Clinical study of the efficacy, duration and adverse effects of hyaluronic acid implants in the oral-maxillofacial area

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ABSTRACT

Clinical, observational and descriptive, longitudinal and prospective study lasting 22 months conducted on 40 patients treated at the School of Dentistry, Universidad de la República.

Objective: To assess the efficacy, duration and adverse effects of hyaluronic acid (HA) implants for nasolabial grooves (NLG).

Methodology: Clinical study of HA implantation in the mid-dermis in cases of deep NLG, grades 2 to 5 in the Wrinkle Severity Rating Scale (WSRS).

Clinical and photographic records of each case were obtained and classified pre and post-application for 12 months using the WSRS, GAIS and PSSS scales. **Results**: expressed in times, percentages and graphs.

Efficacy: very good = 100% cases.

Mean effective clinical duration: 10.5 months.

Adverse effects to the product: none.

Patient rating: Good to very good.

Conclusion: dermal injectable HA (*TEOSYAL Deep Lines*®) is effective to correct deep NLG. Average duration of 10.5 months with a “slow fall”. Adverse reactions: none.

Keywords: hyaluronic acid; nasolabial grooves; regeneration; skin aging.

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1. INTRODUCTION AND BACKGROUND

Longer life expectancies, the aesthetic demands of these times and the advent of oral rehabilitation with dental implants have underscored the need for correcting some soft tissue defects resulting from aging and/or partial or complete edentation[1-8].

The skin aging process involves loss of vasculature, cell reproduction (fibroblasts), elastic and collagen fibers and, essentially, HA, which leads to dehydration and loss of volume(1-6), as shown in ***Fig. 1.a and Fig. 1.b.*** There are numerous cases of patients undergoing dental treatment with aesthetic alterations in the perioral region: NLG (also called nasogenian) folds, thin, flaccid and hypotonic lips, angular cheilitis and loss of the natural tissues support due to aging.

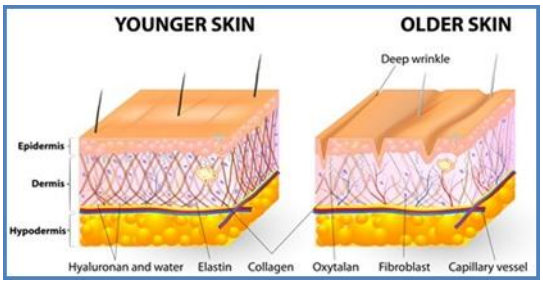


Fig.1a

Adapted from:

https://commons.wikimedia.org/wiki/File:Younger_skin_vs_older_skin.jpg

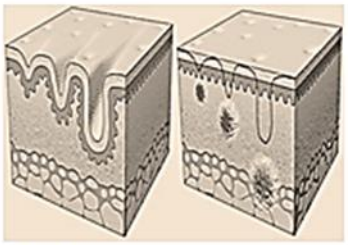


Fig. 1.b

Taken and adapted from: Goldberg D. Rejuvenecimiento facial. Un abordaje completo. Ed. Journal S.A 2010 Argentina

These alterations are often underdiagnosed by dentists and would merit treatment with dermal fillers[3] and other products (botulinum toxin)[7]. HA is currently the most recommended filler and the one that is closest to the ideal implant[5]. It is a natural polysaccharide present in the extracellular fluid of all living beings and it is identical for all species and in all tissues[1-5,8-9-17], therefore, it produces no immune activity. Chemically, it is a "sulfated glycosaminoglycan" composed of repeating disaccharide units: glucuronic acid and N-acetyl-D-glucosamine bound by alternate ligands: heparan, chondroitin, dermatan sulfate and heparin ***(Fig. 2)***. MW_{AH}= 4 million Da and length = 10 microns. It is produced by HA synthases present in the plasma membrane of fibroblasts and released into the extracellular space. It is a linear, uniform, highly acidic molecule with numerous negative charges; it is highly hydrophilic and water-soluble, characteristics that allow it to attract large amounts of water and sodium which, as a consequence, increases skin hydration and elasticity [1-6,8-17]. The molecules form random coils and intertwine to form a network or mesh in the extracellular matrix.

