## ORIGINAL ARTICLE

Revised: 28 June 2023



# How to improve infraorbital hollows with neuromodulators–A clinical prospective interventional study about the application of facial biomechanics

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**Background:** A previous injection algorithm termed the "Toxin Lift" was recently introduced and described volume increases in the midface following neuromodulator treatments of the jawline. Increase in midfacial volume due to soft tissue repositioning could also affect the severity of infraorbital hollows.

**Objective:** The objective is therefore to evaluate whether the severity of infraorbital hollows can be improved by injecting neuromodulators in the supra-mandibular segment of the platysma.

**Materials and Methods:** A total of 35 volunteers (11 males/24 females) with a mean age of 39.8 (9.6) years and a mean BMI of 25.2 (5.2) kg/m<sup>2</sup> were investigated. Bilateral infraorbital regions were evaluated via clinical assessment and semi-quantitative 3D imaging. The applied injection technique targeted the platysma via four injection points administering 5 I.U. per injection point resulting in a total of 20 I.U. per facial side.

**Results:** Volume increase of the infraorbital region was 0.13 cc at 15 days (p=0.001) and was 0.02 cc at 30 days (p=0.452) whereas the skin displacement in cranial direction was 0.54 mm at 15 days (p<0.001) and was 0.31 mm at 30 days (p<0.001). Clinical evaluation revealed a highly statistically significant improvement of the tear trough, palpaebromalar groove, and of the lid-cheek junction when compared to baseline with all p<0.001.

**Conclusion:** The results of this clinical prospective interventional analysis revealed that the "Toxin Lift" injection technique is capable to improve the clinical appearance of infraorbital hollows. The effects can be explained by the concepts of facial biomechanics.

KEYWORDS aesthetic facial procedures, facial aging, facial biomechanics, neuromodulators, tear trough

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# 1 | INTRODUCTION

A recent study has re-introduced the term facial biomechanics to the medical field providing for the first time in literature and definition for this domain: Facial biomechanics is the term used to describe the movement of the facial soft tissues, its causes and effects during facial animation and facial aging.<sup>1,2</sup> The authors described in their hallmark paper a novel injection technique which utilized neuromodulator treatments to increase the volume of the midface by applying the concepts of facial biomechanics. The described injection technique targeted the supra-mandibular portion of the platysma which resulted in weaking of the caudal pull of the muscle and in consequently increased cranial pull of the facial elevator muscles like zygomaticus major, zygomaticus minor, orbicularis oculi, and levator labii superioris alaeque nasi muscles. This shift in balance between in total facial elevators and depressors (comparable to a tug of war) favoring the elevator muscles resulted in increase in midfacial volume, decrease in lower facial volume, and increased gingival show during facial animation. The increase in midfacial volume following neuromodulator treatments was novel and was reproduced in an additional independent study since then.<sup>3</sup>

Clinical implementation of this technique resulted in additional positive effects like reduced severity of the tear trough and elevation of the tail of the eyebrow. However, both effects were not described in the initial study. The observed effects on the tear trough can be explained by applying the concepts of facial biomechanics: the increase in midfacial volume helped to reposition the superficial midfacial fat compartments like the superficial nasolabial and the superficial medial cheek fat compartments towards a more cranial position due to the increased cranial pull of the facial elevator muscles. This resulted in a camouflaging effect of the inferior orbital rim and in a decrease in the clinical presentation of infra-orbital hollows.

To date, this effect was not evaluated in a clinical study design, hence why the present study was conducted. The objective is therefore to evaluate whether the severity of infraorbital hollows can be improved by injecting neuromodulators in the supra-mandibular segment of the platysma. These effects will be evaluated via clinical and semi-quantitative assessment in an objective and independent prospective clinical study.

## 2 | MATERIALS AND METHODS

## 2.1 | Study sample

All participants were screened prior to their inclusion into this study, and it was assured that no previous facial surgical or any type of minimally invasive facial procedures or trauma was present that might influence normal facial anatomy or physiologic facial mobility. Additionally, study volunteers had to have their last neuromodulator treatment 6 months prior to the initiation of the study and had to agree to not undergo any type of facial procedures during the observational period.

Written informed consent was obtained from all volunteers prior to the start of study which allowed for the use of their clinical and imaging-related data for the purposes of this investigation. The study was conducted in the private office of the first author (Sao Paulo, Brazil) and approved by the Hospital Maternidade Leonor Mendes de Barros, Sao Paulo, Brazil under the number: 65738322.9.0000.0063.

## 2.2 | Injection technique

The injection technique was previously described and relied on the superficial injection of neuromodulators 1 cm cranial to the mandibular margin in four locations.<sup>2</sup> The first injection point was located caudal and vertical to the oral commissure targeting the depressor anguli oris muscle whereas the following three points were placed in equidistant locations reaching the angle of the mandible. The injection direction was pointing towards the ear lobe and a strictly superficial product placement was performed to target the superficially located platysma muscle (Figure 1).

