ISSN: 03875547
Volume 45, Issue 07, September, 2022

Evaluation of the efficacy of botulinum toxin type A injection on improving the submandibular approach scars: Randomized controlled trial, Split-Scar

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Keywords:
Botulinum toxin type A, scar, cicatrix, wound healing, submandibular approach wound.

ABSTRACT

This study aims to evaluate the efficacy of early postoperative injection of botulinum toxin type A (BTA) on improving the submandibular approach scars. Fifteen patients who underwent facial surgery through the submandibular approach were enrolled in this study. On the seventh postoperative day, BTA was randomly injected into one-half of each wound. The other half was injected with the same amount of saline alone. The scars were assessed independently by three surgeons at one, three, and six months postoperatively using the visual analogue scale (VAS), the Vancouver Scar Scale (VSS), and the patient and observer scar assessment scale (PSAS and OSAS). All Fifteen patients have completed the clinical study according to the three follow-up periods. Compared to the half injected with saline only, the BTA treated side showed a noticeable improvement and statistically significant difference in most periods, especially at the six-month follow-up appointment. According to the used scales: VAS, VSS, PSAS and OSAS, the results of statistical tests after six months were as follows (P = 0.001, P = 0.009, P=0.004 P=0.001), respectively. BTA early injection into submandibular approach wounds leads to better-looking submandibular approach scars.

1. INTRODUCTION

Scars are formed after surgery, trauma, or some inflammatory conditions. They may produce an aesthetic, functional, and psychological impact, which affects the patient's daily life [1].

Scars are thought to be formed due to abnormal wound healing, including excessive production of fibroblasts and collagen fibers and increased angiogenesis [2]. Skin scars are generally distinguished from the surrounding area by color, thickness, contour and overall aesthetics [3]. Surgical scars associated with facial surgery remain a significant problem for both the surgeon and the patient [4]. Thus, almost all patients desire to improve their facial scars, even if it is a slight improvement [5].

The wound healing process consists of four interrelated phases: the hemostasis phase, the inflammatory phase, the proliferative phase, and the remodeling phase [6]. Any change in these stages can cause an increase or decrease in scarring [7]. In wounds that heal satisfactorily, the inflammatory phase is prolonged and hypertrophic scars and keloids may form [8]. The act of tension on the wound edges is a significant factor in causing the poor appearance of the scars. However, the temporary muscle paralysis induced by botulinum toxin type A (BTA) can reduce movement and tension around the wound. Reducing this tension may help prevent the increased width, enlargement, and hyperpigmentation of facial scars [9]. BTA also reduces scar formation by inhibiting collagen production, delaying the growth of fibroblast cells, and reducing hypertrophic growth of the scar [10]. This study aimed to determine the efficacy of BTA on improving the scars of the submandibular approach.

2. Materials and Methods

2.1 Study design

The study was designed as a double-blind, randomized controlled split-scar model to assess the efficacy of BTA in improving submandibular approach scars compared with normal saline as a placebo. One scar for each patient was symmetrically divided into two halves. Each half was randomly assigned to one of the following: the experimental group injected with BTA and the control group injected with normal saline as a placebo.

2.2 Sample size calculation

The sample size calculation was carried out using G*Power v 3.1.9.7 software based on the study done by [11]. If treatment could improve the VAS visual analog scale score by 1.24, which was considered significant clinically, approximately 12 scars per group were necessary to provide results with a genuine significance (considering the standard α error of 0.01 and a power of 0.8). Assuming a 20% non-compliance rate for follow-up evaluation, the sample size was increased to 15 patients.

2.3 Patients' selection

Between January 2020 and December 2021, patients who required facial surgery through the submandibular approach based on a preoperative assessment by an oral and maxillofacial surgeon were enrolled in this study. Informed consent was obtained from all patients after a detailed explanation of the procedure. The inclusion criteria were as follows: Patients ages above 18 years, fit and well patients, patients who have undergone recent facial surgery through the submandibular approach, the length of the wound is at least 4 cm, and patients who were willing and able to participate in the study and make several visits during the follow-up sessions. The exclusion criteria were as follows: Patients who are known to be allergic to any botulinum toxin, patients who underwent BTA treatment in less than six months, pregnant or breastfeeding women, patients with a history of hypertrophic scar formation or keloid formation, patients addicted to alcohol or narcotic drugs, patients with neurological disorders, patients taking aminoglycosides because this class of antibiotics may interfere with the neuromuscular transmission of the toxin and increase the effect of botulinum toxin [12], and patients with active inflammation or infection at the injection site.

