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GIORIGINAL CONTRIBUTION

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To click or not to click – The importance of understanding the layers of the forehead when injecting neuromodulators – A clinical, prospective, interventional, split-face study

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Abstract

Background: Differences in the effectiveness of neuromodulator treatments for horizontal forehead lines dependent on depth of product administration have been described. However, knowledge in respect to the fascial anatomy of the forehead still remains elusive.

Aims: To relate the fascial anatomy of the forehead to the effectiveness of neuromodulator treatments by conducting a clinical, prospective, interventional split-face study in which injections for the treatment of horizontal forehead lines are performed differently between facial sides.

Methods: This study included a total of n = 14 patients with a mean age of 35.71 (7.8) years and mean body mass index of 21.9 (3.0) kg/m^2. One side of the forehead was injected superficially by positioning the product in the superficial fatty layer, whereas the contralateral side was injected deep targeting the supraperiosteal plane (random selection). The treatment outcome was rated by the physician and by two independent observers according to a forehead line severity scale (0-4) at 14 and at 30 days.

Results: All three observers agreed in their ratings (ICC: 0.942) that the deep injection technique resulted in a superior outcome: D14 (superficial vs deep) 0.17 (0.4) vs 0.14 (0.4; $P = .583$) at rest and 1.26 (0.6) vs 0.43 (0.5; $P < .001$) for frontalis contraction; D30 0.17 (0.4) vs 0.14 (0.3) at rest ($P = .583$) and 1.21 (0.6) vs 0.43 (0.5; $P < .001$) for frontalis contraction.

Conclusion: The results of this study underscore how detailed anatomic knowledge can enhance results of aesthetic interventions, in this case horizontal forehead line treatment with neuromodulators.

KEYWORDS

botulinum toxin, facial anatomy, fascial layers, horizontal forehead lines, neuromodulators

Konstantin Frank is added as co corresponding author.

[Correction added January 9, 2021, after first online publication: Konstantin Frank was designated as corresponding author.]

1 | INTRODUCTION

The injection of neuromodulators for the treatment of facial lines remains the most frequently performed nonsurgical aesthetic procedure in the United States with 1 712 994 procedures in 2019, according to the annual statistics of The Aesthetic Society.[1] These procedures are mostly free of adverse events, which when they occur are generally transient and aesthetic in nature, vs the potentially severe vascular compromise that can occur with soft tissue filler injections.[2,3]

The most frequent areas targeted with neuromodulators include the forehead and the glabellar complex which has been shown to result in a younger overall facial appearance.[4] Recent anatomic research has reported on the bidirectional movement of the frontalis muscle providing evidence for two separate segments of this muscle: eyebrow elevator (lower forehead) vs hairline depressor (upper forehead).[5] To avoid eyebrow ptosis, the authors suggested injecting a reduced amount of neuromodulators in the eyebrow elevation segment of the frontalis muscle via a more superficial product administration.

Recent studies have shown that a more superficial injection technique (= "*intradermal*") for treating horizontal forehead lines can provide safer outcomes and reduced adverse events (eyebrow ptosis) when compared to a deeper injection technique (= "*intramuscular*").[6,7] This indicates that there is a difference in the effectiveness of neuromodulator treatments depending on the layer of product administration. However, the authors of both studies did not relate the observed effects to the underlying anatomy, but rather referred to their outcome as adverse events instead of increased effectiveness of injection points positioned in the eyebrow elevation segment of the frontalis muscle.

It can be hypothesized that the degree and rate of adverse events following neuromodulator treatment of horizontal forehead lines can be reduced by a profound understanding of the underlying anatomy. Therefore, the investigators conducted a clinical, prospective, interventional split-face study whereby neuromodulator injections for the treatment of horizontal forehead lines were performed with the same amount of product and injection sites, superficially on one side and deep contralaterally. The investigators sought to evaluate whether objective clinical differences could be appreciated with differing injection depths and perhaps enhance the understanding and predictability of neuromodulator treatments for horizontal forehead lines.

