The effect of botulinum toxin a (BTX-A) injection into denervated muscles on synkinesis and symmetry in patients with facial nerve paralysis

Abstract

Introduction: Synkinesis refers to an involuntary movement accompanying a voluntary one that is a consequence of facial paralysis. The management of synkinesis is a cosmetic procedure that results in facial symmetry. Botulinum A toxin has been used for more than two decades for resolving asymmetry and synkinesis. However, the endpoints remain to be further explained. The purpose of this study is to analyze research trends on facial synkinesis and asymmetry after facial nerve palsy.


Results: A total of 13 eligible articles, cumulatively examining 332 patients, entered the analysis and were divided into three groups; eight articles were taken as the case series (181 patients) and two compared BTX-A and neuromuscular rehabilitation (61 patients); both these groups had concluded that BTX-A injection can help reduce synkinesis; only three randomized clinical trials were accessed (90 patients) and reported disparate findings.

Conclusion: BTX-A injection cannot yet be proposed as a solution for synkinesis reduction for achieving symmetry and overcoming this complication of facial nerve palsy because of the small number of randomized clinical trials available on the subject; further studies are recommended in order to be able to make such a statement.

Keywords: facial paralysis, botulinum toxin A, synkinesis, facial symmetry

Introduction

Facial nerve paralysis is the most common cranial nerve neuropathy caused by damage to the seventh cranial nerve and its motor nuclei.1–6 There are several etiologies for facial nerve paralysis, with the most common one being acute facial palsy or Bell’s palsy. About 70% of Bell’s palsy patients recover completely within six months. The aberrant regeneration of the nerve fibers after facial nerve paralysis may lead to several adverse consequences, including facial muscle weakness, contracture, hyperkinesia, atrophy, synkinesis and asymmetry in the face muscles.7–9 Synkinesis is one of the sequelae of facial nerve paralysis with its exact cause remaining to be identified. Facial synkinesis is an involuntary movement of a region of the face that occurs as a result of the voluntary movement of another region.10 Synkinesis occurs not only with voluntary movements, but also at sleep, when there is a continuous retraction of the upper and lower lips.11 Synkinesis has a negative impact on the patient’s quality of life. Available treatments for reducing synkinesis include surgery,12 Botulinum Toxin A (BTX-A) injection and neuromuscular retraining; surgical procedures are no longer widely used due to their complications.13

BTX-A injection is one of the most widely-used treatments for synkinesis in medical centers around the globe that was first used in 1970 as a treatment for strabismus.14 This toxin is produced by the bacillus clostridium botulinum under anaerobic conditions.15 The toxin can temporarily block presynaptic- acetylcholine release and lead to muscle paralysis.16–21 Despite its widespread use for reducing or resolving synkinesis and improving facial symmetry, there is some controversy among scholars about the effects, complications and allowed frequency, dose and site of injection of BTX-A.22–24

Furthermore, several animal studies have found destructive effects for botulinum toxin, including decreased muscle mass and strength, decreased contractile material and altered mRNA expression phenotype.25–27 In addition, the results of some electromyographic studies muscle atrophy persisting long after injection; for example, masseter atrophy not resolved even within 25 months;28 other studies have reported a significant reduction in muscle amplitude remaining as long as 12 months after the injection.29 These changes can lead to muscle weakness in the involved side and ultimately cause facial asymmetry during voluntary movements. The aim of therapeutic interventions for facial nerve injuries is to improve facial symmetry by reducing or resolving synkinesis. In one study, BTX-A was found to have a more significant effect on the nerve endings of the synkinesis muscles than the healthy muscles.30 This study seeks to answer the question of how effective BTX-A injection is in improving facial symmetry through a review of literature.
Materials and methods


Results

A total of 483 studies were accessed and all were evaluated by two independent reviewers. The articles that discussed hemifacial spasm, blepharospasm and upper motor neuron lesions and those in which the healthy side was injected were excluded from the analysis and those written in languages other than English were excluded as well, leaving only 13 eligible studies for the analysis. These articles extracted are divided into three groups:

The first group consisted of eight studies Table 1. Four of these studies targeted ocular synkinesis and had BTX-A injected into the muscles around the eyes once or several times. In two other studies, the origin of synkinesis was considered to be the platysma and buccinators and BTX-A was injected into these muscles.31,32 In four other studies, the Facial Grading Scale (FGS) was used and improvements in its score were reported as 11% to 14%. To sum up, the studies in this group found that synkinesis had disappeared or decreased following the given treatments, and some of them also discussed symmetry.

