The role of Botulinum toxin type A for prevention and treatment of cleft lip palate (CLP) post-operative scar: a systematic review

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ABSTRACT

Background: Cleft lip palate (CLP) defects are the common orofacial defects found in newborns. The main treatment is lip and palate surgery, often resulting in a hypertrophic scar that significantly affects the patient's aesthetic appearance. Several studies showed the role of Botulinum toxin type A injections for prevention and treatment of CLP post-operative scar. This systematic review aims to review the role of Botulinum toxin type A for prevention and treatment of cleft lip palate surgery scar.

Method: Online databases were searched for relevant studies from Google Scholar, PubMed, and ProQuest. Data sources were searched using MeSH terms "botulinum toxin," "cleft lip palate," and "surgery scar" for all publications up to October 2022. All English papers regarding the role of Botulinum toxin type A in preventing and treating CLP post-operative scar were included. Papers not available in full text or English and not an experimental study were excluded.

Result: Six studies are included in this systematic review consisting of three randomized controlled trials and three clinical studies. The experimental group received Botulinum toxin type A injections, while the control group received an injection of normal saline or other topical treatment. All of the included studies showed positive results regarding the role of Botulinum toxin type A marked with reduced scar width, good Vancouver Scar Scale (VSS), Visual Analogue Scale (VAS), patient satisfaction and no complications or side effects were found.

Conclusion: The Botulinum toxin type A showed promising results for the prevention and treatment of CLP post-operative scar.

Keywords: Botulinum toxin type A, cleft lip palate, surgery scar.


INTRODUCTION

Orofacial clefts are a group of congenital anomalies that most frequently manifest as a single cleft palate or cleft lip with or without a cleft palate. Orofacial clefts are the second-most common congenital birth abnormality worldwide, affecting about 7,000 newborns annually in the United States. One in 500–2,500 live births worldwide result in cleft lip palate (CLP). According to data from the Centers for Disease Control and Prevention (CDC), there are 4,437 cases of CLP annually or one in 940 live births. The majority of orofacial clefts manifest as cleft lips. A 2:1 ratio of men to women is likelier to have cleft lips. Cleft palate, on the other hand, affects men and women equally.

Due to how the CLP altered the patient's appearance and face structure, it can be a severe psychological and financial hardship for the family. Defects such as cleft lip and palate can interfere with a patient's facial appearance and functions, such as speaking and eating, which substantially impacts the patient's psychosocial growth. Additionally, it was linked to significant healthcare costs and an increase in suicide mortality. Only surgery can rectify CLP, and that's the only therapy option. Because it requires a deep awareness of aesthetics and reconstruction expertise, cleft lip and palate repair is a difficult surgical procedure. Clefts' presentation impacts the reconstruction's complexity, and the results vary depending on the surgeon. However, achieving functional and cosmetic deformities of the cleft lip or palate is the primary aim of cleft lip and palate surgery. One of the side effects of CLP surgery is frequent hypertrophy, which leaves a cleft lip scar. The cleft lip scar developed as a result of the center of the face being exposed to dynamic movement, which has a negative impact on the postoperative wound healing process. The patient's proper facial appearance is badly disturbed by the scar on their face, which has a detrimental effect on their self-esteem and confidence. Additionally, the scar tissue interferes with the orbicularis oris muscle's ability to function, which may restrict the maxilla's ability to grow and develop.

The literature and prior studies have described several techniques to reduce the appearance of the post-operative scar from cleft lip and palate surgery, including scar massage, laser therapy, and graft and flap correction. One of the most recent research
METHODS

Study eligibility
Study eligibility criteria were determined using inclusion and exclusion criteria. The inclusion criteria set include studies regarding Botulinum toxin type A’s role in prevention and treatment. In comparison, the exclusion criteria were studied not available in full text and not available in Bahasa or English and non-clinical study design such as case study, review or meta-analysis. The PICO Criteria used in this systematic review are as follows: P (Population) = cleft lip or palate patients or post-operative CLP patients or animal models with cleft lip defect. I (Intervention) = Botulinum toxin type A injection. C (Comparison/Control) = treatment besides Botulinum toxin injection. O (Result) = objective and subjective evaluation of CLP surgery scar.