2 | MATERIAL AND METHODS

2.1 | Study sample

This study included a total of n = 14 consecutive aesthetic patients with a mean age of (mean value and standard deviation) 35.71 (7.8) years and mean body mass index (BMI) of 21.9 (3.0) kg/m^2. The Fitzpatrick skin types of the included study participants were: Type 1 n = 3 (21.4%), Type 2 n = 4 (28.6%), and Type 3 n = 7 (50.0%); the type of horizontal forehead lines was wavy in n = 9 (64.3%) and straight in n = 5 (35.7%).[8,9]

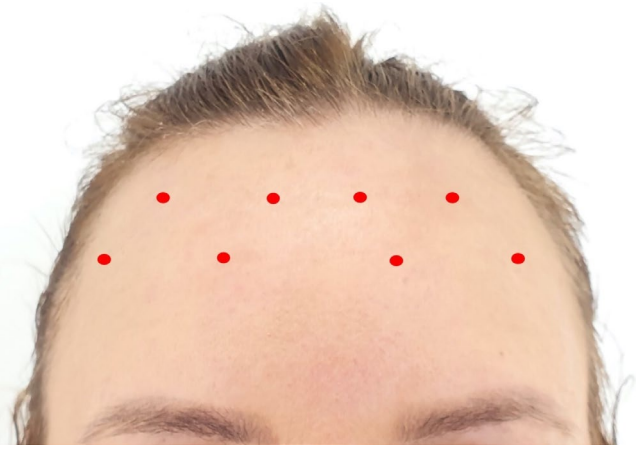

FIGURE 1 Red dots represent injection points treated in this female study participant

Inclusion criteria were no neuromodulator injections of the upper face within 6 months prior, no previous soft tissue filler administration (any type) to the forehead and no history of trauma or surgical procedure of their forehead that could have resulted in a disruption of a normal muscular and fascial frontal anatomy, and no grossly visible asymmetry at rest or at maximal frontalis contraction. No restrictions were set for age, gender or BMI.

Patients were briefed on the aims, scopes, and procedures of the study, and each participant provided written informed consent to be treated according to the explained split-face design study and for the use of both their data and associated images prior to their initiation into the study.

2.2 | Study design

This study was a clinical, prospective, interventional split-face study where the left side was treated differently than the right side of patient's forehead. One side (randomly assigned) was treated with the neuromodulator (Dysport, Galderma; dilution: 500 international units per vial reconstituted with 2.0 cc of saline) injected into the superficial fatty layer (= superficial), while the contralateral side received supraperiosteal plane (= deep) injections.

2.3 | Injection procedure

The injection technique did not differ between the treated study participants. A total of eight injection points (four per side) were performed in each study participant (Figure 1). The injected volume was adjusted to the individual aesthetic needs of every study participant and ranged between 25 and 30 international units per forehead (mean value: 25.73 (1.83) IU).

Superficial neuromodulator placement was achieved by a 45° angle superficial injection utilizing a 30 G 8 mm needle (BD) and verified by a visible small bleb on the skin surface created by injected product and by the absence of a "click"- like sound (Figure 2) indicating contact with bone. Deep neuromodulator placement was accomplished by needle insertion with slight bone contact and verified by a "click"- like sound which indicated that the tip of the needle perforated the subfrontalis fascia and was now contact with the bone (Figure 3). In the interest of patient comfort, firm plunger pressure against the frontal bone was avoided; instead, the auditory and manual feedback was regarded as sufficient to ascertain depth, in addition to the absence of a visible subdermal bleb.