The second group consisted of two clinical studies Table 2. Exercise therapy was the primary treatment in both these studies and BTX-A injection was used only as a complementary treatment. Final appraisals were made within ten to 18 months. Alvaro33 evaluated facial symmetry using the House-Brackmann and Azuma34 studied reductions in synkinesis and symmetry around the eyes only. The contributions of the injections or exercise therapy could not be distinguished, but both studies reported a reduction in synkinesis and an improvement in symmetry was thus inferred.

The third group consisted of three randomized clinical trials (RCTs). Borodic compared BTX-A injection and placebo only in the muscles around the eyes.23 The results of this study showed a significant reduction in ocular synkinesis. Monini35 and Pourmomeny36 obtained similar and comparable results, although they reported different effects for BTX-A injection Table 2.

<table>
<thead>
<tr>
<th>Author</th>
<th>N: Patients</th>
<th>Number injection</th>
<th>Intervention &amp; injection</th>
<th>Outcomes measurement</th>
<th>End of treatment</th>
<th>Main Results</th>
<th>Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mountain37</td>
<td>4</td>
<td>&gt;One</td>
<td>Orbicularis oculi</td>
<td>Photographs</td>
<td>-</td>
<td>All patients showed synkinesis improvement</td>
<td>BTX-A is a effective treatment in reducing synkinesis</td>
<td>There is no report of Objective evaluation</td>
</tr>
<tr>
<td>Roggencamper38</td>
<td>23</td>
<td>&gt;One</td>
<td>Orbicularis oculi</td>
<td>Patients satisfaction</td>
<td>-</td>
<td>Nearly all patients showed synkinesis improvement</td>
<td>BTX-A proves to be an effective treatment for involuntary lid closure</td>
<td>The measurement tool is not clearer The patient without improvement after injection refused further treatment.</td>
</tr>
<tr>
<td>Boroojerdi21</td>
<td>10</td>
<td>One</td>
<td>Orbicular oculi</td>
<td>5 Point scale , videograph</td>
<td>4w</td>
<td>Good to excellent (grades 3 and 4) effect over an average of six months after 91% of injections</td>
<td>BTX-A is an effective treatment in reducing synkinesis</td>
<td></td>
</tr>
</tbody>
</table>

Citation: Pourmomeny AA. The effect of botulinum toxin a (BTX-A) injection into denervated muscles on synkinesis and symmetry in patients with facial nerve paralysis. J Otolaryngol ENT Res. 2018;10(6):388-395. DOI: 10.15406/joentr.2018.10.00388
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Table 2 Groups 2 and 3

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>FRCOphtha</td>
<td>5</td>
<td>One</td>
<td>Pretarsal orbicularis)</td>
<td>3-Point scale</td>
<td>-</td>
<td>All five patients had improvement of the synkinesis</td>
<td>Low-dose BTX-A is an effective treatment in aberrant facial nerve regeneration</td>
<td></td>
</tr>
<tr>
<td>Ito22</td>
<td>11</td>
<td>&gt;One</td>
<td>Synkinesis area</td>
<td>-</td>
<td>-</td>
<td>In seven cases, synkinesis disappeared completely after three or fewer sessions of BTX-A injection</td>
<td>Facial synkinesis can be treated with a lower dose of BTX-A without side effects</td>
<td>Neither measurement tool nor the measurement method is clearly determined.</td>
</tr>
<tr>
<td>Filipo42</td>
<td>41</td>
<td>One</td>
<td>Synkinesis area, FGS, Videotapes questionnaire</td>
<td>Im α</td>
<td></td>
<td>All patients showed some improvement of synkinesis</td>
<td>BTX-A injection is effective in treatment of facial synkinesis &amp; hyperkinesis</td>
<td>Platsma synkinesis had been reduced, platista symmetry at rest had been improved. Score of sunnybrook facial grading scale had been increased</td>
</tr>
<tr>
<td>Angelo31</td>
<td>45</td>
<td>One</td>
<td>Platsma</td>
<td>FGS, (specific platista evaluation)</td>
<td>18 dys α</td>
<td></td>
<td></td>
<td>Buccinator (Intraoral) BTX-A injection is effective in reducing synkinesis of buccinators muscle</td>
</tr>
<tr>
<td>Wei LA32</td>
<td>42</td>
<td>One</td>
<td>Buccinators</td>
<td>Synkinesis , (Synkinesis Assessment Questionnaire + FGS)</td>
<td>-</td>
<td></td>
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</table>