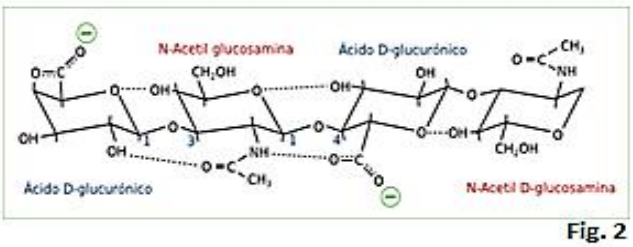


Fig. 2

The body content of HA of an adult is approximately 15 g, with a daily turnover of 2 g. Of the entire body's HA, 56% can be found in the skin. In the dermis and epidermis there are 7 to 8 g with a short half-life of 4 days. It is degraded by endocytosis and then broken down into H_2O and CO_2 by hyaluronidases. With aging, fibroblasts' ability to produce HA decreases and, moreover, the HA produced has a lower MW, which makes the moisturizing effect weaker. The increase of free radicals in the interstitial space also accelerates the destruction of HA molecules[8,14-17].

The objective of this work is to learn the efficacy, duration and adverse effects of the type and brand of HA available in the Uruguayan market (*TEOSYAL*®) injected –in the marked NLG– by a dentist.

2. MATERIALS AND METHODS

Clinical trial conducted by the O.M.S. II Department of the School of Dentistry (Universidad de la República). It is based on the application of HA implants: injectable *TEOSYAL DeepLines*®, into the *mid-dermis* in NLG of 40 patients, in order to, prospectively, carry out a clinical and photographic evaluation of its efficacy, duration and adverse effects.

Population: sample size: 40 patients selected by non-probabilistic sampling. Patients were included through deliberate trickle recruitment, and according to patient demand or convenience during 2015 and 2016. Inclusion criteria: Men and women (n=40) aged 35 to 75 years, with NLG formed by aging in toothed and/or prosthetically rehabilitated patients. The cases included were classified in grades 2 to 5 in the *Wrinkle Severity Rating Scale (WSRS)*[18]. **Fig. 3.** Exclusion criteria: Collagen diseases and other local or systemic, acute/chronic conditions for which the procedure is contraindicated. History or presence, in the area to be treated, of other biodegradable or permanent filler materials. Refusal to give informed consent and/or to clinical and photographic

follow-up which could be published for scientific-academic purposes. Lack of prosthetic rehabilitation that may be necessary.

Study design: Clinical, observational and descriptive, longitudinal and prospective study lasting 12 months for each patient. The study was approved by the Institutional Ethics Committee and authorized by the Board of the School of Dentistry of Universidad de la República. The medical history and informed consent of each patient was obtained, including the authorization to publish the case's photographs. The methodological design included: implantation and clinical and photographic follow-up of each patient for 12 months in 5 (five) stages: 1st stage: trickle patient selection and admission into the department. Medical history, informed consent and scheduling; 2nd stage: HA implantation; 3rd stage: information collection. Capture of pre-, intra- and postoperative data which are classified into immediate (24, 48, 72 h), weekly (1st and 2nd) and monthly, starting on the first month and for 12 months, for each patient. The patients' willingness to repeat the treatment was recorded at the end of month 12; 4th stage: data consolidation; with an analysis of statistical results and presentation of a final report; 5th stage: publication.

The *WSRS*[18] classification was used for the initial and final diagnosis (clinical and photographic) in all 40 cases, which were assigned grades from 2 to 5 by the operator responsible for the research. The following classifications were also used in the postimplant check-ups: *WSRS*, as well as the patient and investigator *Global Aesthetic Improvement Scale* (*GAIS*): 1 to 5; and *the Patient Satisfaction Scale* (*PSSS)*: - 2 to + 2. [19-22]. ***Fig. 3.***

WSRS *CLASS.*	APPEARANCE OF THE NLG	PSSS *CLASS.*	SATISFACTION DESCRIPTION	GAIS *CLASS.*	AESTHETIC IMPROVEMENT
0	**Absent, no visible wrinkle.**	**-2**	**Very dissatisfied**	**1**	**Very much improved (VG)**