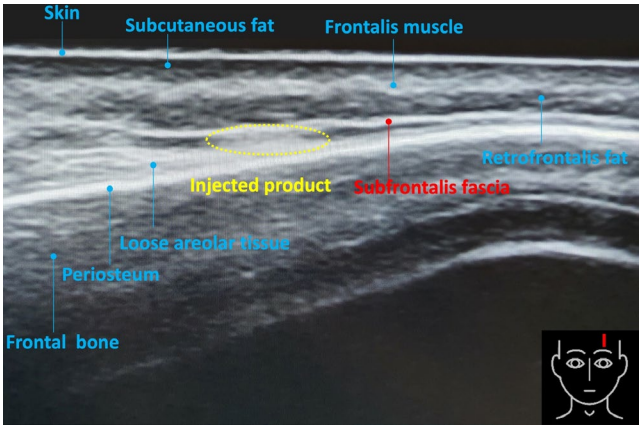

FIGURE 3 Ultrasound verification of the superficial injection technique when performed as control in a healthy volunteer to verify the correct deep (= supraperiosteal) product placement

2.4 | Outcome measurements

2.4.1 | Horizontal forehead line severity scale

The severity of horizontal forehead lines was assessed according to a previously published scale[10] which graded the visible lines at rest and upon maximal frontalis muscle contraction by 5-points: 0 = No lines, 1 = Mild lines, 2 = Moderate lines, 3 = Severe lines, and 4 = Very severe lines. This rating was performed before the treatment, 14 days after the treatment, and 30 days after the treatment.

One rating was conducted by the treating physician (KD) based on visual inspection of the patient at the pretreatment and at the post-treatment follow-up visits. An additional rating was performed by two independent observers who were blinded to the depths of injection; this rating was performed on images without having direct patient contact.

2.4.2 | Ultrasound imaging

The thickness of the forehead was measured in every patient at the injection site (= upper forehead) via ultrasound imaging to identify each participant's individual forehead anatomy. All measurements were conducted with an Acuson Juniper (Siemens Healthineers) device and a 4.5-18 MHz linear transducer (18H5, Siemens Healthineers). Volunteers were positioned supine, and the transducer was positioned into the ultrasound contact gel with minimal skin contact "floating" to avoid tissue compression. All ultrasound-based measurements were conducted by the same investigator (KD) to assure consistency.

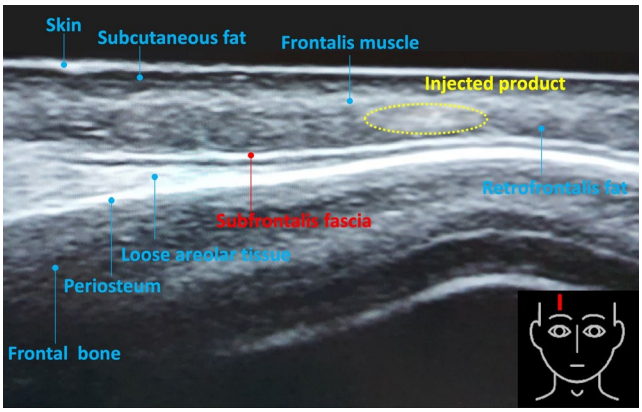

FIGURE 2 Ultrasound verification of the superficial injection technique when performed as control in a healthy volunteer to verify the correct superficial (= subdermal) product placement

2.5 | Statistical analyses

Due to the small sample size, nonparametric analyses were conducted utilizing Wilcoxon signed-rank test. To relate the consistency (= reliability) in the assessment of the observers on the same outcome, the interclass correlation coefficient (ICC) was calculated based on a two-way mixed effect model with absolute agreement for $k = 2$ and 3 raters, respectively.[11] Analyses were performed using SPSS Statistics 23 (IBM), and differences were considered statistically significant at a probability level of ≤.05 to guide conclusions.

3 | RESULTS

3.1 | Baseline assessment

The mean score for baseline severity of horizontal forehead lines (0-4, best to worst) was 2.14 (0.8) at rest and was 3.31 (0.7) upon frontalis muscle contraction ($P < .001$). The ICC (a measure for consistency between ratings of the three different observers) was .888 for the rating at rest and was .971 for the rating upon frontalis muscle contraction, indicating an excellent consistency between the ratings of the three observers.

