Botulinum Toxin and Muscle Atrophy: A Wanted or Unwanted Effect

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Abstract

While the facial rejuvenating effect of botulinum toxin type A is well known and widespread, its use in body and facial contouring is less common. We first describe its use for deliberate muscle volume reduction, and then document instances of unanticipated and undesirable muscle atrophy. Finally, we investigate the potential long-term adverse effects of botulinum toxin-induced muscle atrophy. Although the use of botulinum toxin type A in the cosmetic patient has been extensively studied, there are several questions yet to be addressed. Does prolonged botulinum toxin treatment increase its duration of action? What is the mechanism of muscle atrophy and what is the cause of its reversibility once treatment has stopped? We proceed to examine how prolonged chemodenervation with botulinum toxin can increase its duration of effect and potentially contribute to muscle atrophy. Instances of inadvertent botulinum toxin-induced atrophy are also described. These include the "hourglass deformity" secondary to botulinum toxin type A treatment for migraine headaches, and a patient with atrophy of multiple facial muscles from injections for hemifacial spasm. Numerous reports demonstrate that muscle atrophy after botulinum toxin type A treatment occurs and is both reversible and temporary, with current literature supporting the notion that repeated chemodenervation with botulinum toxin likely responsible for both therapeutic and incidental temporary muscle atrophy. Furthermore, duration of response may be increased with subsequent treatments, thus minimizing frequency of reinjection. Practitioners should be aware of the temporary and reversible effect of botulinum toxin-induced muscle atrophy and be prepared to reassure patients on this matter.

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Since the introduction of botulinum toxin for the treatment of strabismus, there has been an exponential increase in indications for its use. According to the 2014 statistics published by The American Society for Aesthetic Plastic Surgery, botulinum toxin continues to be the most common minimally invasive procedure performed by plastic surgeons in the United States. The injectables market generated 2.3 billion dollars in revenue in 2014 alone.1

While the use of botulinum toxin type A in the cosmetic patient has been extensively studied, there are several interesting questions yet to be completely addressed. This includes, amongst others, the following: (1) does prolonged botulinum toxin type A treatment increase its duration of action; and (2) what is the mechanism of muscle atrophy and what is the cause of its reversibility once treatment has stopped?

The purpose of this article is to review and highlight muscle atrophy as both a wanted and an unwanted effect of botulinum toxin type A in cosmetic patients. We also examine how prolonged chemodenervation with botulinum toxin type A can increase its duration of effect and potentially contribute to muscle atrophy.
THERAPEUTIC BOTULINUM TOXIN-INDUCED MUSCLE ATROPHY

Mandibular Recontouring

Medical management of masseter hypertrophy with botulinum toxin type A was first described in 1994. Although initial management focused on correcting jaw clenching, this quickly evolved into an aesthetic tool for mandibular recontouring (Figure 1). Since then, there have been several series outlining its efficacy and safety profile. Although outcomes in the literature are variable, overall efficacy is generally achieved, and patient satisfaction has been reported to be as high as 80%. Masseter muscle size quantification with CT measurement has shown a progressive reduction of muscle thickness for as long as three months after injection. A visible decrease in masseter size has been reported in as little as two weeks, with maximal aesthetic benefit in approximately 6 to 8 weeks. The recommended treatment frequency is quite varied. In a recent study of 121 patients, the treatment frequency of two to four times per year was suggested in order to maintain a visible result.

A reduction in masseter size is apparent only after continued inhibition of muscular contraction (Figure 2). Therefore the onset of masseter size reduction begins at approximately three months following injection rather than the one week effect seen when botulinum toxin is used for wrinkle ablation. Significant reduction in muscle size has been confirmed following a single injection in ultrasound studies by To et al, demonstrating a maximum of 30% size reduction at three months, with persistence up to six months. The effect of cumulative injections on muscle size, however, was not evaluated. While reduced muscle size persisted, the size reduction dissipated to 13.4% by 12 months post-injection. Further, electromyographic data demonstrated diminution of masster volume even after recovery of muscle function.

