Comparative clinical assessment of two nasolabial hyaluronic acid fillers: A double-blind, randomized controlled trial

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Background: Various fillers have been used for the correction of nasolabial folds. This study investigated the efficacy and safety assessment of two hyaluronic acid (HA) fillers on moderate nasolabial folds.

Methods: This study randomized 10 volunteers, aged 35 to 49 years, with moderate nasolabial folds. Volunteers received injections of HA A and HA B gels into the right or left skin folds. The volume and surface of nasolabial folds were analyzed using CSI computer software and high frequency ultrasonography of these folds before, and 2, 12, and 24 weeks after the injection. The obtained data were analyzed using SPSS software version 20. $P \leq 0.05$ was considered significant.

Results: Evaluation of the nasolabial folds before and after treatment showed significant reduction in volume of wrinkles 24 weeks after injection in both the HA gel A (-29.93±32%, P=0.022) and gel B (-23.60±26%, P=0.019). The surfaces of the wrinkles significantly decreased 24 weeks after injection of HA gel A (-29.90±31%, P=0.012) and gel B (-21.96±26%, P=0.026).

Conclusion: These HA fillers provided a significant, long-lasting correction of moderate nasolabial folds. Overall, we observed no statistically significant differences in any of the measurements between the 2 gels. However, there were more observed changes made by gel A compared to gel B.

Keywords: clinical assessment, hyaluronic acid, nasolabial fold, filler, aging

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INTRODUCTION

Wrinkles are depressions in the skin surface which, depending on their depth, may be coarse or fine. Two of the most considerable coarse wrinkles on the face are lines on either side of the mouth (nasolabial folds) [1]. Age-dependent changes such as nasolabial folds are the results of changes in the fibroblasts - the cells responsible for collagen, elastin, and glycosaminoglycan (GAG) biosynthesis. They include breakdown of collagen and elastin fibers, reduction in skin thickness, loss of hyaluronic acid (HA) with consequent reduction in skin volume and dehydration in the dermis [2-4].

The skin elasticity and hydration is maintained by HA, as the most important GAG. HA can form

complexes with numerous molecules of water to attain a high degree of hydration. HA plays an essential role in cell growth and the formation of the intercellular matrix of the dermis. Additionally, it creates a viscoelastic network for collagen and elastin fibers to connect to each other. These benefits make HA an excellent dermal filler [5,6].

Recent surgical and nonsurgical facial rejuvenation techniques focus more on volume restoration for contour correction such as injectable dermal fillers which reduce wrinkles to produce a younger appearance [7,8]. Injectable fillers (such as HA) in the field of plastic surgery and aesthetic medicine refer to the vast, heterogeneous group of substances which can be applied by various injection techniques to fill wrinkles and improve skin sagging [9,10].

The present study aims to assess two HA fillers in the correction of nasolabial folds by using non-invasive measurement techniques.

PARTICIPANTS AND METHODS

Participants and study design

In this double blind, randomized study, we enrolled 10 (out of 16 screened) healthy 35-49 year old male and female volunteers with moderate nasolabial folds according to the Wrinkle Severity Rating Scale (WSRS). Volunteers were enrolled from June-August 2013 after they provided written informed consent. Exclusion criteria consisted of: any skin diseases, surgical procedure in the previous 3 months, pregnancy or intent to become pregnant, lactation, allergy or sensitivity to HA, any previous injection in the nasolabial folds, laser therapy, peeling, or non-ablative rejuvenation procedures in the year prior to the start day of the study, and a history of smoking.

Prior to the injection, we applied a topical local anesthetic cream that contained lidocaine and prilocaine to the injection sites, after which they were occluded for 30 minutes. Next, we used a table of random numbers to assign the type of gel to be injected. The randomization sequence was placed in separately sealed, numbered envelopes. Patients were unaware of the type of gel injected in each side. We injected 1 ml of one of the two HA fillers, gel A (Hyamax Ultra Deep, Laboratories Hyamed, Switzerland) that contained 2.2% HA or gel B [Yvoire Volume S (HA IDF II), LG Life Sciences, South Korea] that also contained 2.2% HA. The intradermal injections were administered with a linear threading injection technique to each of nasolabial folds.