The mean frontal soft tissue thickness was 4.01 (0.8) mm without statistically significant difference between genders with $P = .088$.

Compared to baseline, all injections independent of technique resulted in a statistically significant reduction in horizontal forehead line severity both at rest and upon maximal frontalis muscle contraction with $P < .001$ for both time points D14 and D30 (Figures 4-6). No eyebrow ptosis or upper eyelid ptosis were observed during the 30 days follow-up period.

3.2 | Day 14 assessment

At 14 days after the neuromodulator treatment, the horizontal forehead line severity at rest was 0.17 (0.4) for the superficial injection and was 0.14 (0.4) for the deep injection with no statistically significant difference between the techniques ($P = .583$; Figure 7). The ICC for the rating of the superficial injection was .840 and was for the deep injection 1.00, indicating an excellent consistency between the ratings of the three observers.

Upon maximal frontalis muscle contraction, the horizontal forehead line severity was for the superficial injection 1.26 (0.6) and for the deep injection was 0.43 (0.5) with $P < .001$ indicating a highly statistically significant difference between the two techniques (Figure 8). The ICC was for the rating of the superficial injection was .977 and for the deep injection 1.00, indicating an excellent consistency between the ratings of the three observers.

3.3 | Day 30 assessment

At 30 days after the neuromodulator treatment, the horizontal forehead line severity at rest was 0.17 (0.4) for the superficial injection and 0.14 (0.3) for the deep injection with no statistically significant difference between the two injection techniques ($P = .583$). The ICC was for the rating of the superficial injection .957 and for the deep injection .835, indicating an excellent consistency between the ratings of the three observers.

Upon maximal frontalis muscle contraction, the horizontal forehead line severity was for the superficial injection 1.21 (0.6) and was for the deep injection 0.43 (0.5) with $P < .001$ indicating a highly statistically significant difference between the two injection techniques. The ICC was for the rating of the superficial injection .947 and was for the deep injection 1.00, indicating an excellent consistency between the ratings of the three observers.

4 | DISCUSSION

This study was designed as a clinical, prospective, interventional split-face study applying neuromodulator injections for the treatment of horizontal forehead lines. The split-face component of the study randomly assigned one side of the patient's forehead to a superficial injection technique and the contralateral side to a deep injection technique. With the superficial technique, the product was injected into the superficial fatty layer, that is, superficial to frontalis muscle, whereas the deep injection technique delivered the product into the supraperiosteal plane, that is, deep to frontalis muscle. However, the injection points (three or four per side) and the amount of administered product (25-30 international units per forehead) did not vary between sides assuring equal neuromodulator concentrations for both sides of the forehead. Applying a split-face study design, inter-individual differences between study participants that could influence the injection outcome (gender, age, soft tissue thickness) were eliminated as the comparisons were made between the left and the right side of the same patient; this should be regarded as a strength of this investigation. This study design provides additionally high validity to the observed outcome despite the small sample size investigated (n = 14). A larger sample size could have enhanced the robustness of the results but recent studies have applied a similar (though not split-face) methodology to investigate neuromodulator injections of the forehead comparing n = 14 foreheads.[6] Due to potential asymmetry of the split-face therapeutic outcome,