Per injection point, five International Units (12.5 Speywood Units) in a volume of 0.05 cc were administered following a reconstitution of 2.0 cc per 500 I.U. of abobotulinumtoxin Type A (Dysport, Galderma). The product was administered via a 6mm, 31G insulin syringe (Becton Dickinson).

All injections were performed by the first author to assure consistency throughout the treatment process.

## 2.3 | Clinical assessment

Clinical evaluation of the injection outcome was evaluated by three independent observers with at least 5 years of facial aesthetic experience based on three-dimensional photographs. All three observers were not involved in the treatment of the volunteers and graded the facial scores based on a 5-point Likert scale ranging from 0 to 4 (best to worst) with 0 = ``No", 1 = ``Mild", 2 = ``Moderate", 3 = ``Severe", and 4 = ``Very Severe". The evaluated scores were as indicated below and were assessed 30 days after the treatment:

- Medial infra-orbital hollowing (= Tear trough severity)<sup>4</sup>
- Lateral infra-orbital hollowing (= Palpaebromalar groove severity)<sup>4</sup>
- Infra-orbital hollowing (= entire lid-cheek junction)<sup>4,5</sup>

## 2.4 | Image analyses

Objective evaluation relied on the semiquantitative analysis of three-dimensional images taken at baseline and at 15 and 30 days

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**FIGURE 1** Graphic illustration showing the injection technique: a superficial injection was performed 1 cm cranial to the bony and thus palpable mandible in four different locations. The first injection point targeted the depressor anguli oris muscle whereas the latter three targeted the supra-mandibular portion of the platysma muscle. Each injection point received 5 units (un).

following the treatment. The imaging-based analysis relied on the computational comparison between the follow-up and the baseline images of each study volunteer. Due to the in-person comparison each volunteer served as its own reference. This methodology relied on passive stereophotogrammetry and included a customized digital camera of 13.524 million pixels (Nikon 3200, Nikon). The region of interest was for both image parameters the infraorbital region which spanned the area of skin between the medial and lateral canthus and extended caudally until the upper margin of the nasal ala. (Figure 2).

Images were compared based on the internal computational algorithm (DermaPix Database for photo documentation, Quantificare) and results were given in volume change (in cc) and skin displacement (in mm) (Figure 3).

#### 2.5 **Statistical analyses**

Descriptive and comparative analyses were conducted using SPSS Statistics 25 (IBM). Comparisons (paired t-test) were performed between the different timepoints of each study participant and results were considered statistically significant with p < 0.05.

#### RESULTS 3

#### **Demographics** 3.1

The study investigated a total of 35 healthy volunteers (11 males/24 females) of Brazilian Caucasian ethnic background. The mean age of the sample was 39.8 (9.6) years, and the mean body mass index was 25.2 (5.2) kg/m<sup>2</sup>. Both infraorbital regions (left and right) in each study volunteer were investigated resulting in a total of n = 70 facial regions investigated.

#### **Objective image analysis** 3.2

The average volume increase of the infraorbital region as measured by semi-quantitative three-dimensional imaging was at 15 days after the initial treatment 0.13 cc (0.3) and was at 30 days 0.02 cc (0.2), with p = 0.001 and p = 0.452, respectively.

The average skin displacement in cranial direction was at 15 days after the initial treatment 0.54 mm (0.4) and was at 30 days 0.31 mm (0.3), with p < 0.001 and p < 0.001, respectively.

#### **Clinical outcome analysis** 3.3

Tear trough severity was at baseline 3.03 (0.7) and was at 30 days follow-up 2.31 (0.6) revealing a statistically significant improvement with *p* < 0.001.

Palpaebromalar groove severity was at baseline 2.24 (0.8) and was at 30 days follow-up 1.75 (0.6) revealing a statistically significant improvement with p < 0.001.

Lid-cheek junction severity was at baseline 2.47 (0.7) and was at 30 days follow-up 2.08 (0.6) revealing a statistically significant improvement with p < 0.001. (Figures 4–7).

#### Adverse events 3.4

Of the 70 evaluated infra-orbital regions, n = 11 (15.7%) presented unexpected clinical outcomes which can be classified as adverse events. Of those were n=1 with asymmetric smile, n=3 difficulties in chewing, and n=7 food accumulation in the oral vestibule (between teeth and lips and cheeks). The adverse events were reported at 15 days following the initial treatment and resolved by itself at the 30 days follow-up without any medical intervention.

FIGURE 2 3D-imaging analysis, showing the measurements conducted (left panel) and the respective volume increase (right upper panel) and the skin vector displacement analysis (right lower panel). The average volume increase measured from the right upper panel image was 0.35 cc for the left patient side.



