Use of botulinum toxin type A to improve treatment of facial wounds: A prospective randomised study

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Summary Background: The tension vectors acting on the wound edges are transmitted to immature collagen fibres synthesised during the normal healing phase. This accounts for scar widening as well as hypertrophic and hyperpigmented scars. The aim of our study was to evaluate whether early injections of botulinum toxin type A (BTA), which induces temporary muscular paralysis, decreases tension vectors on wound edges and enhances scarring of facial wounds.

Patients and methods: Thirty patients with facial wounds were enrolled in this study and randomised into two groups with or without injection of BTA within 72 h postoperatively. BTA was injected into the facial muscles directly or indirectly involved in scar widening. Scars were assessed at a 1-year follow-up visit by patients using the Patient Scar Assessment Scale (PSAS) scale, by an independent evaluator using the Observer Scar Assessment Scale (OSAS) and the Vancouver Scar Scale (VSS), and by a board of six experienced medical specialists using the Visual Analogue Scale (VAS) with standardised photographs.

Results: At the 1-year visit, 24 patients were reviewed and six patients were lost to follow-up. No statistically significant differences were found between the two groups for the PSAS, OSAS and VSS scores. However, the median VAS rated by the six evaluators was 8.25 for the botulinum toxin-treated group compared with 6.35 for the control group. This result was statistically different, demonstrating improved scarring with BTA.

Conclusions: Thanks to chemoimmobilisation, injections of BTA appear to improve cosmesis of facial wounds. Accordingly, they would be beneficial for use in young patients for wounds without tissue loss, lying perpendicular to the reduced tension lines of the skin of the face.

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Unsightly facial scars have a destructive socio-psychological impact. They often occur in wounds perpendicular to the lines of Langer as defined by Karl Langer in 1861. The tension vectors acting on the wound edges are transmitted to immature collagen fibres synthesised during the normal healing phase. This accounts for scar widening as well as hypertrophic and hyperpigmented scars due to increased extracellular collageneous and glycosaminoglycaneous deposits. In 1892, Theodor Kocher, a Nobel laureate in medicine and physiology, was the first to make skin incisions along relaxed skin tension lines. Yet, scar alignment with the lines of Langer does not completely eliminate elastic forces on the wound edges of adjacent skin. Botulinum toxin type A injections induce temporary muscular paralysis, and relieve the tension on wound edges. This relief of tension may help prevent the widening, hypertrophy and hyperpigmentation of facial scars.

The aim of this study is to investigate whether early botulinum toxin type A injections improve scarring of facial wounds.

**Patients and methods**

This study was designed as a prospective, blinded, randomised, controlled, single-institution trial. The level of evidence is II according to the American Society of Plastic Surgeons rating levels of evidence.

Patients older than 18 years presenting to the emergency room at the Lapeyronie Hospital in Montpellier (France) with a facial wound without tissue loss were enrolled from May to October 2009.

The exclusion criteria applied were allergy to botulinum toxin, current pregnancy or breast feeding, myasthenia, previous injection of botulinum toxin within 6 months prior to enrolment and refusal to participate in this trial. Eligible patients were informed about the study protocol in clear, simple language before their informed consent was obtained.

Patients were randomly assigned to one of two groups: the 'toxin' group or the 'control' group. Patients of the 'toxin' group were injected with botulinum toxin in facial muscles directly or indirectly involved in scar widening within 72 h following the suturing of the facial wound. Patients of the 'control' group were not given injections following the suturing of the facial wound.

Data regarding age, sex, phototype according to the Fitzpatrick scale, treatment delay, cause of lesion, wound location and wound length were obtained at an initial clinical examination.

All patients were sutured by the same surgeon in the emergency department using identical facilities, according to a standardised protocol. For local anaesthesia, a solution of 1% lidocaine (LIDOCAINE 10 mg ml; Laboratoire Aquevttant, Lyon, France) was used. A standardised resterilisable suture kit was used for suturing. Subcutaneous suturing for 'deep wounds' involving the hypodermis was realised using simple invasent Polyglactin 4/0 sutures (VICRYL 4/0®, Ethicon Inc., Somerville, NJ, USA). Cutaneous suturing was realised using simple Polypropylene 5/0 sutures (PROLENE 5/0®, Ethicon Inc., Somerville, NJ, USA).

