Dose Higher-doses of botulinum toxin show better intensity and duration in the treatment of Gummy Smile?

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Study Protocol：

The smile is one of the universal facial expressions of humans. Gingival smile is characterized by gingival exposure of >3 mm upon smiling. The degree of gingival exposure can vary substantially between patients, with patients presenting gingival exposure of up to more than 10 mm. The prevalence of gingival smile is 10.57%, and it is more frequently observed in females. Although gingival smile is merely an anatomical variation, it can be considered unattractive, causing significant distress and impacting one's quality of life. Moreover, most orthodontists and dentists regard gingival smile as an important risk factor for dental treatment.

Gingival smile involves a complex interaction between the facial muscles, bone, and skin; specifically, it is related to hypermobility of the upper lip with muscle involvement and alterations in anatomical features, such as a short clinical dental crown, anterior dentoalveolar extrusion, maxillary excess, and a short upper lip. Therapies for gingival smile range from botulinum toxin injections to surgical interventions according to its etiology. Although the outcomes of surgical procedures are long-lasting, botulinum toxin type A treatment is an easy and fast outpatient procedure that requires no downtime and has high efficacy rates. Nevertheless, there are controversies around the optimal dose and injection site of botulinum toxin type A. Moreover, the efficiency of botulinum toxin type A for gingival smile varies markedly between studies, with the improvement rate of gingival exposure ranging from 62.06% to 98%. Sucupira and Abramovitz advocate the use of a low amount of botulinum toxin type A of 1.95 U per side for the treatment of gingival smile. They noted an average satisfaction level of 9.75 on a 10-point scale with this approach. They claimed that higher doses did not provide further benefit, and, in fact, could lead to lip ptosis, asymmetry, and

excessive upper lip length. However, Polo disagreed with their argument, claiming 2-5 U injection of botulinum toxin type A according to the severity of gingival smile. In this regard, Garcia and Fulton showed that low-dose injection of botulinum toxin per muscle (2-5 IU) was as effective as higher doses. Though prior studies have demonstrated a correlation between higher doses of botulinum toxin and intensity and duration of muscle paralyses, no conclusion can be drawn regarding duration and intensity of doses used in the recent studies. A safe approach advocated by some authors consists of starting with low toxin doses initially, with retouching at a later stage if required. In this study, the investigators compared botulinum toxin type A efficiency using the average-dose method (2-5 U botulinum toxin type A per side determined according to the severity of anterior gingival smile) and, the higher-dose method (3-10 U botulinum toxin type A per side determined according to the severity of anterior gingival smile). The investigators aimed to assess the efficiency and duration of these approaches, as well as side effects and patients' satisfaction with treatment.In this prospective self-controlled study, healthy participants with gummy smile underwent two treatment methods.

The inclusion criteria to be considered for the study were as follows: 1) healthy participants with anterior gingival exposure of ⩾3.0 mm during unrestricted, "full-blown" smiling; 2) participants between 18 and 60 years old. The following exclusion criteria were used for the study participants: 1) complications to botulinum toxin A; 2) paralysis of the face; 3) previous disease and/or treatment that affected the position of the gingiva or upper lip; 4) botulinum toxin A injection in the head or neck region within the previous year; 5) are currently receiving or have received active orthodontic treatment, including vertical dimension treatment, for extrusion or intrusion; 6) occurrence of periodontal disease; 7) refused to participate; 8) loss to follow-up.

First, participants were injected with the average-dose, which the dose was individualized according to the severity of anterior gingival exposure pretreatment. For mild gingival smile (3–5 mm), a single-site injection of 2 U botulinum toxin type A [total, 4 U] at both the right and left levator labii superioris alaeque nasi muscles) was administered. For moderate (5–7 mm) and severe (⩾7 mm) gingival smile, 3 U and 5 U of botulinum toxin type A, respectively,

were injected per side (total, 6 U and 10U, respectively). The injection points were located at bilateral levator labii superioris alaeque nasi muscles and at the Yonsei point, with half doses administered at each point. Data were collected at baseline and at four, 12, 48, weeks follow-up.

And 8 months after the first injection, all the patients underwent second injection of the higher-dose method.

With this method, patients were administered botulinum toxin type A after 8 months when the effect of the previous injection had vanished. The injection dose (U) per side was set as the absolute value of the preoperative anterior gingival exposure (mm). For example, if the preoperative anterior gingival exposure was 5mm, then the patient would be injected with 5 U of botulinum toxin per side (total, 10U). The injection points were located at bilateral levator labii superioris alaeque nasi muscles and at the Yonsei point, with half doses administered at each point. Data were collected at baseline and at four, 12, 48, weeks follow-up.

Statistical Analysis Plan：

Data entry will be managed using WJX procedure (Ranxing Information Technology Co., Ltd., Changsha, China) and accuracy was ensured by double entry and validation. All statistical analyses were performed using SPSS software v. 20.0 (IBM Corp., Armonk, NY). The mean and standard deviation were used to describe normally distributed numerical values, and a paired-samples t-test was used to identify differences. The Wilcoxon signed-rank test was used for non-normally distributed numerical values, and the McNemar-Bowker test was used to compare dichotomous variables. A P value of <0.05 was considered statistically significant.