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ORIGINAL RESEARCH ARTICLE

A randomized, double-blind, comparative study for efficacy assessment of two hyaluronic acid nasolabial fillers

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Abstract: Hyaluronic acid fillers are considered safe for use in cosmetics as described in the safety assessment. This study was aimed to assess and compare the efficacy and safety of two hyaluronic acid (HA) fillers on mild nasolabial folds. Ten women aged 30-50 years with mild nasolabial folds participated for injection of A and B gels into right or left nasolabial folds. The volume and surface of nasolabial folds were measured by CSI software and the density and thickness of dermis assessed by skin ultrasonography before and 2, 12, and 24 weeks after injection. The data were analyzed using SPSS software version 20, and p-value <0.05 were considered as significant. Global assessment showed over 50% improvement in patients injected with both gel A and B. At 2 weeks after injecting gel A the volume and surface of wrinkles decreased significantly. In the side injected with gel B, this reduction was significant at 2 and 12 weeks after injection. In addition, 24 weeks after injection of both gels the dermis echo-density increased and the dermis thickness decreased. This study indicated the significant positive filling effect of both HA fillers in decreasing the clinical signs of wrinkles at nasolabial folds. Comparing both fillers, there were not any statistically significant differences in any of measurements, but the persistence of gel B to improve the wrinkle appearance was slightly better than gel A.

Keywords: hyaluronic acid; filler; ultrasonography

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Introduction

Skin aging includes a flattening of the epidermal-dermal interface and some breakdown of the dermal tissue; this layer is a protective and nutritive tissue with main components of collagen, elastin and hyaluronic acid to provide flexibility and elasticity of the skin and protects skin against dehydration[1,2]. The majority of age-dependent changes happen in the dermis and include breakdown of collagen and elastin, reduction in skin thickness, loss of hyaluronic acid and consequently skin volume and dehydration in the dermis which extrinsically lead to create wrinkles[1-3]. Hyaluronic acid is the most important glycosaminoglycan (GAG) which causes skin elasticity and has the unique capacity to contain water and make the skin hydrated. In addition it has a role in cell growth and function of membrane receptors, also leads to stability of cellular structures and creates a viscoelastic network for collagen and elastin fibers to connect to each other; these benefits make hyaluronic acid as excellent dermal filler[4, 5].

One of the signs of aging is vertical lines on either side

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of the mouth which is called nasolabial folds or laugh line. Injectable fillers in treatment for facial rejuvenation have become an increasingly prevalent feature to grow the population wanting to reverse the aging process. Through recent advances in injection techniques, newer types of dermal fillers have been approved, providing practitioners the option of administering soft tissue fillers such as cross linked hyaluronic acids with minimal inconvenience to the patient[6,7]. This study was designed to assess and compare the efficacy and safety of two soft tissue fillers on mild nasolabial folds using non-invasive measurement techniques.

Materials and Methods

Study design and injection technique

This randomized clinical trial was performed in the Pharmaceutical, Cosmeceutical and Hygienic Evaluation Lab (DermaLab) of Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences (TUMS) from May 2013 to April 2014. After signing the written informed consent and according to the Wrinkle Severity Rating Scale, 10 women aged 30-50 years with mild nasolabial folds and and skin type III-IV were recruited. The exclusion criteria were a recent history of any skin disease or operation in the previous 3 months, any systemic disease that can affect skin status, pregnancy, any other previous cosmetic intervention on the nasolabial fold such as HA, collagen and fat injection, laser therapy, peeling, or non-ablative rejuvenation procedures in the year prior to start day of the study and a history of smoking.

Participants received 1 ml of gel A (Hyamax Deep Line manufactured by Laboratories Hyamed, Switzerland) randomly on one of nasolabial folds and gel B (Yvoire Classic S manufactured by LG Life Sciences, South Korea) was injected in the opposite side. Both fillers contained 22 mg/ml HA and all injections were done with standard technique for dermal fillers.

The subjects were uninformed about the gel types and instructed not to use any pharmaceutical, cosmeceutical or hygienic products on their skin on the night prior to the injection. To anaesthetize the region, a thin layer of Janucaine cream (containing lidocaine 2% and prilocaine 2%, Janus pharmaceutical company, Iran) was applied to both nasolabial folds and occluded for 30 minutes.

Assessment

All assessments were done prior to the treatment and 2, 12 and 24 weeks after injections (follow up visits). A front-view digital photo of the face was taken for comparing before-after photos by two independent dermatologists according to the Physician Global Assessment (PGA) five-point scale: 1- Worse: exacerbation, 2- No change: improvement of 24% or less, 3- Fair: improvement of 25-49%, 4- Good: improvement of 50- 74%, 5- Excellent: improvement of 75% or more [8].