1	**Shallow. *Barely visible wrinkle.***	**-1**	**Dissatisfied**	**2**	**Much improved (G)**
2	**Slightly marked. *Mild wrinkle***	**0**	**Moderately satisfied (R)**	**3**	**Somewhat improved (R)**
3	**Moderately marked. *Moderate wrinkle***	**+1**	**Satisfied (G)**	**4**	**No change**
4	**Long and deep with defined edges. *Severe wrinkle***	**+2**	**Very satisfied (VG)**	**5**	**Worse**
5	**Very long and very deep with very defined edges. *Extreme wrinkle***				

Fig. 3

TECHNIQUE: bilateral high terminal infiltration local anesthesia in the bottom of the groove with 0.9 ml of 2% mepivacaine (for dental use). Retro injection of *TEOSYAL Deep Lines*® in the *mid-dermis* of the NLG, using the standard linear and fan techniques[1-6,17], performed by the same operator. The maximum volume of HA applied in each NLG was 1 cc, according to the defect and until it was corrected in the opinion of the professional and patient. The adverse effects of the material and, additionally the adverse events of the application technique, which occurred in some cases, were assessed. In response to the request and needs of the patient, HA was implanted into the lips and other areas with alterations surrounding the groves to provide a comprehensive and aesthetically acceptable rehabilitation. A lower-density HA (*Kiss and/or Global Action*)® was used in these cases.

Information collection: the following four parameters were used to assess the efficacy, duration and safety:

1-Comparison by the operator of the change in the wrinkle assessment scale *(WSRS)* through clinical assessments and photographs.

2-Comparison of the change in aesthetic improvements *(GAIS)* of patients.

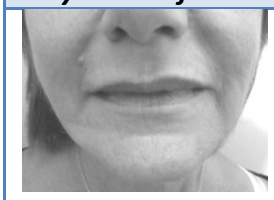
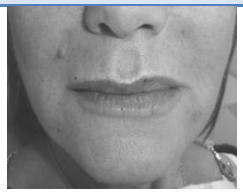
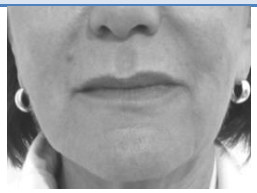
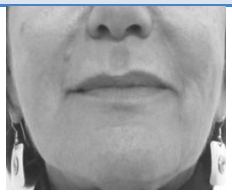
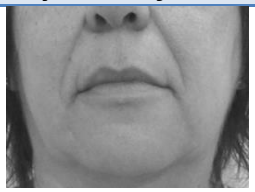
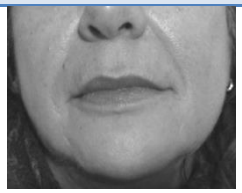
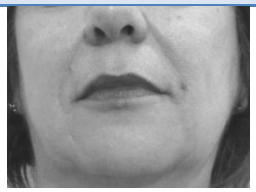
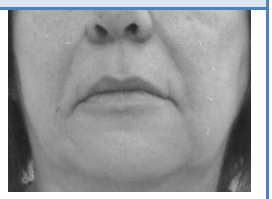
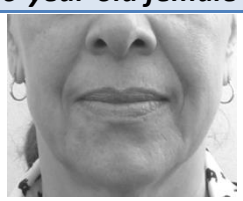
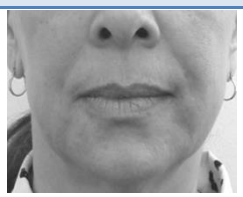
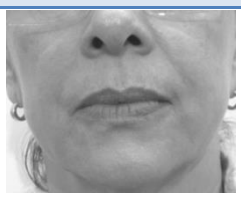
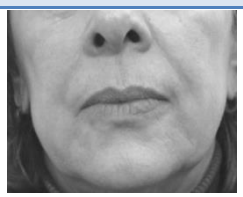
3-Assessment of the patients using the satisfaction scale *(PSSS)* and willingness to repeat the treatment.

The collection of information and variables was carried out in protocolized spreadsheets for all clinical and photographic check-ups (*JPG* software). The (preoperatory) defect was recorded in each spreadsheet, as well as the efficacy of the product in correcting it, the duration of the effect in months and all adverse effects and adverse events starting at intraoperative and 12 months postimplant. Once all the data were collected, they were tabulated using Microsoft Excel. Finally, a descriptive statistics analysis was carried out, using *SPSS* statistical software, version 13.0, to find simple and percentage frequencies of the variables selected.

