Effects of highly concentrated hyaluronic acid filler on nasolabial fold correction: A 24-month extension study

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\section*{ABSTRACT}

\textbf{Background:} A previous 6-month study using a more highly concentrated novel hyaluronic acid (HA) filler, PP-501-B, found nasolabial fold (NLF) improvements with increased tolerability.

\textbf{Objective:} We investigated the long-term efficacy, durability and safety of PP-501-B in the correction of NLFs.

\textbf{Methods:} Subjects completing the initial six-month study were enrolled in this 24-month, randomized, multicenter, double-blind, split-face, extension study. The injection areas and treatment procedures were identical to those of the initial study: each subject was injected with PP-501-B in one NLF and with Restylane Perlane (Q-med) in the contralateral NLF. We reassessed wrinkle improvement using the five-point Wrinkle Severity Rating Scale (WSRS) and changes in the Global Aesthetic Improvement Scale at 12, 18 and 24 months after the initial treatment.

\textbf{Results:} Of the 81 patients enrolled, 72 completed the study. The WSRS score significantly decreased from baseline throughout the follow-up period after retreatment with both fillers. There was no significant difference in the WSRS scores between the two fillers at 24 months. Both fillers were well tolerated with no severe complications or adverse reactions.

\textbf{Conclusion:} The new HA filler PP-501-B is safe and effective in the long term for the correction of moderate-to-severe NLFs, even after a second treatment.

\section*{Introduction}

Hyaluronic acid (HA) filler was first approved for use in 2003 and has since become one of the most widely used treatments for soft tissue filler augmentation\textsuperscript{(1)}. HA is a naturally occurring linear polysaccharide found in the skin. Because unmodified and natural HA has a short half-life of approximately 24 h, various HA fillers have been introduced to improve its resistance to enzymatic and free radical degradation and its longevity by adjusting its chemical and physical characteristics\textsuperscript{(2)}.

There have been many studies of HA fillers, most notably Restylane Perlane (PER; Q-Med, Uppsala, Sweden), which has an average HA concentration of 20 mg/mL. In the present study, we aimed to report the long-term safety, efficacy and persistence of the HA filler PP-501-0B (Cleviel Contour; Pacific Pharma, Seoul, Korea), which has a much higher HA concentration of nearly 50 mg/mL. PP-501-B, a novel biphasic cross-linked HA filler, is manufactured using newly developed solid-phase cross-linking technology\textsuperscript{(3–5)}. Compared with PER, one of the most widely used biphasic cross-linked HA fillers, PP-501-B consists of densely cross-linked HA gel particles at a two-fold higher HA concentration with a smaller particle size and higher cohesiveness. Few commercially used HA fillers have been formally investigated in comparative studies.

We recently reported a multicenter, randomized, double-blind, six-month, split-face comparison study of 103 patients that compared the efficacy and safety of PP-501-B with those of PER in the correction of nasolabial folds (NLFs). In that study, there was no significant difference in the mean improvement in the Wrinkle Severity Rating Scale (WSRS) compared with baseline between PP-501-B and PER\textsuperscript{(3)}. Both fillers were well tolerated and the safety of PP-501-B was not different from that of PER. Although PP-501-B provided satisfactory cosmetic results and safety profiles in the correction of NLFs in that six-month study, the long-term efficacy and safety of PP-501-B should also be assessed. Thus, the aim of our present prospective, randomized, double-blind, split-face study was to extend beyond six months our analysis of the long-term clinical efficacy and safety of PP-501-B in the patients from our original comparative study.

\section*{Materials and methods}

\subsection*{Subjects}

In our previous six-month study, 103 patients were screened and randomized to PP-501-B or PER. Of the 103 treated patients, 90 completed the six-month evaluation. Of the 90 subjects who completed the original six-month trial, 81 subjects were enrolled in the 24-month extension study. All study subjects were healthy Koreans older than 20 years of age with visibly moderate-to-severe NLFs of 3–4 points on the WSRS. This randomized, active-controlled, matched-pair study was conducted at three centers in Seoul.
South Korea and was approved by the relevant institutional boards. All participants voluntarily participated in the study and were required to provide written informed consent after a full explanation of the risks and benefits of the procedure. The study protocol conformed to the guidelines of the Declaration of Helsinki and Korea Good Clinical Practice.

Materials

PP-501-B is a clear, viscoelastic gel that contains HA at a concentration of 50 mg/mL. It was administered through 1.0-mL prefilled syringes with 28-gauge 0.5-inch needles containing 1,4-butanediol diglycidyl ether (BDDE) and phosphate-buffered saline (PBS). PER is a HA generated by a Streptococcus species of bacteria. PER was cross-linked with BDDE, stabilized and suspended in PBS at a concentration of 20 mg/mL in a 1.0-mL prefilled syringe.

