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ORIGINAL ARTICLE NON-SURGICAL AESTHETIC

Hyaluronic Acid Gel Injection for the Treatment of Tear Trough Deformity: A Multicenter, Observational, Single-Blind Study

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Abstract

Background Hyaluronic acid (HA) gel injections were first used to treat the tear trough in 2005 and since then it has been a mainstay of the approach to lower eyelid deformities.

Objective The authors present this retrospective multicentric observational study based on single-blind objective and subjective evaluation and patient satisfaction in relation to the aesthetic improvement of a large group of patients treated.

Methods and materials Between January 2016 and December 2019, 600 patients (468 women and 132 men), were enrolled in this study, and 1200 tear trough deformities were treated with both needle and cannula techniques.

Results Average follow-up time was 12 ± 1 months, and the outcomes were assessed both objectively and subjectively with respect to Hirmand's classification. Statistical analysis shows an inverse correlation between age and class amelioration.

Conclusion HA injection of the tear trough is most effective in patients between 30 and 40 years of age, while its benefits extend to up to 50 years old; afterward, it should no longer be the treatment of choice. This confirms that correction of tear trough with hyaluronic acid injections may provide an option to achieve immediate and durable results for up to one year after the injection.

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Keywords Tear trough · Hyaluronic acid · Lower eyelid

Introduction

Minimal changes in the periorbital region yield great improvement as eyes are a crucial feature when assessing facial aesthetics and appeal, and consequently of major concern for both patients and doctors [1].

The naso-jugal fold was first mentioned by Loeb R in 1981 [2] as the fold caused by the attachment of the lower dermis to the periosteum of the infraorbital margin that accentuates the depression of the eyelids as opposed to the heavier bulk of tissue toward the nasal wall, but further investigation was required before considering it merely as the medial part of the fold described previously [3].

To correct it, fat injection was proposed as a non-vascularized graft option [4]. Once an understanding of the orbitomalar ligament's role in tear trough definition, as well as the role of midface ptosis in its progressive worsening [5], had been gained, the possibility to inject agents other than fat to fill the hollow and rejuvenate the sunken lower eyelid, with the aim of obtaining the same outcome without the known recovery time, became evident.

Hyaluronic acid (HA) gel injections were first used for this purpose in 2005 [6, 7] and, since then, this non-surgical, outpatient procedure has been a mainstay of HA filler treatment for both aesthetic and functional approaches to lower eyelid deformities [8–15], as not all patients require

all steps of surgical blepharoplasty and because surgery may result in the overtreatment of younger patients, who, unlike patients with a history of surgery, affected by residual or worsening tear trough deformity, may prefer to avoid surgery: non-surgical procedures can, therefore, be adopted to treat selected lower eyelid aging in properly selected subjects, as long as key anatomic structures are not jeopardized.

Less-invasive techniques are constantly being pursued with the aim of safely and reliably correcting aesthetic flaws. This is why the authors present their experience with this retrospective multicentric observational study based on single-blind objective evaluation, subjective evaluation and patient satisfaction in relation to the aesthetic improvement of a large group of patients treated with HA gel injections in the tear trough area for cosmetic purposes.

Materials and Methods

Methods

The study protocol followed the ethical guidelines of the Declaration of Helsinki. Patients selected to participate in a retrospective study released written informed consent.

Patients

All patients treated for tear trough deformities with HA dermal filler by three different professionals (a maxillo-facial surgeon, a dermatologist and an aesthetic surgeon) in their own private practices between January 2016 and December 2019 were entered in a clinical database. The information collected included age, sex, amount of filler used, the use of needle or cannula, degree of improvement, adverse events and follow-up. Filters were applied to identify only patients that were eligible to participate in the retrospective study based on inclusion and exclusion criteria.

Inclusion criteria included all patients eligible for tear trough treatment using HA gel.

