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 ORIGINAL ARTICLE

Intradermal Microdroplet Injection of Diluted Incobotulinumtoxin-A for Sebum Control, Face Lifting, and Pore Size Improvement

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ABSTRACT

Background: Intradermal injections of botulinum toxin have been reported to improve sebum secretion, facial skin laxity, and facial pores. However, the effects of Incobotulinumtoxin-A for these indications have not been reported.

Objective: To evaluate the efficacy of Incobotulinumtoxin-A for the improvement of sebum secretion, face laxity, and facial pores.

Materials and Methods: This single-center retrospective study included patients treated with Incobotulinumtoxin-A to improve facial skin laxity, sebum secretion, and facial pores. The microdroplet injection protocol included injection points on the lateral face, anterior medial cheek, mandibular line, depressor anguli oris points, mid-glabella area, and chin. Outcomes were measured using a Sebumeter and three-dimensional scanner and were evaluated by facial laxity ratings and the Global Aesthetic Improvement Scale.

Results: Twenty patients were included in the analysis. Sebum secretion, mandibular length, facial pores, and facial laxity ratings were improved at 1 week and results were sustained through 12 weeks. All outcomes showed maximum improvement after 4 weeks. Evaluation using the Global Aesthetic Improvement Scale showed that all subjects reported at least a score of 2 (improved) after 4 weeks.

Conclusion: This study showed that intradermal injection with Incobotulinumtoxin-A could be effective for face lifting, reduced sebum production, and improved facial pores.

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INTRODUCTION

Botulinum toxin (BTX) has been widely applied for various cosmetic indications, such as glabellar rhytides, crow's feet, eyelid wrinkles, perioral wrinkles, chin rhytides, masseter hypertrophy, and platysmal bands, since its first aesthetic approval by the US FDA in 2002 for the treatment of glabella lines.[1-5] Currently, BTX is one of the most popular minimally invasive cosmetic procedures performed.[6]

The primary mechanism of BTX is muscle paralysis via inhibiting the exocytosis of presynaptic acetylcholine,[7] and wrinkles related to muscular contraction can be improved by intramuscular injection of BTX.[5] More recently, intradermal injection of BTX has been used off-label for various aesthetic conditions, including facial skin laxity, excess sebum production, and enlarged facial pores.[8-13] These effects could be attributed to the paralysis of arrector pili muscles or decreased sebum production via acetylcholine inhibition.[10,13,14] However, previous studies relied on subjective evaluation and lacked long-term clinical data. Regarding sebum production or facial pore reduction, some studies showed conflicting results.[10,15] Additionally, previous studies applied intradermal injections of Abobotulinumtoxin-A (ABO) or Onaboulinumtoxin-A (ONA), but no currently published study used Incobotulinumtoxin-A (INCO) for these indications.

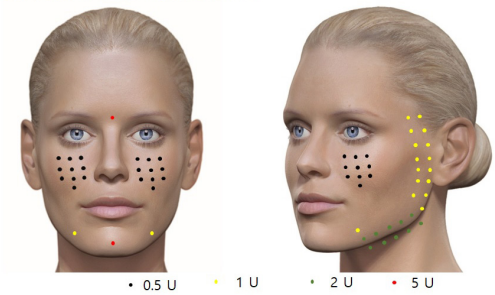
INCO is a highly purified and precisely manufactured BTX type A preparation, which contains the pure 150 kDa active neurotoxin without complexing proteins.[16] Without complexing proteins, INCO is known to have a low antigenicity compared to that of other products of BTX type A.[1,17,18] INCO is also free of other impurities/adjuvants, such as inactive neurotoxin, flagellin, and clostridial DNA contaminants.[17] Here, we retrospectively reviewed patients who received facial treatments with intradermal INCO and evaluated the changes in sebum production, face lifting, and facial pore improvement for up to 12 weeks after a single treatment session.

