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Safety and effectiveness of combining different hyaluronic acid fillers for treatment of facial soft tissue defects: randomized trial, multilayer ("sandwich") approach

Abstract

Hyaluronic acid (HA) has been used as a gold standard for aesthetic facial treatments. Many different HA gels are available, and they differ in their HA concentration and rheological aspects. Treating patients with more than one HA gel in the same session or throughout the patient's life is a common practice. We want to show that a combination of different HA is safe and can have a better outcome regarding results, duration, and patient satisfaction. We have treated 30 patients, split into four groups. Patients were treated with three different HA products selected by their G' to target different facial layers. All products were from the same brand and were injected through a cannula with one point of entry. Patients were evaluated with the WSRS and GAIS scales, showing no difference between groups. A statistically significant difference was seen when compared with basal photos. The follow-up was 12 months. No relevant side effects were detected in all groups. Considering that aging is a transversal process that implicates every facial layer, we conclude that combining different G' HA (multifiller approach) targeting precisecly different layers appears to be well tolerated and increases the average duration of aesthetic effects. More studies should be performed to confirm these preliminary results.

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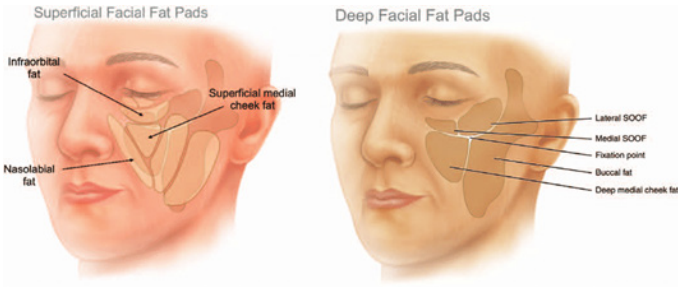
Introduction

Hyaluronic acid (HA) is a glycosaminoglycan found in the extracellular matrix of different tissues: skin, joints, and eyes. It plays a key role in facial structure and skin quality. HA concentration tends to reduce through time, resulting in loss of skin tone, deep wrinkles, and diminished water holding capacity, affecting skin quality and youth aspect.[1,2,3] During the last decades, there has been a huge development of different hyaluronic acid gels with different physical properties, which include particle size, crosslinking degree, active molecule concentration, and manufacturing process. In order to achieve the best cosmetic result, these differences should be considered so as to choose the right product for every facial layer to be treated.[4,5] While those with the lowest G' HA are useful for improving superficial wrinkles in the upper layers and skin quality, those with high viscoelastic properties (high G' HA) are more suitable for deeper planes.[5] We decided to evaluate the consequences of combining several different HA products in the same patient, in the same session, injected through a cannula with a one-point entrance in different layers but in similar anatomical areas. (Sandwich approach). We evaluate duration, adverse effects, and patient satisfaction, as well as possible interactions between the different gels of HA used.

Anatomical background that justifies the approach

Rohrich et al.,[6] et al described the different anatomical compartments of subcutaneous fat of the face. Facial aging is, in part, characterized by how these compartments change with time. The concept of separate compartments of fat suggests that the face does not age as a confluent or composite mass. While superficial compartments mainly sag with time, deep ones undergo atrophic changes, leading to loss of facial volume. Knowledge of this anatomy will lead to better understanding and greater precision when using HA fillers in the face (Figure 1)



From Wan D et al.,[7]

There are four main areas of facial aging that could be addressed:

I. Skin quality
II. Sagging
III. Wrinkles and folds
IV. Loss of volume

HA can be used to improve all of them, but the viscoelastic properties of the gel used should be taken into account.