2.4 Study procedures

The subcutaneous layers were closed with 4/0 Vicryl sutures during the surgical procedure, and the dermal layer was sutured using the interrupted suture technique with 6/0 nylon sutures. The surgical procedure and the suturing were done by the same surgeon for all patients. On the seventh postoperative day, in the suture removal session, the scar was randomly divided into two symmetrical halves. The simple randomization method was used by flipping a coin. Each half was injected with either BTA or normal saline 0.9%. Vials

containing 100 U of BTA (TOXTA JETEMAco. Ltd. South Korea) were mixed with 2 ml of 0.9% saline.

In the experiment group, the injection points were 5 mm away from the edge of the wound, and a space of 1cm was left between each point. Each point was injected with five units of BTA solution. The control group was injected with the exact previous amounts and with the exact dimensions, but with saline only. The first injection site was 5 mm away from the midline on both sides. Injections were administered using 1.0-ml insulin syringes with 8-mm, 31-gauge needles.

2.5 Parameters for outcome assessment

At follow-up appointments in the first, third, and sixth month of observation, three clinicians were asked to separately conduct objective clinical evaluations of each of the two halves of the scar, leaving a 1 cm square in the center of the scar unassessed, using the visual analogue scale (VAS) [13], the Vancouver Scar Scale (VSS) [14] and the patient and observer scar assessment scale (PSAS and OSAS) [15]. Both the observers and the patients did not know in which half the BTA was injected.

2.6 Statistical tests

Each aspect of the results of the visual analogue scale, the Vancouver Scale, and the patient and observer scar assessment scale for each half of the scar between the BTA treatment group and the control group were analyzed using the T student test for paired samples if the data were normally distributed, and its nonparametric Wilcoxon if the data were abnormally distributed. Cronbach's α was calculated to evaluate the internal consistency between the raters. The statistical analyses were conducted using SPSS software version 25.0. Statistical significance was defined if P-value < 0.05.

3. Results

Among the 21 eligible patients with facial surgery through the submandibular approach, four did not meet the inclusion criteria, two patients refused to participate in the study, and 15 patients were enrolled. Fifteen patients finally completed the entire study. (Fig. 1)

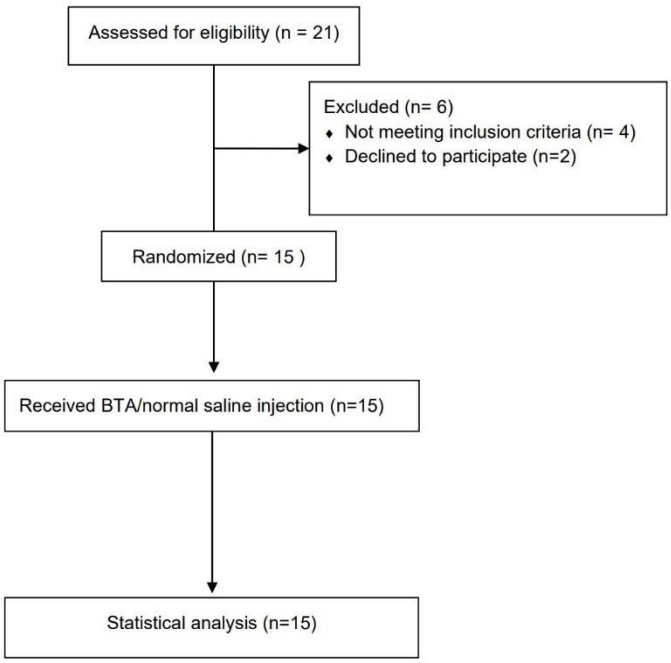

Figure 1: Flow diagram detailing the eligibility, enrollment and randomization process.

The mean age of the study sample was 33.27±14.82. Their ages ranged from 18 to 55 years, 12 males had an average age of 36.83±14.49, and three females had an average age of 19.0±1.00. The surgical procedure performed was reduction and fixation of body and angle fractures of the mandibular. The average length of the scar was 6.16 cm. The injection was performed on the seventh postoperative day. The results showed that 66.7% of the patients were injected with BTA in the anterior half of their scar, and 33.3% were injected with BTA in the posterior half of their scar. There were no obvious serious complications. Only local pain occurred in one patient and itching in another after BTA injection. The symptoms disappeared immediately after a short period without treatment (table1).

All scar assessment scales demonstrated favorable changes for the BTA group compared to the control group in all follow-up periods (Fig. 2).