METHODS

Study Design and Patients

This study was a single-center, retrospective clinical study. The

FIGURE 1. Injection protocol for Incobotulinumtoxin-A. The lateral face (1 U per point), anterior medial cheek (0.5 U per point), mandibular line (2 U per point), and depressor anguli oris points (1 U per point) were injected intradermally with a fixed unit. The mid-glabella and chin area (1 cm above the pogonion) were also injected intramuscularly and intradermally with 5 U per sebum measuring point. The total dose of Incobotulinumtoxin-A injection per protocol was 92 U.



patients who visited Apkoo-Jung Oracle Dermatology Center between August and September 2019, and received facial treatments with INCO for cosmetic purposes, including sebum control, face lifting, and pore size improvement were reviewed. Among these patients, those who had regular follow-ups at the clinic three times (after 1 week, 4 weeks, and 12 weeks) after the procedures were included. If the date of follow-up differed by more than 3 days (after 1 week or 4 weeks) or 7 days (after 12 weeks) of the scheduled date, the results for the patient were not included.This study was approved by the electronic Institutional Review Board of the Korea National Institute for Bioethics Policy (IRB no.: P01-202006-21-005).

Protocol of the Cosmetic Procedure

Each 100-U vial of INCO (Xeomin; Merz Pharmaceuticals GmbH, Hessen, Germany) was diluted using 5 ml of bacteriostatic saline. The face was cleansed with isopropyl alcohol and applied with anesthetic cream (Lidocan cream [lidocaine 96 mg/g]; Daehan Newpharm, Gyeonggi, South Korea) for 30 min before injection. The lateral face, anterior medial cheek, mandibular line, and depressor anguli oris (DAO) points were injected intradermally

FIGURE 2. Measurement of mandibular length by Morpheus 3D. The device automatically measures mandibular length as the lowest border of soft tissue from one side of the gonion via gnathion to the opposite side of gonion (green line). (A) baseline, (B) week 1, (C) week 4, (D) week 12.

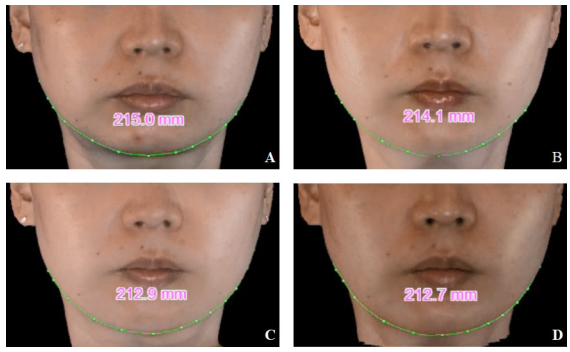


FIGURE 3. Quantification of facial pores. The device automatically counted facial pores on both cheeks where incobotulinumtoxin-A was injected. Analytic images of baseline (A), week 1 (B), week 4 (C), and week 12 (D). Countable facial pores decreased after 1 week (number of pores; 623, density of pores; 21.3%), 4 weeks (number of pores; 413, density of pores; 14.1%), and 12 weeks (number of pores; 649, density of pores; 22.5%) of injection, compared to that of the baseline (number of pores; 906, density of pores; 31.0%). White lines; region of interest, Blue dots; facial pores.

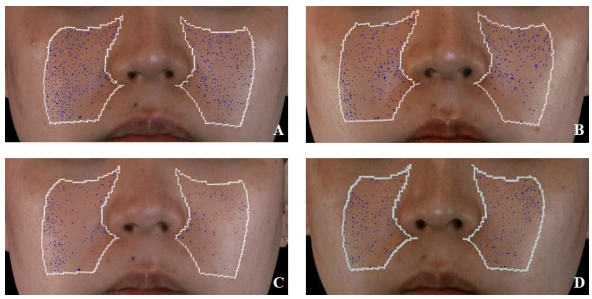
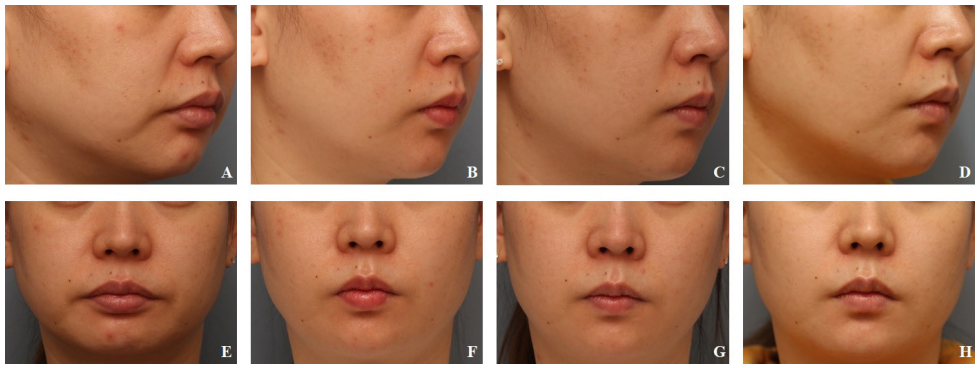


