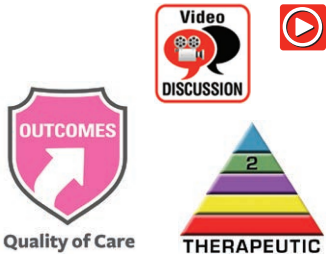
Does Linear or Spot Injection Technique Matter in Upper Face Botulinum Toxin Type A Application? A Split-Face Randomized Trial

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Background: Although the efficacy of botulinum toxin type A (BoNTA) has been shown to vary depending on injection layer, reconstitution volume, and BoNTA formulation, the effect of injection pattern has rarely been mentioned. The authors compared the therapeutic effects in patients treated with BoNTA with retrograde linear and traditional spot injection techniques.

Methods: Twenty-eight participants were enrolled in a split-face, patient-blinded randomized clinical trial. Each patient received BoNTA injected with linear injection technique on one side and with spot injection technique on the other side. Outcomes included wrinkle improvement rates (WIRs) of the 2 injection techniques determined by wrinkle scores derived from an Antera 3-dimensional camera, muscle activity assessed by ultrasound, and patient-reported pain rating on a numeric rating scale.

Results: All participants completed the study. For forehead wrinkles, WIR on the linear side was significantly larger than that on the spot side at 1 week and 1 month ($P < 0.02$). For glabellar wrinkles, WIR on the linear injection side was significantly larger than that on the spot side at 1 week ($P = 0.04$). However, for periorbital wrinkles, WIR on the spot side was significantly larger than that on the linear side at 1 week ($P < 0.03$). No significant difference was observed between the injection patterns in terms of muscle contraction and numeric rating scale pain scores.

Conclusions: Compared with the traditional spot injection, retrograde linear injection was superior in reducing forehead lines and glabellar lines, but less effective in reducing periorbital lines when identical dosages were injected. *(Plast. Reconstr. Surg.* 154: 656e, 2024.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

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Botulinum toxin A (BoNTA) reversibly blocks nerve signals to muscles, creating a temporary weakening or paralyzed effect on muscle activity.[1] Thus, it is widely used in cosmetic procedures to smooth facial wrinkles and

Disclosure statements are at the end of this article, following the correspondence information.

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A Video Discussion by Prakash J. Mathew, MD, accompanies this article. Go to PRSJournal.com and click on "Video Discussions" in the "Digital Media" tab to watch.

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achieve a rejuvenated outcome.[2] Although several guidelines and recommendations have been published,[3,4] the determination of the best treatment protocol regarding the medication preparation, administration method, and BoNTA type requires continuous efforts.[5–7] For example, a previous study preliminarily compared the 2 injection methods and claimed that the retrograde linear injection of BoNTA along the muscle fiber orientations of the orbicularis oculi muscle and corrugator supercilii muscle enabled a larger number of neuromuscular junctions to be paralyzed and thus achieved a marked improvement in terms of reducing periorbital and glabellar wrinkles.[8] However, the study was a retrospective review of the authors' clinical practice, and some linear injection routes were not parallel to the muscle fibers. A prospective study with standard protocol design and systematic efficacy evaluation is necessary. In our study, we improved the retrograde linear injection technique, making its relationship with the injection pattern more reasonable.

Various rating scales, such as the Wrinkle Severity Scale (WSS) and Facial Wrinkle Scale, have been used to evaluate the quality and quantity of facial wrinkles, but subjective assessments are not sensitive enough to detect minor changes, especially static changes.[9] To address this problem, 3-dimensional (3D) measurements, including Visia and Antera, have been developed to provide an objective analysis of skin texture.[10] They have been proven to be sensitive and reliable, and the numeric data derived from them facilitate further statistical analysis.

The aim of the current study was to compare the efficacy of retrograde linear and traditional spot BoNTA injection in the treatment of forehead, glabellar, and periorbital wrinkles based on 3D surface analysis by Antera 3D camera and muscle activity measurement by ultrasound. In addition, pain perception during injection was measured using a numeric pain rating scale (NRS).

PATIENTS AND METHODS

Study Design and Participants

This prospective, single-blind, split-face randomized study was approved by the ethics committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (SK-1556), and registered in the Chinese Clinical Trial Registry (ChiCTR2100046880). All participants provided written consent. The main inclusion criteria were healthy participants, age 18 to 60 years; moderate to severe dynamic forehead, glabellar, and periorbital wrinkles; and no history of BoNTA or dermal filler injections of the upper face. Pregnant or lactating women and people on anticoagulant therapy were excluded. Patients were randomized to 1 of 2 groups. Patients in group A received spot injection on the left side and linear injection on the right side. Patients in group B received spot injection on the right side and linear injection on the left side.