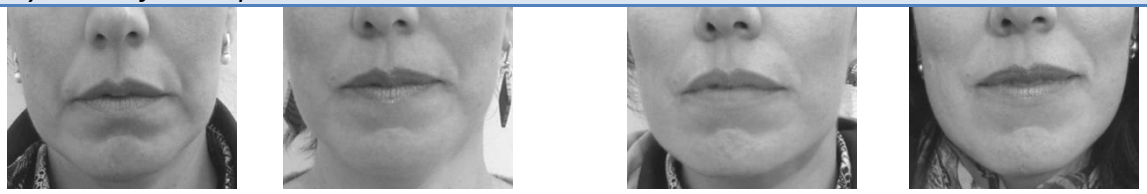
3. RESULTS: Average age of patients (p) 55 years. Women = 95% and men = 5%. Initial mean severity NLG, ***WSRS* = 3.5**. Mean of the immediate efficacy: ***WSRS* = 1.6**. Final mean severity (12 months) ***WSRS* = 2.**

3.a. EFFICACY AND DURATION*:* The correction of the defect, duration and satisfaction were rated, in 100% of the cases, with scores raging from G to VG (*GAIS and PSSS* scales). Results of the check-ups **after 9 months**: *GAIS:* 28p (70%) = VG, 12p (30%) = G; and *PSSS:* 3p (7.5%) = B, 37p (92.5%) = VG. **After 12 months:** *GAIS: 11p (27.5%) = VG, 29p (72.5%) = G; and PSSS: 4p (10%) = G, 36p (90%) = VG;* a very slow fall effect, which did not revert to the preoperative state in any of the cases, was observed after 12 months**.** Four patients are shown in ***Fig. 4.***

The duration of the aesthetic clinical and photographic efficacy which could be appreciated as a result of the NLG implants was, on average, 10.5 months (PERMANENCE).

Efficacy and duration of the HA implant in the NLG of patients in the study			
Pre	***Immediate***	***after 9 months***	***after 12 months***
62-year-old female patient			
			
WSRS=4	***WSRS=1***	***WSRS=2***	***WSRS=2***
57-year-old female patient			
			
WSRS=5	*WSRS=2*	*WSRS=2*	*WSRS=3*
56-year-old female patient			
			
WSRS=5	***WSRS=2***	***WSRS=3***	***WSRS=3***

45-year-old female patient



WSRS=3 ***WSRS=1*** ***WSRS=2*** ***WSRS=2***

Fig. 4

Fig. 5 shows the tables of the pre- and post-implant assessments of the *WSRS, GAIS and PSSS* scales.

Initial classification of NLG according to patient and operator

Initial WSRS CLASSIF	APPEARANCE OF THE NLG	N° Patients = 40
0	Absent, no visible wrinkle	0
Type 1	Shallow, barely visible	3
Type 2	Slightly marked	3
Type 3	Moderately marked	18
Type 4	Long and deep with defined edges	12
Type 5	Very long and very deep with very defined edges	4

Postop. records immediate

WSRS	N° Patients	PSSS	N°Patients	GAIS	N° Patients
0	0	-2	0	1	28
1	10	-1	0	2	12
2	24	0	0	3	0
3	6	+1	2	4	0
4	0	+2	38	5	0
5	0				

Postop Record after 9 months

WSRS	N° Patients.	PSSS	N° Patients	GAIS	N° Patients
0	0	-2	0	1	28
1	14	-1	0	2	12
2	16	0	0	3	0
3	10	+1	3	4	0
4	0	+2	37	5	0
5	0				