Patients randomly assigned to the «toxin» group received an injection of Botulinum Toxin Type A (BOTOX®, ALLERGAN, Westport, Ireland) within 72 h after wound closure. All injections were performed by the same physician experienced in botulinum toxin treatment. The study medication was prepared in proper facilities. The vials contained 100 units of Allergan botulinum toxin type A mixed with 10 ml of 0.9% injectable saline, that is, 1 U of Allergan toxin per 0.1 ml. The vials were refrigerated and used within 4 h. Injections were performed with a 1 ml syringe. The physician injected the amount of botulinum toxin he/she considered necessary to induce paresis of the face muscles directly or indirectly involved in scar widening. Patients received daily standardised antiseptic treatment with Chlorhexidine (BISEPTINE®, Bayer Laboratory, Gaillard, France) for 7 days. At the 7-day follow-up visit, patients were seen and examined for stitch removal and clinical assessment.

Patients were instructed to strictly observe adequate protection with sunglasses and hats and SPF 50+ sunscreen for 1 year. They also initiated a course of 20 manual scar massages 10 days after suturing.

Close-up photographs were taken of the wounds at a 1:1 ratio with a Kodak digital camera (KODAK M1073 IS, Rochester, NY, USA), flash, 10.6-megapixel resolution and blue background prior to wound suturing, following wound suturing, at the 7-day follow-up visit and at the 1-year visit.

At the 1-year visit, the final outcome was evaluated via subjective patient satisfaction rating (very unsatisfied, unsatisfied, satisfied, very satisfied), PSAS completed by patients,10 OSAS completed by an experienced observer in an independent and blinded fashion,10 VSS completed by an experienced observer in an independent and blinded fashion10 and a 1–10 VAS used by a group of three plastic surgeons and three emergency physicians, all experienced in the treatment of facial wounds. VAS scores were determined in a blinded fashion with serialised digital photographs of all patients. The evaluators assessed the scars independently to avoid any influences.

The number of participants to be enrolled in the study was calculated with EPIINFO based on data in a study by Quinn et al.11 A 5% discrepancy between the ‘toxin’ group and the ‘control’ group was expected on the VAS scale. Minimal sample size was estimated at 15 per treatment group assuming a type 1 error level of 5% and an 80% chance of bilateral hypothesis. A 15% loss to the follow-up rate was expected. Data were analysed with the Student t-test or the Wilcoxon rank sum test according to the distribution for the quantitative variables, and with a chi-squared test for the qualitative variables. When chi-squared test validity conditions could not be met, the Fisher exact test was used. The minimal significant difference was 5% for all tests. Statistics were analysed in collaboration with the Department of Medical Information at the Montpellier University Hospital with SAS V9 software (SAS Institute, Cary, NC, USA).

**Results**

Thirty-four patients were assessed for eligibility in this study from May to October 2009. Four patients were
deemed not eligible. Thirty patients underwent randomisation. Fifteen patients were randomly assigned to the ‘toxin’ group and 15 patients to the ‘control’ group. Of the 15 patients in the ‘toxin’ group, four patients were lost to follow-up because they did not attend the 1-year visit. Of the 15 patients in the ‘control’ group, two patients were lost to follow-up for the same reason. Age, sex and phototype according to the Fitzpatrick scale are listed in Table 1.

Cause of lesion, wound location, length and depth (defined by whether subcutaneous suture was used or not) are listed in Table 2. Variances were assessed and found to be similar in the two samples; hence, the two groups were judged comparable.

The mean dose of botulinum toxin injected per patient in the ‘toxin’ group was 20 U Allergan (minimum 15, maximum 40).

On day 7 postoperatively, skin ischaemia at the extremity of a sutured skin flap on the philtrum was observed in one patient in the ‘toxin’ group. Spontaneous healing was necessary, thus affecting final outcome at the 1-year visit. No complications were observed in the ‘control’ group on day 7.

One complication was observed after injections of botulinum toxin on the zygomaticus minor (ZM) and on the levator labii superioris alaeque nasi muscle (LLSAN) to immobilise a wound on the philtrum. An asymmetrical smile was observed on day 7 postoperatively despite bilateral, symmetrical injections (10 U Allergan in the right ZM muscle and 10 U Allergan in the left ZM muscle, 5 U Allergan in the right LLSAN muscle and 5 U Allergan in the left LLSAN muscle). No statistically significant difference was found between the two groups for subjective patient satisfaction based on the Fisher exact test, with 100% satisfaction in the ‘toxin’ group and 92% satisfaction in the ‘control’ group.

