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Abstract

Background: Recently, the efficacy of autologous plasma filler for the reduction of facial wrinkles has been demonstrated. **Objective:** The aim of our study is to validate the efficacy and safety of autologous plasma filler in treating nasolabial fold wrinkles. Material and methods: Twenty Korean patients with moderate to severe nasolabial fold wrinkles were enrolled. The patients were treated in one session of autologous plasma filler. The wrinkle improvement effects were evaluated at 1-week, 4-week, 8-week, and 12-week after the treatment. Three assessment methods were applied. First, two independent dermatologists assessed cosmetic results using a 5-point wrinkle assessment scale. Second, global aesthetic improvement score was used for assessment of final cosmetic results. Third, patient satisfaction was surveyed. And, adverse effects associated to treatment were observed. **Results:** Mean age of the patients was 44.5 years. The average 5-point wrinkle assessment scale score was significantly improved at 1-week, 4-week, 8-week, and 12-week after treatment, comparing to before treatment (p < 0.01). The patients' average GAIS also indicated better cosmetic outcomes. Conclusion: The clinical improvement with sufficient patients' satisfaction and no significant adverse events demonstrated that novel autologous plasma filler could be considered as efficient and safety treatment option for nasolabial fold wrinkles.

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A Clinical Study on the Usefulness of Autologous Plasma Filler in the Treatment of Nasolabial Fold Wrinkles

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Short title: Autologous plasma filler for nasolabial fold

Abstract

Background: Recently, the efficacy of autologous plasma filler for the reduction of facial wrinkles has been demonstrated. Objective: The aim of our study is to validate the efficacy and safety of autologous plasma filler in treating nasolabial fold wrinkles. Material and methods: Twenty Korean patients with moderate to severe nasolabial fold wrinkles were enrolled. The patients were treated in one session of autologous plasma filler. The wrinkle improvement effects were evaluated at 1-week, 4-week, 8-week, and 12-week after the treatment. Three assessment methods were applied. First, two independent dermatologists assessed cosmetic results using a 5-point wrinkle assessment scale. Second, global aesthetic improvement score was used for assessment of final cosmetic results. Third, patient satisfaction was surveyed. And, adverse effects associated to treatment were observed. Results: Mean age of the patients was 44.5 years. The average 5-point wrinkle assessment scale score was significantly improved at 1-week, 4-week, 8-week, and 12-week after treatment, comparing to before treatment (p < 0.01). The patients' average GAIS also indicated better cosmetic outcomes. Conclusion: The clinical improvement with sufficient patients' satisfaction and no significant adverse events demonstrated that novel autologous plasma filler could be considered as efficient and safety treatment option for nasolabial fold wrinkles.

Keywords: Autologous plasma filler, nasolabial fold, wrinkle

Introduction

Nasolabial folds are the folds on both sides of the face that start from the outer corners of the nose and run down to the corners of the mouth. There is an increasing demand for aesthetic correction of deep nasolabial folds because of the association with age. Dermal fillers are one of the nonsurgical options for soft tissue augmentation (1). As it can be performed on an outpatient basis owing to the ease of the procedure, there has been an increasing preference for injectable dermal fillers among both dermatologists and patients recently. Among the widely used dermal fillers, including bovine collagen, human-derived collagen, hyaluronic acid, liquid silicone, and calcium hydroxylapatite, heterogeneous materials like collagen and gelatin might induce rejection reactions (2). Autologous fat graft was introduced as the filler of choice in patients with collagen vascular disease or proven allergic reactions to collagen or hyaluronic acid, but a more involved surgical procedure was necessary than that for the previously discussed fillers (2).

Most recently, several new approaches based on autologous plasma fillers have been introduced. By using autologous concentrated platelet-rich plasma as dermal fillers, this procedure could be performed on an outpatient basis at a moderate cost, without any rejection reactions (3). However, there are few clinical studies that objectively confirm the efficacy and safety of autologous plasma filler in treating nasolabial fold wrinkles.