Exclusion criteria included previous lower eyelid surgery, any treatment six months prior to baseline, including Botulinum toxin type A injections in the periocular area, facial soft tissue filler, laser, facial ultrasound or radio frequency treatment, and treatment with isotretinoin or oral acne medications. Lastly, patients with local dermatitis were excluded.

A total of 600 eligible Caucasian patients were randomly selected from this clinical database: 468 women and 132 men. The men (22%) were aged between 34 and 55 (mean, 42 $\pm$ 5.71) and the women (78%) were aged between 29 and 58 (mean 41.6 $\pm$ 7.42). Demographic data are presented (see Table, Supplemental Digital Content 1).

The tear trough patterns, pre- and post-treatment, were categorized according to Hirmand's classification system (see Table, Supplemental Digital Content 2, summarizing Tear trough deformity assessment according to Hirmand's classification system).

Patient photographs were taken using a Nikon SLR D90 12.3 Mpixel digital camera (Nikon, Tokyo, Japan).

Photometric Evaluation

Documentation with full-size 1:1, standardized photograph (Frankfurt horizontal plane parallel to the floor) of each patient looking straight ahead in the standing position.

Position, facial expression, focal distance and camera settings were standardized and photographs were sized with Adobe Photoshop CC (Adobe Systems Inc, San Jose, CA) to ensure that initial proportions were maintained.

To allow objective evaluation, the photographs were randomized, and case assessment was performed 8 weeks and 12 months after injection by an independent blind investigator.

Treatment

A total of 1200 tear trough deformities were treated using HA dermal filler (Teosyal PureSense Redensity [II], Teoxane SA, Geneva, Switzerland).

Treatment was performed with the patient seated in a semi-reclined position, following thorough disinfection of the injection sites.

Neither topic nor infiltrative anesthesia was used.

Injections were performed using 30G, 13-mm-long needles in 428 sites and 25G, 40-mm-long cannulas in 772 sites.

The injected areas were gently massaged immediately after injection.

Statistical Analysis

PLUM ordinal logistic regression was carried out to test the effects of patient age and gender, amount of filler injected and injection device on class improvement after treatment. Binary logistic regression was performed to analyze the relationship among the above-mentioned predictor variables and occurrence of adverse reaction.

The IBM SPSS Statistics (ver. 26) software package was used to perform all these analyses.

Results

The tear trough deformities of the 1200 treated eyelids were assessed before injection: 84 Class I (7%), 804 Class II (67%) and 312 Class III (26%).

A total of 1200 sites were injected with HA gel.

Injections were performed with a needle in 428 out of 1200 (35.7%) sites, and with a cannula in 772 out of 1200 (64.3%) sites.

Patients were monitored up to 52 weeks after injection: average follow-up time for all patients was 12 ± 1 months (range, 4–17 months).

A mean volume of 0.33 ± 0.05 ml (range 0.2–0.45 ml) per site was injected, and a mean touch-up volume of 0.18 ml (range, 0.1–0.2 ml) was reinjected after 18 ± 1 days (range, 7–30 days).

The total volume injected per site during the 12-month follow-up was 0.35 ± 0.1 ml (range 0.2–0.65ml)

The clinical data recorded are listed (see Table, Supplemental Digital Content 3, summarizing clinical data).

Efficacy Assessment

The final outcomes were assessed both objectively and subjectively.

In order to avoid potential bias, objective evaluation was carried out by a blind investigator, a medical professional to whom patient photographs taken before, and then eight and 52 weeks after injection were sent by the authors. Blind evaluation was carried out by the investigator using the Global Aesthetic Improvement Scale (iGAIS) to assess treatment outcome as: "very much improved," "much improved," "improved," "no change" or "worse."

After eight weeks, the blind investigator (Table 1) rated maximum improvement in 10.7%, great improvement in 49% and improvement in 37.6% of all patients treated. After one year, the outcome was confirmed as maximum in 0.8%, great in 9.9% and improved in 35.9%, considering only the 242 patients available for the clinical check.