Clinical assessment

We assessed the volume and surface of the nasolabial folds by taking a digital photo at baseline, and 2, 12, and 24 weeks after the injections. The photos were analyzed by Complete Skin Investigation (CSI) software (CK Electronic GmbH, Cologne, Germany). The change in volume and surface of the wrinkles at each time point after the injection were calculated as:

Value after injection–value before injection/ value before injection

Patients underwent ultrasonography (22 MHz, DUB Skin Scanner, tpm, Luneburg, Germany) of the nasolabial folds at baseline and the final visit (24 weeks after injection) to measure the dermis echo density and thickness [11].

The participant's satisfaction was assessed by a Visual Analogue Scale (VAS) [12] where a score of 0 indicated no satisfaction at all and a score of 10 was the ideal result.

Physician global assessment (PGA) was performed by a dermatologist blinded to the treatments using five-point scales at 2, 12, and 24 weeks after treatment. The PGA was scored as: 1. worse (exacerbation), 2. no change (improvement of ≤24%), 3. fair (improvement of 25%-49%), 4. good (improvement of 50%-74%), 5. Excellent (improvement of 75% or more) [13]. Possible adverse effects were assessed and recorded throughout the trial duration according to a 0-3 scale, as follows: 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Statistical analysis

For the descriptive analysis, quantitative variables were described by number of subjects, mean and standard deviations. Qualitative variables were described by number of subjects and percentage. For statistical analyses, we used IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, US) version 20 and the clinical efficacy was analyzed with the paired t-test. Statistical significance was defined as $P<0.05$.

Ethical considerations

The study protocol was reviewed and approved by the Ethical Committee in Medical Research, Tehran University of Medical Sciences, Tehran, Iran. All participants provided written informed consent.

RESULTS

In present study, we randomly injected the nasolabial folds on either the right or left sides of 10 participants. There was no deviation from protocol or loss to follow up during the study. According to Table 1, after injecting HA gel A, the wrinkle volume had statistically significant decreases at week 2 (-39.24±31%, *P*=0.010), week 12 (-47.96±25%, *P*=0.001), and week 24 (-29.93±32%, *P*=0.022). We observed significant decreases in the surfaces of the wrinkles at 2 (-39.58±31%, *P*=0.008), 12 (-48.38±23%, *P*=0.001), and 24 (-29.90±31%, *P*=0.012) weeks after injecting HA gel A compared to baseline.

In the side injected with HA gel B, we observed significant reduction in volume at 12 (-45.58±26%, *P*=0.002) and 24 (-23.60±26%, *P*=0.019) weeks after the injection. The surfaces of the wrinkles showed significant reductions at 12 (-46.26±23%, *P*=0.001) and 24 (-21.96±26%, *P*=0.026) weeks after injection. We compared the changes at the injection sites for both gels. Although these changes were greater after injection of the HA gel A compared to the HA gel B, the differences were not statistically significant (Table 1). The echo-density of the dermis showed nonsignificant increases 24 weeks after injection of HA gel A (9.57±35%) and HA gel B (9.52±39%). There was a significant decrease in the dermis thickness after injection of both HA gel A (-13.41±17%, *P*=0.044) and HA gel B (-8.99±9%, *P*=0.015). A comparison of the changes of ultrasound parameters between the two gels did not show any significant differences.

Table 1. The change in the surface and volume of nasolabial folds as well as echo-density and thickness of dermis 2, 12 and 24 weeks after injecting gel A in comparison with gel B

Variable	Wrinkle volume	Wrinkle surface
The change of gel A after 2 weeks (%) ± SD	-39.24±31	-39.58±31
P (before-after comparison)	0.010	0.008
The change of gel B after 2 weeks (%) ± SD	-34.29±30	-34.23±28
P (before-after comparison)	0.19	0.16
P (fillers comparison)	0.487	0.528
The change of gel A after 12 weeks (%) ± SD	-47.96±25	-48.38±23
P (before-after comparison)	0.001	0.001
The change of gel B after 12 weeks (%) ± SD	-45.58±26	-46.26±23
P (before-after comparison)	0.002	0.001
P (fillers comparison)	0.646	0.670
The change of gel A after 24 weeks (%) ± SD	-29.93±32	-29.90±31
P (before-after comparison)	0.022	0.012
The change of gel B after 24 weeks (%) ± SD	-23.60±26	-21.96±26
P (before-after comparison)	0.019	0.026
P (fillers comparison)	0.569	0.401