3.1 The effectiveness of BTA in improving scar according to VAS

The VAS score in the experimental group was significantly better than the control group at the three follow-up appointments (p=0.001, p=0.000, p= 0.001), respectively, as shown in (tables 2 and 3). Interobserver consistency in using VAS was high (Cronbach α= 0.808).

Table (1)
Patients' characteristics and treatment records.

Patient number	gender	Age year	Wound length	Injection side	Complication
1	F	18	5.5	anterior	None
2	M	40	6	anterior	None
3	M	19	6	anterior	None
4	M	19	5.5	posterior	None
5	M	55	5	posterior	local pain
6	M	54	5	anterior	None
7	F	19	12	anterior	None
8	M	41	6	anterior	itching
9	M	44	5	anterior	None
10	M	44	5.5	anterior	None
11	M	23	6	anterior	None
12	M	21	5	anterior	None
13	F	20	5.5	posterior	None
14	M	32	5.5	posterior	None
15	M	40	9	posterior	None

ISSN: 03875547
Volume 45, Issue 07, September, 2022

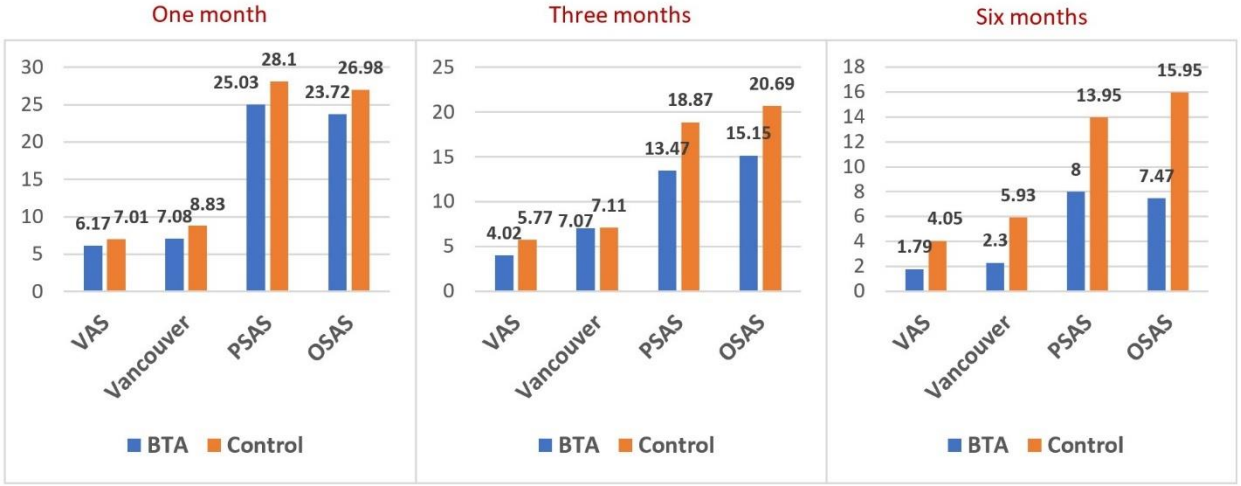

Figure 2: Improvement of scat assessment scales of BTA (left) and control group (right). Left: one month after treatment. Center: three months after treatment. Right: six months after treatment.

3.2 The effectiveness of BTA in improving scar according to Vancouver

The VSS score in the experimental group was significantly better than in the control group at the three follow-up appointments (p=0.000, p=0.017, p= 0.009), respectively, as shown in (tables 2 and 3). Interobserver consistency was high (Cronbach α= 0.911).

3.3 The effectiveness study of BTA in improving scar according to the OSAS

The OSAS score in the experimental group was significantly better than the control group at the three follow-up appointments (p=0.028, p=0.001, p= 0.001), respectively, as shown in (tables 2 and 3). Interobserver consistency for OSAS was high (Cronbach α= 0.97).

3.4 The effectiveness study of BTA in improving scar according to the PSAS

The PSAS scores in the experimental group were significantly better than in the control group at both the second (p= 0.001) and third points (p=0.004), as shown in (tables 2 and 3).

Table (2)

Statistical results of scar scales on both groups at the first and the second time point for the normally distributed data.