Table 1 Outcome assessment according to iGAIS 8 and 52 weeks after injection (blind investigator)

Grade		
	8 weeks	52 weeks
Very much improved (pts/site)	64/128	2/4
Much improved (pts/site)	294/588	24/48
Improved (pts/site)	226/452	87/174
No change (pts/site)	16/32	129/258
Worsen (pts/site)	0	0
Total	600/1200	242/484

In addition, the outcome was assessed blindly by the authors too, using Hirmand's classification, eight and 52 weeks after treatment.

The objective outcome assessments are given in Tables 1 and 2.

Furthermore, 600 and 306 out of the 600 treated patients were available for a satisfaction interview at 8- and 52-week follow-up visits, respectively. Subjective patient satisfaction was evaluated using the Freiburg questionnaire (sGAIS). Patients were interviewed to judge their level of satisfaction as: "very satisfactory," "satisfactory," "poorly satisfied" or "not at all satisfied."

Precisely, in order to fulfill outcome assessment, the 52-week clinical check with a survey carried out in the form of a patient satisfaction interview held on the telephone, allowed the authors to consider 306 questionnaires, adding 64 telephone questionnaires to the 242 filled out in person.

Eight weeks after treatment, 67% of patients claimed to be very satisfied and 28.17% to be satisfied, while after 52 weeks, 67% and 28.1%, respectively, of the interviews confirmed the satisfaction rate.

Patients that were poorly satisfied accounted for 3% after eight weeks and 2.94% after 52 weeks, while unsatisfied patients accounted for 1.83% after eight weeks and 1.96% after 52 weeks.

The subjective outcome assessment is presented (see Table, Supplemental Digital Content 4, presenting outcome assessment according to patient satisfaction (sGAIS) eight and 52 weeks after injection).

Statistical Analysis

Descriptive statistics are shown (see Table, Supplemental Digital Content 5–7, illustrating descriptive statistics):

Table, Supplemental Digital Content 5, presenting Case Processing Summary, summarizes general data after eight weeks, as follows:

Twenty-two patients (3.7%) showed class upgrade "0," therefore no improvement;

Five hundred and sixty-seven patients (94.5%) showed class upgrade "1," an improvement of one class with respect to the classification mentioned;

Eleven patients (1.8%) showed class upgrade "2," therefore an improvement of two classes with respect to the classification mentioned.

The data in the Table, Supplemental Digital Content 6, shows an ordinal regression model which significantly fitted the data and Nagelkerke's pseudo $r^2 = 0.31$ indicated an overall good proportion of explained variance. Patient age

Table 2 Outcome assessment according to Hirmand's classification at 8 and 52 weeks after injection compared to pre-treatment baseline (carried out blindly by the Authors)

Hirmand's class	Pre-treatment class number (%)	8-week post-treatment class number (%)	52-weeks post-treatment class number (%)
Class I	42 (7%)	395 (65.8%)	9 (3.7%)
Class II	402 (67%)	138 (23%)	182 (75.2%)
Class III	156 (26%)	18 (3%)	51 (21%)

Table 3 Post-treatment complications collected by investigators immediately after injection or at the first follow-up visit within 1 month based on treatment with needle or cannula.

Type	Treatment with needle		Treatment with cannula	
	Number	Percentage (%)	Number	Percentage (%)
Swelling	5	2.3	11	2.8
Bruising	6	2.8	0	0
Redness	5	2.3	9	2.3
Pain	6	2.8	11	2.8
Blue discoloration	0	0	27	7
Hypercorrection	0	0	26	6.7
Malar edema	0	0	0	0
Inflammation	0	0	1	0.2
Total	22	5,1	85	11

was the only predictor variable with a significant effect on class improvement ($p<0.001$). As shown by negative parameter estimates (−0.26), the probability of class improvement decreases with an increase in age.