Such results are likely responsible for a sustained effect of botulinum toxin type A on muscle contouring when compared to its other cosmetic applications, most of which rely on a reduction of muscular contraction rather than muscle volume. Adverse effects include difficulty chewing, speech disturbances, and muscle fatigue. These are all related to muscle weakness caused by the initial treatment, and while inconvenient they are self-limited.

Calf Recontouring

When used for treating lower extremity spasticity due to cerebral palsy, intramuscular injections of botulinum toxin type A were noted also to produce calf muscle atrophy. These findings led to a popular alternative to surgical calf denervation (Figure 3). The initial muscle targeted in calf recontouring is the medial head of the gastrocnemius; however, some practitioners recommend targeting both lateral and medial heads. Regardless of administering technique, weakening of the neighboring soleus and plantaris muscle remain a known risk. This can be minimized by appreciating muscle anatomy and understanding that botulinum toxin diffuses approximately one centimeter from its injection site.

The major difference in treating the gastrocnemius compared to the masseter or mimetic facial muscles relates to its size and muscle area. Enough toxin has to reach the targeted calf muscles to induce noticeable muscular atrophy without causing a functional deficit of the surrounding muscles.

Figure 1. (A) A 31-year-old woman with complaints of a “squared” lower face. The patient underwent two separate treatments with 50 units of botulinum toxin type A separated by three months. (B) A smooth, slimmer face can be appreciated at six months after initiation of treatment.
structures. Dilution has been proposed to address this issue; inadvertent diffusion of the diluted solution to the soleus and plantaris would not be potent enough to cause functional muscle weakening.5

Literature on calf recontouring is limited, with proposed doses initiated by either anecdotal evidence or small case series. In addition, muscle size presents a second variable to standardizing both dosage and frequency of injection. Suggested doses range from 32 to 100 units of botulinum toxin type A per calf.9,11 This dosage varies significantly when compared to the cerebral palsy literature, where the recommended dose can reach up to 210 units of botulinum toxin type A per side.12 Botulinum toxin-induced atrophy has been reported as early as one month after injection, and is well maintained for 6 months. In some cases, variable degrees of atrophy were noted up to one year after a single administration.11

Overall, the use of botulinum toxin type A in calf recontouring is well tolerated and adverse effects including gait disturbances and muscle fatigue are self-limited and temporary.5,6 Further studies and follow-up are needed to address ideal dosage, dosage interval, and long-term effects of this muscle recontouring therapeutic modality. Experience thus far is too limited to determine whether repeated, long-term treatment will allow dose reduction.

**INADVERTENT BOTULINUM TOXIN-INDUCED MUSCLE ATROPHY**

Despite its widespread use for facial rhytid reduction, there is limited documentation of botulinum toxin-induced facial muscle atrophy. Guyuron et al described the “hourglass deformity” due to temporalis atrophy caused by repeated doses of botulinum toxin type A when treating migraine headaches. While this was noted by 28% of patients, subtle atrophy was noted by the treating physician in all patients in a series of 92 individuals injected with 25 units of botulinum toxin type A per side.13 Botulinum toxin-induced atrophy has been observed as early as one month post-injection, resolved in all patients several months after recovery of muscle function.13

In some instances, temporalis atrophy is the desired outcome. Ali et al described a patient with bilateral temporalis hypertrophy of unknown etiology that was successfully treated with botulinum toxin type A (80 units/side). This was a significantly higher dose to that causing the “hourglass deformity” in the Guyuron study (25 units/side). In this case report, resolution of muscle hypertrophy was noted within 4 weeks of treatment.14

To the best of our knowledge, there is only one published case of inadvertent botulinum toxin-induced atrophy of a facial mimetic muscle. This occurred in a 29-year-old female treated with botulinum toxin for chronic headaches.
Each corrugator supercili muscle was injected with 2.5 units at two different sites, for a total of 5 units per muscle. Two and a half months post-treatment, visible depressions at the lateral aspect of both corrugators were detected. Although no further injections were performed, the patient still exhibited significant atrophy six months after therapy. At the one-year follow-up, facial defect was no longer apparent. Since this publication, we have also treated a patient who developed facial atrophy following prolonged botulinum toxin type A injection for hemifacial spasm (Figure 4).