Search strategy and study selection
The MeSH terms “botulinum toxin,” “cleft lip and palate,” and “surgical scar” were used in the search strategy study to cover all articles up to October 2022. Three electronic databases—Google Scholar, PubMed, and ProQuest—were searched for the study. Duplicate studies from the search results were removed. The study also carried out an abstract screening to determine its applicability to the study’s subject. To eliminate bias, two researchers conducted a literature review. The studies that made it past the abstract screening were then carefully studied to see if they met the requirements for eligibility. The studies that satisfied the eligibility requirements were further examined to produce a literature review. The Preferred Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) diagram, as seen in Figure 1, were used to choose the studies.

Study quality assessment
Study quality was assessed using a modified Jadad scale from the Oxford quality scoring system for the randomized controlled trial (RCT) study. This scale consists of 8 questions. While the other clinical study used criteria from Joanna Briggs Institute (JBI) for the quasi-experimental study that consists of 9 criteria. Each item on the checklist is worth one point if it satisfies the requirements, and the study is deemed acceptable if it earns at least half of the maximum possible points. To prevent bias, two writers independently evaluated the study’s quality.

Synthesis of the study
The narrative synthesis was then completed with all pertinent research that satisfied the eligibility requirements. This systematic review gathers study data on the use of injections of botulinum toxin type A for the prevention and treatment of CLP post-operative scars as qualitative research. We gathered information about the authors, study designs, sample sizes, intervention and control groups, measured outcomes, and study findings from the studies included in the analysis.

RESULTS

Study characteristics
Based on the search results on three electronic databases, we found 1,640 studies that matched the search keywords. After excluding 104 duplication studies, 1,728 were screened for abstracts to determine the suitability of the study with the research topic. A total of 1,690 studies were excluded from the abstract screening, so 38 studies were analyzed for the eligibility criteria. A total of 32 studies did not meet the eligibility criteria, as shown in Figure 1, so in the last phase, only six were included in the final analysis.

Of the six studies, three were randomized controlled trials, and the other three were clinical pilot studies. Studies from several countries such as Ecuador, India, Iran, Mexico, Taiwan, and the USA were published up to October 2022, as stated in Table 1. Study quality
Quality assessment of the RCT study using a questionnaire from a modified Jadad scale done by two authors to prevent bias. The modified Jadad scale comprises eight questions: 1) Was the research described as randomized? 2) Was the approach of randomization appropriate? 3) Was the research described as blinding? 4) Was the approach of blinding appropriate? 5) Was there a presentation of withdrawals and dropouts? 6) Was there a presentation of the inclusion/exclusion criteria? 7) Was the approach used to assess adverse effects described? 8) Was the approach of statistical analysis described? And 9) Was the approach of statistical analysis described? All of the studies were classified as good research with a point range from 6-8.

Sample characteristics
This systematic review comprised 118 humans and 40 Wistar rats as the study sample. Five studies used humans as the study’s sample ranging from infant to adult patients. One study by Chang et al. used 58 adult patients who had undergone cleft lip scar revision (CLSR) surgery. Four studies by Galárraga et al., Navarro-Barquín et al., Orvakonde et al., and Tollefson et al. used infants and children ages 3-24 months as the study subject. Three studies, including patients only with cleft lip and two studies by Galárraga et al. and Navarro-Barquín et al., involved patients with cleft and lip palate. Only one study in our systematic review by Namdar et al. did a study on an animal model using 40 Wistar rats with triangular incisions in the upper lip for a cleft lip model. In their study, to induce cleft lip deformities, ketamine hydrochloride (0.5
measured outcome