**FIGURE 3** 3D-imaging analysis showing the average volume increase of a female patient following the performed injection technique at 30 days follow-up. The average volume increase measured was for the right side 0.08 cc whereas it was for the left side 0.10 cc.



# 4 | DISCUSSION

The results of this interventional prospective clinical study revealed that the concepts of facial biomechanics are applicable to minimally invasive procedures utilizing neuromodulators. The applied injection technique targeted bilaterally the supra-mandibular portion of the platysma muscle via four injection points administering 5 I.U. per injection point to the superficial (= supra-platysmal) plane resulting in a total of 20 I.U. per facial side and 40 I.U. per patient. The clinical outcomes were observed in the tear trough, the palpaebromalar groove, and along the entire lid-cheek junction despite the jawline was injected with neuromodulators. The objectively measured volume increase of the infraorbital region was 0.13 cc at 15 days (p=0.001) and was 0.02 cc at 30 days (p=0.452) whereas the skin displacement in cranial direction was 0.54 mm at 15 days (p < 0.001) and 0.31 mm at 30 days (p < 0.001). These changes are interesting because the jawline was treated with neuromodulators and the effects were observed in the infraorbital region. Additional aesthetic effects were observed in the 35 treated patients which included improved jawline contouring, increase in midfacial volume, and elevation of the tail of the eyebrow. However, these effects were not quantitatively assessed and therefore no numeric values can be provided to those additional clinical effects.

This study was designed as a follow-up study of the recently described "Toxin-Lift" injection technique, published in 2022 by Hernandez et al.<sup>2</sup> The initial study was a modification of the original Nefertiti injection algorithm from 2007 and of its various alterations which followed in 2017 and 2019 for jawline contouring and neck rejuvenation.<sup>6–8</sup> It has to be noted that none of the above-mentioned studies aimed at increasing the midfacial volume or at improving the infraorbital region, which underscores the uniqueness of the investigated "Toxin Lift" injection technique. In the initial study, Hernandez et al. reported an average volume increase of the midface by 0.46 cc and a lower face volume decrease of 0.30 cc after the administration of 16.6 I.U. for both facial sides in total. The authors however, did not investigate the effects of the "Toxin Lift" in the infraorbital region but focused on the middle and lower face exclusively, which is why the present study was carried out.

In this study a total of 40 I.U. were administered which is significantly more than initially recommended. It is therefore not surprising that an adverse event rate of 15.7% was noticed at 15 days follow-up which however resolved by itself at the 30 days visit and



**FIGURE 4** Bar graphs showing the change in severity score for the three assessed scores (tear trough, palpaebromalar groove, and lidcheek junction severity scales) at baseline and at 30 days follow-up. Note the statistically significant change in all scores with *p* < 0.001.



**FIGURE 5** Baseline (before the treatment) and 30 days follow-up (after the treatment) images showing the full-face outcome of a male patient following the administration of neuromodulators with the toxin lift injection technique.

which is identical to the "Toxin Lift" adverse events rate of 0% at 30 days as described initially. The adverse events can be explained by the extended effects of the neuromodulator product: an asymmetric smile can be explained by the affection of the risorius muscle which is located in the superficial plane of the lateral face and is located slightly cranial to the upper margin of the platysma muscle. It seems therefore most likely that the product diffused cranially and affected this muscle which is important for lateral movements of the modiolus and thus the oral commissure. Another adverse event was described as difficulty during chewing which might be related to the involvement of the masseter muscle. The masseter muscle is located deep to the platysma muscle and two out of the four injection points apply the product in its closest proximity. The separating layer between platysma and masseter muscles is the parotideomasseteric fascia which is thin and might not be substantial enough to form a barrier for the diffusing neuromodulator. It seems therefore most likely that the product diffused into deeper planes and affected the masseter muscle which was in return perceived by the patient as difficulty during chewing. The last adverse event described was food accumulation within the oral vestibule; this effect is most likely related to the relaxation of the depressor anguli oris, orbicularis and potentially buccinator muscles. Despite the latter is located deep within the cheek, product diffusion from the modiolus towards deeper planes is possible resulting in a inability to contract and reduce the size of the oral vestibule to remove and to propel food towards the pharynx or to the oral cavity proper. **FIGURE 6** Baseline (before the treatment) and 30 days follow-up (after the treatment) images showing the infraorbital outcome of a female patient following the administration of neuromodulators with the toxin lift injection technique.

FIGURE 7 Baseline (before the treatment) and 30 days follow-up (after the treatment) images showing the infraorbital outcome of a female patient following the administration of neuromodulators with the toxin lift injection technique.