In the study conducted by Mountain, the aim of treatment was to reduce ocular synkinesis; for this purpose, BTX-A was injected into the orbicularis oculi of four patients and again repeated after seven months. The results were examined through photography and the patients reported a subjective improvement in their synkinesis.

In a retrospective study, Roggencamp et al. examined the results of 23 patients with ocular synkinesis who had been paralyzed for 12 months and injected BTX-A into their orbicularis oculi muscle. Almost all the patients reported an improvement in their synkinesis. After 19 weeks, some of the patients requested a second injection, as they were satisfied with the results of their first injection.

In another study, Boroojerdi injected BTX-A into the orbicularis oculi of ten patients with ocular synkinesis; six of these patients were videotaped before their injection and again two to four weeks after their injection, and the width of their affected lid was compared with that of their healthy side during movements. A five-point scale was used to evaluate the effectiveness of the treatment for synkinesis and all the patients ended up with a moderate to good improvement in their synkinesis.

FRCOphtha evaluated the effect of low-dose BTX-A injection in five patients with ocular synkinesis. In this study, the patients were examined for signs of reduction in their symptoms two to three months after the treatment. A three-point scale was used to evaluate the patients and the results showed that low-dose BTX-A injection is an effective treatment for reducing ocular synkinesis in patients with facial paralysis.

Ito evaluated the effect of low-dose BTX-A injection on oral and ocular synkinesis in 11 patients with facial nerve palsy. Signs of synkinesis disappeared in the patients two to three days after the injection. Another round of BTX-A injection was performed in order to maintain the effect of the injection and the interval between these two injections was 14.5 weeks. In seven patients, synkinesis disappeared completely after about three sessions of BTX-A injection. The results of this study suggest that low-dose BTX-A injection can be effective in reducing synkinesis without leaving any side-effects.

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<tbody>
<tr>
<td>III</td>
<td>Pourmomeny</td>
<td>34</td>
<td>one</td>
<td>BTX-A +biofeedback</td>
<td>FGS, videotape, Photoshop software</td>
<td>4 m</td>
<td>there were more improvements of facial synkinesis in patients who received BTX-A in addition to neuromuscular retraining</td>
<td>Biofeedback rehabilitation is as effective as biofeedback rehabilitation treatment along with BTX-A injection</td>
</tr>
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The effect of botulinum toxin a (BTX-A) injection into denervated muscles on synkinesis and symmetry in patients with facial nerve paralysis

11,19,24,47

27,52

35

49

41

18,24,30,41,44-46

The effect of BTX-A injection into denervated muscles on synkinesis and symmetry in patients with facial nerve paralysis. The researchers believed that the buccinator has an important role in facial expressions and so injected BTX-A into the subjects’ buccinator as well as the synkinetic muscles around their eye and mouth. All the evaluations were performed before and after the treatment using FGS and the Synkinesis Assessment Questionnaire. Statistically significant improvements were observed in both scales. According to the results, the administration of BTX-A into the buccinator increase in both scores and is therefore an appropriate treatment for patients with facial synkinesis.

Alvaro31 believed that neuromuscular retraining is an effective treatment for facial synkinesis and that BTX-A injections can be considered a complementary treatment. In this study, 48 patients with severe Bell’s palsy underwent BTX-A injection and neuromuscular retraining by a physiotherapist at the hospital and also in the form of home exercise. The patients were assessed at the onset of their paralysis until 12-18 months after the injection and until they achieved complete recovery. The mean score in the final FGS was 56.9%.