Scales		BTA side			Saline side			Differences between means						
		number of cases	Mean	Standard deviation	number of cases	Mean	Standard deviation	Mean	Standard deviation	95% CI min	95% CI max	Calculated |"t."	p-value	differences significance
VAS	T1	15	6.17	0.9	15	7.01	0.7	-0.85	0.8	-1.3	-0.4	-4.127	0.001	*
	T2	15	4.02	0.7	15	5.77	0.9	-1.75	0.9	-2.2	-1.3	-7.911	0.000	*
OSAS	T1	15	23.7	6.1	15	26.9	7.2	-3.3	5.2	-6.1	-0.4	-1.339	0.028	*
	T2	15	15.2	3.4	15	20.7	5.7	-5.5	5.1	-8.3	-2.7	-4.234	0.001	*

PSAS	T1	15	25.03	6.5	15	28.1	7.4	-3.1	7.6	-7.3	1.1	-1.561	0.141	NS
	T2	15	13.5	4.2	15	18.9	5.4	-5.4	4.7	-7.9	-2.8	-4.473	0.001	*
Vancouver	T1	15	7.08	1.6	15	8.83	1.7	-1.8	1.2	-2.4	-1.1	-5.857	0.000	*

Student's Paired Samples Test, T1: after one month, T2: after three months, (*): significant at P<0.05

Table (3)

Statistical results of scar scales on both groups at the second and the third time point for the abnormally distributed data.

Scales			P-value	significance
Vas	T3	BTA side – Saline side	0.001	*
OSAS	T3	BTA side – Saline side	0.001	*
PSAS	T3	BTA side – Saline side	0.004	*
Vancouver	T2	BTA side – Saline side	0.017	*
	T3	BTA side – Saline side	0.009	*

Wilcoxon Signed Ranks Test, T3: after six months, (*): significant at P<0.05

The results showed a general improvement in the scar during the three follow-up periods on both sides. However, the side injected with BTA, compared with the other side injected with saline, showed a clear superiority in favor of the first. (Fig. 3)

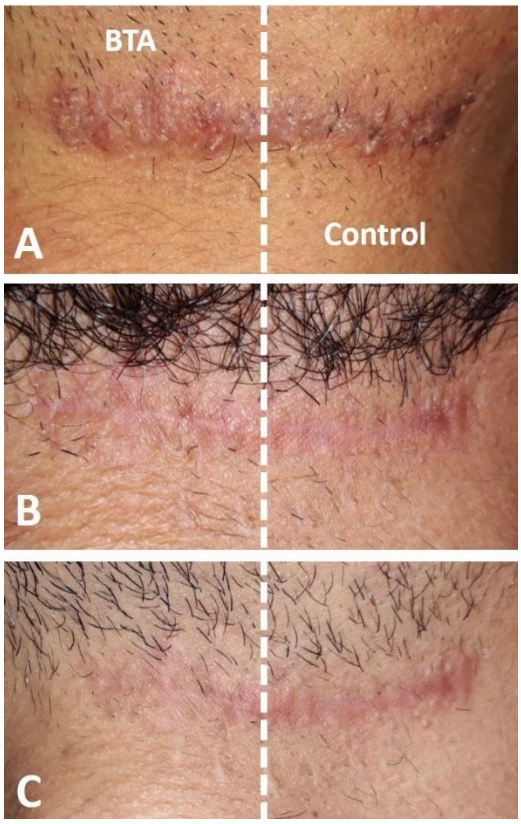

Figure 3: submandibular approach scar (A) After one month, (B) After three months, (C) After six months follow up. The left half treated with BTA, and the right half treated with normal saline.

4. DISCUSSION

A scar is the only lasting product after surgical treatments [16]. Incision anatomical location, patient's race,

surgical techniques, and postoperative infections are all factors that contribute to an undesirable scar [17]. Poor cosmesis scars, especially in visible areas like the neck and face, may cause distress, psychological problems, and functional disorders [18], [19]. To our knowledge, this is the first study that has an objective and subjective evaluation of scars following BTA injection into submandibular approach wounds using VAS, VSS, PSAS, and OSAS.

4.1 Injection time

In previous studies, times for BTA injection ranged from immediately after skin closure to 14 days [11], [16]. BTA reduces the infiltration of inflammatory cells during wound healing; as a consequence, healing time is prolonged [20]. During the wound healing process, the inflammatory phase endures from three to five days [6]. Thus, in our study, we chose to perform the injection on the seventh postoperative day. This is consistent with the study of [21], who performed the injection on days 6 to 7 postoperatively and reported excellent results.

4.2 Dosage and diffusion

In previous research, there was no consensus regarding the dose of BTA for scars [9]. In these previous studies, the injection dose ranged from two to 10 units at each point, with a distance of approximately 1 cm between each point. The distance from the wound edge ranged from 5 to 10 mm [3], [9], [16]. In our study, we injected five U/cm at the site 5 mm away from the wound edges with an interval of 1 cm, and the first point near the midline was about 5 mm away from it on both sides to reduce the possible carry-across effect. This distancing was based on several studies that found the diffusion of BTA after administration stays within a range of 1 cc approximately [22- 25].