The purpose of this study was to validate and confirm the efficacy and safety of autologous plasma filler in treating nasolabial fold wrinkles.

Materials and methods

1. Study population

From February 2010 to June 2010, twenty women were injected with autologous plasma fillers into the nasolabial fold area for aesthetic reasons. Patients included in this study were healthy adults (aged 20 years) with moderate to deep nasolabial folds who had not undergone facial augmentation within 6 months or had not received botulinum toxin A within 4 weeks. Exclusion criteria included women who were pregnant or nursing; history of hypersensitivity or anaphylactic shock, autoimmune, collagen vascular, or connective tissue disease or bleeding disorder; active skin disease on or near the nasolabial folds within 6 months before the study; any clinically significant disease as determined by the investigator; treatment with immunosuppressive drugs, chemotherapy, or systemic steroids within 3 months or with anti-inflammatory drugs within 10 days before or 1 week after injection; or receiving desensitization injections.

The Human Subjects Review Committee of the Institutional Review Board at Kangbuk Samsung Hospital in Seoul, Korea, approved the study.

2. Study design

1) Preparation of autologous Plasma Filler

Ten cubic centimeters of the patient's blood was drawn via venipuncture in the upper arm. To obtain platelet-poor plasma, the blood was centrifuged and separated using a lithiumheparin tube (BD Vacutainer[®] LH PST[™] Tubes). After the plasma contained in the injection syringe was warmed up using an ALSA system (ALSA S-1[®], Genexel-Seine) for 12 minutes, preparation of the injectable autologous plasma filler (gel type) was complete (Figure 1).

2) Techniques for Application

Each patient was treated in only one session. During the time needed for preparation of the autologous plasma filler, the patient was anesthetized with topical lidocaine cream. In case of intolerable pain, more lidocaine injections were administered. After the patient was seated at a 30-degree angle, the same amount of autologous plasma fillers was injected intradermally or subdermally below the nasolabial folds on both sides. All nasolabial folds were treated to full correction only from the alar crease to the level of the oral commissure, until immediate correction of 1-point decrease on the 5-point wrinkle assessment scale was achieved. After administering the injections, the dermatologist performed a massage of the treated area to correct the irregular surface and to prevent the possible subcutaneous nodules. The same dermatologist performed all procedures using the same technique.

3) Efficacy assessments (the 5-point wrinkle assessment scale)

The follow-up phase consisted of visits at week 1, 4, 8, and 12 after the injection treatment. Standardized photographs were taken at all treatment and follow-up phase visits. Two independent dermatologists assessed the cosmetic results using a 5-point wrinkle assessment scale: no wrinkles (0), shallow and just perceptible wrinkles (1), moderately deep wrinkles (2), deep wrinkles with well-defined edges (3), very deep wrinkles, redundant folds (4). These results were compared with the untreated wrinkles (Table 1).

4) Global aesthetic improvement score

The wrinkle improvement effects were evaluated at one week, 4 weeks, 8 weeks, and 12 weeks after the treatment. The patients assessed the final cosmetic results by assigning a global aesthetic improvement score (GAIS) using questionnaires: no improvement (0) to excellent improvement (100).

5) Satisfaction degree of patients

Satisfaction degree of patients was surveyed using questionnaires at 12 weeks after the injection treatment: very unsatisfied (0) to very satisfied (10).

6) Safety assessment

At screening, the patient's medical history and prior or concomitant medications and treatments were assessed, and a physical examination was performed. During all subsequent visits, patients were interviewed regarding treatment success and adverse events. Potential adverse effects related to filler treatment such as pain, itching, delayed erythema and edema, bruising, subcutaneous nodule, and pigmentary alteration were registered throughout the study. Severity and duration of injection- and procedure-related adverse events were

surveyed using questionnaires at 12 weeks after the injection treatment: none (0), mild (1), moderate (2), severe (3) (Table 2).