Azuma34 studied 13 patients with ocular synkinesis who received a single dose of BTX-A injection as well as 30 minutes of daily mirror biofeedback for a total of ten months. The patients’ facial movements in the frontal view were recorded using a videotape and through photographs. Their eye opening symmetry was calculated by measuring the ratio of their interpalpebral space width in the affected eye to that of the normal eye in percentage. The results showed that mirror biofeedback after a single dose of BTX-A can be a treatment with lasting effects for cases of established facial synkinesis.

In a study by Monini,35 20 patients with facial palsy who had undergone Kabat physical rehabilitation for one year and who were final House-Brackmann (HB) grade II and III after recovery were randomized into two groups. To assess the efficacy of BTX-A treatment on the final synkinesis score after neuromuscular rehabilitation, the patients in the experimental group received one dose of BTX-A before neuromuscular retraining and those in the control group received neuromuscular retraining only. Both groups of patients were assessed once before and then 90 days after the treatment using the FGS. Significant differences were observed between the results of the treatments, as synkinesis improvement was greater in the experimental group compared to the control group.

Borodic23 performed a double-blind, placebo-controlled trial assessing the efficacy of BTX-A injection. The 36 subjects in this study received injections into the muscles around their eye with BTX-A or normal saline in the case of the control group. The patients were assessed once before and then two weeks after the treatment using the Physicians Grading Scale and palpebral asymmetry during facial movements and the level of synkinesis were measured on a scale from 0 to 6 by videotaping. A questionnaire containing items on the problems faced due to facial synkinesis was also used to subjectively evaluate the patients. The data showed a significant improvement in ocular synkinesis while the controls showed no improvements.

Discussion

The main goal of this study was to analyze papers that have reported the effects for BTX-A on facial nerve damage. BTX-A injection was introduced in 1991 in papers published in German aiming to control synkinesis and improve facial symmetry.41 The most important complication of facial nerve damage is asymmetry and weakness in the muscles damaged due to incomplete regeneration and synkinesis due to mal-regeneration or ephaptic transmission between adjacent axons or nuclear hyperexcitability. No matter the cause of this damage, those papers were analyzed that had used BTX-A injections in the synkinetic muscles to reach facial movement symmetry. Except in special cases (such as the hyperlacrimation phenomenon), the patient’s expectation or the researcher’s goal was to achieve symmetry during rest position and during active movement. Numerous studies had even recommended BTX-A injection into the healthy side or both sides for achieving.9,42,43 Needless to say, BTX-A injection cuts the chemical connection between the nerve endings and the muscular fibers and leaves part of the muscle paralyzed. After this connection is re-established at the chemical synapses, movement or synkinesis is established once again. The effect of BTX-A has been reported to last for three to seven months,18,24,30,41,44-46 and re-injection is needed to continue this effectiveness. Nonetheless, as the body develops an antibody to botulinum toxin, its effectiveness will further decline following each injection.11,19,24-47 Moreover, Dressler found that if BTX-A is injected into human body tissues for a prolonged period, permanent muscle atrophy becomes a possibility.46 In some of the studies conducted, atrophy and a considerable reduction in muscle amplitude were reported after BTX-A injection with no restoration for months, which is consistent with the hypothesis put forward by Dressler.

Yaraskavitch observed that BTX-A injection reduces the strength of the muscle adjacent to the site of injection (after four weeks of injection) in animals.40 Ansved and Girlanda proposed that atrophy could also be developed in the other muscles following BTX-A injection.50-51 In two studies, Fortuna showed that following three injections in the quadriceps of animals, atrophy is observed along with a significant decline in muscular strength, particularly in the third injection; what is interesting is that muscular strength declines even for the muscles that have not had injections.27,28 Toffola argued that synkinesis intensity gradually declines with repeated BTX-A injections because of the progressive atrophy of the muscle injected.46
The effect of botulinum toxin a (BTX-A) injection into denervated muscles on synkinesis and symmetry in patients with facial nerve paralysis

The results obtained by Couch showed that, as BTX-A is injected into the synkinetic muscles, symmetry in the dynamic movements (standard expressions) also declines significantly after 35 days in addition to the reduction in synkinesis. Although various studies have been conducted to reduce or eliminate synkinesis, few clinical trials have examined the effectiveness of this treatment. Moreover, there is no consensus about the injection dosage and some researchers have even questioned the site of injection. Angelo and Wei found platysma and buccinator to be the cause of synkinesis, respectively, and Filipo found injection technique and depth to affect the results. Ito argued that the effect of lower doses is just as long-lasting as high doses or even more. Nonetheless, most of these studies have examined improvements in synkinesis rather than symmetry.