We have chosen fillers composed of HA with concentrations between 12 and 20 mg/ml and the percentage of particulate crosslinks and calibration are specific to each product- Restylane line from Galderma. These hyaluronic acids are non-animal, stabilized, and are manufactured according to the NASHA technology. Restylane has two additional presentations: Restylane Lift ™ for deep skin layers and Restylane Vital ™ for superficial. The hyaluronic acid concentration in these products is 20 mg/ml. Restylane family includes OBT technology developed fillers: REFYNE, DEFYNE, KISSE and VOLIME. These HA gels also have 20 mg/ml and their

viscoelastic properties are different for each of them. Previous studies have demonstrated the safety and efficacy of Restylane ™ use for face rejuvenation as **"monofiller".**[1-5]

Considering this fact

Low G', low crosslinking, small particles HA (Restylane Vital) has been employed for upper layers. Intermediate G' and crosslinling either NASHA or OBT has been employed for folds and deep wrinkles. High G' High crosslinked and big particle size either NASHA and OBT has been employed to fill deep compartments. Though there have been several reports that compare different dermal fillers with each other and with other products, there are few publications that compare their combination capability. The primary aim of this study is to prove the efficacy and compatibility of different gels of Restylane combined and injected through a single point of entry in multiple skin layers in the same patient ("sandwich technique"). Secondary aims include evaluation of the safety and tolerability of a single point of entry injection technique, evaluation of patient satisfaction, and evaluation of clinical results at twelve months follow-up.

Materials and methods

Study design

A randomized twelve month duration open label pilot study was conducted in two centers in Buenos Aires, Argentina. Subjects were randomized to receive injection of fillers in a consecutive fashion into one of the four categories:

I. Restylane lift ™ for deep layer and Refyne ™ above; Vital Restylane ™ for superficial layer.

II. Restylane REFYNE ™ for deep layer and Restylane ™ volume above; Restylane ™ vital for superficial layer.

III. Restylane volyme ™ for deep layer and Restylane Refyne™ above; Vital Restylane ™ for superficial layer.

IV. Restylane Lift ™ for deep layer and Restylane ™ above; Vital Restylane ™ for superficial layer.

Procedures were performed by two independent injectors (E.S – P.M). Blinding was not performed due to different packaging of the products. Patients were evaluated by medical teams in which the two injectors were not included. The evaluating team was forbidden to access information regarding the type of filler injected. This ensured the blinding of the evaluating team. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and local regulatory requirements. All patients provided their written informed consent prior to entering the study. Subjects were free to withdraw from the study at any time and for any reason.

Subject selection

Eligible patients were men or women between 18 and 70 years old with nasogenian and accessory folds suitable for treatment with dermal fillers, and a WSRS ranging from 2 to 5. Exclusion criteria included active hematologic disease, a history of disease or current treatment with antiplatelet or anticoagulant that cannot be interrupted, active treatment with corticosteroids, allergy or known hypersensitivity to AH, known autoimmune diseases (excluding thyroid pathology), skin rash at the injection site, presence of a prior permanent filler at the injection site, AH-injection performed within six months prior to the procedure, history of hypertrophic scarring, pregnancy or breastfeeding period, any other chronic disease where AH injections may otherwise be considered a risk. 30 patients from the period between April and June 2020 were included in the study.

Treatment and injection technique

Anesthesia cream was applied at the injection site in a standardized fashion 30 minutes prior to the procedure. A single point of entry technique was used. Entrance point was performed 1cm lateral to the labial angle, aimed towards layer 2 (subcutaneous tissue). 21 G cannulas were used for the application of Restylane Volyme ™ in groups B and C. 25G cannulas were utilized for Lift ™ in groups A and D. Through the same entrance point, nasogenian folds and marionette lines were filled with Restylane ™ for groups B and D, and Restylane Refyne ™ for groups A and C. The last step consisted of applying Restylane VITAL™ in superficial dermis of the middle and lower third of the face with a 27G cannula and a fan technique through the same entrance point. Volume was at the discretion of the injector, with a maximum of 2ml of each filler to be applied per patient. Follow up visits included an evaluation at three weeks in which touch ups were performed if needed. Subsequently, four follow-up visits were to be held at 3, 6, 9 and 12 months after initial treatment.

Assessments

Efficacy was evaluated by blinded evaluators and subjects based on the severity of subject's nasolabial folds according to the WSRS and GAIS subjective and global scores. Tolerability and safety were assessed based on the subject's diary, which documented the severity of possible complications, ranging from none to severe. Adverse events were recorded by the evaluating investigators at each visit. Additionally, patient evolution was recorded photographically in each visit. At the end of the treatment, patients answered a questionnaire about their satisfaction with the procedures.