Postop Records after 12 months

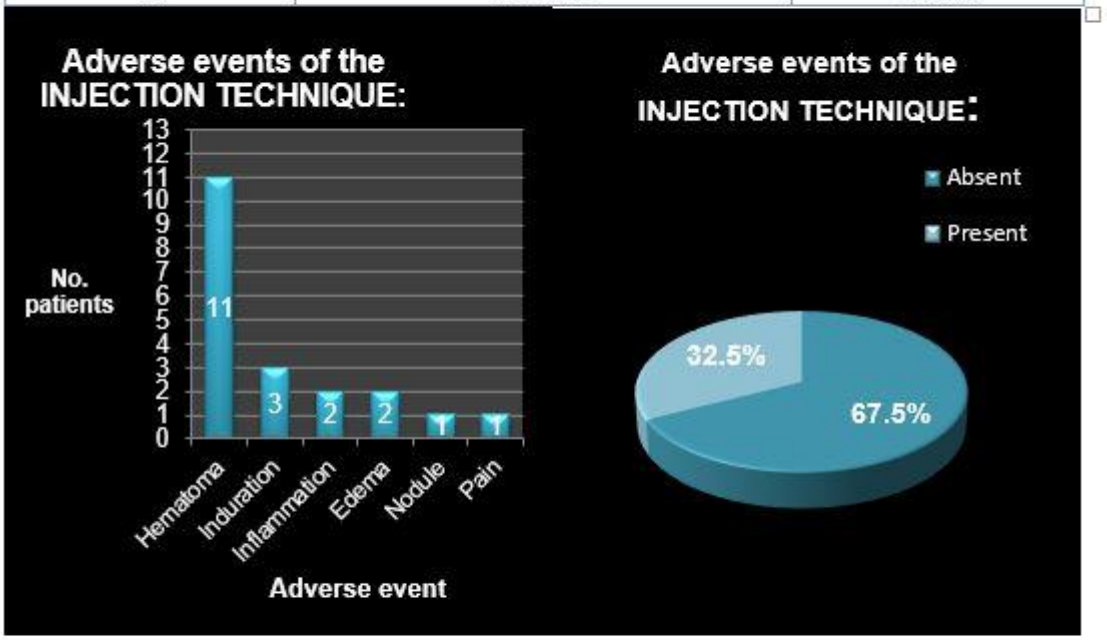
WSRS	N° Patients	PSSS	N° Patients	GAIS	N° Patients
0	0	-2	0	1	11
1	10	-1	0	2	29
2	24	0	0	3	0
3	6	+1	4	4	0
4	0	+2	36	5	0
5	0				

3.b. ADVERSE EFFECTS to HA (material): **NONE were observed**.

Due to the **injection technique** used for implanting the HA (40 patients), some ***adverse events*** were reported.

There were **no** adverse events in **27** patients (67.5%). There **were adverse events** in **13** patients (32.5% of the cases treated), remitted after 1 to 15 days, except for two nodules that one patient had, which resolved over three months. In some of the 13 cases there were coexisting ***events***: bruising (11), induration (3), inflammation with/without redness (2), edema (2), nodule (1) –deposition outside of the plane of the material– and pain (1). Described in **Chart 1**.

Adverse events of the INJECTION TECHNIQUE		
No. of patients	Clinical signs and symptoms	Percentage
27	Absent	67.7%
13	Present	32.5%



4. DISCUSSION: The results of this study support the indication and validation of the treatment of marked NLG with HA implants in the discipline of dentistry. Among the aspects that should be discussed are the efficacy, duration and adverse effects of the product.

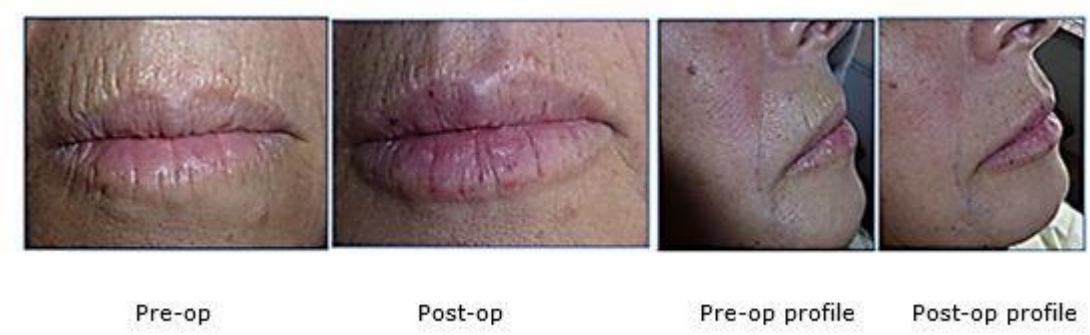
EFFICACY. Although the literature suggests numerous materials[1-17, 20-76] for increasing the volume of soft tissues, HA[1-6,10-17,20-52], silicone[1,5,53-54], polylactic acid[5,12,55-61], autologous fat[1,5,12,62-64], collagen[1,5,12,65-70], Ca hydroxyapatite[1,5,12,71-75], polymethacrylate[1,5,12,76], etc., none of them meet 100% of the properties that could be expected from an ideal implant[1,3,5,12,15,17]. These are: biocompatibility (with no allergic, toxic, pyrogenic or teratogenic effects), being safe and inert, without adverse effects or complications (does not trigger chronic inflammations: granulomas, fibrosis, necrosis, etc.). Not migrating or moving around, giving always natural-looking results. Not being permanent and lasting two[17] to five[1,5] years, or close to that.