The parameter used to measure the effectiveness of Botulinum toxin type A as prevention and treatment of CLP post-operative scar, in general, consisted of objective and subjective evaluation. Several methods were used, such as the Vancouver Scale (VSS), Visual Analogue Scale (VAS), measurement of scar width using photographic plus ultrasound, electromyographic examinations for assessing wound tension, and subjective evaluation using a patient’s satisfaction questionnaire. The VSS comprises several components such as pigmentation, vascularity, pliability and scar height, which lower VSS score implicated a better result. While for the VAS score, the higher, the better. The photographic evaluation examines the white roll match, vermillion match, scar appearance, cupid’s bow form, and lip length were all assessed by two independent observers, who then gave each of these variables a score as shown in Table 2. The EMG examination was done before and after surgery to measure the upper lip tension, representing muscular activity. Subjective evaluation was done through a patient’s satisfaction questionnaire consisting of several questions regarding satisfaction with scar color, texture, width and thickness.

In the Namdar et al. study, they did histopathologic examinations in the rats regarding the inflammation rate, cellular proliferation, fibroblast proliferation and collagen deposition.

study result

Based on our qualitative analysis, all studies showed positive results regarding the role of Botulinum toxin type A injection in preventing and treating CLP post-operative scar. The Botulinum toxin types A injection significantly can reduce the scar width in the experiment more than in the control group. In Chang et al. study, the experimental group had a significantly lower VSS score and better VAS score than the control group. A lower VSS score represents a better result. While better VAS was marked by a higher score, which was evaluated from the scar’s photographs and graded from 0 (worst possible scar) to 10 (best possible scar).

Identified studies form electronic database (n=1,831)
- Google Scholar (n=1,640)
- PubMed (n=3)
- ProQuest (n=189)

Duplicated studies (n=104)

Studies included in abstract screening (n=1,728)

Studies assessed for eligibility criteria (n=38)

Studies included in the final analysis (n=6)

Studies in human (n=5)

Study in an animal model

Excluded studies (n= 1,690)

Studies did not meet eligibility criteria (n=32)
- Non-clinical trial study (n=24)
- Study not available in full text (n=3)
- Study not available in English or Bahasa (n=5)

Figure 1. The PRISMA flowchart of our systematic review.

mL) and xylazine hydrochloride (0.1 mL) were intraperitoneally injected into the rats. Then, the hair on the rats’ faces was shaved, and triangle incisions measuring 7 mm by 7 mm by 4 mm were made at the left side of the top lip of the rats.

The intervention used in all of the studies was Botulinum toxin A injection. Five studies on humans injected Botulinum toxin into the upper lip part, exactly in the orbicularis oris muscle. While Namdar et al. injected the Botulinum toxin straight into the rat’s wound region. Study by Chang et al. did the Botulinum toxin injection after the CLSR surgery or secondary cheiloplasty. Six injections of encoded vial content (0.1 ml for each injection site) were given to the orbicularis oris muscle. While Namdar et al. injected the Botulinum toxin type A on the seventh postoperative day.

Three out of the six included studies used a control group. In a study by Chang et al. and Navarro-Barquin et al., the control group was injected with normal saline into the orbicularis oris muscle. Study by Orvakonde et al. used a modified Millard approach for cleft lip correction and injected 6-8 units of Botulinum toxin type A on the seventh postoperative day.