Technique

A total of 100 U of BoNTA (Botox; Allergan) was diluted in 2.5 mL of 0.9% saline to a final concentration of 4.0 U/0.1 mL. Compound lidocaine cream (Tongfang Pharm Group) was applied half an hour before injection. On the spot injection side, injections were performed with a 1.3-cm-long 30-G needle, (Becton Dickinson Labware). For the forehead wrinkles, 6 injection sites were determined with 0.5 U at each spot subcutaneously (3 U in total). For the glabellar lines, injections were performed deep to the periosteum at the origin of the corrugator supercilii muscle and subcutaneously at the insertion of the corrugator supercilii muscle with 4 U on each site (8 U in total). For the periorbital wrinkles, the injection sites were determined around the lateral canthus evenly, with 2 U on each site subcutaneously (6 U in total). On the linear injection side, injections were performed with a 30-G needle, 2.5 cm in length (Becton Dickinson Labware). An equal dosage of BoNTA was injected into corresponding injection sites (Fig. 1). For forehead wrinkles, 3 injection routes were recognized accordingly, with 1 U at each route subcutaneously (3 U in total). The needle was introduced at a 15- to 25-degree angle and traveled along the orientation of muscle bundles for about 2 cm, and the medication was evenly administrated while the needle was slowly withdrawn. For glabellar lines, the needle was inserted from the middle of the eyebrow, at the insertion of the corrugator supercilii muscle, and advanced toward the beginning of the eyebrow for about 2.5 cm, at the origin of the corrugator supercilii muscle, until the needle tip reached the periosteum. A total of 8 U of medication was evenly administrated while the needle was slowly withdrawn. For periorbital wrinkles, 2 injection routes were recognized accordingly, with 3 U at each route subcutaneously (6 U in total). The injection was performed in a similar fashion to the forehead wrinkles. (**See Video 1 [online]**,

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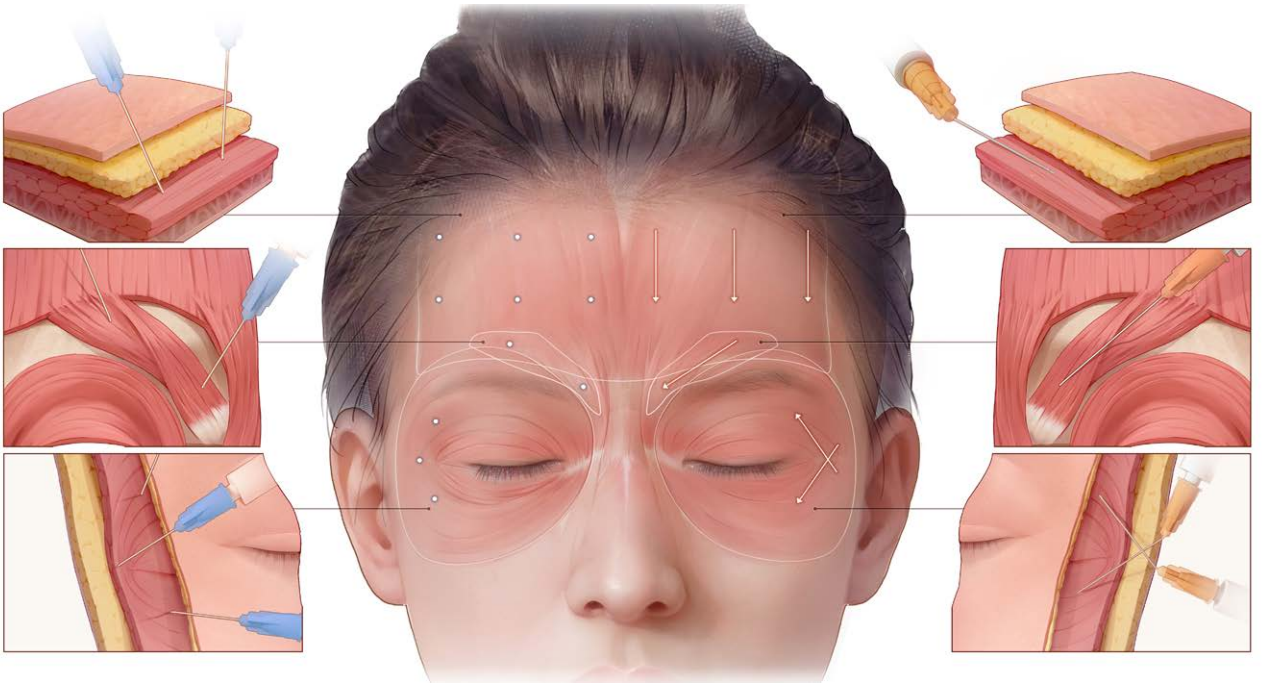


Fig. 1. Patients were randomized to receive the traditional spot injection of BoNTA on one side of the face and the retrograde linear injection on the contralateral side to treat forehead, glabellar, and periorbital wrinkles.

which demonstrates linear and spot injection techniques.) All injections were performed by an experienced plastic surgeon (Y.L.).