The first aspect to be discussed is whether the HA implanted in the perioral region at different levels of the dermis has the characteristics listed above as ideal , with EFFICACY to correct the volume defects in the NLG without altering the muscles of facial mimicry in the region[17]. As for the RELEVANCE of HA and not other products, we can say that, because it is a component of the extracellular matrix of all vertebrates,

it is biocompatible, resorbable and does not pose a risk to the health of individuals, as demonstrated by different researchers[1-17,23-25,31].

The four clinical cases in Fig. 4 support the efficacy obtained in correcting the NLG in all patients. ***Fig. 1.b.*** shows a diagram of the skin sectors in which the HA can be applied[1-5,17,25]: *superficial*, *middle* (for NLG) and *deep*. The clinical case presented in ***Fig. 6***, shows, aside from a correction of the NLG, an implantation of HA in the *superficial and mid-dermis* of the lips and perioral region, where the aesthetic improvement achieved was very significant (front and profile of the patient).

Fig. 6



Historically, the first uses of HA for medical purposes at its beginnings (1990s) were in ophthalmology and orthopedics[1,3,5,17]. It was first used for aesthetic purposes in Europe in 1995, and in stomatology towards the 2000s. In the last decade its use quickly spread to dermatology and dentistry. *The Telegraph*, newspaper, published in London, dated May 4, 2008, cites Prof. Dr. Bob Khanna as one of the first British dentists to offer anti-aging therapies through the art of “lip sculpting”[3].

The use of HA has a skin rejuvenation effect scientifically proven by WILLIAMS S. et al. (2009)[24]. Other studies also cite an increase in the number of cells, fibers, moisture, etc.[23,31-38].

The literature review carried out in Uruguay found no treatments with injectable HA in scientific dentistry publications *(Pub Med; Timbó, Google Scholar and Bireme)*. This

clinical trial would be the first to be published in the discipline of dentistry in Uruguay. A brand commercially available and authorized by the *Ministry of Public Health of Uruguay* (*TEOSYAL®*), which is available in different densities, for varying defects, was used in the study.

Both aesthetics and function are simultaneously included in the rehabilitation of all dental treatments. ***Fig. 7.C*** shows, for a clinical case, the improvement achieved with the aesthetic facial rehabilitation treatment performed only with conventional dentures and then with the addition of HA. ***Fig. 7.D***.