Three out of the six included studies used a control group. In a study by Chang et al. and Navarro-Barquin et al., the control group was injected with normal saline into the orbicularis oris muscle. The RCT study by Namdar et al. divided the sample into 4 groups, with one group receiving Botulinum toxin type A injections in the wound area and the other three groups receiving one of the topical treatments in the wound area using topical chitosan hydrogel (CHIT), folinic acid chitosan hydrogel (FOLCHIT) or gauze moistened with normal saline as stated in Table 1.
Table 1. Detailed the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size (n)</th>
<th>Type of cleft</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Outcome measured</th>
<th>Follow up time</th>
<th>Result</th>
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<tr>
<td>Chang et al., 2014, Taiwan, RCT.</td>
<td>Fifty-eight adult patients undergo cleft lip scar revision (CLSR) surgery.</td>
<td>Unilateral cleft lip.</td>
<td>30 patients M/F: 12/18 L/R cleft: 20/10 Treatment: Six injections of Botulinum toxin type A (each 0.1 ml) into the orbicularis oris muscle after CLSR surgery.</td>
<td>28 patients M/F: 14/14 L/R: 20/8 Treatment: Injection of normal saline after CLSR surgery.</td>
<td>VSS, VAS and scar width.</td>
<td>6 months.</td>
<td>- The VSS score in the experimental group was lower than in the control group (2.45±1.52 vs. 3.50±1.88; p=0.023).&lt;br&gt;- VAS score in the experimental group was better than the control group (7.47±0.64 versus 6.10±1.06; p&lt;0.001).&lt;br&gt;- Scar wound significantly narrower in the experimental group than control group both in the first and second point of evaluation (0.62±0.18 mm vs. 0.95±0.31 mm; p&lt;0.001) and (0.63±0.18 mm vs. 0.92±0.36 mm; p&lt;0.001).&lt;br&gt;- There was a significant decrease in orbicularis activity of the lips after the Botox injection, especially during rest (p&lt;0.039).&lt;br&gt;- No complication was found after the treatment.&lt;br&gt;- The FOLCHIT group showed faster initial regeneration by higher inflammation and cellular proliferation but has a higher tendency for scar formation through higher fibroblast proliferation and collagen deposition.&lt;br&gt;- The injection of botulinum toxin A provides less fibroblast proliferation and collagen deposition and, thus, a lower potential for scar formation than the other groups.</td>
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<tr>
<td>Galárraga et al., 2009, Ecuador, Clinical study</td>
<td>Five children aged &lt; 6 months years old.</td>
<td>Complete cleft lip and palate.</td>
<td>Injection of 10 units of Botulinum toxin into orbicularis oris muscle during cheiloplasty surgery, EMG performed before and after surgery.</td>
<td>No control groups.</td>
<td>Decrease in the orbicularis oris muscle, complication.</td>
<td>10 days after surgery.</td>
<td>- The FOLCHIT group showed faster initial regeneration by higher inflammation and cellular proliferation but has a higher tendency for scar formation through higher fibroblast proliferation and collagen deposition.</td>
</tr>
<tr>
<td>Namdar et al., 2022, Iran, RCT.</td>
<td>Forty Wistar rats with triangular incisions in the upper lip, ten rats in each group.</td>
<td>Unilateral cleft lip.</td>
<td>Group I: Topical chitosan hydrogel (CHIT) with gauzed soaked in normal saline after wound closure. Group II: Topical folic acid chitosan hydrogel (FOLCHIT) with gauzed soaked in normal saline after wound closure. Group III: injection of 3 units of botulinum toxin A in the wound region.</td>
<td>Topical treatment using a gauze pad soaked with normal saline for 5 min immediately after wound closure.</td>
<td>Fibroblast proliferation, collagen deposition, inflammatory cell infiltration, neovascularization, and epithelial proliferation.</td>
<td>28 days.</td>
<td>- The injection of botulinum toxin A provides less fibroblast proliferation and collagen deposition and, thus, a lower potential for scar formation than the other groups.</td>
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<td>Author</td>
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| Navarro-Barquin et al., 2019, Mexico, RCT. | Twenty-two patients aged 4-24 months | Unilateral or bilateral cleft lip and palate | 11 patients M/F: 5/6 L/R cleft: 6/5 Treatment: Injection of 8 IU Botulinum toxin types A at a dilution of 100 IU/1 ml into both orbicularis oris muscles. | 11 patients M/F: 8/3 L/R: 9/2 Treatment: Injection of normal saline bilaterally into the orbicularis oris muscle. | Vancouver scale, scar width and adverse outcome. | 3 and 6 months. | • Scar width evaluation in 3 months dan 6 months showed significantly narrower scars in the experimental than in the control group (1.70± 0.67 vs. 4± 1.65 mm; p=0.003) and (1.90± 0.56 vs. 3.89± 1.69 mm, p=0.008), respectively.  
• Vancouver scale was significantly lower in the experimental group than the control group on 3- and 6-month evaluation (2.0± 1.05 vs. 3.78 ±1.20 mm, p=0.004) and (1.10± 1.05 vs. 3.22±1.20 mm; p=0.002), respectively.  
• No adverse outcomes were found.  
• Based on the photographic evaluation, most patients had either excellent or good aesthetic outcomes.  
• Based on subjective evaluation, all patients were happy or very happy with the surgical results.  
• Botulinum toxin can be used safely in infants with cleft lip deformities for chemo-immobilization after surgery to reduce the surgery scar.  
• Early aesthetic results were satisfactory.  
• No complication was found. |
| Orvakonde et al., 2020, India, Clinical study | Thirty patients aged 3-6 months | Unilateral left cleft lip. | The sample was undergone modified Millard technique surgery and injection of 6-8 units of Botulinum toxin A on the 7th postoperative day. | No control groups. |Photographic and subjective evaluation by two independent observers. | 1 year. |                                                                      |
| Tollefson et al., 2006, USA, Clinical study. | Three infants aged 3-6 months | Bilateral and unilateral cleft lip. | Botulinum toxin (1-2 U/kg at 25 U/mL) was injected into the bilateral aberrantly oriented orbicularis oris muscles via 4 superficial injection sites seven days before the surgical repair. | No control groups. | Lips tension before and after the treatment, patient satisfaction and complication after the treatment. | Not stated. |                                                                      |

