Comparing the efficacy, safety, and satisfaction for moderate to severe glabellar frown lines between abobotulinum toxin A and incobotulinum toxin A: a multicenter randomized study

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INTRODUCTION
Facial wrinkles, particularly permanent glabellar lines, can age a person’s appearance and give them a perpetually angry or annoyed look. These lines result from the activity of muscles in the glabella region, specifically the frontalis, procerus, and corrugator superciliii. To address this, botulinum toxin injections are frequently employed. Notable types include onabotulinum toxin A (Botox, Allergan), incobotulinum toxin A (Xeomin, Merz), and abobotulinum toxin A (Dysport, Ipsen). Botox was the first botulinum toxin approved for the cosmetic treatment of glabellar lines in the 1990s, with Xeomin and Dysport later receiving approval and becoming widely used both in Korea and internationally [1].

Background Botulinum toxin type A is widely used to improve facial wrinkles associated with aging, and various types are available. However, the efficacy, particularly the duration of effect, varies among these types, and research on this subject is limited. This study aimed to compare the efficacy and safety of incobotulinum toxin A and abobotulinum toxin A.

Methods This prospective analysis included cases of moderate to severe glabellar lines treated with either incobotulinum toxin A or abobotulinum toxin A. After a 24-week follow-up, clinical photos were taken at each visit. The severity of the glabellar lines was evaluated by three groups: the investigator, the patients, and an independent evaluator.

Results The study included a total of 42 patients. When comparing the improvement rates of glabellar lines at maximum frown for both groups at the week-4 visit, which was the primary efficacy endpoint, no statistically significant difference was observed. However, the abobotulinum toxin A group demonstrated a higher improvement at the week-24 visit, as evaluated by the investigator, and this difference was statistically significant.

Conclusions Overall, the abobotulinum toxin A group exhibited a higher improvement rate in the glabellar lines at the frown state. The difference in the improvement rate at the week-24 visit was 36.86%, which was statistically significant.

Keywords Botulinum toxins / Skin aging / AbobotulinumtoxinA / IncobotulinumtoxinA
toxin, molecular weights, and three-dimensional structures [3,4]. Direct comparative data on these products are currently lacking. This study aimed to evaluate the efficacy and safety of incobotulinum toxin A and abobotulinum toxin A in the treatment of moderate-to-severe grade glabellar frowns.

**METHODS**

**Participants and eligibility criteria**
This study was a prospective, randomized controlled, multicenter, single-blind study that assessed the effectiveness and patient satisfaction of botulinum toxin injections for glabellar lines. Participants with moderate to severe frown lines, classified as grade 2 or 3 in the maximum frown state, who sought treatment for glabellar frown were enrolled. Eligibility was determined based on medical history and any prior surgeries or procedures in the glabellar or forehead areas. The evaluation utilized a 4-point grading system: grade 0, no alteration in lines or skin texture; grade 1, skin texture changes to a vertical shape without visible lines; grade 2, clear lines and a noticeable base of the frown becoming visible; grade 3, deep lines with an imperceptible base of the frown (Fig. 1).

The exclusion criteria included conditions that could affect neuromuscular function, such as myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, and motor neuropathy. Additionally, individuals who had taken medications like curare-like agents or neuromuscular junction inhibitors (including muscle relaxants, anticholinergics, benzodiazepines, benzamides, tetracyclines, and lincomycin) within 4 weeks prior to screening were excluded. Participants who had taken aspirin, other nonsteroidal anti-inflammatory drugs, or anticoagulants within 7 days before the screening were also excluded. Other exclusion criteria encompassed individuals with adverse skin reactions at the injection site, such as infections, dermatitis, or scarring, as well as those with facial nerve palsy or eyelid ptosis. Individuals undergoing face-lifting treatments, those with permanent implants in the glabellar area, or those who had undergone other procedures that could affect wrinkles in the glabellar area or forehead within the previous 6 months were also excluded. Additionally, those who had received botulinum toxin treatment within the past 3 months were not eligible. Only participants who met the eligibility requirements, agreed to participate in the clinical trial, and did not meet any of the exclusion criteria were randomly assigned to either the incobotulinum toxin A group or the abobotulinum toxin A group, based on the order of their participation in the clinical trial.

**Procedure**
In this study, 100 U of incobotulinum toxin A was diluted in 2.5 mL of 0.9% sodium chloride to achieve a concentration of 4 U/0.1 mL. Similarly, 500 U of abobotulinum toxin A was diluted in 5 mL of 0.9% sodium chloride to achieve a concentration of 10 U/0.1 mL. Each study vial contained either 50 U of abobotulinum toxin A or 20 U of incobotulinum toxin A per 0.5 mL. On the baseline day (day 0), participants received an injection of either incobotulinum toxin A or abobotulinum toxin A. The total volume administered was 0.5 mL, distributed in 0.1 mL increments across five predetermined sites in the glabellar region: two injections in each corrugator muscle and one in the procerus muscle (Fig. 2) [5,6]. After the injection, an ice pack was applied for cooling for 10 minutes, and participants were monitored for any adverse effects for 30 minutes.