Inadvertent botulinum toxin-induced atrophy was also noted in a patient being treated for palmar hyperhidrosis. She received injections every nine months for a period of four years. Hand weakness and bilateral thenar atrophy became noticeable two years after initiating treatment. Three months after injection cessation, moderate improvement of the atrophy was noted.

**DISCUSSION**

Muscle atrophy can be an intended or non-intended outcome of botulinum toxin type A treatment. In either case, the result is temporary and reversible, and the patient should be counseled accordingly. Preliminary evidence suggests that both the unintended degree of muscle atrophy and the intended wrinkle reduction can be affected by altering dosage and/or dosage intervals. Tables 1-2 detail recommended dosage interval and range for facial contouring and wrinkle ablation respectively.
While investigating the effect of botulinum toxin type A on glabellar lines, it was found that after six or more injections, administering intervals were extended up to seven months while the cosmetic effect was maintained.\textsuperscript{17,18}

In their review, Gordon and Barron examined the effectiveness of repeated botulinum toxin type A treatments for a variety of conditions in over 44 studies. Ten of these studies demonstrated a significant increase in efficacy of botulinum toxin type A over time. Only one of the 44 investigations addressed botulinum toxin type A for rhytide reduction; the remainder investigated spastic disorders.\textsuperscript{19}

Several theories have been postulated for why repeated botulinum toxin type A treatment might increase its effective duration. Some have suggested that chemical muscle paralysis is similar to true muscle denervation. At the time of re-injection full recovery of neuronal function may not yet have occurred.\textsuperscript{20} Others suggest that repeat injections affect additional previously unaffected neuromuscular junctions; thus, causing a more extensive and long lasting denervation.\textsuperscript{18}

Using magnetic resonance imaging to look at recovery of muscle atrophy after a single injection of onabotulinumtoxin A into the procerus muscle, Koerte et al found that muscle atrophy lasted approximately twelve months with a decrease in muscle volume of 46% to 48%. In contrast, muscle function and glabellar line severity returned in about six to ten months.\textsuperscript{17} A possible explanation for this temporal gap is that of local plasticity, where neighboring neuromuscular junctions that have not been inactivated by the toxin play an initial agonistic and compensatory role in such recovery.\textsuperscript{20}

In one animal study, Fortuna et al looked at changes in muscle mass and contractile properties in rabbit muscles receiving repeat injections of botulinum toxin. Injections were administered at month intervals and measurements were taken at one, three, and six months. A dramatic loss in muscle mass reaching peak value of approximately 60% after 3 months was noted. Interestingly, in the latter study, muscle volume loss was also associated with distinct histologic changes. Botulinum toxin type A injections not just caused a dramatic loss in muscle mass, but at 6 months, a greater percentage of muscle mass was primarily attributed to fat rather than muscle.\textsuperscript{21} Such histologic changes seem contrary to the eventual return of muscle mass noted after cessation of treatment. In essence this reversibility of muscle atrophy remains unexplained.

Practitioners should be aware of the temporary and reversible effect of botulinum toxin-induced muscle atrophy as well as the beneficial effect of wrinkle reduction, and be prepared to reassure patients on this matter. While the question of what might predispose patients, particularly those undergoing the same treatment, to have such varied degrees of atrophy is one that has yet to be answered. It has been postulated that this may be related to the amount of soft tissue overlying the muscle. Heavier patients experience a much lesser degree of visible atrophy.\textsuperscript{13,15} In addition, clinical experience suggests that males require larger doses of botulinum toxin type A than females if similar responses are to be obtained. Furthermore, there is evidence that male subjects also exhibit a longer duration response (4-6 months) than females.\textsuperscript{18}

Potential limitations of this work exist. Although it may appear as a meta-analysis, it is rather a topic review. While we believe the review was complete, our effort could be criticized for this reason. Unfortunately, the majority of the papers available were either case reports or small series, making a meta-analysis impractical.