The PGA showed stability of both gels at 2, 12, and 24 weeks after injection (Table 2). Improvement was fair or good (25%-75% improvement) 2 weeks after the HA gel A injection in 7 patients, as well as in 9 patients after 12 weeks, and in 9 patients after 24 weeks out of 10 patients. Of the 10 patients that received the HA gel B injection 7 had fair or good improvement after 2 weeks; this finding was present in 9 patients after 12 weeks and in 10 patients after 24 weeks (Figure 1 and Table 2). The means of the PGA scores were not significantly

Table 2. Physician global assessment (PGA) of correction level and stability of hyaluronic acid (HA) gels A and B at 2, 12, and 24 weeks after injection.

Grade**	Week 2 (n*=10)		Week 12 (n=10)		Week 24 (n=10)	
	Gel A	Gel B	Gel A	Gel B	Gel A	Gel B
1	-	-	-	-	-	-
2	2	2	1	1	1	-
3	6	5	5	6	5	7
4	1	2	4	3	4	3
5	1	1	-	-	-	-
Mean PGA	3.1	3.2	3.3	3.2	3.3	3.3

*n: Numbers of participants; 1: Worse (exacerbation); 2: No change (improvement of ≤25%); 3: Fair (improvement of 25%-49%); 4: Good (improvement of 50%-74%); 5: Excellent (improvement of 75% or more)