Statistical analysis

Data analysis was done using non-parametric tests due to the lack of normal distribution among groups and the small sample size. In order to test efficacy, comparisons between WSRS scores pretreatment and at twelve months follow-up were performed. This was achieved with the two sided Wilcoxon Sign Rank Test. Differences in WSRS scores regarding pretreatment values were estimated and recorded as the delta value for each patient. Differences between treatment groups at twelve months were evaluated with the Kruskall Wallis test. Differences between groups in GAIS subjective and global score at twelve months were estimated with the Kruskall Wallis test. P values < 0.05 were considered statistically significant. Adverse events were analyzed descriptively. No considerations were made for missing data. Data was analyzed with Real Statistics Resource Pack 2016.

Results

Patient demographic characteristics

The demographic characteristics of the population treated eligible for further analysis are summarized in Table 1. 30 patients were included in the study. Mean age was 52.41 years (range 36 to 74 years). All patients were female and Caucasian. WSRS score was distributed evenly amongst the patients, with 67% corresponding to a grade III scale.

Efficacy

The mean improvement in the investigator-evaluated WSRS from baseline was from 3.14+-0.74 to 1.77+-0.87 at twelve months ($p<0.001$). At twelve months, 81% of the treated patients were classified as WSRS grade I or II (46% and 35%, respectively). This data contrasts to a 67% of WSRS grade III of patients at baseline, and demonstrates an overturn towards better scores after twelve months

Citation: Escobar SO, Pelli MJ, Rey AB. Safety and effectiveness of combining different hyaluronic acid fillers for treatment of facial soft tissue defects: randomized trial, multilayer ("sandwich") approach. *J Dermat Cosmetol.* 2022;6(4):118–122. DOI: 10.15406/jdc.2022.06.00223

of the initial treatment (Figure 2). In order to evaluate statistical differences between groups, the mean delta ratio between baseline data and data observed at 3, 6, 9 and 12 months was estimated. Overall, there was a 45, 5% mean difference between baseline and twelve months scores ($p<0.001$) (Figure 1). The Kruskall-Wallis test, performed on data from four groups over a twelve-month period, demonstrates that there is no statistically significant data to state statistical differences between groups ($p=0.12$). GAIS subjective and global scores were evaluated and are presented at Figure 3. There was a mean GAIS subjective and global score of 1.86+-0.16 and 1.73+-0.19 at twelve months follow-up. Kruskall Wallis test performed on the treatment groups showed there is no statistical data to prove statistical differences between groups for GAIS subjective and global scores ($p=0.39$ and $p=0.57$, respectively). Subjective efficacy was also evaluated through a patient satisfaction survey at twelve months follow-up (Table 2).

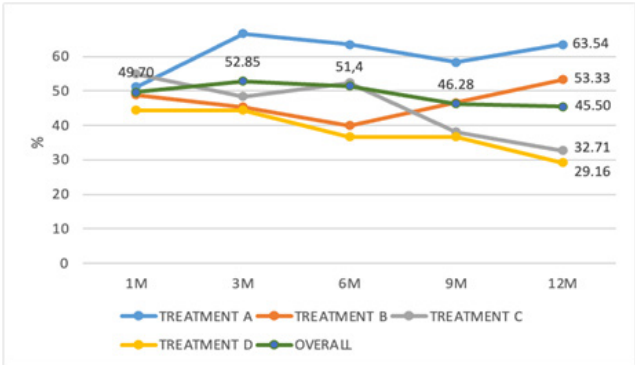


Figure 1 Mean differences in delta WRSS between groups and overall (estimated in percentages).

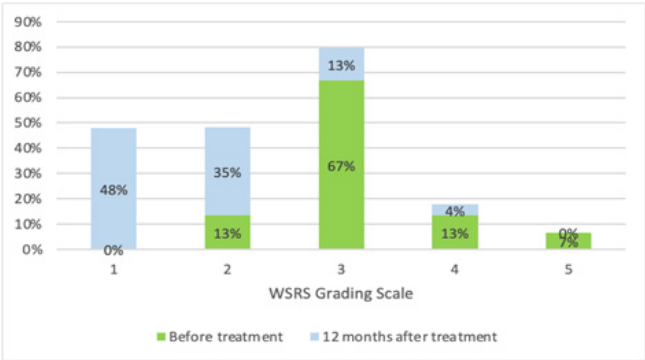


Figure 2 Distribution of patients according to WSRS before treatment and at 12 months follow-up.