Abbreviation: CHIT= chitosan hydrogel; CLSR= cleft lip scar revision; E=Electromyographic; F=female; FOLCHIT= folinic acid chitosan hydrogel; IU= International Unit; L=left; M=male; mm= millimetre; R=right; RCT=Randomized controlled trial; USA=United States of America; VAS=Visual Analogue Scale; VSS=Vancouver Scar Scale.
Hypertrophy with disturbance
No disparity
2 mm
Equal length on cleft and
3
10
2
2 > 2 mm
>2 mm
3
Scalp appearance
No hypertrophy
1
Hypertrophy with no disturbance of
cupids bow or columella
2
Hypertrophy with disturbance of
cupids bow or columella
3
Cupids bow form
No disparity
1
Distortion on cleft side < 2 mm
2
>2 mm
3
Lip length
Equal length on cleft and
cupids bow or columella
1
Shortening on cleft side > 2 mm and
< 5 mm
2
Shortening on cleft side > 5 mm
3
Total
5
10
15

Interpretations: 5 = Excellent; 6-10 = Good; 11-15 = Poor.

Study by Navarro-Barquin et al. also found a similar result, the stated a significantly narrower scar and lowered VSS sore in the experimental than the control group, as stated in Table 1.8 Study by Galárraga et al. found a significant decrease in orbicularis activity of the lips after Botox injection, especially during rest. The decreased tension of the lip muscle helps the wound-healing process and decreases scarring.1 From the subjective evaluation, a study by Orvakonde et al. stated that the majority of the study subjects were satisfied with the wound color (50%), wound texture (63.3%), wound width (66.6%) and wound thickness (56.6%).10 In an animal model study by Namdar et al., they found the injection of botulinum toxin A provides less fibroblast proliferation and collagen deposition and, thus, a lower potential for scar formation compared with the other groups.11 All studies did not find any complications and side effects regarding the Botulinum toxin type A injections, such as redness and necrosis.7,11,14

**DISCUSSION**

This systematic review aims to review the role of Botulinum toxin type A in preventing and treating CLP post-operative scar. Based on the results, Botulinum toxin type A showed promising results in preventing and reducing post-operative scarring. The CLP post-operative scar is recognized due to its location in the face. In addition to being functionally limited and possibly leading to psychosocial disengagement in certain individuals, facial scars can be disfiguring visually. Differences in color, thickness, contour, compliance, and overall cosmetic and functional drawbacks, such as contracture formation, help to distinguish cutaneous scars from surrounding normal skin.15