Despite the initial study described a range between 16 and 20 I.U. for the bilaterally performed "Toxin Lift" technique, the present study increased the dose to evaluate its effectiveness; this was suggested by the authors of the initial study to investigate various dosages to identify whether more product would result in more lifting effects. Based on the results of the present study it has to be concluded that more product (40 vs. 20 I.U.) does increase the rate of adverse events and not necessarily the clinical benefits. However, it must be emphasized that at 30 days, both adverse events rates were 0% and that the study by Hernandez et al. did not evaluate specific adverse events at 15 days following the treatment. It could be also possible that the adverse effects at 15 days might be rather adjustment effects in which the patient perceives differences in their facial muscle tone and soft tissue positions until re-balancing or re-adaptation effects take place following the treatment. This could explain why no adverse effects were described at 30 days follow-up.

The clinical effects observed in this study revealed a highly statistically significant improvement of the infraorbital region when compared to the baseline status with all p < 0.001. This is remarkable as the infraorbital region was not targeted directly neither with soft tissue fillers nor with neuromodulators but only the jawline was treated with neuromodulators. This effect is in line with the following biomechanical concept: relaxation of the platysma muscle allowed the facial elevators to relatively increase their upwards pull which resulted in repositioning of the superficial midfacial fat compartments. The repositioning of the superficial fatty layer was effected by the transverse facial septum and the zygomaticus major muscle which is incorporated into the midfacial SMAS.<sup>9,10</sup> The latter is connected to the platysma and to the orbicularis oculi muscles and allows for force transmission between the lower face and the infraorbital region. It is therefore plausible that relaxation of the major facial depressor results in volume increase of the infraorbital region and in cranial skin displacement as measured here.<sup>11</sup>

The longevity of the clinical outcome could have been investigated with a longer follow-up period (3 or 6 months) which should be considered as a limitation of the study. However, the purpose of this study was not to investigate the effectiveness of the utilized product but to evaluate the biomechanical concept behind the applied injection technique. The biomechanical concepts have been revealed to be correct and applicable to the infraorbital region and future studies will need to identify the most optimal dosage and type of product for this injection technique. Another limitation of the study is the investigated study population and its respective sample size; it could be assumed that a larger sample size with more mature patients and a higher degree of skin Journal of

laxity or of soft tissue sagging might have different outcomes with potentially reduced effectiveness. Future studies will need to investigate this aspect to provide reliable information about the subset of patients which might benefit most or might be most prone for adverse events.

## 5 | CONCLUSION

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This study sought to investigate whether the "Toxin Lift" injection technique for neuromodulator treatments of the jawline is capable of improving the aesthetic appearance of the tear trough, the palpaebromalar groove, and the lid-cheek junction. The results revealed that a statistically significant improvement in all three evaluated scores occurred with p<0.001 for all scores at 30 days follow-up. Three-dimensional imaging additionally showed that a volume increase and a cranially directed skin displacement effect occurred at 30 days follow-up which supports the effectiveness of the performed injection algorithm. However, an adverse events rate of 15.7% was observed at 15 days which resolved by itself at 30 days and reduced to 0%; this might be most likely due to product diffusion rather that the performed injection technique.

## AUTHOR CONTRIBUTIONS

Marcelo Germani, Sebastian Cotofana, and Jeremy B. Green conceived the idea for the study. Nicholas Moelhoff, Michael Alfertshofer, Kristina Davidovic, and Sebastian Cotofana conducted the statistical analysis and interpreted the results. Marcelo Germani, Victor R. M. Munoz-Lora, Victor Rogério, Michael Alfertshofer, and Sebastian Cotofana drafted the initial manuscript. Claudia C. M. S. Almeida, Victor R. M. Munoz-Lora, Nicholas Moelhoff, David L. Freytag, Jeremy B. Green, and Victor Rogério critically revised the manuscript for intellectual content. Sebastian Cotofana, Michael Alfertshofer, Nicholas Moelhoff, David L. Freytag, and Kristina Davidovic provided administrative support and coordination. Sebastian Cotofana, Marcelo Germani Claudia C. M. S. Almeida, and Victor R. M. Munoz-Lora supervised the project. David L. Freytag, Jeremy B. Green, and Kristina Davidovic, contributed to the interpretation of the results.

### FUNDING INFORMATION

This study received no funding.

## CONFLICT OF INTEREST STATEMENT

None of the other authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

The study was conducted in the private office of the first author (Sao Paolo, Brazil) and approved by the Hospital Maternidade Leonor Mendes de Barros, Sao Paolo, Brazil under the number: 65738322.9.0000.0063.

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How to cite this article: Germani M, Almeida CCMS, Munoz-Lora VRM, et al. How to improve infraorbital hollows with neuromodulators–A clinical prospective interventional study about the application of facial biomechanics. *J Cosmet Dermatol*. 2023;22:2950-2956. doi:10.1111/jocd.15970