Evaluation of the duration of injectable hyaluronic acid in nasolabial folds and perioral rhytids

Avaliação da permanência do ácido hialurônico injetável no sulco nasogeniano e rítides labiais

**ABSTRACT**

**Introdução:** Hyaluronic acid has been increasingly used in aesthetic procedures.

**Objective:** To evaluate the degree of improvement and duration of results in patients who received treatment for wrinkles with hyaluronic acid.

**Methods:** Prospective, open, non-randomized, non-controlled study of 20 female patients who presented superficial wrinkles in the superior lips contour and a prominent nasolabial fold. The efficacy of hyaluronic acid was assessed using the Wrinkle Severity Rating Scale. The duration of results was assessed through biopsies. Safety was evaluated through clinical observation and reports of adverse events.

**Results:** A significant clinical improvement was observed after 15 days, which was sustained for 4 months. A minor worsening was observed after that period, although patients still presented favorable aesthetic results up to 12 months after the procedure. A majority of patients (n = 17) had a biopsy in the left retro-auricular region 180 days after the procedure. From this group, the substance was observed in 13 slides (76.4%).

**Conclusion:** Hyaluronic acid is an effective and safe product. This study has proven that the product remains in the dermis for up to 6 months.

**Keywords:** hyaluronic acid; residence time; skin.

**RESUMO**

**Introdução:** O ácido hialurônico vem sendo utilizado em escala crescente em procedimentos estéticos.

**Objetivo:** avaliar o grau de melhora dos pacientes submetidos à aplicação do AH e o tempo de permanência do produto.

**Métodos:** estudo prospectivo, aberto, não randomizado e não controlado. Incluídas no estudo 20 pacientes do sexo feminino que apresentavam rugas superficiais no contorno labial superior e sulco nasogeniano proeminentes. A eficácia foi avaliada pela escala de classificação de gravidade das rugas (Wrinkle Severity Rating Scale - WSRS). O tempo de permanência foi avaliado através de estudo anatomopatológico, e a segurança, por observação clínica e relato de eventos adversos.

**Resultados:** Após 15 dias constatou-se importante melhora clínica que se manteve durante quatro meses, identificando-se, então, discreta piora; ainda assim, os pacientes apresentavam resultados estéticos favoráveis até 12 meses. Dezessete pacientes foram submetidas à biópsia na região retroauricular esquerda 180 dias após o procedimento. Nesse grupo, observou-se depósito de material em 13 lâminas (76,4%).

**Conclusões:** O ácido hialurônico é um produto seguro e efetivo, e este estudo comprovou sua permanência na derme por período de até seis meses.

**Palavras-chave:** ácido hialurônico; tempo de permanência; pele.
INTRODUCTION

Hyaluronic acid (HA) was first described by Karl Meyer as a substance contained in the vitreous humor of cats’ eyes, in 1934. A natural polysaccharide, it is part of the intercellular matrix of the dermis and can also be found in the conjunctive tissue, bones and interstitial membranes.

It is an extremely biodegradable and biocompatible substance with a chemical structure that is consistent among all animal species. Its invariable chemical structure decreases the risk of immunological reactions, which is an advantage when compared to other filling substances. Cutaneous tests are not usually necessary before HA injections.

Dermatologists and plastic surgeons have used HA for cosmetic purposes since 1996, to fill wrinkles and scars, and increase the volume of lips, for example. Since then, different companies in the pharmaceutical industry have developed their own products with HA as the active ingredient. HA is a powerful water retainer and is effective in adding volume to injected tissues. However its non-modified form has a short half-life, and is eliminated rapidly in the dermis. To be used as a filling agent to improve rhytids and scars or add volume, HA should be stabilized to give it a long half-life. The stabilization process varies by manufacturer and brand, which explains the differences in the viscosity of HA and the duration of the effects that are found in the diverse products on the market. Since HA fillings are not permanent, the procedure must be repeated at variable intervals, according to the need (a few months on average). HA is currently the safest agent used in cosmetic fillers, and rarely presents adverse effects, which the physician must be aware of and inform the patient about before using the product. Most complications are not serious – primarily erythema or a burning sensation at the site of injection – and disappearances when the product is degraded. Although the duration of the effect is limited, products containing HA are the most popular among cosmetic fillers. They produce considerably significant results and few undesirable reactions. Physicians and patients prefer fillers containing HA due to their good tolerance, natural effect and few side effects.

OBJECTIVE

To evaluate the degree of improvement in patients who received HA injections in the nasolabial fold (NLF) and in the superficial rhytids of the upper lip margin (ULM) and the duration of the product in the retroauricular region.

METHODS

Female patients (n = 20) from the Dermatology Outpatient Clinic of the Complexo Hospitalar Santa Casa de Porto Alegre who presented superficial wrinkles in ULM and prominent NLF were included in this prospective, open, non-randomized and non-controlled study. Patients who were pregnant, had acute or chronic disorders that could influence the evaluation of results, presented with a personal or family history of keloids or allergy to HA, and those who had previously been treated with any type of filler in the areas to be studied were excluded.

The present study was submitted to and approved by the Research Ethics Committee of the Complexo Hospitalar Santa Casa de Porto Alegre. All patients signed a term of free and informed consent prior to the start of the treatment.

The patients were photographed in frontal and angled perspectives, in a standardized way, on each visit with a Canon Rebel XT camera. A stereotactic device that allows the standardization of the positioning of the head and focal distance was used.