Assessments

Five evaluations were performed: baseline, follow-up visit 1 (1 week after the procedure), follow-up visit 2 (1 month after the procedure), follow-up visit 3 (3 months after the procedure), and follow-up visit 4 (6 months after the procedure). Photographic assessments (Canon D80) were performed at rest and at maximum muscle activity.

An Antera 3D camera (Miravex) was used to capture 6 areas on the face at rest and at maximum muscle activity. The areas include the left forehead, mid-forehead, right forehead, glabellum, left lateral canthus, and right lateral canthus. The steps were repeated 3 times. The acquired images were converted into wrinkle images, and wrinkle scores (wrinkle score $_{static}$ and wrinkle score $_{max}$) derived from the camera were recorded for further quantitative analysis.

Based on the follow-up photographs, a blinded physician assessed wrinkles and graded them separately with either side of the face according to the WSS as follows: 0, no wrinkles; 1, minimal wrinkles; 2, mild wrinkles; 3, moderate wrinkles; or 4, severe wrinkles.[9]

To obtain maximum contraction of the frontalis and corrugator supercilii, M-mode ultrasound imaging with a 12-H linear probe (E-cube 7; Alpinion Co.) was adopted to measure the change in muscle thicknesses before and after contraction at maximum force. The differences between peak and valley values were measured using on-screen calipers and recorded as muscle contraction.

To estimate how experiences of pain vary in relationship to injection patterns, the patients were asked to rate the pain on either side of the face based on NRS ranging from 0 to 10, with 0 representing no pain and 10 being the greatest imaginable pain. Meanwhile, participants rated their satisfaction separately with either side of the face as follows: 0, very dissatisfied; 1, dissatisfied; 2, neutral; 3, satisfied; or 4, very satisfied at follow-up visit 4. Any complications occurring during the trial were recorded.

Minor Iodine Starch Test

To further understand the field effects of the 2 injection patterns and discover a mechanism that might help explain the different performances of the 2 injection patterns, the minor iodine starch test was performed on 5 additional participants. The retrograde linear injection of 4 U BoNTA was performed on the right side of the forehead. Meanwhile, the spot injection of 2 U BoNTA on 2 corresponding sites was performed on the left side. Participants were evaluated at baseline, 1 week, and 1 month. They were asked

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Table 1. Change in Wrinkle Improvement Rate at Each Visit[a]

Wrinkle Improvement Rate	Linear (n = 28)	Spot (n = 28)	P
Forehead			
Follow-up 1	89.55 (71.57, 95.89)	63.43 (40.43, 78.45)	<0.007
Follow-up 2	72.77 (56.28, 90.87)	52.36 (35.73, 70.26)	<0.02
Follow-up 3	42.43 (16.38, 69.02)	33.56 (−2.99, 73.26)	>0.05
Follow-up 4	15.25 (−8.97, 46.64)	10.22 (−43.48, 46.07)	>0.05
Glabellar			
Follow-up 1	83.06 (67.10, 90.13)	75.30 (56.67, 92.00)	0.044
Follow-up 2	81.57 (59.44, 91.14)	71.81 (48.94, 88.40)	>0.05
Follow-up 3	44.86 (3.58, 73.93)	38.70 (7.77, 59.84)	>0.05
Follow-up 4	11.4 (−27.17, 34.03)	0.53 (−31.48, 27.61)	>0.05
Periorbital			
Follow-up 1	25.86 (2.13, 53.26)	48.06 (25.89, 77.27)	<0.03
Follow-up 2	22.48 (−4.51, 59.94)	43.69 (7.97, 65.01)	>0.05
Follow-up 3	20.63 (−4.29, 39.93)	27.21 (4.69, 68.89)	>0.05
Follow-up 4	18.13 (−25.67, 33.17)	13.07 (−3.54, 31.68)	>0.05

[a]Data are presented as median (interquartile range).

to run until sweating. Then the sweat was wiped, and a 0.5% complex iodine solution was applied, followed by a thin layer of starch with a powder puff. The rationale is the action between iodine and amylose precipitated by sweat. Thus, sweating areas would be determined by a blue–black color, whereas areas of anhidrosis would not, forming a halo.[11] Photographs were taken, and Image J 1.80 (National Institutes of Health) was used to measure the areas of the halo.

Statistical Analysis

The wrinkle scores in different areas were defined as follows: wrinkle $score_{max}$ − wrinkle $score_{static}$. An index called the wrinkle improvement rate (WIR) was introduced to describe the effect of injection patterns on the wrinkles: ([wrinkle score at follow-up visit − wrinkle score at baseline]/wrinkle score at baseline). The WIRs of the first 4 patients at visit 1 were used to calculate the sample size. A sample size of 6, 18, and 168 patients was required to detect a difference in treating the forehead, glabellar, and periorbital lines, respectively, at 80% power. An index called the muscle contraction reduction rate was introduced to describe the paralyzing effect of injection patterns on the muscles: ([muscle contraction at follow-up visit − muscle contraction at baseline]/muscle contraction at baseline). Shapiro-Wilk test was performed to detect the normality of the collected data. All data were expressed by median (interquartile range). Mann-Whitney U test was used to compare the variables between different groups. $P < 0.05$ was statistically significant. Python 3.8.5 was used to analyze the data.