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**Table 1. Recommended Dosage and Administration Intervals for Muscle Mass Reduction**

<table>
<thead>
<tr>
<th>Administration Intervals</th>
<th>Dosage</th>
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</thead>
<tbody>
<tr>
<td>Mandibular Recontouring</td>
<td>4-12 mo</td>
</tr>
<tr>
<td></td>
<td>125-180 units botulinum toxin type A per hemiface\textsuperscript{4}</td>
</tr>
<tr>
<td></td>
<td>100-140 units botulinum toxin type A per hemiface\textsuperscript{6}</td>
</tr>
<tr>
<td></td>
<td>50-150 units botulinum toxin type A per hemiface\textsuperscript{9}</td>
</tr>
<tr>
<td>Calf Recontouring</td>
<td>6-15 mo</td>
</tr>
<tr>
<td></td>
<td>60-140 units botulinum toxin type A per calf\textsuperscript{11}</td>
</tr>
<tr>
<td></td>
<td>50-60 units botulinum toxin type A per calf\textsuperscript{9}</td>
</tr>
<tr>
<td></td>
<td>90 units botulinum toxin type A per calf\textsuperscript{22}</td>
</tr>
</tbody>
</table>

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**Table 2. Recommended Dosage and Administration Intervals for Rhytid Reduction\textsuperscript{23}**

<table>
<thead>
<tr>
<th>Administration Intervals</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glabellar Lines</td>
<td>3-4 mo</td>
</tr>
<tr>
<td></td>
<td>Women: 20-30 units total Men: 30-40 units total</td>
</tr>
<tr>
<td>Frontalis Muscle</td>
<td>3-6 mo</td>
</tr>
<tr>
<td></td>
<td>Women: 10-20 units total Men: 20-30 units total</td>
</tr>
<tr>
<td>Crow’s Feet</td>
<td>3 mo</td>
</tr>
<tr>
<td></td>
<td>6-15 units per side</td>
</tr>
<tr>
<td>Bunny Lines</td>
<td>3 mo</td>
</tr>
<tr>
<td></td>
<td>2-5 units total</td>
</tr>
<tr>
<td>Perioral Areas</td>
<td>2-3 mo</td>
</tr>
<tr>
<td></td>
<td>4-10 units total</td>
</tr>
<tr>
<td>Mentalis Muscle</td>
<td>3-4 mo</td>
</tr>
<tr>
<td></td>
<td>Women: 2-6 units Men: 2-8 units</td>
</tr>
<tr>
<td>Plastysmal Bands</td>
<td>3-4 mo</td>
</tr>
<tr>
<td></td>
<td>Women: 10-30 units Men: 10-40 units</td>
</tr>
</tbody>
</table>
The purpose of our paper was twofold: (1) to highlight lesser appreciated uses of botulinum toxin type A to the practice of plastic surgeons; and (2) to emphasize the fact that muscle atrophy can be both a benefit and untoward effect of chronic treatment. We believe the plastic surgeon should be aware of both. The mechanism of muscle atrophy deserves further thought.

**CONCLUSION**

Numerous reports demonstrate that muscle atrophy after botulinum toxin type A treatment occurs and is both reversible and temporary. This can be wanted or unwanted sequelae of treatment. Current literature supports the notion that repeated chemodenervation with botulinum toxin type A is likely responsible for both therapeutic and incidental temporary muscle atrophy. Several studies, predominantly those related to spastic disorders, have shown that with repeated treatments of botulinum toxin, duration of response may be increased thus minimizing frequency of reinjection. This suggests a similar situation probably occurs in the aesthetic sphere.

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**REFERENCES**