The patients received an intradermal application of 0.1 ml of Perfectha Derm® (Comedix Com Produtos Médicos e Farmacêuticos, Brazil) in the right and left retroauricular regions. In order to evaluate allergic reactions and to proceed the subsequent histological examination, the product injected behind the ears belonged to the same batch as the material involved in the study. The histological examination aimed to detect granulomas and verify the product’s duration. Later on, the patients were given injections of Perfectha Derm® in the superficial rhytids of the ULM or in the NLF. The treatment’s objective was to completely correct the rhytids, while avoiding overcorrection.

The sites to be treated were swabbed with chlorhexidine before each application. The patients who had HA treatment in the NLF received topical 4% lidocaine cream (Dermomax®, Laboratório Ache, São Paulo, Brazil) before the procedure. The patients who received HA in the ULM had a regional block of the infraorbital nerves with 2% lidocaine, without vasoconstrictor. The HA was injected in the NLF and in the ULM with 27G and 30G needles, respectively. The treated sites were massaged immediately after the injection. The HA was injected in the medium-deep dermis using the retroinjection technique, with the needle’s bevel preferentially turned upward, according to the manufacturer’s recommendation.

The patients were photographed in frontal and angled perspectives, in a standardized way, on each visit with a Canon Rebel XT camera. A stereotactic device that allows the standardization of the positioning of the head and focal distance was used.

The biopsy of the right and left retroauricular regions was also carried out at 30 and 180 days after the procedure, respectively. Before the biopsies, those areas were anesthetized with 2% lidocaine without vasoconstrictor and a 2mm punch. The material that was obtained underwent histological evaluation. Adverse effects and severity level were appropriately reported.

RESULTS

Female patients (n = 20) aged 35–49 (average age 43) were included in the study. Eleven (55%) had treatment of the NLF, and nine (45%) received treatment of the ULM. Five patients (four from the NLF group and one from the ULM group did not complete the protocol, and were therefore excluded. The
DISCUSSION

The results of this study confirm the efficacy of HA in the correction of NLF and ULM, proving it is a well tolerated treatment. The positive clinical improvement persisted for more than six months in most of the cases. Such results are in line with those obtained by Beer and Carruthers and others in previous studies. An interesting fact was the observation of intact material in the biopsies carried out in the left retroauricular region, proving that the product can remain in the dermis for up to six months.

The absence of deposited material in some slides can be explained by the fact that the material was obtained using superficial biopsies. The material was most likely present but was not captured due to insufficient depth in the collection procedure.

The durability of the product in the skin depends on the rate of degradation of the substance, the structure of the particle of the HA used and its concentration. Maintaining the treatment effect also depends on the texture of the skin, the type and severity of the problem to be corrected, the patient’s age and the technique employed. The site to be treated is also an important factor, for areas that move more frequently tend to present less durable results.

The data reinforce that the use of HA produces good results in the correction of the nasolabial fold and labial rhytids.

Table 1. Wrinkle Severity Rating Scale (WSRS)

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<th>Description</th>
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<tbody>
<tr>
<td>5</td>
<td>Extreme: extremely long and deep creases with impairment of the physionomy, variable “V” shaped fold, of 2 to 4 mm, when skin is stretched</td>
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<tr>
<td>4</td>
<td>Severe: very long and deep creases, prominent physionomy, fold shorter than 2 mm when skin is stretched</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: moderately deep creases, absence of folds when skin is stretched</td>
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<tr>
<td>2</td>
<td>Light: superficial yet noticeable crease; minor influence on the physionomy</td>
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<tr>
<td>1</td>
<td>Absent: absence of noticeable crease</td>
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Volume of HA injected in each NLF varied from 1.6 to 2.3 ml (average 2 ml). In the ULM, it ranged from 1.1 to 1.7 ml (average 1.5 ml).

A significant degree of clinical improvement was observed after 15 days, which remained stable for approximately four months. Although a minor worsening was observed after that period, the patients presented favorable aesthetic results that lasted up to 12 months (Graph 1).

BIOPSIES

Eighteen patients had a biopsy in the right retroauricular region on the 30th day after the procedure. The analysis of the material, carried out by an experienced pathologist, demonstrated deposits of HA on 13 slides (72.2%).

The rest of the patients (n = 17) had a biopsy in the left retroauricular region 180 days after the procedure. In that group, deposited material was observed on 13 slides (76.4%) (Figure 1). The formation of foreign body granulomas was not observed in any case.

Adverse effects associated with HA and the procedure itself included ecchymoses, edema, erythema and local pain. These findings were of mild to moderate intensity, with a duration of a few days. Only one patient who received filling of the NLF presented the formation of a nodule around 30 days after the application of the product; the nodule disappeared after 15 days of massage with medium potency corticoid.
Graph 1 - Curves representing the median, and minimum and maximum values of the scores in the Wrinkle Severity Rating Scale in the sites (A) lip margin (n = 8) and (B) nasolabial fold (n = 7). Comparison of time points (using Wilcoxon’s test)

0 vs 2: (A) p = 0.038 and (B) p = 0.024
0 vs 12: (A) p = 0.014 and (B) p = 0.025

Figure 1 - Retroauricular region biopsy at 180 days demonstrating the presence of HA in the dermis

REFERENCES