Lastly, the data in the Table, Supplemental Digital Content 7, shows a binary logistic regression model that significantly fitted the occurrence of adverse reactions. However, as shown by the value of Nagelkerke's pseudo-r^2 (0.052), only a small proportion of the variability in the dataset can be explained by the predictor variables that were included. A significant effect was detected for needle injection, which decreased the probability of adverse reaction compared to cannula injection, and for gender, with females being more likely than males to suffer adverse effects.

The data collected after 52 weeks were not subject to statistical analysis as 358 dropouts were recorded at the time of clinical check.

Discussion

Following its first mention in 2005, interest in tear trough rejuvenation carried out with hyaluronic acid injection peaked around the year 2012 and has continued its ascending trend ever since [16].

Multiple classifications of tear trough deformity have been presented since then [17, 18], although a standard has yet to be established, and the Hirmand Classification [19] has been chosen in this paper for its reliability and ease of application.

The study presented offers the highest numerosity ever published on tear trough treatment, as the average study population of papers related to this topic is 71.37 ranging from 3 [20] to 400 [11] patients treated.

Nowadays, the standard rule for tear trough treatment outcome evaluation is to carry it out subjectively, clinically [11, 12, 21, 22], using bidimensional photographs [15, 23–26], via Assessment Scale as evaluated by both patients and doctors [24–28], with questionnaires [29] and even by telephone calls [30]. Here, the patient group was evaluated along a 12±1 (range, 4–17 months) month follow-up, and the outcome assessment was corroborated by a single-blind evaluation.

Results collected by the authors (Table 2) and their statistical analysis (see Table, Supplemental Digital Content 5, presenting Case Processing Summary) allow observation of an improvement of one class with respect to the Hirmand classification in most of the cases treated (94.5%), eight weeks after treatment.

Improvement of more than one class was recorded in 1.8% of patients, mainly young people: indeed, age has been shown to inversely correlate with the chance of improvement in the whole study population, being the only predictor variable with a significant effect on class improvement ($p<0.001$) as the probability of improvement decreases with an increase in age (see Table, Supplemental Digital Content 6, presenting Class improvement: ordinal regression model).

No correlation was found between gender and an improvement in class.

In view of the results recorded and their statistical validation, it can be stated that HA injection of the tear trough is most effective and should therefore be indicated, in patients between 30 and 40 years of age, and while its benefits extend to patients aged up to 50 years old (Fig. 1); afterward, it should no longer be the treatment of choice as the descent of the sub-orbicularis oculi fat and the deep medial cheek fat are responsible for its worsening and the tethering action of the underlying ligament overwhelms the correction achievable with hyaluronic acid injection alone.

With the aim of corroborating evaluation after eight weeks with a longer follow-up period, both subjective and objective assessment at 52 weeks, performed by a single-blind evaluator, were included (Tables 1 and 2).

Only 242 patients were available for clinical evaluation 52 weeks after treatment; therefore, the data were recorded without being subject to statistical analysis. It did, however, infer a positive outcome of the treatment.

In the population examined, hyaluronic acid injection was performed with both cannula (Figs. 2 and 3) and needle (Figs. 4 and 5).

In this study, 35.7% of sites were treated using the needle, which allows the injection of a single bolus of hyaluronic acid directly into the deepest part of the tear trough onto the periosteum and used to be the technique of choice, from publication of the very first article in 2005 until 2019 [11–15, 22, 27].

Conversely, the use of the cannula was first reported in 2012 and, since 2017 [21, 31–33], retrograde injection, reaching the bony orbital ridge and placing the hyaluronic acid again deeper than the orbicularis oculi muscle, with an entry point located below the external canthus, has been strongly advocated; in this population, 64.3% of sites were injected using a cannula.

To obtain the results presented, a total volume of 0.35 ± 0.1 ml (range 0.2–0.65ml) was injected per site during the 12-month follow-up and, interestingly, injection with needle did not require touch up, while cannula injection was followed by additional treatment in 142 areas (18.4%) within one month of primary treatment.