RESULTS

Clinical Characteristics

There were 28 participants enrolled, with ages ranging from 21 to 50 years (mean, 31.2 years), including 21 women and 7 men. Data were collected from April 24, 2021, to May 20, 2022. After randomization, the linear injection was performed on the left side of the face in 11 participants and on the right side of the face in 17 participants, with the contralateral side receiving the spot injection. All 28 participants completed the photographic, 3D camera, and ultrasound assessments.

Wrinkle Assessment

The objective severity of the wrinkles was determined by the wrinkle scores derived from the Antera 3D camera as previously described. The wrinkle scores and the WIRs of different wrinkles are presented in Table 1 and Figure 2 For forehead and glabellar wrinkles, both injection patterns were significant at 1 week, 1 month, and 3 months ($P < 0.03$). For periorbital wrinkles, the spot injection technique showed a statistically significant improvement from baseline at 1 week, 1 month, and 3 months ($P < 0.03$), whereas the assessment of the linear injection only showed a statistically significant improvement from baseline at 1 month ($P < 0.05$). For forehead wrinkles, the WIR of the linear injection side was significantly larger than that of the spot injection side at 1 week and 1 month over baseline: 89.55 (71.57, 95.89) versus 63.43 (40.43, 78.45) ($P < 0.007$) and 72.77 (56.28, 90.87) versus 52.36 (35.73, 70.26) ($P < 0.02$). The difference, however, diminished, and

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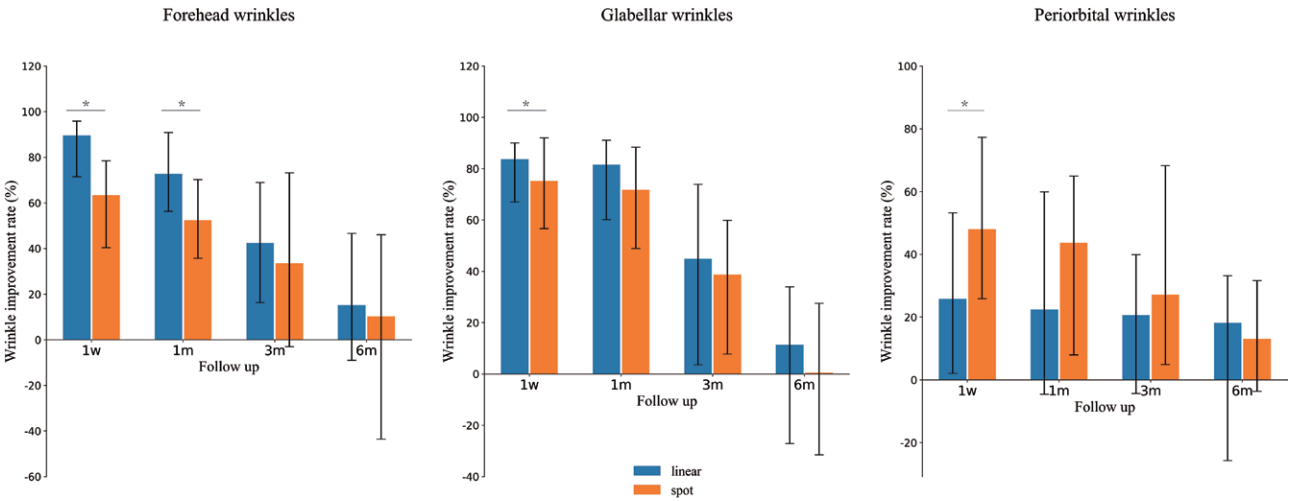


Fig. 2. WIRs of different wrinkles for linear injection (*blue*) versus spot injection (*orange*). (*Left*) WIR of forehead wrinkles. (*Center*) WIR of glabellar wrinkles. (*Right*) WIR of periorbital wrinkles. *$P < 0.05$.

fell below significance at the remaining follow-up visits. For glabellar wrinkles, the WIR of the linear injection side was significantly larger than that of the spot injection side at 1 week over baseline: 83.06 (67.10, 90.13) versus 75.30 (56.67, 92.00) ($P = 0.04$). The difference fell below significance at the remaining follow-up visits. For periorbital wrinkles, the WIR of the spot injection side was significantly larger than that of the linear injection side at 1 week over baseline: 25.86 (2.13, 53.26) versus 48.06 (25.89, 77.27) ($P < 0.03$). The difference diminished and fell below significance at the rest of the follow-up visits.