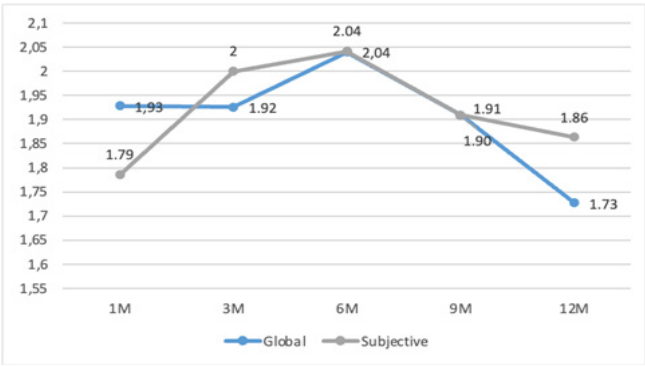


Figure 3 Overall mean improvement in GAIS subjective and global score at months 1,3,6,9 and 12.

Table 1 Baseline characteristics

Baseline characteristics	Value (N=30)
Age, year	
Mean + SD	52,41 +- 1.49
Min, Max	36 – 74
Gender, N (%)	
Female	30 (100%)
Race, N (%)	
Caucasian	30 (100%)
Evaluators WSRS, (%)	
5 Score	2 (7%)
4 Score	4 (13%)
3 Score	20 (67%)
2 Score	4 (13%)

Table 2 Personal satisfaction index

	Personal Satisfaction index (N=30)
Very satisfactory	92.50%
Satisfactory	7.50%
Marginally satisfactory	0%
Unsatisfactory	0%

Local tolerability and safety

The average injection volume for each treatment group is summarized in Table 4. The number of treatment related adverse events was 8 (26%). The products were well tolerated, with only a few mild to moderate reactions observed during the follow-up period. All complications resolved ad-integrum without additional treatment. Our reported complications include mild and moderate hematomas in 20% of the patients, one case of mild swelling (3%), and one case of mild hypotension during the injection session (3%). Our study shows that the single point of entry injection technique that we describe in our study proved no severe adverse reactions at twelve months follow-up (Table 3).

Before and after photographs

In the following pictures you can see the before and after photographs of some representative patients that participated in the study at basal and 12 months after treatment.

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Table 3 Report of treatment related adverse events and review of literature

Authors	Study design	No Patients	Injection Technique	Type of complications	Bruising	Oedema	Others
Escobar et al. 2016	Ranzomized double blinded controlled trial.	N= 30	Lineal threading - Monopuncture	Mild 5 (16%) Moderate 3 (10%) Severe: None	Mild 3 (10%) Moderate 3 (10%)	Mild 1(3%)	Mild hypotension 1(3%)
Ascher et al.[4]	Split face one side blinded Prospective Cohort (Emervel Deep vs Restylane Perlane)	N= 133	Not specified (Determined by each injector)	None - Mild (54-96%) Moderate (3-40%) Severe (0.7-6%)	None – Mild 96 (72%) Moderate 54 (0%) Severe 7 (5%)	None – Mild 72 (54%) Moderate 54 (41%) Severe 7(5%)	Erythema 39 (29%) / 8 (6%) Pruritus 4(3%) /1 (0.7%) Pain- Tendernes 36 (27%)/ 5 (3.7%)
Brandt et al.[3]	Prospective Cohort (Restylane and/or Perlane)	N=20	Lineal threading + multiple punctate pools	Mild (100%) Moderate (0%) Severe (0%)	19 (95%)	8 (40%)	Headache 2 (10%)
Heden et al. 2010	Split face double blinded prospective cohort (Restylane Perlane w/ Lidocaine vs Restylane Perlane wo/ Lidocaine	N=43	Fan and/or lineal threading	Mild 42 / 41 (97% / 95%)	21 / 25 (49% / 58%)	38 / 37 (88% / 86%)	Tenderness 25 / 31 (58% / 72%) Redness 26 / 25 (60% /58%) Itching 11 / 12 (26% / 28%) Pain 8 /10 (19% /23%)
Lindqvist et al.[2]	Split face Randomized double blinded controlled trial (Perlane vs Zyplast)	N= 68	Not specified (linear threading and/or serial puncture)	Total: 12 (18%) / 21 (31%) Mild: 9 (79%) / 13 (60%)	Not specified	6.8% / 15.9%*	Redness 11.4% / 15.9% Pruritus 9.1%/13.6%. Skin induration 2.3% / 13.6%. Injection site pain 0 / 6.8%.*
Narins et al.[1]	Split face Randomized double blinded controlled trial (Restylane vs Zyplast)	N=134	Not specified (linear threading and/or serial puncture)	38.4% (27% / 39%)	After initial treatment 52.2% / 48.6% At 6 months 4.2% 4.8%*	After initial treatment 87% / 74% At 6 months 6.3%/ 7.0%*	Redness 85%- 85% / 19% - 27% Pain 57% - 42% / 0%-0.7% Pruritus 30%- 24% / 3%-6%* *(reported as incidence).

