

Deep Facial Wrinkle Treatment Outcome After First Injection of Reticulated Hyaluronic Acid

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Skin aging is a complex multifactorial biological process that affects different skin components. Even if the skin aging mechanism is not fully elucidated yet, it is shown that with time, the epidermis loses the hyaluronic acid (HA), resulting in decreased skin tonicity and hydration level. HA properties – as glycosaminoglycan, present in all conjunctive and epithelial tissues and as biological skin moisturizer that attracts and retains averagely 70% of its weight in water – lead to its usage as dermocosmetic. When talking about wrinkles incidence, they can appear in all persons, depending on age, genes, environmental and dietary factors, etc. The present study is about the use of reticulated HA of non-animal origin in treating deep wrinkles, assessing its effects in time, as well as the side-effects. The study was conducted in aBeauty Clinique centres in Romania, on 164 subjects. Treatment outcomes were evaluated according to biological factors, habits or lifestyle as risk factors, tolerability, effectiveness, lastingness, adverse reactions and complications, and HA dosage.

Keywords: skin, aging, wrinkles, fillers, hyaluronic acid

With aging, loss of collagen in the dermis leads to loss of skin elasticity (elastin fibers) and moisture (hyaluronic acid), progressing to a wrinkled appearance. Dermal filling, for different skin defects, is a method that has been used for decades in soft tissue augmentation. Recently, this technique was introduced in dermocosmetic. Nowadays there is a broad variety of filler materials and products but hyaluronic acid is the most well-known choice. Nevertheless, controversies and discussions on this topic exist, regarding the use of different types of hyaluronic acid, its indications and contraindications [1]. Among them, it is worth mentioning a recent study showing that hyaluronic acid, besides filling effect, stimulates neocollagenesis [2]. Despite all this, the specialty literature is scarce in clinical studies based on injectable administration of the reticulated hyaluronic acid. In this context, the present study brings a comparative analysis of treatment effectiveness, tolerability, lastingness and complications that may appear after first injection of reticulated hyaluronic acid.

Experimental part

Material and method

The study was conducted in aBeauty Clinique centres in Romania from 1.04.2012 to 31.12.2014 on a lot comprising 164 persons, 27 males (16.74%) and 137 females (83.54%), aged between 27 to 69 (mean 45.7 years). Subjects diagnosed with cutaneous infections at the initial examination were not admitted in study. As wrinkles fillers, Juvéderm Ultra 4, Teosyal Deep Lines and Restylane were used by intradermic injection, quantities varying from 1 to 6mL/session. Treatment was applied most often in nasolabial, glabellar and forehead areas, under local anaesthesia. All subjects experienced the treatment for the first time. Treatment outcome was assessed considering both favouring factors in wrinkled appearance and factors that may determine a rapid absorption of HA. As risk factors, smoking (more than 10 cigarettes/day for

a minimum of 10 years or over 20 cigarettes/day for a minimum of 5 years), excessive sun exposure (over 30 days of sunbathing/year, minimum 5 years or professional UV exposure for long periods of time), frequent intake of antibiotics (more than 21 days/year, in combination of two or more kinds) and anti-inflammatory drugs were analysed. For statistical analysis, *SigmatStat 3.5* software was used.

Results and discussions

Risk factors

In the study lot, 107 (65.25%) subjects were smokers: 23 males (21.5%) and 84 females (78.5%). Excessive sun exposure were registered for 146 (89%) subjects, that acknowledged sun exposure up to 3 months per year: 17 males (11.65%) and 129 females (88.35%). A number of 36 persons (21.95% of the study lot), 5 males (13.88%) and 31 females (86.12%) declared frequent intake of antibiotics. Anti-inflammatory drugs intake was more frequent, according to statements of 69 subjects (42%) – 9 males (13%) and 60 females (87%).

Dehydrated skin was observed in 52 persons (31.70%), most female (47 subjects, 90.38%). Between the 164 subjects analysed, 152 have been treated for nasolabial folds (the most frequent). Obviously, the thickness of the cheek fat is involved in the formation of these wrinkles: the thicker is fat cheek; the sooner and deeper folds appear, due both to superficial muscular aponeurotic system weakening (by forcing) and to gravitation (in orthostatism). Based on wrinkle depth and Smith et al. model [3], a wrinkles severity classification was created (table 1), which reveals 113 subjects with an advanced degree of cellulitis and/or inchoate obesity (score 3 and 4).