Treatment

In the previous six-month trial, the subjects were randomized with a computer-generated code to determine which NLF, right or left, would receive PP-501B. The opposite NLF received PER according to the split-face comparison study method. The participants were unaware of which treatment was given to which side of the face. After enrolling in this extension trial, patients received a second injection on the same NLF as the initial treatment. This retreatment was performed nine months after the initial treatment. The lower half of the subjects’ face was photographed at pretreatment and at each visit. Subjects were evaluated 12, 18 and 24 months after their initial treatment. The independent evaluating investigators and subjects were blind to the treatments. The treating investigators were not blind to the therapies used as the mode of administration was at their discretion in order to ensure the optimal correction for each subject. The injection amount was determined according to the width, length and depth of the NLF.

Efficacy measures

The primary efficacy measurement was the improvement in baseline WSRS scores, determined by the independent evaluating investigators at 24 months. The secondary efficacy measurement used both the point improvement in baseline WSRS scores and changes in Global Aesthetic Improvement Scale (GAIS) scores measured through self-assessment of subjects at 12, 18 and 24 months after the initial treatment. Pretreatment photographs of each subject were taken and assessed during each visit to serve as controls.

Safety measures

The safety of the treatments was assessed through laboratory tests and physical examinations. All abnormal side effects were recorded.

Statistical analysis

Efficacy analyses were based on changes in WSRS and GAIS scores. Evaluating investigators assessed the WSRS and the subjects in a blind manner and treating investigators assessed the GAIS at 9, 12, 18 and 24 months. Inter-treatment differences were validated with the Wilcoxon signed-rank test. Safety analysis of all subjects was completed for local injection site reactions and systemic adverse events using McNemar’s test. The one-sided 97.5% confidence interval of the mean between-treatment difference (PP-501-B vs. PER) was calculated and non-inferiority was declared if the lower limit of the interval was greater than $-0.29$ in both the full analysis set and per protocol populations. The non-inferiority test was subject to a 97.5% one-tailed confidence interval, whereas other comparisons were subject to two-tailed tests with a 5% significance level.

Results

Of the 90 subjects who completed the original six-month trial, 81 subjects were enrolled in the 15-month extension study. All subjects received a touchup treatment of both NLFs nine months after the initial treatment. A total of 72 participants (70 females and 2 males; mean age, 45.92 ± 7.58) completed the additional 24-month follow-up (Figure 1). The average filler volumes injected in the retreatment were 0.97 mL and 0.99 mL for the PP-501-B and PER groups, respectively.

Efficacy

Clinical improvement evaluated by independent evaluating investigators and treating investigators showed no differences in terms of the pretreatment WSRS scores between the two groups (Figure 2). By the six-month follow-up examination, there was a significant improvement in the average WSRS value, as assessed by independent evaluating investigators. In the subsequent 24-month study, WSRS scores in the two groups significantly decreased from baseline throughout the follow-up period after retreatment and were 2.32 ± 0.70 and 2.23 ± 0.77 in the PP-501-B and PER groups, respectively. However, there was no significant difference in the WSRS score between the groups at any follow-up visit ($p = 0.66$, 0.13 and 0.24 at the 12-, 18- and 24-month follow-ups, respectively).

The proportion of subjects who showed changes in the WSRS score of more than 1 point from baseline was evaluated by treating investigators (Figure 3(a)). Based on treating investigator assessment, the proportion of subjects with WSRS scores of 1 point or higher than baseline was between 79% and 100% throughout the study period. There was no significant difference between the groups at any follow-up visit. The independent evaluating investigators judged that more than 90% of subjects maintained WSRS decreases from baseline of 1 point or greater throughout the study period in both groups. The assessment of the treating investigators showed a similar tendency. There was no significant difference in the proportion of subjects with a more than 1-point improvement, but the proportion of subjects was significantly different between the two groups at the 12-month follow-up visit ($p = 0.03$) (Figure 3(b)). Additionally, a similar proportion of subjects showed an improvement in WSRS scores greater than 2 points from baseline (Figure 3(c)).

Figure 4(a) and (b) show the GAIS score assessed by treating investigators and study subjects at each visit. The GAIS score rated by treating investigators and study subjects was not significantly different between the two groups.

Safety

Both PP-501-B and PER treatments were well tolerated, with only transient mild-to-moderate reactions localized to the injection sites. There was no treatment-related systemic adverse event throughout the 24-month study period. After either PP-501-B or PER treatment, eight subjects experienced local adverse reactions at the injection site, including three incidences of hematoma, one hemorrhage, one discomfort, one pain and one inflammation.
The local adverse events were mild and self-limiting, except in one patient with moderate local injection site inflammation. This patient developed inflammation over the PP-501-B injection area without bulla or crust formation that resolved within four weeks without additional treatment. All subjects with local adverse events continued with subsequent treatments.