At each visit, a physician-reported wrinkle severity score was given, and the significant wrinkle-soothing effect lasted until week 24 in both groups for all 3 wrinkle areas, but there were no significant differences between the 2 injection patterns at any time point. (**See Table, Supplemental Digital Content 1**, which shows WSS of forehead lines for linear injection versus spot injection, ***http://links.lww.com/PRS/G981***. **See Table, Supplemental Digital Content 2**, which shows WSS of glabellar lines for linear injection versus spot injection, ***http://links.lww.com/PRS/G982***. **See Table, Supplemental Digital Content 3**, which shows WSS of periorbital lines for linear injection versus spot injection, ***http://links.lww.com/PRS/G983***.)

Representative before and after photographs of each of the 3 wrinkle areas recorded are shown in Figures 3 and 4. (**See Figure, Supplemental Digital Content 4**, which shows digital and 3D photographs of a 30-year-old man who received the retrograde linear injection on the right side of the face and the spot injection on the left side of the face before treatment [*above*] and 1 month after treatment [*below*], ***http://links.lww.com/PRS/G984***. **See Figure, Supplemental Digital Content 5**, which shows digital and 3D photographs of a 52-year-old woman who received the retrograde linear injection on the left side of the face and the spot injection on the right side of the face before treatment [*above*] and 1 month after treatment [*below*], ***http://links.lww.com/PRS/G985***.)

Muscle Activity

Contraction of the orbicularis oculi was too minor to be well captured by the ultrasound; thus, only the contraction of the frontalis and corrugator supercilii was recorded and analyzed further (Table 2). (**See Video 2 [online]**, which shows contraction of the frontalis on M-mode ultrasound imaging. **See Video 3 [online]**, which shows contraction of the corrugator supercilii on M-mode ultrasound imaging.) For the frontalis, both injection patterns reduced muscle contraction significantly at 1 week, 1 month, and 3 months over the baseline ($P < 0.001$). There was no significant difference between the muscle contraction reduction rates of the 2 injection patterns at any time point. For the corrugator supercilii, the linear injection demonstrated a longer lasting paralysis effect than the spot injection; the former significantly reduced the muscle contraction at 1 week and 1, 3, and 6 months ($P < 0.001$) over the baseline, but the latter only significantly reduced the muscle contraction at 1 week, 1 month, and 3 months ($P < 0.03$). However, there was no significant difference between the 2 injection patterns at any time point.

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Fig. 3. Photographs show a 30-year-old man who received the retrograde linear injection on the right side of the face and the spot injection on the left side of the face. (*Left*) Before treatment. (*Right*) 1 month after treatment.

Fields of Anhidrotic Effect

Five additional participants completed the minor iodine starch test. Fields of anhidrotic effect (FAEs) on the side of the retrograde linear injection were linear, whereas the FAEs on the side of the spot injection were round. (**See Figure, Supplemental Digital Content 6**, which shows FAEs 1 month after the retrograde linear injection of 4 U BoNTA on the right side and the spot injection of 2 U BoNTA on 2 corresponding sites on the left side, ***http://links.lww.com/PRS/G986***.) The area of the former was slightly larger than the area of the latter, but the difference was not significant: 3.56 (2.98, 4.12) versus 2.78 (2.32, 3.14) ($P > 0.05$).

Safety and Patient Satisfaction

One patient (3.5%) reported a sense of eyelid heaviness 3 days after administration on the linear injection side. No blepharoptosis was noted. The symptom spontaneously resolved in 3 weeks. No other complications, including headache, visual field change, eyebrow ptosis, or allergic response, were reported.

NRS was higher on the linear injection side (**see Figure, Supplemental Digital Content 7**, which shows NRS scores for linear injection versus spot injection, ***http://links.lww.com/PRS/G987***), but there was no significant difference ($P > 0.05$). The safety profile of both techniques was excellent.