FIGURE 4. Close-up photos of the patient who is the same as that in Figure 2 and 3. The baseline facial laxity rating (FLR) scale was grade 4 (A, E). After Incobotulinumtoxin-A injection, the FLR grade was 1 after 1 week (B, F), and this was sustained through week 4 (C, G) and 12 (D, H). Both investigator and subjective Global Aesthetic Improvement Scale were grade 4 (very much improved) throughout the follow-up period.



with fixed predetermined doses using a 31G needle (Figure 1). This protocol included injection points that mainly targeted the platysma, DAO, and mentalis muscle, as well as sebaceous glands and enlarged pores in the anterior medial cheek.The mid-glabella area and chin area (1 cm above pogonion) were also injected intramuscularly and intradermally (2.5 U each) with a total of 5 U for sebum measuring points. In total, the patient was injected 92 U of INCO using the microdroplet technique.[19,20]

Assessments of Facial Lifting, Sebum Control, and Facial Pores

The clinical outcome was evaluated at baseline and each follow-up visit. Sebum production was measured using a Sebumeter (SM815; Courage and Khazaka, Cologne, Germany) on the forehead and chin as previously described,[21,22] over the same area where INCO was injected. Mandibular length and facial pore (count and density) were evaluated using a three-dimensional scanner (Morpheus 3D; Morpheus Co., Gyeonggi, South Korea).[23-25] This device contained software that automatically analyzed three-dimensional facial images, including measurement of mandibular length and facial pores. The mandibular length was calculated as the lowest border of soft tissue from one side of the gonion via gnathion to the opposite side of gonion (Figure 2). Facial pores were counted on both cheeks, where INCO was injected (Figure 3).

A facial laxity rating (FLR) scale of the lower face was evaluated by an investigator (J.Y. Park) based on photography. The FLR scale graded the laxity of the face from no laxity (class 0) to severe laxity (class 9), including the upper face, middle face, lower face, and neck.[26] Additionally, the Global Aesthetic Improvement Scale (GAIS) was scored by the investigator (Investigator's GAIS, IGAIS) and each patient (Subject's GAIS, SGAIS), which was scored as follows; 4; very much improved, 3; much improved, 2; improved, 1; no change, 0; worsened.

TABLE 1.

Comparison of Mandibular Length, Sebum Secretion, and Facial Pores between the Baseline and After Incobotulinumtoxin-A Injection (Week 1, Week 4, and Week 12)

Baseline		Follow-up after Incobotulinumtoxin-A injection					
		Week 1	p-value	Week 4	p-value	Week 12	p-value
Sebum (Forehead, μg/cm²)	121.5±37.6	99.1±37.2	<0.001	91.8±39.7	<0.001	96.0±35.7	0.010
Sebum (Chin, μg/cm²)	72.5±43.0	59.7±43.6	0.001	56.5±41.6	0.002	60.5±35.3	0.013
Mandibular length (mm)	241.6±21.4	240.2±21.4	<0.001	239.1±20.4	<0.001	240.1±20.0	0.026
Pore (count)	1805.0±478.7	1515.4±472.1	<0.001	1371.2±443.0	<0.001	1584.8±440.1	0.002
Pore (density, %)	43.9±11.5	36.8±10.9	<0.001	33.3±10.2	<0.001	38.6±10.7	0.003

mean ± standard deviation

TABLE 2.