7) Statistical analyses

All efficacy analyses were performed on the intent-to-treat population, defined as all patients who were randomized, received study treatment, and had baseline evaluations. The *t*-test was performed to compare the within-treatment changes from baseline, being 2-sided with a significance level of 0.05.

Results

1. Patients' clinical characteristics

Twenty females were selected for treatment and their mean age was 44.5 years (range, 27-60 years). There was no case of dropout throughout the study period. None of the patients had severe underlying disease except for two patients with well-controlled hypertension and one patient with gastroesophageal reflux disease.

2. Clinical assessment of wrinkles before treatment

Before the treatment, 20 females were examined by a dermatologist to assess the severity of nasolabial fold wrinkles. Ten females (50%) had moderate nasolabial fold wrinkles, 9 females (45%) had severe nasolabial fold wrinkles, and 1 female (5%) had extremely severe nasolabial fold wrinkles. All patients had moderate to severe degree of nasolabial fold wrinkles.

3. The injected volume of autologous plasma filler

The patients received autologous plasma filler injections into the nasolabial folds on both sides. Mean volume injected into each side was 0.34 cc (range, 0.2-0.5 cc).

4. Clinical efficacy

1) The 5-point wrinkle assessment scale

Two independent dermatologists who did not perform the procedure assessed the clinical improvement using the 5-point wrinkle assessment scale (Figure 2). There was a significant reduction in mean scores for wrinkles. Mean score was 2.55 before treatment, and at 1 week, the score was 1.35. The score was 1.55 at 4 weeks (mean reduction was 1.0), 2.0 at 8 weeks (mean reduction was 0.55), and 2.15 at 12 weeks (mean reduction was 0.4). The improvement persisted for 3 months. All results showed a significant improvement (p < 0.01). Especially between 4 and 8 weeks after treatment, the reduction in mean scores for wrinkles was remarkable (Figure 3).

2) Clinical improvement (%)

On assessing the improvement in nasolabial fold wrinkles, it was observed that the improvement was the highest (47.1%) at 1 week, remained highly significant up to 12 weeks (15.7%) (p < 0.01). Also, reduction in the improvement of wrinkles was significant between 4 and 8 weeks after treatment (Figure

5. Patient self-assessment

1) Patient global aesthetic improvement score

Patients performed a self-assessment of their overall improvement at the final 12 weeks of the study, no improvement (0) to excellent improvement (100). Average score was 56.5 out of 100 (Figure 5).

2) Patient satisfaction degree

Satisfaction degree of the patients was surveyed using questionnaires at the final 12 weeks of the study, very unsatisfied (0) to very satisfied (10). Average score was 6.3 out of 10 (Figure 6).

6. Adverse effects

1) Evaluation of adverse effects

All patients had erythema and edema on the treated sites on the day of injection. Erythema and edema disappeared without treatment in 1-2 days. Seven patients (35%) had a subcutaneous nodule at the treated sites that persisted for 4 weeks. None of the patients had a subcutaneous nodule that persisted for 12 weeks. There were 5 patients (25%) who experienced a localized bruise and one patient (5%) who experienced itching. None of the patients experienced pigmentary alteration. Meanwhile, one patient (5%) experienced a moderate adverse effect. Subcutaneous nodule, bruise, erythema, edema, and signs of inflammation appeared on the 3rd day after the treatment. Symptoms disappeared after the administration of antibiotics and NSAIDs for 1 week.

2) Patient's assessment of adverse effects (Table 2)

Severity and duration of adverse events were surveyed using questionnaires at 12 weeks after the injection treatment: none (0), mild (1), moderate (2), severe (3). The mean score was 0.25 and it was very low.

Discussion

There are more than 200 commercial products which are used for soft tissue augmentation, such as bovine collagen, the first developed material, porcine collagen, human-derived collagen, hyaluronic acid, liquefied silicone, calcium hydroxylapatite, poly-L-lactic acid and so on (2). Various types of fillers were developed depending on the properties of longevity, potentiality for causing allergic reaction, safety, possibility of application, indication, and physicians can select the most suitable agent for each patient by considering the advantage and disadvantage. The ideal fillers have lower immunogenicity; thus, they induce low incidence of allergic reaction. Also, non-carcinogenic and nonteratogenic features are important. And, they have to be appropriate for biomedical use, nonmovable, and they should take longer time for resorption.