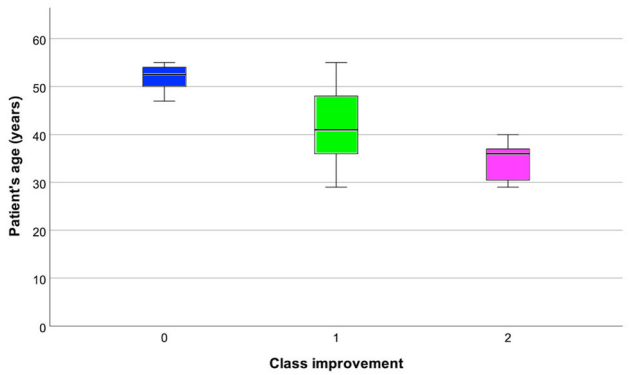

Fig. 1 Correlation between age and class amelioration

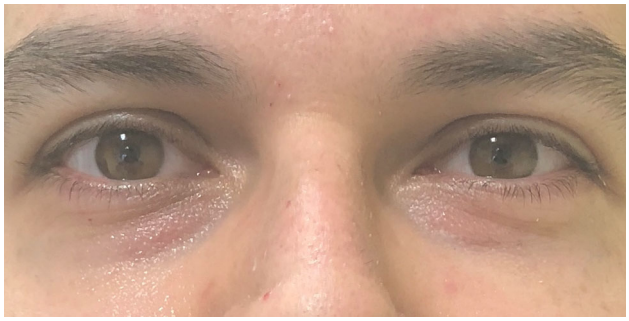

Fig. 2 Patient 1, before treatment (cannula)

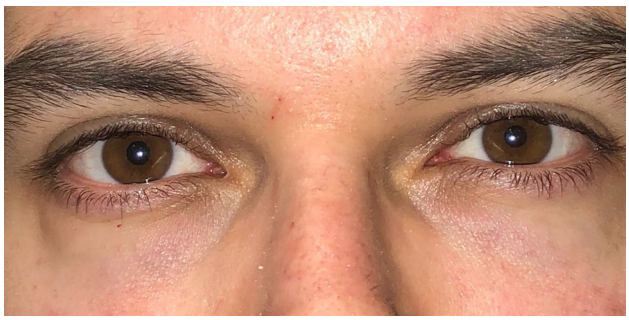

Fig. 3 Patient 1, 8 weeks after treatment (cannula)

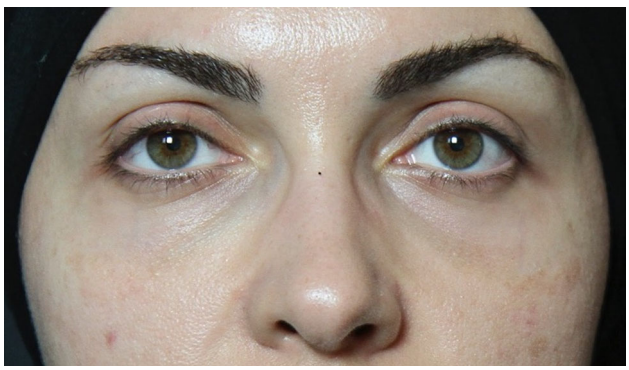

Fig. 4 Patient 2, before treatment (needle)

Fig. 5 Patient 2, 8 weeks after treatment (needle)

It is the authors' opinion that the efficacy of injection by needle is supported by a more precise and localized delivery of hyaluronic acid, which remains confined within the surrounding tissues following the injection.

When the cannula is adopted, attention must be paid to inject small boluses of hyaluronic acid rather than a linear deposit as the latter often remains visible, with less support of the overlying tissues.

The need for touch-up is secondary to this erroneous placement of hyaluronic acid, which often requires injection of a larger amount in order to fully correct the area treated.