Trends in Facial Laxity Rating Scale and Global Aesthetic Improvement Scale Before and After Incobotulinumtoxin-A Injection (Week 1, Week 4, and Week 12)

		Baseline	Week 1	Week 4	Week 12
Facial laxity rating (FLR) scale	1	0 (0%)	3 (15%)	3 (15%)	2 (10%)
	2	1 (5%)	10 (50%)	12 (60%)	6 (30%)
	3	6 (30%)	5 (25%)	3 (15%)	9 (45%)
	4	10 (50%)	2 (10%)	2 (10%)	2 (10%)
	5	2 (10%)	0 (0%)	0 (0%)	1 (5%)
	6	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Investigator's Global Aesthetic Improvement Scale (GAIS)	0 (worse)	--	0 (0%)	0 (0%)	0 (0%)
	1 (no change)	--	1 (5%)	0 (0%)	0 (0%)
	2 (improved)	--	4 (20%)	3 (15%)	11 (55%)
	3 (much improved)	--	8 (40%)	10 (50%)	8 (40%)
	4 (Very much improved)	--	7 (35%)	7 (35%)	1 (5%)
Subjective Global Aesthetic Improvement Scale (GAIS)	0 (worse)	--	0 (0%)	0 (0%)	0 (0%)
	1 (no change)	--	1 (5%)	0 (0%)	0 (0%)
	2 (improved)	--	3 (15%)	4 (20%)	11 (55%)
	3 (much improved)	--	9 (45%)	9 (45%)	8 (40%)
	4 (Very much improved)	--	7 (35%)	7 (35%)	1 (5%)

Statistical Analysis

IBM SPSS version 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis. The Wilcoxon signed rank-sum test was performed to compare the difference between the baseline and follow-up periods. The differences in outcomes were considered significant if $P<0.05$. All continuous variables are expressed as the mean ± standard deviation.

RESULTS

Thirty-two patients were injected with INCO using the aforementioned protocol over the study inclusion period. A retrospective chart was reviewed to confirm that the patients were suitable for study inclusion. Twelve were excluded because they did not regularly follow-up on the visiting schedule. A total of 20 patients (18 females and 2 males) fulfilled the inclusion criteria. The mean age was 35.7 ± 6.4 (mean ± standard deviation) years. Sebum secretion was significantly reduced at week 1 (99.1 ± 37.2 and 59.7 ± 43.6 μg/cm^2, $P<0.001$ and = 0.001), week 4 (91.8 ± 39.7 and 56.5 ± 41.6, $P<0.001$ and = 0.002), and week 12 (96.0 ± 35.7 and 60.5 ± 35.3, $P= 0.010$ and = 0.013) compared to that at baseline (121.5 ± 37.6 and 72.5 ± 43.0) for both the forehead and chin (Table 1). In particular, at 4 weeks, sebum secretion decreased by 24.4% on the forehead and 22.1% on the chin.

Similarly, mandibular length and facial pores (both number and density) also showed a significant decrease after 1 week (240.2 ± 21.4 mm, 1515.4 ± 472.1 count, 36.8 ± 10.9 %, $P< 0.001$ in each), 4 weeks (239.1 ± 20.4, 1371.2 ± 443.0, 33.3 ± 10.2, $P< 0.001$ in each), and 12 weeks (240.1 ± 20.0, 1584.8 ± 440.1, 38.6 ± 10.7, $P= 0.026$, 0.002, 0.003) of INCO injection compared to that at baseline (241.6 ± 21.4, 1805.0 ± 478.7, 43.9 ± 11.5). All variables showed the most improved results after 4 weeks.

Change in facial laxity evaluated by the FLR scale was significantly improved after INCO injection ($P< 0.001$ at week 1, week 4, and week 12) (Table 2). At baseline, there was no FLR scale grade 1 and only 1 subject (5%) had a grade 2; however, at week 4, 75% of the subjects were grade 2 or less, with 3 (15%) having grade 1 and 12 (60%) having grade 2. Both GAIS by investigator and patients showed at least a score of 2 (improved), except for one patient with no change (score 1) at week 1. At week 4 and 12, both GAIS by investigator and patients scored grade 2 or more. FLR scale and GAIS showed the best results at week 4 (Figure 4). No adverse reaction or complication was reported during the 12-week follow-up period after intradermal microdroplet injection of INCO.

DISCUSSION

In this study, INCO injection improved facial laxity, sebum secretion, and facial pore count up to 12 weeks after injection. This is the first study with INCO to date using intradermal microdroplet injection for these indications.