**Evaluation**
After receiving treatment, all participants returned to the hospital for follow-up visits at 2 days, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 24 weeks to assess improvement. During each visit, both the investigator and the participants evaluated the scales for the maximum frown state and resting state. An independent evalu-
ator, who was not involved in the treatment process, assessed the scales using photographs. Additionally, participants were evaluated for their satisfaction and any side effects they experienced.

The primary efficacy criterion was defined as the improvement in wrinkles, quantified by achieving a glabellar frown scale score of 0 or 1. The investigator assessed the improvement rate at the fourth week. Other metrics were used for the secondary efficacy evaluation.

After the conclusion of the clinical trial, photo data of participants collected from all participating institutions were deemed suitable for evaluating glabellar wrinkles. Independent evaluators assessed the glabellar lines without sharing their opinions. The participant photos were randomly organized, with no regard to participant number or sequence, to ensure an unbiased evaluation. In instances where the evaluations from the two reviewers differed, a consensus was reached to determine the final outcome.

Statistical analysis
All statistical analyses were conducted using Rex Excel-based statistical analysis software, version 3.6.0 (RexSoft, http://rexsoft.org/), which is based on R version 4.0.0 (R Foundation for Statistical Computing). The data on improvement rates from all study visits for the incobotulinum toxin A group were compared with those from the abobotulinum toxin A group. P-values were determined using the Pearson chi-square test and Fisher exact test, with a threshold for statistical significance set at 0.05. Confidence intervals were two-tailed and set at a 95% level.

RESULTS
A total of 44 participants, with 22 in each group, were enrolled in the study. At the 4-week mark, the primary efficacy full analysis set (FAS) analysis group excluded one participant who was not evaluated, resulting in 22 participants in the abobotulinum toxin A group and 21 in the placebo group. In the per-protocol set (PPS) analysis, after excluding one participant from the FAS analysis group due to the concomitant use of a contraindicated medication, there were 22 participants in the abobotulinum toxin A group and 20 in the placebo group.

Of the 43 participants, 41 were women and two were men. The two men were included only in the incobotulinum toxin A group. The mean ages were 48.95 years (range, 32–65 years) for the abobotulinum toxin A group, and 43.43 years (range, 30–64 years) for the abobotulinum toxin A group. The initial results from the scale of glabellar frowns for each group are presented in Table 1.

In the primary efficacy evaluation, which assessed the improvement rate of glabellar lines at maximum frown at week 4, the rates were 81.82% and 95.24%, respectively. Although the abobotulinum toxin A group demonstrated a tendency toward greater improvement, this difference was not statistically significant (P = 0.401).

As part of the secondary efficacy evaluations, both the investigator and the participants assessed the improvement rate of glabellar lines in a frown state and at rest, along with their satisfaction at each visit. Independent evaluators also reviewed clinical photographs post-trial. The investigator noted that the abobotulinum group consistently showed a higher improvement rate in the frown state at all time intervals. Specifically, at 24 weeks, the improvement rate was 13.64% for the incobotulinum group compared to 50.5% for the abobotulinum group, demonstrating a statistically significant difference (P = 0.027). The assessments by independent evaluators aligned with the investigator’s observations, with the abobotulinum group exhibiting higher improvement rates at all intervals. At the 12-week mark, the improvement rates were 47.62% for the incobotulinum group and 90% for the abobotulinum group, again showing a statistically significant difference (P = 0.013). However, the participants’ self-assessments showed reversed results at the 8-week and 24-week evaluations, with no statistically significant differences noted between the two groups (Fig. 3).

In the resting state, the investigator’s evaluation indicated that the abobotulinum group consistently outperformed across all intervals, achieving a peak improvement rate difference of 27.06% on day 2, although these differences were not statistically significant (P = 0.069). The participants’ evaluations also revealed smaller differences between the groups compared to the frown state, and the independent evaluator’s assessment showed almost no difference (Fig. 4).

Participant satisfaction was assessed at each visit using a scale ranging from 1 to 7, with an improvement indicated by a score of 6 or higher. Although there was a variance of up to 30.52% at the week 1 visit, this difference was not statistically significant (P = 0.114) (Fig. 5).