In terms of safety, the highest injected dose in our study was 50 units. This was much lower than the maximum dose of 200 units/month reported by [16].

4.3 Efficacy and evaluation

The first reported use of BTA to reduce wound complications was in 1997 by [26] after eyelid reconstruction in 11 patients. In [27] studied the efficacy of BTA in improving the appearance of skin scars in primates and proved that it could effectively improve their appearance. Since then, multiple studies have been conducted on animals and have demonstrated that BTA can improve wound healing and reduce scarring [28], [29].

In 2006, Wilson found that the result of BTA type A injection into facial scars during reconstructive surgeries was very satisfactory [30]. Similar results were found by [31] for BTA in the treatment of facial wounds. The first split-scar, double-blind, randomized controlled trial was published by [32]. BTA was injected into 15 thyroidectomy scars. In the sixth month of follow-up evaluation, a significant improvement was noted in half treated with BTA, with slight changes in the control group.

In our study, the overall median VAS, VSS, OSAS, and PSAS scores at follow-up visits were significantly different between the BTA and control groups.

As for VAS, the results showed a statistically significant difference between the two sides during the follow-up periods. This is consistent with all the previous similar studies [3], [9], [11], [19], [21], [31], [33]. The reason is that VAS appears to be suitable for assessing the scars of simple facial wounds because it is sensitive, ready to use, easy to use, and its results are reproducible [3], [31].

In regard to VSS, we also found a statistically significant difference between the two sides of the wound

during the observation periods, and we agreed with [9], [21], [34]. This is because BTA injections inhibit the proliferation of fibroblasts, the expression of transforming growth factor beta-1 (TGF-B1) [35], and the differentiation of fibroblasts into myofibroblasts [16], which may protect the reduction of vascularity [36] and significantly reduce wound tension [21], [37]. Therefore, it contributes to improving the overall Vancouver Scale score.

We disagree with [9], [11], [31], [38]. This may be attributed to the fact that Phillips et al. injected BTA into the midline, so the crossover effect cannot be prevented. Furthermore, the injection was in a lower part of the neck that is more proposed to movement and leads to more tension in the area. As for [39] he injected BTA after cleft lip repair, which is known to be under tension and is subject to poorer scaring. The low vascularity in the forehead could be the reason for the disapproval of Li Hu. Plus, he did not report how he managed the possible crossover effect. For [31], the lack of agreement could be because he injected BTA into different facial wounds and did not use the split scar method.

The OSAS and PSAS results showed a statistically significant difference between the two sides during the follow-up periods, except for the first period of PSAS. This is the opposite of the similar studies performed by [3], [31], [38]. For Kim et al., the discrepancy may be due to their injection technique that avoided the occurrence of muscle paralysis. Also, he did not use the split scar method. The disapproval with Ziade and Philipe could be for the same reasons discussed before.

4.4 Effect mechanism

The act of pulling on the wound's edges is an essential factor in the bad appearance of scars after wounds [39]. BTA causes temporary muscle paralysis and thus reduces tension on the wound's edges [37], [40]. Thus, it eliminates dynamic tension on the edges of the wound. It can also significantly reduce collagen deposition and thus prevent and reduce scarring [41]. Recently, BTA has been found to inhibit the proliferation of fibroblasts and inhibit the expression of transforming growth factor beta-1 (TGF-B1) [35]. Furthermore, BTA directly inhibits the differentiation of fibroblasts into myofibroblasts [16]. Hence, we believe that the BTA properties of tension-relieving, along with its direct inhibitory effects on fibroblasts and transforming growth factor-beta-1 support its use in the prevention of submandibular approach scars.

4.5 Limitations

There are some limitations to this study. First, no histological study of the scar tissue was conducted at the end of the observation period. Second, the majority of patients who were enrolled in the study were males. Third, the patients we studied had a wide range of ages.

5. Conclusions

This study indicates that early postoperative injection of the BTA results in a better submandibular approach scar. Accordingly, we recommend conducting additional studies that compare the effects of BTA injections at different anatomical levels and locations of the face.

Institution where the work was done:
Oral and maxillofacial surgery Damascus university hospital.

Ethical considerations:
Informed consent was obtained from all participants according to the protocols and regulations of the institutional review board and ethics committee of the Damascus University, Damascus, Syria.

Declaration of competing interest:
The authors declare no conflict of interest.

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