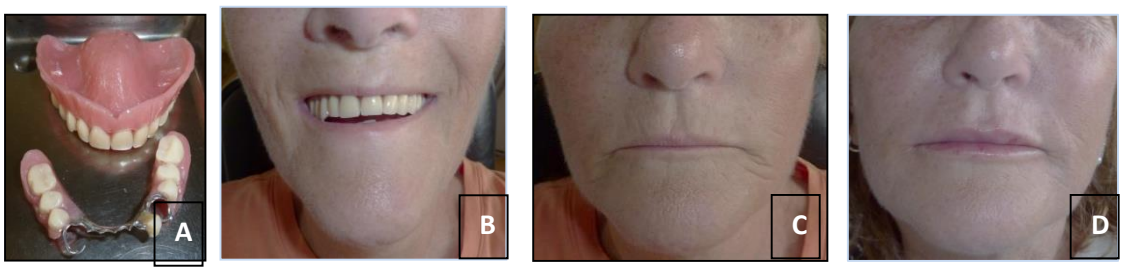
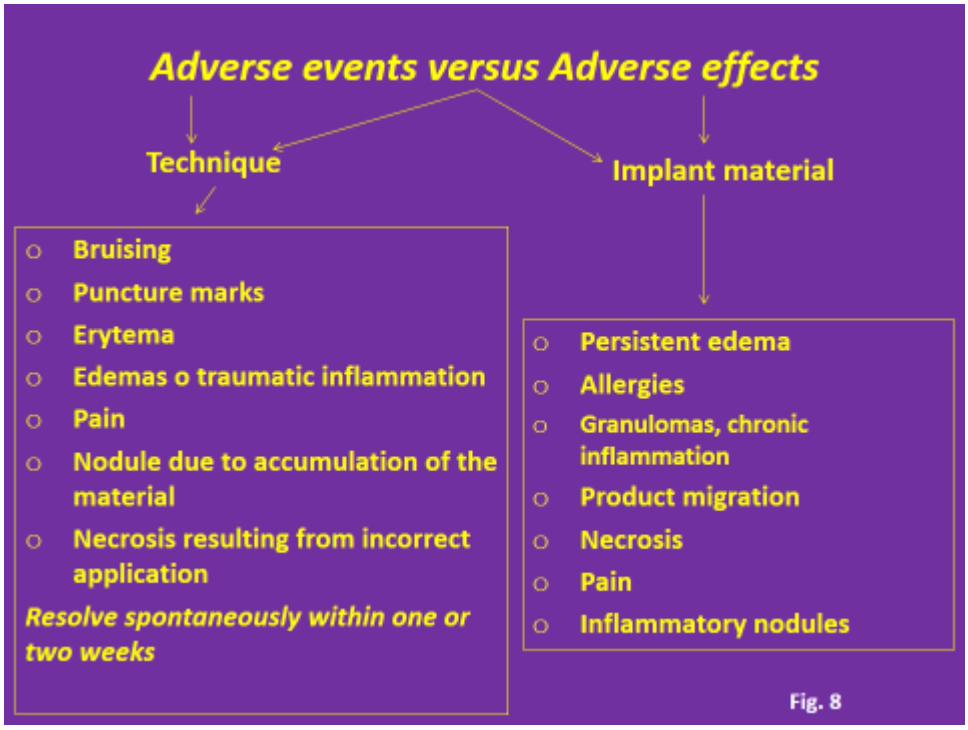


Fig.7. Aesthetic efficacy of the HA in patient with A prosthesis. B-. Functional appearance with prosthesis in place. C- Static appearance with prosthesis in place. D- Aesthetic static appearance of the patient with AH implant

Therefore, for some cases of soft tissue collapse in the perioral region due to aging and/or edentation, HA implants are the only treatment that can lead to a dental discharge with a comprehensive rehabilitation, from an aesthetic and functional perspective. There are reports of anomalies resulting from volume losses in swallowing[77], as well as in phoniatric difficulties[78] pronouncing bilabial phonemes: ***P-B-M***; or labiodental phonemes: ***F***, due to very thin and incompetent lips, which can go unnoticed by dentists and can be solved with HA implants.

Regarding the **Adverse Reactions** caused by the implant materials, there are some conflicting reports, perhaps because many authors and translations use the following terms interchangeably: *Adverse reaction* and *adverse event* **(*Fig. 8)***. According to some sources used, the prevalence of adverse effects to HA is estimated to be below 1%[79] and for others, according to the brand employed, it is up to 3%[80], with the effects being easily manageable and without consequences[5,12]. For this study we have considered the definitions given by WHO**[81]** and PAHO**[82]** to "***adverse reaction****: a response to a drug, which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, therapy...". An* ***adverse event***[83] unlike an *adverse reaction* is not related to the material but to the **technique used**[83]**,** therefore, it will disappear in a few days, even if the product remains implanted, except in the cases of "necrosis" caused by a very superficial placement of the material or embolization of the material. There are reports which do not differentiate both eventualities clearly[84], in the way they are presented in **Fig. 8**, the concepts of which are applied to the work submitted.