At the 1-year visit, the overall median PSAS score was 9 in the ‘toxin’ group (Minimum 6, Maximum 18) compared with 8 in the ‘control’ group (Minimum 6, Maximum 26), with no significant difference between the two groups based on the Wilcoxon rank sum test. At the 1-year visit, the overall median OSAS score was 8 in the ‘toxin’ group.
Early injection of botulinum toxin type A appears to enhance healing of facial wounds. In our study, the overall median PSAS, OSAS and VSS scores at the 1-year visit were not statistically significantly different between the 'toxin' group and the 'control' group. This is due to the fact that the validated assessment scales routinely used to evaluate the healing outcome of complex wounds (burns, loss of bulk) are not discriminant enough to compare two groups of patients with simple facial wounds without tissue loss and sutured in good conditions.

The PSAS, with six items on a 1–10 scale (pain, pruritis, colour match, induration, elevation and regularities), includes one item for painful scars and another item for scar pruritis, both uncommon symptoms with simple facial wounds.

### Discussion

(Minimum 6, Maximum 13) compared with 9 in the 'control' group (Minimum 5, Maximum 24), with no significant difference between the two groups based on the Wilcoxon rank sum test. At the 1-year visit, the overall median VSS score was 3 in the 'toxin' group (Minimum 1, Maximum 4) compared with 2 in the 'control' group (Minimum 1, Maximum 9), with no significant difference between the two groups based on the Wilcoxon rank sum test.

The overall median VAS score was 8.25 in the 'toxin' group (minimum 6, maximum 10) compared with 6.38 in the 'control' group (minimum 2, maximum 9), with a significantly more favourable result in the 'toxin' group based on the Wilcoxon rank sum test ($p < 0.001$) (Table 3) (Figure 1).

### Table 3

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![Figure 1](image1.png) A 37-year old male (upper left) and a 51-year-old male (lower left) with a 2.2 cm long contused wound of the right eyebrow and a 2.6 cm long contused wound of the left eyebrow. The first patient is randomised in the 'toxin' group and 17.5 U Allergan of botulinum toxin A are injected 6 h postoperatively in the frontalis muscle and 2.5 U Allergan in the orbicular muscle of the eyelid. The second patient is randomly assigned to the 'control' group. Final outcome at 1 year postoperatively (right).
wounds 1 year postoperatively. Both items were rated by all 24 patients with the minimal score of 1. Scores for the four other PSAS items (colour match, induration, elevation and regularity) varied a lot, reflecting subjective experience more than the actual aspect of the scar. For instance, for patient #2 overall PSAS was 18/60 within particular 5/10 for the colour whereas the independent surgeon’s more objective overall OSAS was 7/50 with 1/10 for the colour as it was found to be normal.

The OSAS scores, with five items on a 1–10 scale (vascularisation, pigmentation, width, elevation and thickness), were not statistically significantly different between the two groups. Thus, most of the independent evaluators’ scores ranged from 1 to 3, due to an absence of the major scarring problems found in hypertrophic scars or burns, for which this scale would be more suitable.

The VSS scores, with four items ranging respectively from 0 to 2, 0 to 5, 0 to 5 and 0 to 3 (pigmentation, vascularisation, elasticity and elevation) were not significantly different between the two groups. Items are not rated with enough accuracy to show a statistically significant difference between the ‘toxin’ group and the ‘control’ group. For instance, there are only four ratings on the scar elevation scale (0 mm, 0–2 mm, 2–5 mm and over 5 mm). As all of the scars in this study were lower than 2 mm, all of the independent evaluators’ rates ranged between 0 and 1 point for this item.

On the other hand, the VAS scores, previously validated for scar assessment,16,17 were significantly favourable to the ‘toxin’ group. The intraclass correlation coefficient between the average VAS ratings of the plastic surgeons and the average VAS ratings of the emergency physicians was 0.97, corresponding to strong concordance between both categories of specialist evaluators. This is likely to be due to the fact that scar ratings were carried out with slides of the 24 patients shown successively, so that evaluators could assess the scars with a more relevant range. Moreover, the slides shown to evaluators included photographs of the wounds prior to suturing. Evaluators could therefore assess 1-year visit photographs more accurately in view of the initial wounds. Of all the wound assessment scales used in this study, the VAS appears to be more suitable for the assessment of simple facial wounds because it is ready to use, easy to use, sensitive and its results are reproducible.