**Discussion**

The interest in cosmetic treatments to achieve a younger appearance is steadily increasing as the world population rapidly ages. Mid-facial aging leads to sagging and atrophy of the malar fat pad, causing infraorbital hollowing, tear trough deformity and NLF deepening, particularly in darker skin-type patients (6). Numerous fillers can be used to replace lost fat and collagen to correct NLFs. Darker skin-type patients may develop more gravitational descent of facial soft tissues over time due to the combination of dense, heavy subcutaneous tissue and a weaker facial bony support (6,7). Hence, they have an increased need for soft tissue augmentation for aesthetic purposes. However, the long-term effects and safety of the widely used HA fillers have not been reported previously in Asians.
In our original six-month study, the patients’ NLFs were treated with PP-501-B and PER using a split-face method. The average WSRS values of the two groups showed that the efficacy and safety of PP-501-B were comparable to that of PER at six months (3). In our present extension study, our subjects received a second injection at the same site nine months after the initial treatment. PP-501-B was found to be as effective as PER in treating moderate-to-severe NLFs with comparable WSRS and patient-assessed GAIS scores. The proportion of subjects with a decreased score of more than 1 point from baseline based on the WSRS was between 79% and 100% throughout the study period. Moreover, the proportion of our subjects with a WSRS score decrease of more than 2 points was also similar in subgroup analysis. There was no significant difference in the WSRS score between the two groups at any follow-up visit.

PP-501-B was generally well tolerated and safe with only transient, mild-to-moderate reactions localized to the injection sites. There were no treatment-related systemic adverse events throughout the 24-month study period. One patient in our present study complained of moderate local injection site inflammation. This patient developed inflammation over the PP-501-B injection area without bulla or crust formation that resolved without additional treatment. Considering its self-limiting nature and relatively short duration, this local reaction was thought to be related to the procedure rather than the product itself.

Figure 3. (a) Proportion of subjects with changes of more than 1 point on the Wrinkle Severity Rating Scale (WSRS) as assessed by treating investigators over a 24-month period. (b) Proportion of subjects with a change of more than 1 point on the WSRS as evaluated by the independent evaluating investigators over a 24-month period. (c) Proportion of subjects with changes of 2 points or more on the WSRS over a 24-month period. The white bar represents the test filler treatment group (PP-501B). The black bar represents the control filler treatment group (Restylane Perlane). Retreatment was performed at nine months. *p < 0.05 vs. PER.

Figure 4. (a) Global Aesthetic Improvement Scale (GAIS) as evaluated by investigators over a 24-month period. (b) GAIS as evaluated by subjects over a 24-month period. The white bar represents the test filler treatment group (PP-501B). The black bar represents the control filler treatment group (Restylane Perlane). Retreatment was performed at nine months.
Although HA fillers are considered immunologically inert, there are some studies that demonstrated delayed-onset nodule formation following the usage of HA fillers. The reported symptoms include lumps, sterile abscesses and firm nodules (8,9). The reported incidence of these reactions was very low (0.5–0.8%) and the range of time to resolve these reactions was 1–52 weeks. In the present study, we did not experience any delayed nodule formation during the 24-months follow up, even though this novel filler consists of higher HA concentration. The injection technique, location, inflammatory and/or immune reaction, infection and foreign-body granulomas are known to be the causes of these nodules (9,10). It is important to keep a sharp technique during the procedure and use smaller boluses of filler to avoid these delayed inflammatory nodules (8–11). More studies with a larger sample size and longer follow up may be necessary to determine if the concentration can affect the formation of these nodules.

HA fillers are widely used for their low immunogenicity, ease of use and relative longevity. Although many kinds of commercial HA fillers have been used for many years, there are few long-term, split-face comparative studies (12–14). Large-scale studies composed of Caucasian patients are more common, but very few studies have assessed the efficacy and safety of HA fillers in darker skin types such as Fitzpatrick skin types III–VI (15–17). Moreover, although a number of comparative studies in Asian patients using HA fillers have recently been published, most follow-up periods were just six months (11,18).

In our current extension study, we determined that the improvements in moderate-to-severe NLFs in Asian patients treated with PP-501-B and PER were similar in longevity and safety until 24 months. This result can be explained by the physical properties of the two fillers. Although the particle size of PER is significantly larger (650 μm) than that of PP-501-B (250 μm) (19), PP-501-B has a total HA concentration that is 2–3 times higher than the usual commercial filler and has a densely packed structure of gel particles (3,20). These physical properties are thought to be one of the reasons that the two fillers show similar longevity over 24 months. From an aesthetic perspective, the two HA fillers used in our current analyses significantly improved the appearance of NLFs at 24 months. Similar volumes were used for the two fillers to achieve full correction. These results suggest that both the efficacy and the safety of the two fillers are roughly equivalent.

Conclusion

Our present 24-month study provides a long-term assessment of the efficacy, safety and durability of PP-501-B in treating moderate-to-severe NLFs in Asians. PP-501-B was found to be safe and effective during the 24-month treatment. This is the first report of the use and long-term evaluation of repeated treatment with HA filler at a concentration of 50 mg/mL for soft tissue augmentation in Asian skin.

Disclosure statement

The authors report no conflicts of interest and no funding source.

References