At first, HA was of animal origin (rooster combs, fish eyeballs, etc.) and would carry certain antigenic impurities which affected the safety of the product[3,5,12,17,84]. Therefore, at the time, the literature reported various adverse reactions to HA: hypersensitivity, granulomas, necrosis, etc. These occurrences were overcome in time using bioengineering to synthesize the HA[3-s5,12,15,17,84]. Other currently used filler materials still cause diverse, significant adverse reactions[1,5,17,84-100], therefore, it is not advisable to combine HA with other materials, or brand names that are not subject to stringent quality controls[1,4-5,84,87,93].

Nowadays, HA is obtained by biotechnology[3-5,9-12,15-17,84]. It is a “NASHA” product (non-animal hyaluronic acid). It is obtained from strains of bacteria grown under very rigorous conditions, resulting in a pure HA, which is why it is currently the most used filler material, with the advantage that it does not require an allergy test prior to application[17,84]. It is a clear viscoelastic gel in a sterile, very easy to use, 1 cc syringe. When placed in the dermis, it acts by filling the space between the collagen fibers and elastin in the skin, thus restoring the natural volume and moisture of the skin ***(Fig. 1)***, which has been lost over the years[23-24]. It also stimulates cell proliferation and the neosynthesis of collagen from mature fibroblasts, thus rejuvenating the skin[23-24,27-28,31]. In general, the only shortfall of current hyaluronic acids is their DURATION, because they do not reach the ideal permanence standard established (2 to 5 years) for dermal implants[3,5-7,12,17,26]. Some studies report that the duration that is visible and effective at the beginning of the treatment is short, lasting approximately 6 months[3,5-17], but with the advantage that it disappears gradually, without a sudden fall effect. It is progressively reabsorbed together with the endogenous HA, although more slowly, via an enzymatic process (hyaluronidases, beta-D-glucoronidase, etc.) which results in H_2O and CO_2. Nowadays the various brands compete and seek to extend the

duration of the product through different mechanisms. Some products which have already been approved by the FDA have a minimally altered HA molecule in order to achieve a different and more stable physical form, which increases the time of permanence in the tissues[84]. All brands have different formulations regarding the size of the particles and the density of the HA, resulting from crosslinking the chains (reticulation process). The degree of viscosity of the HA depends directly on the crosslinking of the chains and the reticulate or mesh they form[3,5,9-11,17,25-26,36,84]. Those more tightly crosslinked achieve better duration results because the degradation of the injected gel is delayed. Also, because they have larger particles, they are even more dense and are indicated for deeper grooves or depressions[20,22,43,46,84], as is the case of the NLG treated in this study with *TEOSYAL Deep Lines*®. Lightly crosslinked HA, with small and middle-sized particles, are more fluid and are indicated for lips and other treatments[3,5,17,22,25-26,36-39,84] ***(Fig. 6-7)***. Different studies agree[1,20-23,84] that the mean duration of HA, regardless of the type and brand, is multifactorial and also depends on: the skin type, habits of the patient, age, depth of the wrinkle, volume injected and the different levels of dermal application (*superficial, middle or deep*). A single brand was used in this study (*TEOSYAL Deep Lines®)*, at the level of the *mid-dermis of the NLG* and results ranging from good (G) to very good (MG) were immediately obtained. These scores were maintained for 12 months later, according to the observations of the operator and patients**.** Average acceptable aesthetic duration of the total number of cases: 10.5 months.

CONCLUSIONS:

1- HA of the NASHA kind, used in dentistry, was EFFECTIVE in correcting NLG, achieving aesthetic improvements from G to VG according to the *WSRS, GAIS*

and PSSS scales. *Mean initial severity* ***WSRS = 3.5;*** *Mean immediate correction* ***WSRS = 1.6;*** *Mean severity after one year* ***WSRS = 2.***

2- No ADVERSE REACTIONS were reported in the total of cases treated with *TEOSYAL*®, therefore, the material is SAFE, while adverse events related to the technique were reported in 32.5% of cases.

3- The DURATION of the good aesthetic effect which could be appreciated clinically and photographically in the NLG was, on average, 10.5 months (PERMANENCE). A “very slow fall” effect was observed in all cases, and all patients showed willingness to undergo the treatment again after one year.

4- New clinical studies are necessary to gather evidence and compare results using other variables, such as brand names, different maxillofacial areas, etc.

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