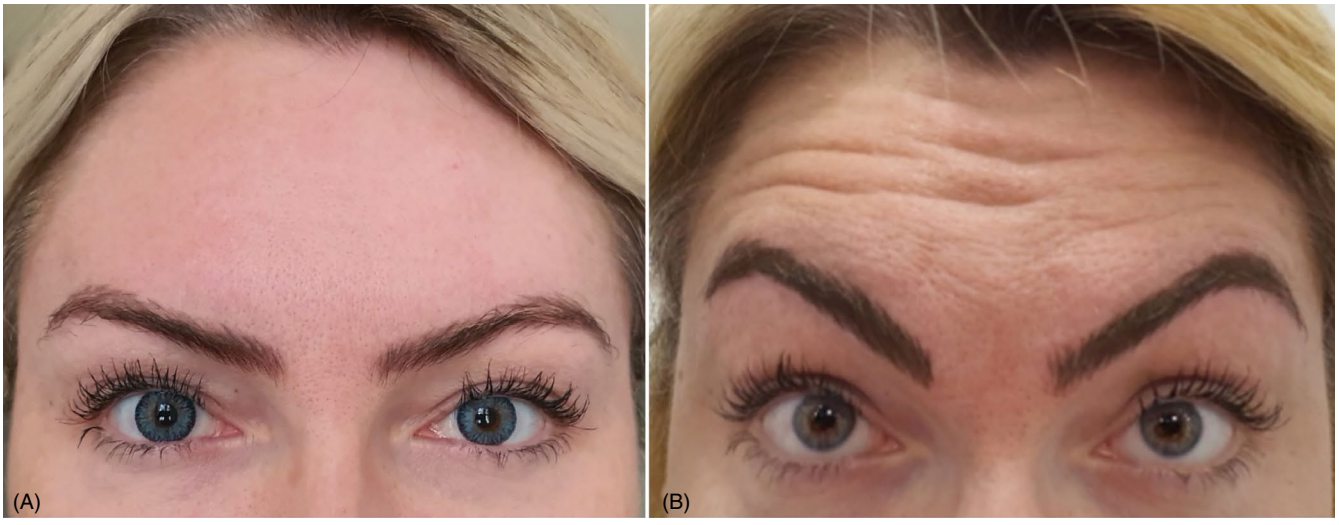

FIGURE 4 Before treatment images of a female study participant at rest (A) and at maximal frontalis muscle contraction (B)

FIGURE 5 Day 14 after the treatment images of a female study participant at rest (A) and at maximal frontalis muscle contraction (B). Note the hyperelevation of the eyebrow (Mephisto sign) on the side treated with the superficial injection technique. This indicates that the central and the contralateral portion of the forehead was treated with greater effectiveness by the deep injection technique resulting in the observed compensatory effect of the remaining active frontalis muscle

FIGURE 6 Day 30 after the treatment images of a female study participant at rest (A) and at maximal frontalis muscle contraction (B). Note the hyperelevation of the eyebrow (Mephisto sign) on the side treated with the superficial injection technique. This sign indicates that the central and the contralateral portion of the forehead was treated with greater effectiveness by the deep injection technique resulting in the observed compensatory effect of the remaining active frontalis muscle

the recruitment of volunteers for split-face studies is difficult and limits large samples which was shown in a previous split-face study design likewise focusing on the forehead with n = 3.[7] However, the present study received no funding from industrial partners and was sponsored by the authors of the study themselves. This limited the number of volunteers included into this study but increases the degree of objectivity of the results presented and may be regarded as another strength of this study. The glabellar complex was not conocomitantly injected as is common in clinical aesthetic practice; however, the investigators sought to ascertain whether depth of neuromodulator injections into the forehead influenced efficacy on the frontalis muscle contraction, and treating the glabellar complex could have confounded the results.

The results of this investigation confirmed that neuromodulator injections (independent of their applied technique) result in a reduction of the severity of horizontal forehead lines both at rest and at maximal frontalis muscle contraction with $P < .001$ (Figures 7 and 8). However, a highly statistically significant difference between the two utilized injection techniques (superficial vs deep) was observed upon maximal frontalis muscle contraction with $P < .001$ indicating