High-resolution images of the nasolabial fold were taken by VisioFace (CK electronic GmbH, Cologne, Germany) then the volume and surface of wrinkles were measured by the related Complete Skin Investigation (CSI) software. The change in volume and surface of wrinkles at each time point after injection were calculated as:

Value after injection – value before injection / value before injection

Furthermore 22 MHz skin ultrasonography (DUB Skin Scanner, tpm, Luneburg, Germany) of nasolabial folds dermis were done at baseline and final visit (24 weeks after injection) to measure the dermis echo-density and thickness[9]. The subject's satisfaction of treatment was assessed by Visual Analogue Scale (VAS)[10] on a 0-10 scale which 0 is dissatisfied and 10 is extremely satisfied. Finally any possible adverse effects were asked and recorded on the 1-3 scale (1: mild, 2: moderate, 3: severe).

Statistical analysis

The obtained data were entered in SPSS software version 20 and then mean score of parameters before and after intervention was analyzed by the paired T-test and p-value <0.05 was considered significant.

Ethics

The study was conducted in accordance with the ethical principles provided by Good Clinical Practice (GCP) and the Declaration of Helsinki and all volunteers provided written informed consent.

Results

All volunteers completed study period and there was no deviation from protocol. Regarding the safety, one participant reported mild bruising and the other one reported swelling, pain and mild stiffness at injection sites of gel A, which cleared spontaneously in a few days.

As depicted in figure 1, the volume and surface of wrinkles at 2, 12 and 24 weeks after injecting gel A decreased compared to baseline, which was statistically significant only 2 weeks after injection (-45.94±20.74%, p–value = 0.000 for volume of wrinkles and -45.02±20.43%, p–value = 0.001 for surface of wrinkles). In the side injected with gel B; this reduction in wrinkles objective parameters was significant at week 2 (-39.67±21.51%, p –value = 0.003 for volume of wrinkles and -39.56±17.16%, p–value = 0.001 for surface of wrinkles) and week 12 (-31.6±31.37%, p –value = 0.019 for volume of wrinkles and -34.68±23.59%, p–value = 0.004 for surface of wrinkles); 24 weeks after injection gel B, just the reduction in surface of wrinkles was significant (-22.23±23.14%, p–value = 0.037).

In addition, 24 weeks after injection of gel A the echo-density of dermis increased significantly (119.32±164.8%, p–value = 0.028), and there was a non-significant decrease

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in the dermis thickness. The same changes occurred after injecting gel B, significant increase in dermis density (78.00±97.06%, p–value = 0.036), and non-significant decrease in the dermis thickness (**Tables 1**). Comparing both fillers, there were not any statistically significant differences in any of measurements.

The results of PGA considered the grade of correction of nasolabial folds and stability of both gels at 2, 12 and 24 weeks after injection (**Table 2**). This improvement was good or excellent (over 50% improvement) in 8, 6, and 6 of 10 patients injected with gel A, and in 9, 7 and 7 of 10 patients injected with gel B after 2, 12, and 24 weeks, respectively (**Figure 2** and **Table 2**). The mean of PGA scores were not significantly different between two gels.

The mean patient satisfaction score at 2, 12 and 24 weeks after injection of gel A were 6.25 ±1.75, 7.88 ± 2.02 and 7.6 ±1.89, respectively. 2, 12 and 24 weeks after injecting of gel B, these records were 7.4 ±1.34, 7.44 ±1.66 and 7.5 ±1.95, respectively ($p < 0.05$).

Discussion

In the past decade there has been a major shift in facial rejuvenation toward less invasive and even nonsurgical procedures with less downtime and less pain[11]. It is understandable that increased popularity of soft-tissue fillers is due to the effective results of restoring lost volume and correcting contour deficiencies to the aging face[12]. Due to the fact that aging is a continuous process, temporary fillers should be preferred over permanent ones[13]. Hyaluronic acid (HA)-based gels are now the gold standard and most commonly used dermal fillers in the US[14].

In this before-after trial, the volume and surface of wrinkles in nasolabial folds have been reduced both objectively and subjectively 2, 12, and 24 weeks after injection of two HA fillers (**Figure 1**). These results can be due to the restoration of volume using dermal fillers which can rebalance facial proportion, increase symmetry and by reducing wrinkles, produce a younger appearance[11].

The obtained results have been confirmed by physician assessments (**Table 2**), in accordance with biometric assays. In addition there was not any statistically significant difference between these two products, and both of them were able to reduce the symptoms of wrinkles.

