of neurotransmitters and neuropeptides, such as glutamate and substance P, which also would explain its anti-inflammatory and analgesic actions. Accordingly, inhibition of the local release of pain-inducing neuropeptides from free endplates would prevent local sensitization of nociceptors. In line with this mechanism of action, intra-articular BTX-A injection recently decreased joint pain in patients with chronic arthritis, thereby confirming an earlier study conducted in a mouse model.

Study Limitations

This study was conducted on a small number of patients using different commercial formulations of BTX-A without an estimate of dosage equivalence. Therefore, other larger studies are required to evaluate a specific range of dosages for different formulations of BTX-A. Finally, in this pilot study, we chose to focus on the pain referred to by the patients by using a VAS score. However, it would be interesting to evaluate other pain measures, as well as daily life activities, range of movement, and other shoulder joint function measures.

CONCLUSIONS

Intra-articular BTX-A injection might be a new strategy for the treatment of refractory HSP. However, its efficacy should be evaluated better in randomized blind controlled studies.
References