Some studies even proposed BTX-A injection in the opposite side for creating symmetry and found that it led the muscle function in the healthy side to the damaged side. In the present analysis, studies in which the injection had been made in the healthy side were excluded in order to identify the effects of BTX-A and its durability (for temporary or permanent paralysis) for symmetry. To increase the durability of BTX-A, some therapists increase its dosage, but this measure also increases the side-effects and may result in systemic toxicity. Cakmak argued that a comparison of hemifacial spasms and Bell’s damage to the facial muscles shows significantly more complications after BTX-A injection, which could be due to the nature of the nerve damage in facial palsy. Nonetheless, it is not clear what will happen with injection into muscles that have previously been denervated and become regenerated.

In some studies, the goal was to reduce ocular synkinesis and increase symmetry, but these studies may not have been thorough, because synkinesis can be observed in three upper and lower parts of the face. These studies reported the prevalence of synkinesis in the muscles around the mouth when raising the eyebrows or in the voluntary closing of the eyes as 85-89% while the prevalence of ocular synkinesis was reported as 82%. The FGS is currently the most suitable instrument that can demonstrate three situations (facial symmetry at rest, five normal standard expressions and the intensity of synkinesis) distinctly in the peripheral neuropathy and has a good validity. This instrument was used in only four studies and the maximum improvement was reported as 14%.

As for those studies in which the researchers had not prescribed a regimen for correcting facial movements alongside their prescribed BTX-A injection, it is difficult to conceive of any patient who would not check his facial movements in the mirror and exercise. In other words, the question is how much mirror biofeedback has contributed to the improvements observed in these patients. In studies conducted by Alvaro and Azuma, BTX-A was introduced as a complementary treatment along with neuromuscular exercises. Alvaro believed that the efficacy of this rehabilitation was high and proposed muscle retraining as the essence of treatment. Azuma assessed the percentage of ocular symmetry after injection and exercise therapy. Improvements in symmetry were reported in both studies, but the contribution of each of the two treatments could not be distinguished.

Only three English RCTs had been indexed. Borodic compared BTX-A injection and placebo only in the muscles around the eye and provided no reports of total face symmetry, whereas synkinesis may occur in the platysma muscle in addition to one half of the face. The patients in this study were appraised only in a two-week interval. Monini and Pourmomeny reported different effects for BTX-A; Monini’s patients were selected from grade II and III only and were examined using the House-Brackmann scale, while Pourmomeny reported BTX-A to be not effective after four months according to the three measurement instruments used and believed only muscle retraining to be effective. MehdiZadeh argued that when neuromuscular exercise does not show a speedy recovery in some patients, BTX-A may be able to reduce the tension so that neuromuscular therapy can work faster.

Conclusion

BTX-A injections currently target temporary and permanent paralysis; in other words, they aim to remove muscular fibers receiving BTX-A, and with repeated injections, this process continues in a defective cycle, and it is not clear to what extent the sprouting mechanism occurs afterwards, and to what extent the phenomenon of neuroplasticity occurs in the patient with neuromuscular exercise (whether the therapist has prescribed it or not). The researchers’ 14 years of clinical experience supports this claim; that is, the damage becomes fixed within months to two years in patients who do not fully recover within the first few months, and after receiving several sets of BTX-A injection over one to two years, the patient eventually gives in to the complications, unless receiving BTX-A becomes a motivation for neuromuscular exercise and the complications are controlled or reduced by neuroplasticity. Further biochemical and pathological animal studies or human clinical trials are recommended in order to achieve evidence-based results.

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Conflicts of interest

All the authors have no conflict of interest.

References


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