Table 4 Injection volume for each group (expresed in means)

	Superficial Filler	Deep Filler No1	Deep Filler No2
Treatment A	Restylane Vital = 0.94cc	Restylane Refyne = 0.85cc	Restylane Lift =0.97cc
Treatment B	Restylane Vital = 0.96cc	Restylane = 0.96cc	Restylane VOLIME = 1.9cc
Treatment C	Restylane Vital = 1.05cc	Restylane Refyne = 0.91cc	Restylane VOLIME = 1.87cc
Treatment D	Restylane Vital = 1cc	Restylane = 1.16cc	Restylane Lift = 1.14cc

Discussion

The findings of this study are consistent with previous studies that compared AH with different physical properties to other dermal fillers and against them.[8,9] Recently, a "sandwich" approach has been published by Tingson et al in J Cosmet Dermatol.[10] This study proves that combinations of deep and superficial dermal fillers are safe and effective. Different types of HA, when applied to the correct layer, can be used simultaneously. For short and middle term evaluation, our results are consistent with previous studies showing a significant mean improvement in WSRS from baseline for Restylane Defyne and Restylane Lift at 3 months and 6 months follow-up.[1] We have demonstrated that different G" Restylane can be combined in the same session, and the final outcome at 12 months is good. We have also assessed the main differences in GAIS global and subjective scores, proving that there is a sustained increase in GAIS scores throughout the twelve month period, with no statistical differences between groups. It can be stated that the combination of different types of Restylane results in a subjective perception of improvement in the patient that lasts up to twelve months. This data is consistent with our previous findings. Our study shows fewer adverse effects than previous studies reported in the literature. We have reported a 26% complication rate, of which 16% were mild and 10% moderate. We have had no severe adverse reactions throughout this study. We believe this is due to the standardized single point of entry multilevel injection technique. A review of the literature reveals that injection technique is a critical factor that has not been adequately controlled in previous studies, either because it was not specified or because it was left to the discretion of each injector during the procedure. Though this is a comparative evaluation of the descriptive data reported in each study,

our differences with other studies in treatment related adverse events open the possibility of an association between injection technique and adverse effects rather than the type of dermal filler applied.

Further randomized controlled trials should be performed in order to state the burden of the injection technique on treatment related adverse events. Our personal satisfaction index performed at twelve months show there was a 92.5% of highly satisfied patients, proving that our standardized injection technique has been widely accepted by our patients, and, together with our reduced incidence of adverse events, could be recommended for dermal filling of nasolabial and accessory folds in patients. Limitations of this study include: small sample size restricts statistical evaluation through parametric testing and might underestimate statistical significance. Further randomized controlled trials with larger sample sizes should be performed in order to contribute to our initial investigation.

Conclusion

We demonstrated the efficacy and compatibility of different G' HA combinations. Good results were seen up to twelve months after the procedure. Our standardized single point of entry multilevel injection technique proved to be a safe alternative for treatment of nasolabial and accessory folds, filling deep fat compartments, and improving skin texture and global appearance, with high levels of acceptance among the patients studied.

Acknowledgments

None.

Conflicts of interest

Authors declare there is no conflict of interest.

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