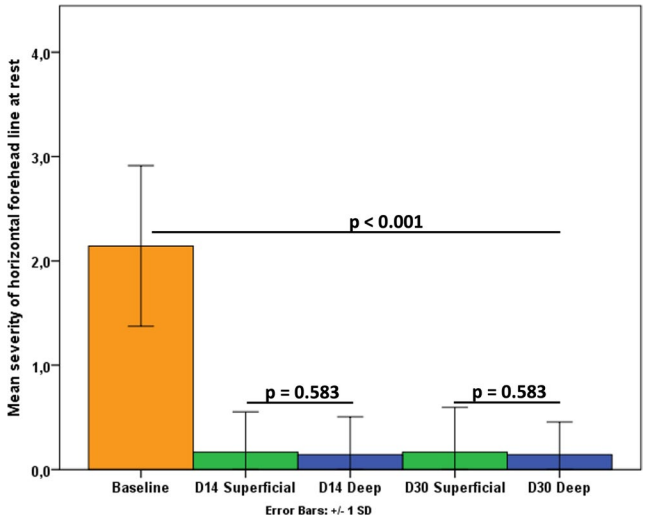

FIGURE 7 Bar graphs showing the mean and the respective standard deviation for the forehead line severity scale at rest (0-4, best to worst) at baseline (orange bar) and at D14 and D30. Green bars indicate the superficial injection technique whereas blue bars indicate the deep injection technique

that there is a measurable difference in the treatment outcome depending on depth of injection. All three observers agreed in their rating with an ICC of .942 for all conducted ratings that the deep injection technique resulted in a superior outcome when the outcome was assessed by the forehead lines severity scale published by Flynn and colleagues.[10] The level of agreement between the performed ratings can be classified as "excellent consistency" which supports the validity of the results presented.[11]

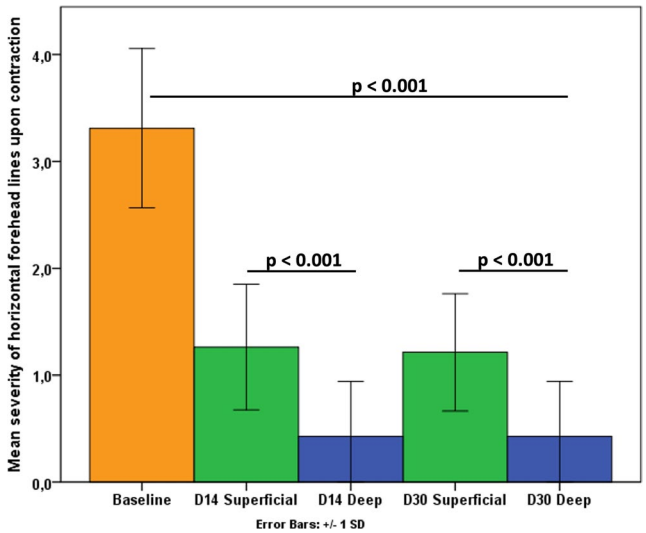

FIGURE 8 Bar graphs showing the mean and the respective standard deviation for the forehead line severity scale at maximal frontalis muscle contraction (0-4, best to worst) at baseline (orange bar) and at D14 and D30. Green bars indicate the superficial injection technique whereas blue bars indicate the deep injection technique

The superficial injection technique administered the product in the superficial fatty layer of the forehead superficial to the frontalis muscle. Here, the product is located between the dermal underside and the suprafrontalis fascia. The suprafrontalis fascia is the superficial continuation of the galea aponeurotica and covers the frontalis muscle on its superficial surface.[12] This fascia connects the frontalis muscle via thin septae also termed retinacula cutis to the frontal skin underside and is responsible for the direct force transmission between the moving muscle and the overlying skin[13]; this enables the overlying skin to reflect directly on the contraction pattern and on the level of contractility of the underlying muscle.[8,9] Positioning the product superficial to the suprafrontalis fascia and into the superficial fatty layer seems to yield reduced efficacy in affecting the contractility of the frontalis muscle when compared to the deep injection technique. The product is separated by the intact fascia which was not penetrated by the needle and can thus limit the efficacy to paralyze the muscle.