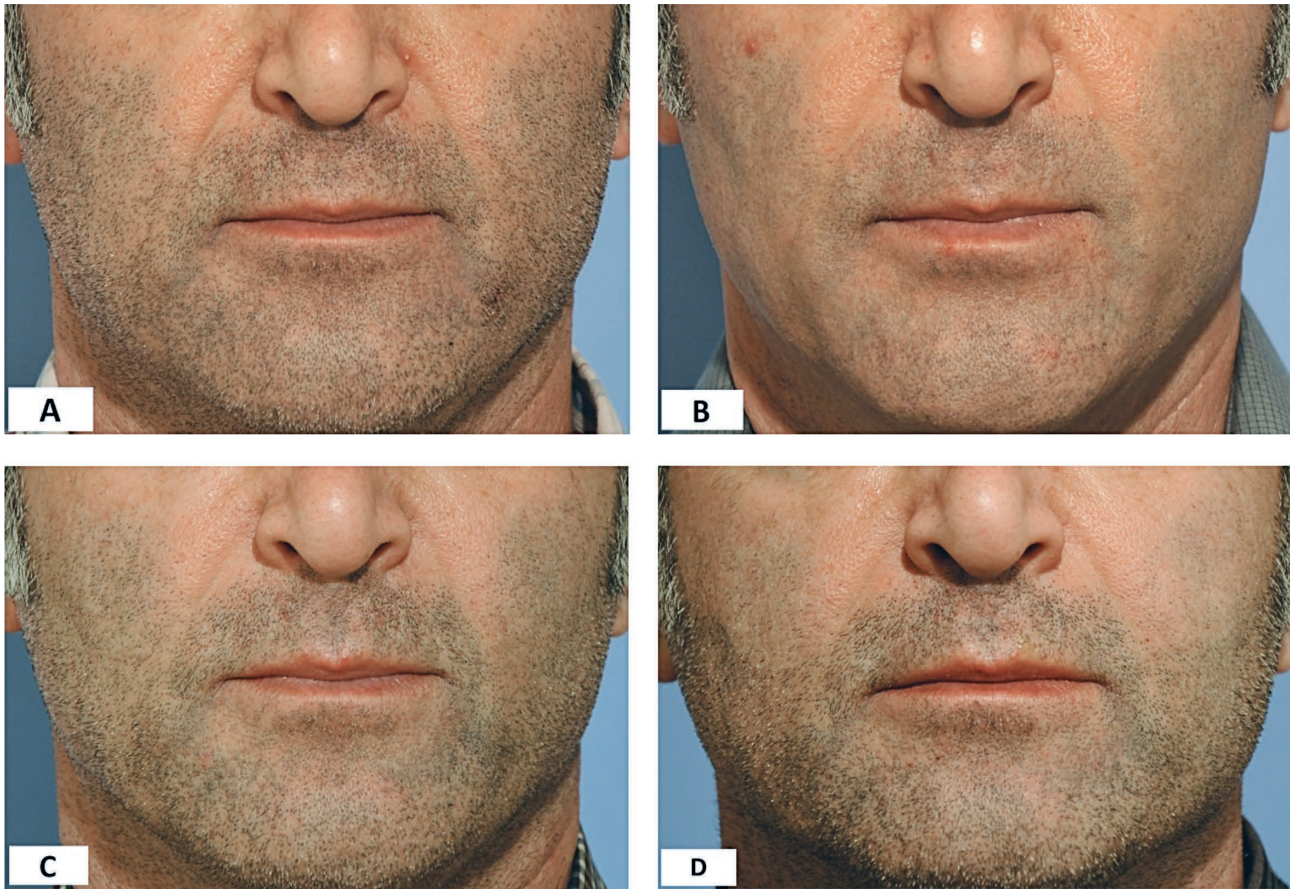

Figure 1. Photographs of a study participant at baseline (A), 2 weeks (B), 12 weeks (C), and 24 weeks (D) after injection of hyaluronic acid (HA) gel A (left nasolabial fold) and HA gel B (right side).

different between the two gels.

The mean scores of subject satisfaction rate after injection of HA gel A were 7.7±1.41 (2 weeks), 7.6±0.96 (12 weeks), and 7.15±2.16 (24 weeks). These figures were 7.7±1.41 (2 weeks), 7.4±1.17 (12 weeks), and 6.95±2.45 (24 weeks) for HA gel B ($P<0.05$).

There were 2 participants who reported an adverse event of mild bruising at the injection site of HA gel A which disappeared spontaneously after a few days. No patient reported this adverse event at the site of the HA gel B injection.

DISCUSSION

A large component of the skin's natural aging process is manifested by volume loss. Due to this fact that aging is a continuous process, temporary fillers should be preferred over permanent ones [14]. Over the last decades, the safety and efficacy of dermal fillers have improved which has bled to a major shift in facial rejuvenation toward less invasive and even nonsurgical procedures for correction of wrinkles and folds [15]. HA-based gels are now the gold standard and most commonly used dermal fillers in the US [16].

In this comparative study, the volume and surface of wrinkles in nasolabial folds reduced according to objective and subjective assessments at 2, 12, and 24 weeks after injection of two HA fillers (Table 1). There were no statistically significant differences between these two products.

If a filler stay for a long time in the dermis it, leads to a prolonged compression of the tissues that induces a biological response to foreign body. Stimulation of new fibrous tissue is induced. This stimulation of collagen production caused by cross-linked HA dermal filler injections and collagen lead to increased dermis density to the mentioned rate. Therefore, the increased echo density of the dermis in this study might be due to the presence of HA [17,18]. In line with previous

reports, both gels reduced the dermis thickness at the injection sites due to the pressure effect of fillers on the dermis as the main role of fillers used to treat wrinkles [19]. A comparison of the two HA fillers showed no statistically significant differences between them, however the better results of HA gel A could be due to the different, complex, multi-step manufacturing processes which might result in different biological activity, safety, and effectiveness of the final product. Therefore, these results showed that each biological product (HA gel) had its own unique features which resulted from the variability associated with its manufacturing processes [20].

The main limitation of our study was low sample size, which made it difficult to compare two products; therefore future studies should be performed with larger sample sizes.

Our results indicated an improvement in the appearance of wrinkle in subjects with moderate clinical signs of nasolabial folds. The differences between baseline and after the injection showed that these two HA fillers could be safe, effective products to remove the appearance of wrinkles at the nasolabial area.

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