Nevertheless, it is advisable to avoid injections of excessive amounts of hyaluronic acid in a single session, and even though the average amount reported in the literature is 0.56 ml, ranging from 0.2 [12] to 2.0 ml [24] per side, satisfactory results were experienced by the authors with a smaller mean volume of 0.35 ± 0.1 ml (range 0.2–0.65ml) per site.

The choice between needle and cannula is based on personal experience and preference. However, in the authors' practice, the use of the cannula leads to overcorrection and Tyndall effect in 6.7% of cases secondary to its superficial misplacement, while needle injections tend to avoid such complications secondary to superficial migration, provided that the product is injected in a plane deeper than the orbicularis oculi muscle [14, 32, 34, 35] down to the inferior orbital rim [11, 13, 15, 23].

Tyndall effect, a blue-gray dyschromia, and contour irregularities are the most frequently reported complications [22, 36–39] with injection into this site, being referred in up to 30.5% of cases [37].

Being careful with the amount of hyaluronic acid injected has allowed the authors to avoid malar edema, the third reported complication [22, 40–43], which occurs in up to 11% of cases [37], taking advantage of the low percentage (2.8%) of bruising with needle injection, which may cause lymphatic vessel compression with a greater risk of edema.

In the authors' experience, the use of the cannula makes it possible to avoid bruising and ecchymosis, while post-injection swelling, redness and pain are recorded in 2% to 3% of cases, regardless of the injection technique.

With respect to the results here presented, post-injection complications encountered (Table 3) with needle use occurred in 5.1% of cases, compared to cannula use in 11% of cases, and they are usually transient and self-limited within hours (swelling, bruising, redness and pain).

The statistical analysis related to needle/cannula injections, the presence and type of complications and the amount of material injected confirm that needle injection decreases the probability of adverse reaction compared to cannula, and further shows that females are more likely than males to suffer adverse effects (see Table, Supplemental Digital Content 7, presenting Occurrence of adverse reaction: binary logistic regression model).

Major complications have nevertheless arisen following the use of cannulas (Figs. 6 and 7) when the hyaluronic acid is placed too close to the surface or above the tear trough ligament, leaving it visible and often palpable. Touch-ups were necessary in up to 18.4% of cases.

So why are we still injecting the tear trough using the cannula? It is the authors' opinion that growing awareness of the relevant anatomy [33, 44, 45] has supported the use of blunt cannulas as the safer choice to avoid lesions of the infraorbital and angular vessels. This somewhat coincides with the increasing number of related papers after 2017 [16]. Nevertheless, to date, there has been no publication specifically regarding arterial embolism or intravascular injection secondary to tear trough injection since the very first articles on complications published in 2012 [38, 46] and subsequently [22, 36, 37, 40, 41], up to 2020 [42].

This evidence confirms that the technical complexity of this treatment requires adequate skill for it to be properly performed. Therefore, it is strongly recommended that it be carried out by experienced injectors only.

Lastly, the authors believe that it is mandatory to distinguish between the surgical and non-surgical approach to tear trough deformity, as the first must follow principles of ligament release to achieve the detethering of the superficial layers, while its correction with hyaluronic acid is used to provide camouflage, masking the skin depression caused by deep ligament retention; to bridge this gap and simulate the surgical result, some forms of cannula subcision have been performed, the results of which have been published [21] but should, however, be further investigated in future studies.

This paper does have some limitations, as its level of evidence with respect to the Levels of Evidence