During the study, adverse events were reported in seven partici-
pants with 13 incidents in the incobotulinum group, and in eight participants with 22 incidents in the abobotulinum group. According to the system-organ-class classification, dry eye was the most frequently reported adverse event in the incobotulinum group, occurring in two incidents involving one participant. In the abobotulinum group, allergic rhinitis was reported in three incidents across two participants, and thermal burn was reported in two incidents across two participants. All adverse events were classified as mild in severity, and their causality was assessed as "none." No adverse drug reactions or serious adverse events were reported during the clinical trial period.

**DISCUSSION**

Botulinum toxin, a protein produced by *Clostridium botulinum*, a Gram-positive bacterium, is classified into seven antigen types, ranging from A to G. For cosmetic applications, botulinum neurotoxin types A and B are utilized, with type A being the preferred choice due to its longer-lasting effects [7]. In Korea, the commercialized botulinum toxin products include Dysport, IPSEN France, Xeomin, MERZ Germany, Botox, and Botulax (Hugel). Abobotulinum toxin A, marketed as Dysport in the United States and Azzalure in Europe, is produced by Ipsen Biopharm Ltd. as a powder-for-reconstitution formulation. It was approved in Korea in 2009,
Botulinum toxin A was adjusted to 10 units per 0.1 mL to standardize injection volumes in a single-blind study design.

In the primary efficacy evaluation conducted at week 4, which assessed the improvement rate in the maximum frown state, there was no significant difference between the groups. However, in the ongoing trial, the overall improvement rate was higher in the abobotulinum group, with statistically significant differences noted at two time points. While these findings might suggest that abobotulinum toxin A has a longer-lasting effect, careful interpretation is necessary. Initially, the distribution of the glabellar frown grades in the maximum frown state showed that 36.36% of the incobotulinum group were at grade 2 and 63.63% at grade 3. In contrast, the abobotulinum group had 47.61% at grade 2 and 52.38% at grade 3. This difference indicates that the abobotulinum group had a relatively lower severity, potentially making it easier to demonstrate effectiveness.

The rate of improvement in the resting state was significantly lower, with no periods showing statistically significant differences. This likely stems from the selection of participants who exhibited moderate to severe maximum frown states, with about 62% already at grade 0 or 1 in their initial resting state, which made it difficult to observe significant differences.

In general, compared to placebo, the treatment is effective, and patient satisfaction is high. This satisfaction often remains even after the treatment’s effects have diminished [17-19]. In this study, satisfaction rates fell to below 30% around week 16, coinciding with a reported decline in frown state improvement by the participants. By week 16, the improvement in frown state at rest had returned to levels similar to those seen before week 12, yet satisfaction had decreased. This suggests that patients are more likely to judge the effectiveness of botulinum toxin based on the appearance of frown state wrinkles rather than the resting state.

This study has several limitations. First, it was conducted with a relatively small sample size. Additionally, there was a disparity in the initial severity of glabellar frown grades between the incobotulinum group and the abobotulinum group. Second, the study was single-blinded, and a potential source of bias arises from the fact that statistical significance was noted only in the evaluations conducted by the investigators, who were the only ones not blinded among the investigators, patients, and independent evaluators. In the evaluation of the resting state, both the participants and independent evaluators observed minimal differences between the incobotulinum and abobotulinum groups. In contrast, the investigator’s assessments consistently indicated a superior performance by the abobotulinum group across all areas.

It is widely recognized that men require a higher dose of botulinum toxin than women to achieve the same effect [20]. In this study, only two male participants were included, both in the incobotulinum group, which could potentially lead to gender bias. Although both men exhibited positive effects on frown lines in the glabella area for approximately 12 weeks, it is crucial to address gender bias...
by implementing stratified randomization in the study design.

In addition, to conduct a single-blind study on a patient, the dose of abobotulinum toxin A was diluted to 0.1 mL from 0.05 mL by mixing it with sodium chloride. This deviates from the clinically labeled method for abobotulinum toxin A, and no experiments have been conducted to determine how this adjusted dose might impact efficacy.

Despite these limitations, this article is notable for its direct comparison of the effectiveness of two botulinum toxin products, incobotulinum toxin A and abobotulinum toxin A, in reducing glabellar frown lines. Both products demonstrated significant improvements in glabellar frown lines over a 3-month period. The group treated with abobotulinum toxin A exhibited slightly better improvement rates at certain intervals, particularly during maximum frown, with statistically significant differences. However, the differences were minimal when the participants were at rest. Further research involving larger sample sizes and efforts to overcome these limitations is essential to reinforce these findings.

NOTES

Conflict of interest
Eun Soo Park is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Ethical approval
This study received approval from the Institutional Review Board (IRB) of the Soonchunhyang Medical Center Office of Human Research Protection Program (IRB No. 2018-01-002) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

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