Autologous plasma filler, harvested from the patient's own blood, is a new cosmetic technique, and is relatively cheap, and the process of production is simple. Because a small amount of blood is enough to extract the plasma filler content, better patient compliance of the procedure would be expected. Furthermore, it is auto-transplanted, and hence, there is an

advantage of absence of graft rejection or there is no risk of transmission of contagious disease.

Autologous plasma filler was first introduced by Krajcik et al. in 1999, and they confirmed its safety and efficacy in comparison with the bovine collagen filler (Zyderm[®] and Zyplast[®]) by injection into hairless mice (4). According to the results, they could identify the autologous plasma filler injection site even after 550 days, and they reported that the autologous plasma filler had greater longevity than the bovine collagen filler. Also, they showed that it maintained a good response when it was injected into the wrinkles at 3 to 6 months interval, for 2 years, 0.05-0.1 cc in deep wrinkles at 5-10 mm distance and 0.02-0.05 cc in shallow wrinkles at 3 mm distance. There was no significant side effect (4).

Sclafani presented a clinical report after a single application of autologous platelet-rich fibrin matrix (5), as in our study, on deep nasolabial fold wrinkles, and it showed a statistically significant improvement in wrinkles up to 12 weeks after application ($\rho <$ 0.001). On comparison with the status before application, the degree of improvement in wrinkles at 2 weeks, 6 weeks, and 12 weeks after application was better with passage of time than that at 1 week after application. All patients showed no adverse effects, and the author suggested that it can be used effectively for soft tissue augmentation as it has the advantage of being foreign body-free (5). The difference between this study and our study is that, in our study, although the highest degree of improvement in wrinkles was observed after 1 week and the lowest degree of improvement in wrinkles was observed after 12 weeks, a statistically significant improvement was observed throughout the study period. Also, we could observe a notable decrease in improvement in wrinkles (39.2% to 21.6%) from 4 weeks after application to 8 weeks after application. We thought that our study showed different values for maintenance of improvement compared to the study by Sclafani as we did not perform over-correction during treatment of nasolabial fold wrinkles and set the endpoint of treatment as a decrease of one degree on the 5-point wrinkle assessment scale for nasolabial folds in gross findings immediately after treatment.

Nasolabial fold wrinkle is a mixed type of wrinkle with the dynamic rhytide which is caused by muscular effects like crow's feet, glabellar wrinkle, forehead wrinkle, and the static rhytide which is caused by gravity and ultraviolet light. The dynamic rhytide is mostly treated with botulinum toxin, while the static rhytide is treated with soft tissue augmentation with a filler (6). The treatment selection is influenced by not only the etiology of wrinkles but also by the figure of wrinkles; the filler which is injected into the dermis (almost in the upper portion of the dermis) is selected in case of thin and shallow wrinkles, and the filler which is injected in the lower dermis or the subcutaneous fat layer is selected in case of thick and deep wrinkles (7). The autologous plasma filler, which was used in this study, is mostly injected into the dermis and recommended to inject into the lower dermis or the upper portion of the subcutaneous fat layer (5). We selected the lower dermis injection rather than

the upper dermis injection as some subcutaneous nodules can develop frequently, the patient appeared to have moderate to severe wrinkles, and the anatomical position of nasolabial fold wrinkles in which the filler was injected had a relatively short longevity.