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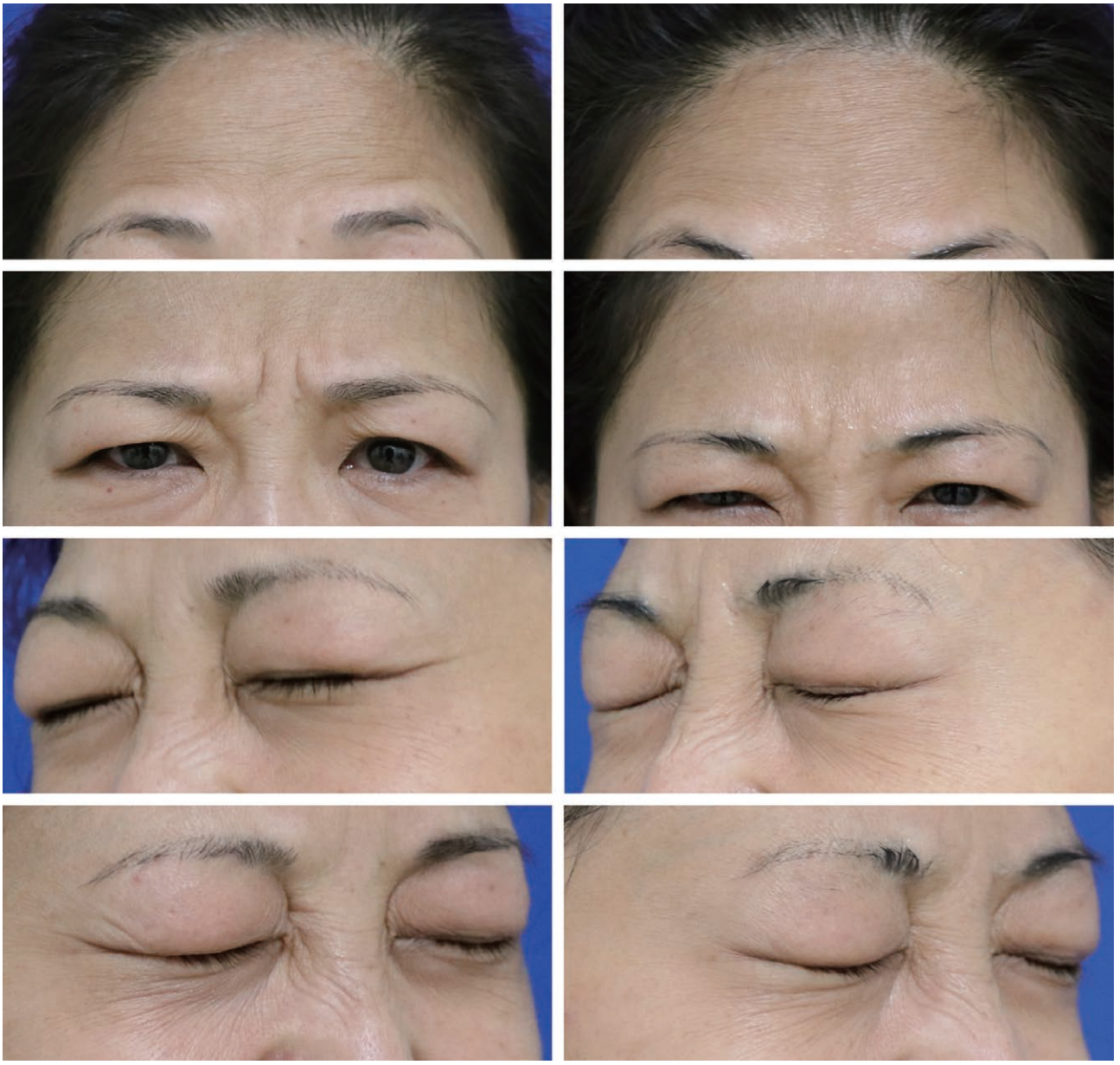


Fig. 4. Photographs show a 52-year-old woman who received the retrograde linear injection on the left side of the face and the spot injection on the right side of the face. (*Left*) Before treatment. (*Right*) 1 month after treatment.

Table 2. Change in Muscle Contraction Reduction Rate at Each Visit[a]

Muscle Contraction Reduction Rate	Linear (n = 28)	Spot (n = 28)	P
Frontalis			
Follow-up 1	66.26 (59.75, 75.23)	65.79 (48.72, 70.67)	>0.05
Follow-up 2	55.14 (38.57, 59.78)	51.52 (41.78, 57.32)	>0.05
Follow-up 3	20.51 (11.29, 34.28)	20.56 (11.54, 28.26)	>0.05
Follow-up 4	5.88 (0.9, 14.46)	2.94 (1.28, 10.66)	>0.05
Corrugator supercilii			
Follow-up 1	78.12 (74.07, 85.71)	70.37 (62.5, 78.26)	>0.05
Follow-up 2	56.25 (48.15, 69.23)	50.00 (41.38, 65.38)	>0.05
Follow-up 3	37.50 (22.58, 53.33)	28.57 (15.62, 42.31)	>0.05
Follow-up 4	9.68 (0, 30.77)	13.51 (3.84, 29.16)	>0.05

[a]Data are presented as median (interquartile range).

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For the spot injections, participants rated their satisfaction at 3.04 (2.17, 3.86). For the linear injections, the satisfaction rating was 3.00 (2.10, 3.43). The difference in patient satisfaction was not statistically significant ($P > 0.05$).