The concept of face lifting by BTX is to correct the imbalance between the activity of levator and depressor muscles in the face.[27] Aging progression, along with gravity causes dominant depressor muscle activity and a downward movement vector; thus, this results in sagging and drooping. Although the intradermal injection of 20–25 U/side of ONA to temporal areas and cheek showed no significant face lifting effect,[28] a more recent study showed that intradermal injection of 50 U/side ONA or 125 U/side ABO showed comparable and significant efficacy in face lifting.[15] Consistently, Petchngaovilai retrospectively reported intradermal injections of 100–140 U ABO to the platysma and orbicularis oculi, which led to midface lifting in 90% of patients lasting 10 to 14 weeks.[27] A split-face trial involving 22 subjects showed that intradermal injection of ABO to the superior portion of the frontalis, corrugator supercilli, lateral part of the orbicularis oculi, and platysma was associated with face lifting in 40.9% of patients after 2 weeks.[8] Another split-face study found that intradermal injection of different dilutions (50 U or 100 U/side) of ABO were similarly effective in reducing facial laxity and wrinkles.[29] However, only subjective assessments, such as photographic comparison or grading were performed in previous studies, without objective quantification using validated devices. In the present study, the degree of face lifting was evaluated by both subjective (FLR scale) and objective measurements (mandibular length) using a 3D scanner. Time point of peak efficacy for face lifting, sebum secretion, and facial pores observed in this study was 4 weeks, which is similar to that of the follow-up results from previous BTX studies for wrinkle reduction.[30]

Several studies reported decreased sebum production or improved facial pores by intradermal injection of BTX. The mechanism of BTX effects on sebum production has not been fully elucidated; however, sebocyte differentiation and sebum production may be disturbed by inhibition of acetylcholine release by BTX.[14,31] Shah[9] reported that intradermal injection of BTX improved skin oiliness and facial pores in 85% of patients (17/20), although the study was designed retrospectively and no objective evaluation was included.[9] The other two studies examined the efficacy of BTX on forehead sebum production by intramuscular injection of ONA[11] or intradermal injection of ABO.[12] In both studies, decreased sebum production measured by Sebumeter showed a peak after 1 month and was maintained until approximately 2–3 months after injection.[11,12] Although intradermal injection of 50 U/side ONA or 125 U/side ABO failed to show significant efficacy in sebum and facial pore reduction,[15] a recent split-face study showed that the intradermal BTX injected-side showed a significantly greater reduction in seborrhea at 1 month compared to that of the saline injected-side.[10] However, there was a limitation in that seborrhea was evaluated by a 4-point score rather than by objective quantification.

Because the size of facial pores is affected by sebum output,[32] the effect of intradermal BTX injection on facial pores could be directly relaxing arrector pili muscles or indirectly reducing sebum production.[9,13,14,33] In this study, the changes in both sebum secretion and the reduction in facial pores began from 1 week and were evident at 4 weeks. There was no tendency for sebum reduction to precede changes in facial pores. This finding suggests that INCO injection independently affects arrector pili muscles and sebaceous glands.

There have been previous studies on the improvement of facial laxity, sebum secretion, and facial pores by applying a BTX other than INCO. When BTX was used for face lifting, approximately 100 U of intradermal injection was required per session.[27,29] As INCO has no unnecessary proteins and other impurities such as inactive neurotoxin, flagellin, and clostridial DNA contaminants,[17] the low antigenicity of INCO may have an advantage in procedures requiring administration of large units of BTX, such as face lifting.[16,17,34]

Moreover, the exact intradermal depth injection is very important in this procedure. The intradermal injection can show greater direct effects to the dermis and epidermis, and more natural results, which affect only the superficial layer of facial muscles. However, it is believed that intradermal injection of BTX might be more immunogenic than an intramuscular or subcutaneous injection because the dermis contains more dendritic cells to facilitate antigen presentation.[35] Therefore, in terms of preventing immunogenesis, it might be prudent to use a highly purified BTX preparation containing only the 150 kDa neurotoxin to ensure effective, durable, and well-tolerated treatment outcomes over repeated injections.[18,36]

This study has some limitations. First, this study was a single-center retrospective study. Second, the efficacy of INCO was evaluated without a control group. However, this study demonstrated the effects of INCO on face lifting, sebum control, and facial pores up to 12 weeks after injection by using both objective and subjective scales simultaneously.

In conclusion, this study, which showed that intradermal microdroplet injection with INCO could be effective for reducing sebum production, face lifting, and improvement of facial pores. The improvements persisted up to 12 weeks after a single injection.

DISCLOSURES

The authors have no relevant conflicts to report.

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