Complex Regional Pain Syndrome (CRPS) is an incompletely understood, frequently devastating condition characterized by severe neuropathic pain. Associated features include autonomic dysregulation (increased sweating, increased temperature of the affected area, edema), motor symptoms (weakness, tremor, dystonias) and trophic changes (e.g., loss of hair, nail changes, skin atrophy) (1,2). The exact pathophysiology of CRPS is not known. Sensitization of the nociceptive system,
both peripherally and centrally, is believed to be a key pathogenic process (3). The frequently excruciating pain is difficult to treat, and the natural history of CRPS is marked by unremitting worsening of the pain (1).

The most widely known action of Botulinum toxin A (BtxA) is its relaxing effect on skeletal muscles. BtxA is therefore widely used for the symptomatic relief of spasticity, dystonias, and other movement disorders. Recently there has been great interest in the use of BtxA for chronic pain. This interest stems from the fact that BtxA seems to have an early anti-nociceptive action that is independent of its muscle relaxing action and may be due to inhibition of central and peripheral sensitization (4-9). It has been previously hypothesized that the anti-nociceptive action of BtxA may be beneficial in CRPS (10).

We conducted a retrospective chart review of CRPS patients with pain and dystonia of neck and upper limb girdle muscles treated with intramuscular BtxA injections to ascertain the benefits and risks of this treatment.

**METHODS**

Thirty-seven patients were included in the study of whom 35 (95%) were females. All participants in this study were initially seen in the pain clinic, and had CRPS as their primary diagnosis. All patients met the IASP criteria for CRPS (11) with 26/37 (70%) of participants diagnosed with CRPS Type 1, and 11/37 (30%) of participants with CRPS Type 2. Ten (27%) of the participants had localized CRPS predominantly involving one or both upper limbs. CRPS involved the entire body in 27 (73%) of the patients.

Participants with spasm or dystonia in the upper limb girdle muscles were referred for BtxA treatment. Based on previous literature, it was believed that participants with spasm/dystonia in the upper limb girdle muscles were most likely to benefit from BtxA treatment. These participants subsequently had electromyography (EMG) guided BtxA injections into these muscles.

**Botulinum injections**

Participants were treated with intramuscular BtxA injections into specific upper limb girdle and neck muscles. EMG was utilized for injection of BtxA into the targeted muscles. Muscles were selected by patient complaints, hypertrophy, spasm and/or tenderness on palpation. The injecting needle also functioned as a monopolar recording electrode, and the reference electrode and ground electrode was a surface electrode placed close by. The needle was inserted into the targeted muscle using bony and soft tissue landmarks. The position of the needle in the targeted muscle was confirmed by asking the participants to activate the muscle and confirming the presence of motor unit potentials on the EMG monitor. Based on the size of the muscle, 10-20 units of BtxA were then injected through the needle. This procedure was repeated for all muscles injected. The total amount of BtxA used per participant was 100 units.

We tabulated the specific sites of injection, which are listed in Table 1.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trapezius</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>2. Splenius Capitis</td>
<td>37</td>
<td>98</td>
</tr>
<tr>
<td>3. Levator Scapulae</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td>4. Longissimus Capitis</td>
<td>17</td>
<td>46</td>
</tr>
<tr>
<td>5. Obliqus Capitis</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>6. Scalene</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>7. Semispinalis</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>8. Obliqus Capitis</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>9. SCM</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>10. Paraspinals, not specified</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

The majority of participants were injected on only one side - the right side in 15 (41%), and the left in 17 (46%). Eight (22%) had bilateral injections. The specific sites of injection are listed in Table 1.

**Pain-scores**

Pain scores were recorded based on the participant’s report of local pain on an 11-point Likert scale, where a score of zero meant the participant had no pain, and a score of 10 was the worst pain imaginable. Pre-treatment pain scores were collected immediately prior to the injections. Post-treatment pain scores were collected 4 weeks after the BtxA injections. None of the study participants had significant medication changes in the 4 weeks after BtxA injection. Participants who had significant medication changes, or had possible disease modifying treatments such as ketamine infusions, were excluded from this study. A participant was classified as “improved” if the decrease in pain scores was 2 or more. This was based on the results of a recent meta-analysis of pain studies by Farrar et al (12) that demonstrated a 2 point decrease to be clinically significant.
Statistical Analysis:

All statistical analysis was done using STATA 9 (Stata-Corp, College Station, TX). The student t-test was used for comparing means, the rank-sum test was used for comparing continuous variables for small samples, and the chi-square test was used for comparing proportions.

IRB Approval:

This study was approved by the Institutional Review Board of the Drexel College of Medicine.

Results

Pain relief

All participants reported severe local pain at baseline, which was 8.2 ± 0.8 (range 7 to 10). The mean local pain score after the BtxA was 4.5 ± 1.1 (range 2 to 8). On an average, there was a 43% (range 11% to 78%) decrease in local pain scores. This difference was statistically significant (P <0.001). These results are illustrated in Fig. 1.

By Farrar’s criterion (i.e., a decrease in local pain score by 2 or more points), 36/37 participants (97%) reported significant improvement in local pain.

Side-effects:

One out of the 37 participants (2.7%) developed a transient neck drop after BtxA injection. This participant required a non-invasive plastic neck brace after BtxA injections. The neck drop resolved spontaneously 2 weeks after the BtxA injection without any further complications.

None of the participants reported new onset dysphagia after the injections. No other serious side-effects developed after the intramuscular BtxA injections.

Factors affecting improvement:

Age, sex, extent of CRPS, CRPS type, number of extremities affected, and the duration of disease were not found to affect the magnitude of pain decrease seen after BtxA injections.