DISCUSSION

To accurately predict the efficacy of BoNTA in treating facial wrinkles, several factors should be taken into consideration, including injection layer, reconstitution volumes, and BoNTA brands. Although intramuscular and subcutaneous injection of BoNTA present equivalent antidynamic wrinkle effects, the prominent role of the intradermal injection technique is to decrease microwrinkles and improve skin texture.[12,13] Previous studies implied that BoNTA prepared in lower concentration and higher volume resulted in greater diffusion and a larger affected area.[14] Differing brands of BoNTA might not exert the same efficacy, mainly because of different molecular potency. Generally, increased molecular potency shortens the time of onset and increases the duration of effect.[15] Despite the great effort invested so far in optimizing injection protocols of BoNTA, the effect of injection patterns has been rarely mentioned. Based on the motor end plate distribution theory, Labbe et al.[8] suggested that retrograde linear injection of BoNTA along the muscle fiber orientations of the upper facial muscles potentialized the dose delivery through influence over a higher number of neuromuscular junctions; thus, it achieved a more remarkable antiwrinkle effect around the eyes and between the eyebrows than the spot injection technique. However, their injection pattern did not strictly follow the muscle fiber direction, as it was almost perpendicular to the frontalis muscle. In our study, a traditional multispot injection was performed on half of the patients' faces, and on the other half, a retrograde linear injection was performed. Both techniques made the best use of the muscle fiber directions.

The wrinkle scores derived from the Antera 3D camera confirmed that both injection techniques resulted in significant wrinkle improvement. Compared with spot injection, linear injection was superior in reducing forehead lines and glabellar lines, but less effective in reducing periorbital lines. We theorized that the relationship between the diffusion of BoNTA and the muscle shape was key to BoNTA efficacy. As indicated by the minor iodine starch test, the diffusion shape of BoNTA was consistent with the injection pattern. When BoNTA was injected following a linear pattern, the FEA was linear. Similarly, when it was injected at spots, the FEA was round. For the frontalis, which is a broad muscle, the linear injection allows the toxin to diffuse evenly along its muscle fiber and paralyzes more motor end plates to reach a better effect. A noteworthy advantage is that injecting larger muscle with the linear technique permits lower toxin doses to be injected with good clinical efficacy while minimizing the common side effects associated with overdoses, such as brow ptosis, and reducing treatment costs. For the corrugator supercilii, a slender-shaped muscle, the effect of the linear injection is also more prominent than the spot injection. For the orbicularis oculi, which is a sphincter muscle, the linear injection demonstrated a poorer effect than the spot injection. The orbicularis oculi is a complex of muscles that encircles the eye and is composed of 3 independent quadrants that interlace and give only an appearance of circularity.[16] Thus, the contraction of the muscle is more unpredictable, and is the result of the antagonistic and synergistic effects among multiple regions.[17] A monolinear injection in the direction of a bundle of muscle fibers may not be adequate to achieve a more satisfactory effect.

Treatment with both injection patterns resulted in significant wrinkle improvement from baseline assessed by WSS. However, there was no significant difference seen between the 2 injection patterns. The reasons behind this might be that a 5-point grading scale was only sensitive enough to detect improvement after treatment, but not able to compare 2 similar treatments, even though the differences were obvious to the eye, as shown in our figures.

Some participants were given a higher wrinkle score at the 6-month follow-up compared with the baseline, possibly because as the study progressed, it became easier for them to make facial expressions following the instructions.

In terms of muscle activity, a significant decrease in muscle contraction from baseline was observed on both injection sides, as demonstrated by ultrasound recordings. Although the linear injection side had more reduction in muscle contraction compared with the spot injection side, the difference was not significant. In fact, compared with the large muscle groups in other parts of the body, the activity of facial muscle groups is extremely subtle, inflicting mounting challenges in accurately capturing tiny changes. Previous work has used the amplitude of evoked compound muscle action potentials by electromyography to evaluate the effect of BoNTA on muscle

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activity.[6] Further study could be launched to compare the effect of 2 injection patterns on muscle activity based on evoked compound muscle action potentials.

Another important factor to consider is whether the retrograde linear injection triggers more clinically significant pain. During the practice, a subset of participants reported more pain in the linear injection side, whereas the other subset felt the opposite, possibly because some people were more sensitive to the friction feeling of a needle sliding in the subcutaneous tissue during the linear injection, whereas some were more sensitive to the pressure when administrating medicine during the spot injection.

Clinical details of the linear injection technique are as follows: onset of the linear injection results is faster, allowing patients to experience the effect of wrinkle reduction earlier; the medication is more evenly distributed, avoiding an uneven injection that leads to muscle strength imbalance in regions of the target muscle; the linear injection evades the pain and discomfort caused by repeatedly piercing the skin in the traditional spot injection, and as for subcutaneous advancement in the linear injection, the patients in this experiment had a similar perception of linear and spot injection; and the linear injection has a higher technique requirement and a longer learning curve.

When applying the treatment, an ideal goal is to distribute BoNTA evenly into the targeted muscle, and the injection pattern is one of the nonnegligible factors that will influence the outcome. During hyaluronic acid filler treatment, experienced doctors are familiar with cannulas (which inject fillers mainly in a linear fashion) and sharp needles (which inject fillers mainly in a bolus fashion), and have excellent results with a combination of these 2 skills, although different doctors may have their own preferences. Similarly, the linear injection in BoNTA treatment may be advantageous, considering different treatment targets and goals; the clinical decision depends on the doctor's preferences and the patient's expectations. The results of our study provide a new option for aesthetic practitioners.