Tolerability

In terms of tolerability, only 1 female subject, with multiple allergies, presented light intolerance to the product, manifesting erythema and important facial oedema that reabsorbed under conventional treatment

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Score	Severity descriptions	Descriptions	Cases
4	extreme	Very deep wrinkle, redundant fold (overlapping skin)	27
3	severe	Deep wrinkle, well-defined edges (but not overlapping)	86
2	moderate	Moderately deep wrinkle	35
1	mild	Shallow, just perceptible wrinkle	4
0	none	No wrinkle	0

	1	2	3	4	5
Subjects (no/%)	-	-	-	29 (17.69%)	135 (82.31%)
Physician (no/%)	-	-	-	21 (12.80%)	143 (87.20%)

Table 1
POINT WRINKLE ASSESSMENT
SCALE FOR NASOLABIAL FOLDS
SEVERITY

Table 2
TREATMENT EFFECTIVENESS
APPRECIATION

(Xyzall and hydrocortisone hemisuccinate) in a couple of days. The rest of the subjects have shown not systemic intolerance.

Effectiveness

Evaluation of the embellishing is often relative and differently appreciated by subjects and physicians. Evaluation of the treatment effectiveness was carried out on two considerations: subject's personal appreciation, on a scale from 1 to 5, and physician's objective appreciation, also on a scale from 1 to 5. The results shown in the table 2 are, from our point of view, the most important appreciation criterion. ($p \leq 0.05$).

Physicians didn't succeed to correctly meet the subjects' expectancies in 8 cases, who anticipated a much higher level of satisfaction. Also it should be noted that among the subjects who achieved the score 4 from the physicians, 19/21 have not complied with the medical indications concerning the required amount of filler because financial reasons, receiving, consequently, 1-2 mL less HA.

Lastingness

Lastingness, as well as effectiveness, is relatively evaluated. Reappearance of wrinkles occurs gradually, within months, differing from subject to subject. From this point of view, we have appreciated the lastingness taking into consideration only the subjects' opinion as final beneficiary of the treatment. The evaluation was performed statistically by months and facial areas, as shown below (fig. 1, table 3). The treatment lastingness following injection was 4-16 months (average 10.5 month), with small variation depending on wrinkle types and individual variation. As a parallel observation, has been observed that after the following injections, the lasting period may increase up to 14 months but only for non-smokers and for subjects who were not exposed to excessive sunlight.

Adverse reactions and complications

The following complications have been considered: asymmetries after injection, post-injection nodes, ecchymosis, oedema, hematoma, skin necrosis, infections and inflammatory masses. Statistically, no immediate

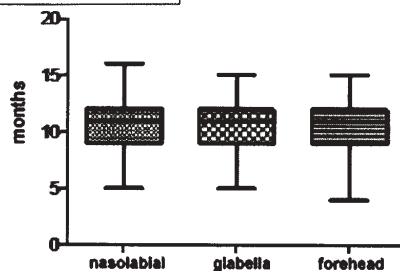


Fig. 1. Graphical representation of HA lastingness

facial asymmetries have been registered, strictly due to the injection technique. Although, in 18 cases (10.97%) asymmetrical absorption has been registered, immediately resolved by re-injection of HA. The rest of complications have been distributed as follows: no cases of skin nodules, 39 cases (23.78%) with post-injection ecchymosis, one case (0.6%) of subcutaneous hematoma – developed in the left nasolabial area, resorbed without complications – no skin necrosis and cutaneous infections. A number of 11 subjects (6.70%) presented important oedema after injection, spontaneously resorbed in 48 h. Expected mild inflammations, some accompanied by mild pain, have been registered in almost all subjects and progressively improved in the next 2-5 days. They were not included as complications.

HA dosage

HA dosage and subjects distribution on Fitzpatrick skin typing test are shown in tables 4 and 5.

Women were always concerned about beauty and changes occurred with the passing years. Along the time, different methods of rejuvenation and cosmetology have been tested in order to cheat time. In over 20 years ago, fillers appeared as purpose to fill wrinkles, skin depressions and later, to facial augmentation. Different types of fillers have been conceived, some permanent, e.g. silicone or collagen, others semi-permanent, with different durability in time. Nowadays, the most used dermal fillers are HA and calcium hydroxyapatite [4,5]. Dermocosmetic, as well as aesthetic surgery and geriatrics, have tried to identify factors that favour the aging process. Speciality literature indicates as favouring factors in the aging process smoking, long sunlight exposure, frequent intake of antibiotics and