Fig. 1. Pre-BtxA and post-BtxA local pain scores.
**Discussion**

In this retrospective study, we found that intramuscular injection of botulinum toxin in the upper limb girdle muscles was beneficial for short term relief of pain caused by CRPS. Participants in this study were diagnosed with CRPS by strict application of IASP criteria by a single expert (RJS), minimizing diagnostic variability. All EMG-guided BtxA injections were administered by a single individual, who was well acquainted with the procedure. There was a 43% decrease in local pain scores 4 weeks after intramuscular BtxA injections. The incidence of serious side effects associated with this therapy was low (2.7%). There was no clinical prognostic marker for success of treatment. A previous study of the natural history of CRPS demonstrated little change of symptom severity after 1 year (1).

In most patients, CRPS is initiated by trauma to the body, a surgical procedure or fracture (1). The inciting event can produce neuropathic pain by peripheral and central sensitization. Peripheral sensitization lowers the threshold for nociceptor discharge by inducing changes in the receptors themselves (autosensitisation) and/or by increasing the excitability of the pain terminal membrane (heterosensitisation) (13). In CRPS, there is evidence of immune mediated inflammation, a process which is likely to be self-sustaining (3). Substance P and CGRP peptides are the vasoactive neuropeptides thought to be most active in the process of neurogenic inflammation (2,14) which might also enhance the “afferent barrage” to the dorsal root ganglia (DRG) and dorsal horn of the spinal cord. This induces central sensitization of pain transmission neurons which is pivotal to the maintenance of neuropathic pain (3,13).

Botulinum Toxin A acts by cleaving the SNAP-25 (Synaptosome-associated protein of 25 kd) complex in the presynaptic terminal, which prevents formation of the SNARE (soluble N-ethyl maleimide sensitive factor-attachment protein-receptor) system. As a consequence, neurotransmitter vesicles do not fuse with the presynaptic membrane, which decreases the release of neurotransmitters at the synaptic cleft. This mechanism decreases the release of acetylcholine, CGRP, substance-P and glutamate which may decrease the nociceptive fiber discharge (9,15-17).

Dystonia occurs in approximately 20% of CRPS patients (18,19). This abnormal, sustained contraction of skeletal muscles can reasonably be assumed to be a significant source of pain in CRPS patients. In the past, intrathecal baclofen and intrathecal glycine have been evaluated for relief of CRPS associated dystonia. In larger case series, the former was found to be effective (20,21), but was associated with a high complication rate in at least one study (21); while the latter was ineffective in relieving either pain or dystonia (22). In our study, we postulate that the relief of CRPS induced pain by intramuscular BtxA injection is multifactorial: 1) relief of neurogenic inflammation (23-25), 2) relaxation of dystonic muscles that may decrease the afferent nociceptive barrage from sensitised A-delta and C fibers, 3) a distinct antinociceptive action which is distinct from these above mentioned mechanisms (4-6).

There are a significant number of clinical studies on the use of BtxA in neuropathic pain, that includes 2 recent randomized controlled trials. Yuan et al (26) demonstrated in a placebo-controlled randomized trial of 18 patients that intradermal BtxA is effective in relieving painful diabetic neuropathy with results showing 44% of patients receiving BtxA reporting significant relief of pain, as compared to 0% in the placebo group. Ranoux et al (6), in another placebo-controlled randomized trial of 29 patients, showed that intradermal BtxA was effective in post-herpetic neuralgia or posttraumatic/postoperative neuropathic pain. In this study, 40% of patients receiving BtxA reported significant improvement at the end of 2 weeks, as compared to 14% of the patients receiving placebo. The relief of pain was sustained for 6 months after the initial injection. Multiple other non-randomized studies demonstrating the antinociceptive action of BtxA in neuropathic pain caused by diverse clinical conditions have been summarized (27).

In contrast, the use of BtxA for pain relief in CRPS has only been described in 5 small studies, which are summarized in Table 2.

In contrast to earlier studies of BtxA in CRPS, a recent randomized trial failed to find improvement in pain after intradermal BtxA injections (29). The authors postulated that failure was due to the very severe/advanced nature of CRPS in their study participants, and the mode of administration of BtxA (intradermal-subcutaneous rather than intramuscular). This study was followed up quickly by the same group by a small case series describing 2 patients who were treated with intramuscular instead of intradermal BtxA (28). Both patients had improvement in pain, skin discoloration and swelling which is in agreement with the earlier study by Argoff (10).
There are several limitations of this study. These include its retrospective nature, the lack of a control group, and the possibility of a placebo effect. The study does not provide information on the efficacy of this treatment after one month. The current study was unable to identify predictors of pain relief after BtxA injection. Further studies are essential to determine these patient characteristics, and define subgroups of CRPS patients that are most likely to benefit from intramuscular BtxA injections.

This study is the largest study to date that documents a potentially useful therapy for a disease characterized by devastating and frequently intractable pain. In view of its limitations, this retrospective study provides data to justify a larger prospective randomized control trial. Further studies need to a) confirm these results, b) identify the subgroups of CRPS patients and modes of BtxA administration that optimize pain relief, c) assess

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**Conclusion**

There are several limitations of this study. These include its retrospective nature, the lack of a control group, and the possibility of a placebo effect. The study does not provide information on the efficacy of this treatment after one month. The current study was unable to identify predictors of pain relief after BtxA injection. Further studies are essential to determine these patient characteristics, and define subgroups of CRPS patients that are most likely to benefit from intramuscular BtxA injections.

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changes in other symptoms of CRPS (sudomotor, vaso-
motor, trophic) and associated conditions (migraine), d) assess its use as an adjunct with other treatments such as
ketamine to increase the efficacy of these medications, or to prolong their effect by decreasing the chronic pain stimuli that lead to central sensitization (32,33).

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