Limitations

The study was designed to compare 2 different injection patterns of BoNTA in 28 healthy volunteers and reveal the possible mechanisms behind their differences in effects. Despite efforts to collect a sufficient amount of data for analysis, we were only able to successfully perform the minor iodine starch test in 5 participants, and could not analyze the muscle contraction of the orbicularis oculi because of the limited instrument sensitivity. In addition, follow-up assessments started 1 week after the procedure; as a result, early responses could not be analyzed.

CONCLUSIONS

Compared with the traditional spot injection, the retrograde linear injection was superior in reducing forehead lines and glabellar lines, but less effective in reducing periorbital lines, when identical dosages were injected. The results of this study introduce unique insights into the customizable treatment protocol for facial wrinkles by BoNTA.

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DISCLOSURE

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Kumar R, Dhaliwal HP, Kukreja RV, Singh BR. The botulinum toxin as a therapeutic agent: molecular structure and mechanism of action in motor and sensory systems. *Semin Neurol.* 2016;36:10–19.
2. Michaels BM, Csank GA, Ryb GE, Eko FN, Rubin A. Prospective randomized comparison of onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) in the treatment of forehead, glabellar, and periorbital wrinkles. *Aesthet Surg J.* 2012;32:96–102.

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3. Carruthers J, Fagien S, Matarasso SL; Botox Consensus Group. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. *Plast Reconstr Surg.* 2004;114:1S–22S.
4. Ahn BK, Kim YS, Kim HJ, Rho NK, Kim HS. Consensus recommendations on the aesthetic usage of botulinum toxin type A in Asians. *Dermatol Surg.* 2013;39:1843–1860.
5. Kassir R, Kolluru A, Kassir M. Triple-blind, prospective, internally controlled comparative study between abobotulinumtoxinA and onabotulinumtoxinA for the treatment of facial rhytids. *Dermatol Ther.* 2013;3:179–189.
6. Hexsel D, Hexsel C, Siega C, Schilling-Souza J, Rotta FT, Rodrigues TC. Fields of effects of 2 commercial preparations of botulinum toxin type A at equal labeled unit doses: a double-blind randomized trial. *JAMA Dermatol.* 2013;149:1386–1391.
7. Kim YJ, Lim OK, Choi WJ. Are there differences between intradermal and intramuscular injections of botulinum toxin on the forehead? *Dermatol Surg.* 2020;46:e126–e131.
8. Labbe D, Abdulshakoor A, Fernandez J. Retrograde vs spot botulinum toxin facial injection. *Ann Chir Plast Esthet.* 2021;66:223–233.
9. Rappl T, Wurzer P, May S, et al. Three-dimensional evaluation of static and dynamic effects of botulinum toxin a on glabellar frown lines. *Aesthetic Plast Surg.* 2019;43:206–212.
10. Linming F, Wei H, Anqi L, et al. Comparison of two skin imaging analysis instruments: the VISIA from Canfield vs the ANTERA 3D CS from Miravex. *Skin Res Technol.* 2018;24:3–8.
11. Jiang HY, Chen S, Zhou J, Leung KK, Yu P. Diffusion of two botulinum toxins type A on the forehead: double-blinded, randomized, controlled study. *Dermatol Surg.* 2014;40:184–192.
12. Gordin EA, Luginbuhl AL, Ortlip T, Heffelfinger RN, Krein H. Subcutaneous vs intramuscular botulinum toxin: split-face randomized study. *JAMA Facial Plast Surg.* 2014;16:193–198.
13. Diaspro A, Calvisi L, Manzoni V, Sito G. Microbotulinum: a quantitative evaluation of aesthetic skin improvement in 62 patients. *Plast Reconstr Surg.* 2020;146:987–994.
14. Hsu TSJ, Dover JS, Arndt KA. Effect of volume and concentration on the diffusion of botulinum exotoxin A. *Arch Dermatol.* 2004;140:1351–1354.
15. Nestor MS, Arnold D, Fischer DL. The mechanisms of action and use of botulinum neurotoxin type A in aesthetics: key clinical postulates II. *J Cosmet Dermatol.* 2020;19:2785–2804.
16. Tong J, Lopez MJ, Patel BC. Anatomy, head and neck, eye orbicularis oculi muscle. In: *StatPearls.* Treasure Island, FL: StatPearls Publishing; 2022.
17. Li Y, Cai L, Zhang X, et al. Types of periocular wrinkles based on anatomical and contractile characteristics of participating periocular muscles: a modified classification method and personalized injection technique. *J Cosmet Dermatol.* 2022;21:5591–5600.

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