In our study, there was 47.1% improvement in wrinkles after 1 week of treatment, and also there was maintenance of improvement in wrinkles at 39.2% after 4 weeks, 21.6% after 8 weeks, and 15.7% after 12 weeks in the physician's objective assessment. All these values were statistically significant (p < 0.01). In the patient's subjective assessment, there was 56.5% improvement in wrinkles after 12 weeks of treatment, and also 6.3 points (total 10 points) for the satisfaction value, showing that the patient satisfaction is high with the treatment. The most common adverse effect associated with the treatment of nasolabial fold wrinkles with the autologous plasma filler was erythema and edema (100%), and every cases were recovered spontaneously within 1-2 days. Seven patients (35%) had a subcutaneous nodule after treatment and it disappeared in an average 4 weeks without complications, and some localized bruises were observed in 5 patients (25%), and prufitus was noted in 1 patient (5%). In one patient, there was much more than a moderate adverse effect (subcutaneous nodule, bruise, localized inflammatory reaction with edema and erythema) at 3 days after treatment, but it disappeared in 1 week with systemic administration of antibiotics and antiinflammatory agents. In the assessment of adverse effects and complications after 12 weeks, 95% of the patients replied that only a less than mild degree of adverse effect was observed.

The best advantage of the autologous plasma filler is its cost-effectiveness. After the FDA approval for the first developed dermal filler for wrinkle treatment in 1985, bovine collagen material was generally used for treating nasolabial fold wrinkles (7). But it has disadvantages, such as low cost-effectiveness, short longevity and variable results depending on the physician's procedure (2,8). So far, there have been many studies on the usefulness of many types of fillers made from porcine collagen (1), hyaluronic acid⁹, and poly-L-lactic acid (10,11) for the treatment of nasolabial fold wrinkles, but there was a limitation in selection because of the expensiveness. On the contrary, autologous plasma filler harvested from the patient's own blood; thus, it is economical. However, it has the disadvantage of the need for repeated treatment due to short longevity.

In conclusion, based on the results of this study, we suggest that the treatment of nasolabial fold wrinkles with the autologous plasma filler is a relatively safe and satisfactory treatment option and maintenance of the effect is observed for at least 3 months. The longevity is similar and the cost is much less than that of the existing collagen filler. But, there are limitations regarding the precise assessment of longevity of the autologous plasma filler as we conducted this study over a relatively short follow-up period (12 weeks); hence, we suggest that there is a need for clinical trials with a longer follow-up period in the future. **Disclosure of Interest**

The authors report no conflicts of interest.

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Figure Legends

Figure 1. Preparation of the injectable autologous plasma filler. (A) Patient's blood is drawn. (B) Centrifugal separation: patient's whole blood is centrifuged and separated using a lithium-heparin tube (BD Vacutainer[®] LH PSTTM Tubes). Platelet-poor plasma was obtained after centrifugation. (C) Warming up of the plasma contained in the injection syringe using an ALSA system (ALSA S-1[®], Genexel-Seine) for 12 minutes. (D) Preparation of the injectable autologous plasma filler (gel type) is complete.









Figure 2. Clinical photographs of nasolabial fold wrinkles at baseline (left) and 12 weeks (right) after the correction using the autologous plasma filler. Note the improvements in depths and contours of the nasolabial fold wrinkles. Pt 3 (A), pt 5 (B), and pt 14 (C) are shown.



Figure 3. Change in the 5-point wrinkle assessment scale as noted by two blinded independent dermatologists (${}^*p < 0.01$).



Figure 4. Percentage of improvement in the 5-point wrinkle assessment scale score, as shown by change from baseline according to visits (p < 0.01).











Table Legends

Wrinkle assessment scale	Grade	
No wrinkles	0	
Shallow and just perceptible wrinkles	1	
Moderately deep wrinkles	2	
Deep wrinkles with well-defined edges	3	
Very deep wrinkles, redundant folds	4	

 Table 1. The 5-point wrinkle assessment scale for assessing the cosmetic results.

Score (adverse effect)	Number of patients	Percentage (%)
0 (No adverse effect)	16	80
1 (Mild)	3	15
2 (Moderate)	1	5
3 (Severe)	0	0
Total	20	100

Table 2. Adverse effects related to filler treatment that were surveyed at 12 weeks after the correction.