Wrinkle	Nasolabial fold	Glabellar area	Forehead lines
Total number of values	164	164	164
Number of excluded values	0	0	0
Minimum	5.0	5.0	4.0
25% Percentile	9.0	9.0	9.0
Median	11.0	11.0	11.0
75% Percentile	12.0	12.0	12.0
Maximum	16.0	15.0	15.0
Mean	10.5366	10.4146	10.5061
Std. Deviation	2.45797	2.05717	2.09146
Std. Error	0.191935	0.160638	0.163315
Lower 95% CI of mean	10.1576	10.0974	10.1836
Upper 95% CI of mean	10.9156	10.7318	10.8286

$p=0.3151$

Table 3
ANALYSIS OF HA TREATMENT
LASTINGNESS

Type	No. of subjects (%)
I	-
II	47 (28.65%)
III	105 (64.02%)
IV	12 (7.31%)
V	-
VI	-

Table 4
LOT SUBJECTS DISTRIBUTION
BASED ON FITZPATRICK
PHOTOTYPING SCALE

ml HA	No. of subjects (%)
1	-
2	7 (4.26%)
3	31 (18.90%)
4	98 (59.75%)
5	9 (5.48%)
6	18 (10.97%)

Table 5
LOT SUBJECT DISTRIBUTION
BASED ON HA DOSAGE

anti-inflammatories, genetic inheritance for dry skin, chronic streptococcal infections that secrete streptokinase, able of cleavage of skin HA [6]. Our study noted a very high percentage of smokers (65.25%) and subjects that throughout their lives exposed excessively to the sun (89%), such factors being considered, without any doubt, as favouring factors in wrinkles appearance. With regards to the antibiotics intake, we consider the result unconvincing, with only 21.5% of the total subjects. Dry skin and an exaggerate use of anti-inflammatory drugs may be considered as favouring factors but to a lower degree than smoking or sun exposure. Nasolabial folds were the most frequent type of wrinkles met in subjects and reason of addressing for facial treatment. About one fifth of cases belong to class 2 and a half to class 3 score of severity.

Tolerability was excellent, with only 0.6% intolerability rate due to predisposition to allergies – and even in this case, the results were very good without further complications.

In terms of effectiveness, as previously mentioned, the percentage of 82% subjects who appreciated the treatment is a very good one [7,8]. It should be noted that 19 subjects did not respect physician indication regarding HA dosage – if those indications would have been followed, the percentage raised as high as 95%.

Concerning described complications, they seem adverse reactions, rather than complication. Practically, the only worrisome complication was ecchymosis. It's important to mention that there were no registrations of post-injection cutaneous infection or skin necrosis, although there are mentions in the literature [9-12]. Like most of the authors, we strongly believe that paying attention to the subjects' individual conditions and the correct application of injection technique can eliminate these two complications [13]. Last but not least important, the quality of the injected products compete to avoid complications. Other complications mentioned by specialily literature are atrophic lesions (10.5%), skin depigmentation (13.1%) or ulcerations (5.3%) [14]. HA injections can cause an extremely severe complication such as blindness (when injection in glabellar area penetrate ophthalmic artery, leading to thrombosis) [2,15]. Another extremely rare complication is the ischemia of the oculomotor nerve together with the oculomotor paralysis, manifesting as diplopia [16,17]. A special attention should be paid in cases of accelerated resorption: some studies have shown that some persons may develop antibodies to hyaluronic acid [18].

Ultimately, we left the discussions about sustainability, considering being the main element of the assessment of the cost / effectiveness. There are many studies that indicate the lastingness of the hyaluronic acid. All these studies certify good results at 6 months [19] or even at 12 months [20,21]. From this point of view, with a mean

persistence of 10.5 months, our results are similar to those of the literature. As previously mentioned, the persistence of hyaluronic acid grows with time, after further injections [3].

Given that most Romanian subjects come from sunny area as Black Sea or the Lower Danube, it should be emphasized that sunlight contributes greatly to skin aging and destruction of hyaluronic acid.

Conclusions

Cross-linked hyaluronic acid, used as filler in treatment of facial wrinkles, has a high tolerability and it is safe. Administered correctly and following the specific indications and contraindications, complications are almost removed. Also, if the right quantity of HA is administered, there may be excellent results up to 95% of the cases. The treatment persistence in time is conditioned by some factors as smoking or excessive sun exposure, but also personal organic factors including the production of antibodies anti-hyaluronic acid. Excessive subcutaneous adipose tissue or important weight variations, determine the accentuation of nasolabial wrinkles. Also taking into account the geographical characteristics, the persistence of the effects for a mean 10,5 month is considered as a very good result.

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