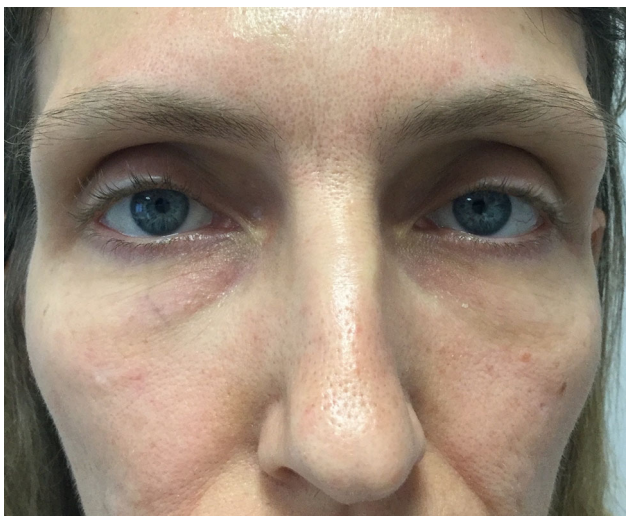

Fig. 6 Patient 3, Tyndall effect before treatment

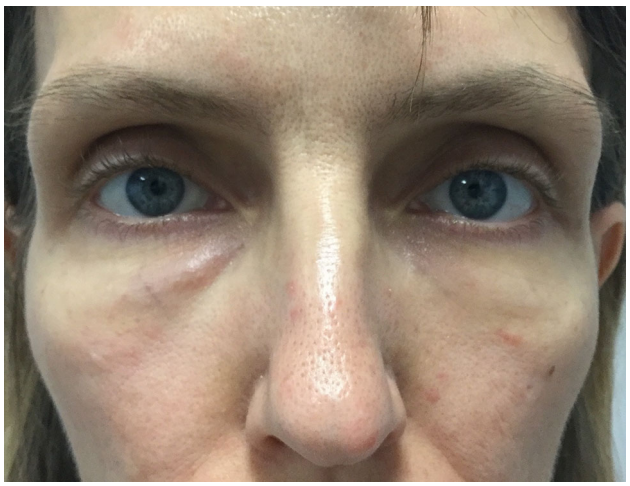

Fig. 7 Patient 3, Tyndall Effect 4 weeks after treatment (right eyelid, whereas the patient did not require correction)

classification of the Oxford Centre for Evidence-based Medicine (OCEBM) [47] is 4.

However, this is the first multicenter study focused on hyaluronic acid for tear trough treatment, with the largest sample and a single-blind outcome evaluation providing for the best reliability of the results presented.

Unfortunately, there are different classifications of the severity of tear trough deformities [17, 18] and, as long as a standardized and universally accepted grading system continue to be absent from current literature, it will be impossible to raise the level of evidence of the related research.

It must be considered that the classification mentioned includes every pathological condition of the tear trough deformity but does not consider its absence; therefore, patients rated "Class I" prior to treatment remain "class I" even if improvement occurs, while the groups rated "Class II" and "Class III," respectively, improve to "Class I" and "Class II."

Eight weeks after the treatment, 33% of patients were not very satisfied: a touch-up, defined as additional treatment, was in fact performed in 142 areas (18.4%) within one month of treatment, and it is therefore suggested that this be included in the treatment plan.

The authors have shared the reliability and efficacy of this treatment up to 52 weeks after treatment, according to the average follow-up of the literature published; however, only approximately half of the study population was available to check the treatment outcome at that time.

The paper presented confirms that non-surgical correction of tear trough deformity with hyaluronic acid injections may provide a reliable and viable option for achieving, when properly performed by experienced injectors, immediate and durable results for up to one year after injection, with great satisfaction among patients and doctors.

Conclusions

Correction of the tear trough deformity with hyaluronic acid injections provides a reliable and viable option based on the evidence presented, and its efficacy is inversely correlated with patient age at the time of treatment, until the aging process requires further surgical treatment to properly address the underlying tethering action of the ligament responsible for the deformity and for the recorded loss of clinical outcome and patient satisfaction with non-surgical treatment.

Corroboration is provided by the statistical analysis results.

The encoding of a standardized grading system will make it possible to highlight its effectiveness with prospective, randomized controlled studies; to date, this multicentric, single-blind study presents the largest available sample to support validation of the procedure and its expected outcomes.

Disclosures

Dr. Calvisi is a consultant for Allergan, Inc. The other authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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