The increased echo density of dermis can be due to the presence of hyaluronic acid composition in mentioned area. Furthermore, HA in the dermis can stimulate collagen synthesis; the cumulative effect of hyaluronic acid and collagen lead to the increase in the dermis density to mentioned rate (**Table 1**)[15]. In contrast, both gels reduced the dermis thickness at the injection area due to the pressure effect of fillers on dermis which is the main role of fillers to treat the wrinkles. This finding has been reported previously[16]. The participant's satisfaction after injecting both fillers was considerable and no significant side effects

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

Variable	The % of change of gel A after 24 weeks Mean ± SD*	*P –value* (before-after comparison)	The % of change of gel B after 24 weeks Mean ± SD	*P –value* (before-after comparison)	*P –value* (before-after comparison)
Dermis density	119.32% 164.80±	0.028	78% ±97.06	0.036	0.178
Dermis thickness	-10.90% ±19.61	0.081	-8.35% ±16.26	0.127	0.697

Table 2. The physician global assessment of correction level and stability of gels A and B 2, 12 and 24 weeks after injection

	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- Worse: exacerbation	-	-	-	-	-	-
2- No change: improvement of 24% or less	-	-	1	1	1	1
3- Fair: improvement of 25-49%	2	1	3	2	3	2
4- Good: improvement of 50-74%	7	8	5	6	6	6
5- Excellent: improvement of 75% or more	1	1	1	1	-	1
The mean of PGA	3.9	4	3.7	3.9	3.5	3.7

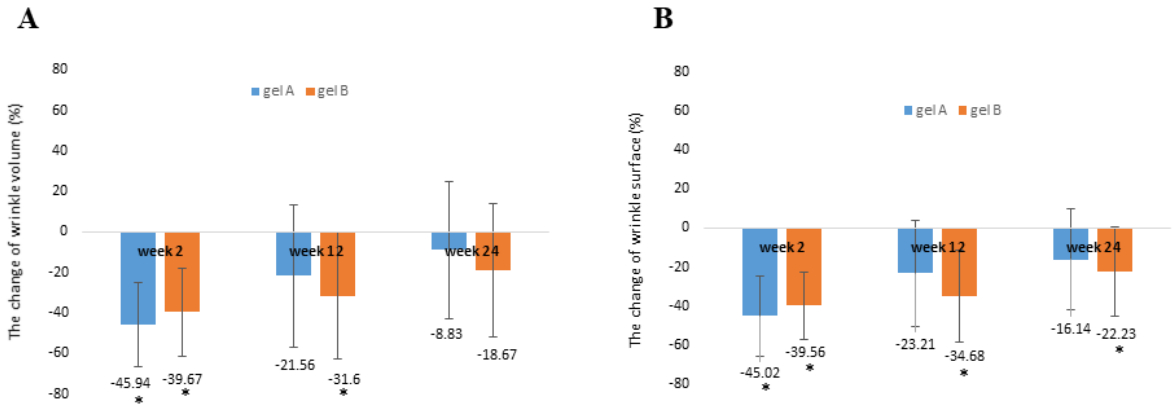

Figure 1. The change in the A) volume and B) surface of nasolabial folds 2, 12 and 24 weeks after injecting gel A in comparison with gel B. *: considered as significant percent of the change (p-value< 0.05)

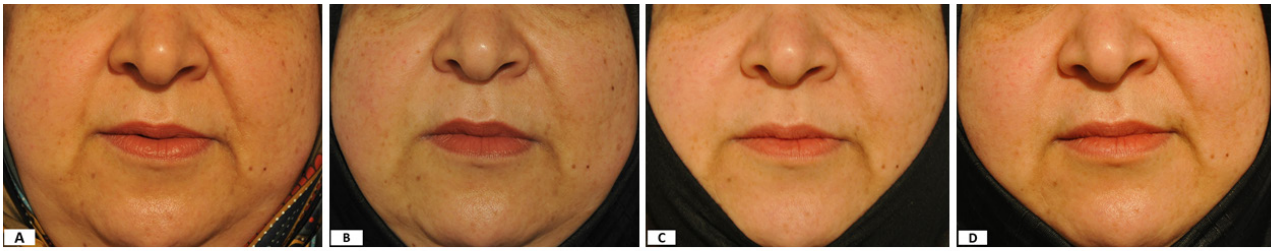

Figure 2. The photographs of nasolabial folds of a representative participant at baseline (A), 2 weeks (B), 12 weeks (C) and 24 weeks (D) after injection A and B gels. The nasolabial folds were treated on contralateral sides of the face with gel A in the participant right side and gel B in left

were reported after injection. Bruising at the injection site was infrequent and disappeared spontaneously in a few days.

Our obtained results indicate no statistically significant difference between two HA fillers but a little better results of gel B in reducing wrinkle volume and surface compared to gel A can be due to different manufacturing processes with major influence on the characteristics of the biopharmaceutical final product, so even minor manufacturing processing differences may impact biological activity, safety and effectiveness of finished product[17].

Conclusion

In conclusion due to the differences between before and after injection and lack of major side effects in both gels, they can be safe and effective products to remove the wrinkles at nasolabial area. Totally because of the superior beauty results of HA fillers, they are still the best dermal aesthetic device to increase the volume of soft tissue. On the other hand they are absorbed and therefore cannot be a permanent solution to remove wrinkles.

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