The mean dose injection of botulinum toxin per patient in the ‘toxin’ group was 20 U Allergan. The mean cost of this injection per patient is therefore, at the time of study, 41 euros. In light of the benefits encountered by these injections on wound scarring, this overcost is acceptable, especially if a scar revision at 1 year can be avoided.

The first study in which botulinum toxin was tested to improve facial wound scarring was carried out in 1997.19 In this study without case controls, Choi reported the cases of 11 patients presenting for palpebral reconstruction followed by tarsorrhaphy. Botulinum toxin was injected into the orbicular muscle to obtain chemoimmobilisation and enhance wound scarring. Overall results showed improvement in wound scarring and no complications were reported. Nevertheless, the uncontrolled nature of this study raises concerns regarding whether botulinum toxin was responsible for the improved outcome.

In a trial on primates by Gassner in 1999,20 six pairs of Y-shaped excisions were performed with a template on either side of the forehead of six Macaca fascicularis monkeys. All excisions were then sutured using the standard surgical technique and subsequently randomly injected with 0.9% saline on one side and with botulinum toxin type A on the other side (7 UI per excision, i.e., 21 UI per half forehead). Three blinded experienced maxillo-facial surgeons were asked to evaluate the quality of the six scars on each monkey’s forehead at 1, 4 and 12 weeks postoperatively on a VAS (1–10) with regard to scar width, elevation and colour match. The blinded observers were also asked to rate each scar compared to its symmetric counterpart on the other side of the forehead. Results confirmed that botulinum toxin significantly improved the cosmetic appearance of cutaneous scars (p = 0.01). This blinded, randomised, placebo-controlled animal trial yielded positive results. Testing on humans was still necessary as these results could not be transposed to humans, given anatomical and physiopathological differences between the two species.

In 2006,7 Gassner tested whether postoperative injections of botulinum toxin type A improved facial wounds scarring on patients with forehead lacerations and excisions. Thirty-one patients were included in this prospective, blinded, randomised, placebo-controlled, single-institution trial. This trial constitutes the most direct benchmark with our study, with the primary difference being that Gassner performed his injections directly in wound edges, while our injections were done in specific muscles that acts on wound edges, which were defined after a surgeon’s testing and prior to wound suturing. The final cosmetic outcome of Gassner’s study was assessed using the VAS (0–10) at the 6-month follow-up visit. Two maxillo-facial surgeons were asked to assess the digital photographs (all taken by one photographer with a single camera) in an independent and blinded fashion. The overall median VAS for the botulinum toxin-treated group was 8.9 compared with 7.2 for the placebo group, with a statistically significant difference (p = 0.003). The findings of this study match the results in a previous study by Gassner 3 years earlier.21,22 However, these findings remain questionable as most patients enrolled in this study were subject to skin excisions, which lie parallel to skin tension lines and generally heal well.

In 2006, Wilson evaluated whether postoperative botulinum toxin type A injections improved scarring of facial wounds and skin tumour excisions.18 Patient age ranged from 11 to 72 years in this non-controlled trial involving 40 participants. Scar outcome was assessed using pre-operative and 6-month postoperative photographs by the surgeon and by the patient using a VAS of 1–5. The outcome was considered highly satisfactory by 90% of the patients (5/5 on the VAS scale). This study was neither randomised nor controlled, and mainly evaluated skin excisions that heal well. Moreover, the enrolment of children under 15 years of age with different healing processes, including a tendency for scar hypertrophy, may have skewed the results.

In a preliminary study published in 2006,23 Tollefson et al. described encouraging results with the first two cases of pre-operative botulinum toxin type A injections for cleft
lips is a critical factor in achieving a good cosmetic outcome. The use of botulinum toxin type A injections prior to wound closure can enhance healing and minimize scarring. However, complications such as reduced tension on the face may occur, and patients should be informed of these potential outcomes.

Conclusions

Early botulinum toxin type A-induced chemoinhibition appears to enhance the final cosmetic outcome of facial wounds. The 3–6-month paralyzing effect of botulinum toxin type A matches well with the duration of primary healing. Muscular paralysis of the musculature underlying cutaneous wounds results in less tension on wound edges during healing. However, more ample research is being carried out to also investigate the biological effects of botulinum toxin type A on wound healing that goes beyond immobilisation. Considering previous studies on primates and humans as well as this current study, we believe that this treatment improves scarring and cosmesis. It appears safe and justified to expand its use in the hands of an experienced surgeon, in particular in young patients with wounds without tissue loss, lying perpendicular to the lines of reduced tension on the face.

Conflict of interest

None.

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