The deep injection technique administered the product into the supraperiosteal plane and resulted in highly statistically significantly better outcomes when compared to the superficial injection technique. The confirmation of the deep plane injection was based on manual feedback as the needle was inserted perpendicular to the skin surface until bone contact was established and could not be inserted further. During the insertion process, a click-like sound was heard in 100% of the performed injections; this sound resulted from the penetration of the subfrontalis fascia by the needle. This fascia is thick and substantial in texture and is the deep continuation of the galea aponeurotica. The subfrontalis fascia covers the deep surface of the frontalis muscle and separates the muscle from the loose areolar tissue of the forehead which is located in the supraperiosteal plane.[12] The performed deep needle injection technique perforates all layers of the forehead including the subfrontalis fascia and creates a perpendicular injection canal connecting the supraperiosteal plane to the skin surface. The application of the neuromodulator product which has viscoelastic properties close to water results in the distribution of the product retrograde along the created injection canal. This retrograde distribution behavior was previously documented for filler injection on the forehead[14] and confirmed in several consecutive studies investigating materials with different viscoelastic properties.[15,16] These studies have provided evidence that injected products with low viscoelastic properties (= low G-prime), that is, fluid products migrate more easy along the created injection canal as products with high viscoelastic properties (= high G-prime) with a correlation coefficient of $r_p = -.651$ and $P < .001$ between G-prime and retrograde product spread. Due to the perpendicular injection technique, the applied neuromodulator can migrate into more superficial layers via the injection canal and reach the frontalis muscle and thereby be in direct contact with the muscular tissue. The influence of the injection angle was previously investigated, and the authors reported that the degree of retrograde product migration with a perpendicular needle approach was increased by the odds of OR 10.0 (95% CI, 7.11-14.09) and $P < .001$ when compared to a 10° needle injection[17]; this can be confirmed by the results of the present study

as the deep injection technique resulted in statistically significant better outcomes compared to the superficial injection technique.

Clinically, the results of this and previous split-face studies indicate that the effectiveness of forehead neuromodulator injections depends highly on the depth of product administration.[6,7] The same amount of neurotoxin in the same anatomic location (forehead) can have different effects when injected superficially or deep. Treating the forehead on an individual basis and not following rigid "cookbook" injection schemes does require a targeted and precise approach which should be guided by a profound understanding of anatomy. Recent research has provided new insights into the functional anatomy of the frontalis muscle when describing the line of convergence.[5] In the clinical conclusion of their article, the authors indicated that inferior to the line of convergence a more superficial injection should be attempted to lightly affect the frontalis muscle in order to eliminate horizontal forehead lines but to not cause eyebrow ptosis. This present study provides scientific evidence for their claims as it was shown that a superficial injection can result in equal outcomes at rest but in reduced frontalis muscle paralysis when assessed by the forehead lines severity score at maximal frontalis contraction.[10] In areas of the forehead where predominately a surface effect is desired, but with limited influence on the contractility of the frontalis muscle to avoid adverse events (ie, brow ptosis), a superficial injection should be performed. On the contrary, a deep injection should be performed when a substantial effect on frontalis muscle action is desired; this can be performed most safely in the location at the aforementioned line of convergence or above (= 60% of the total forehead length).

5 | CONCLUSION

This study was designed as a clinical, prospective, interventional split-face investigation of the effects of neuromodulator injections for the treatment of horizontal forehead lines at varying depths. The results revealed that the deep injection technique with product administration into the supraperiosteal plane resulted in a statistically significant better outcome at 14 and 30 days after the treatment upon maximal frontalis muscle contraction. At rest, no statistical difference between the superficial and the deep injection techniques was observed. The results of this study underscore how detailed anatomic knowledge, in this case regarding the layers of the forehead, may guide therapeutic techniques in order to optimize clinical outcomes.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

AUTHOR CONTRIBUTIONS

KD, DVM, KF, DG, JBG, DLF, SH, TP, MHG, and SC have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. KD, DVM, KF, DG, JBG, DLF, SH, TP, MHG, and SC have been involved in drafting the manuscript or revising it critically for important intellectual content and given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL STATEMENT

The study was approved by the ethical committee of the university of Belgrade (Ethics approval number: 5H09M77KS0241/2020).

DATA AVAILABILITY STATEMENT

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

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