The most prevalent complication of CLP surgery is the presence of a hypertrophic scar, which places the patient at a significant social disadvantage and causes discomfort. The cleft scar excision, orbicularis oris muscle anatomical repair, and correction of asymmetries found in the Cupid bow and philtral columns are the tenets of CLP surgery. The orbicularis oris muscle, which is adjacent and constantly used for talking, eating, drinking, blowing, sucking, and a variety of facial gestures, pulls perpendicular to the line of wounds caused by CLP surgery. These frequent bursts of distracting tensional forces cause micro-trauma to the healing site, prolonging the inflammatory response and, ultimately, causing greater fibrosis.2,3

Botulinum toxin type A is a neurotoxic protein secreted by the bacteria Clostridium botulinum. In both medicine and dentistry, Botulinum toxin type A is frequently employed. Botulinum toxin type A's principal effect is to prevent the release of acetylcholine from neuromuscular junctions, which temporarily paralyzes the muscles. The main mechanism driving the scar’s enlargement in the face region, particularly in CLP scars, is the strain of the orbicularis oris muscle. Continuous use of this muscle while eating, speaking, or expressing emotion increases skin tension along the borders of the wound, which encourages fibroblast proliferation and excessive collagen fiber deposition in the newly created tissue.6,13,16

Our analysis showed the role of Botulinum toxin type A in decreasing lip tension and muscular activity after CLP surgery. To obtain a functional and aesthetically attractive upper lip contour, the repair of cleft lip abnormalities necessitates precise attention to recreating the 3-dimensional characteristics of the lip and nasal tissues. The degree of wound tension present during healing is one of the numerous elements impacting the outcome of cleft lip repair. When sealing a widely divided cleft lip, excessive tension can lead to unsightly scars and, rarely, wound collapse (fistula or dehiscence). Thus, decreasing tension helps reduce the wound tension and the risk of scarring.11

The Botulinum toxin type A significantly reduced scar width and gave better results from the objective and subjective evaluation both in human and animal models. This mechanism can be explained according to a study by Hu et al. They stated that Botulinum toxin type A could reduce scars and stop skin contractions throughout the healing process by changing the signaling route in fibroblast.17 Botulinum toxin type A has been shown by Xiao et al. to reduce muscular tension and alter the distribution of fibroblasts produced from hypertrophic scars.18 Another study by Carrillo et al. demonstrated that botulinum toxin enhances the wound's microenvironment by developing richer vascular support, increasing the production of pro-angiogenic factors, and decreasing muscular contraction, thereby reducing the tension at the wound’s edges and resulting in less ischemic environment. The Botulinum toxin's increased expansion of the CD31 messenger's ARN ensures a superior healing process, which also lowers the hypoxic condition and sustainably enhances angiogenesis. Clinically, this might mean improved muscle recovery, a reduction in whistling deformity, better collagen alignment, and a more effective remodeling phase due to
increased oxygen supply and nutrients by improved vascularity.\textsuperscript{11,19}

Botulinum toxin type A injection, both before and after CLP surgery, has no negative side effects, improves surgical outcomes, and produces a more aesthetic scar with a lower likelihood of hypertrophic scar, increasing patient and family comfort and lowering the stigma associated with cleft lip. It is also safe for use with infants and children beginning at 3 months of age.\textsuperscript{6,11} Additionally, botulinum toxin is more comfortable for the patient and their parents than other treatments like silicon plates or tension bands. It is a cost-effective method of lowering the likelihood of subsequent surgeries. It also represents a one-time intervention in a population with limited access to specialized treatment.\textsuperscript{7,10}

CONCLUSION
Botulinum toxin type A showed promising results as a modality to prevent and treat the CLP post-operative scar. It significantly reduces scar width and better scar wounds through objective evaluation using VSS, VAS score and photographic evaluation. It also improves patient satisfaction and is safely used for infants older than 3 months without causing side effects or complications.

CONFLICT OF INTEREST
The authors declare that there is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION
All of the authors contributed to the study from the conceptual framework, data gathering, and analysis until the study’s results were interpreted upon publication.

REFERENCES