



# aesthetic medicine

Official Journal of the  
International Union of Aesthetic Medicine UIME



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# aesthetic medicine

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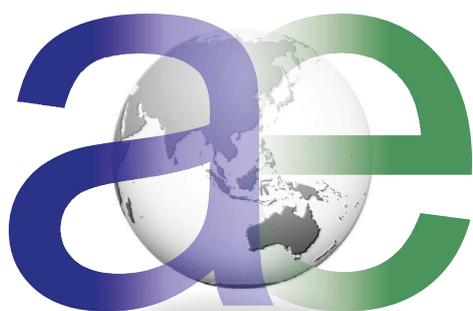
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## Contents

Original Article

### **Forehead contouring with fillers: early experience with 18 consecutive cases**

Verega Grigore, Giovanni Francesco Nicoletti, Nicola Zerbinati, Samuel Staglianò, Pierfrancesco Bove,  
Romolo Fragola, Raffaele Rauso

**pag 11**

Original Article

### **The art of aesthetic neuromodulation and facial perception**

Meghann M. Reller, Nancy Bredenkamp, Cathy Carrico

**pag 24**

Original Article

### **Facial aging in patients with schizophrenia**

Tal Friedman, Avshalom Shalom, Alex Aviv, Yoram Barak, Yonit Wohl

**pag 32**

Case report

### **Clinical and histochemical response to an automated microneedling therapy in the treatment of traumatic scars**

Inas Shaker, Hisham Ali Shokeir, Nevien Ahmed Sami, Sara Bahaa Mahmoud, Rana Fathy Hilal, Safinaz Salah EL Din Sayed,  
Samia Esmat

**pag 37**

Case report

### **Evaluation of the beneficial impact of atopic dermatitis treatment with high- and low-molecular-weight hyaluronic acid hybrid stable cooperative complexes: a case report**

Gabriel Siquier-Dameto

**pag 45**

**Courses and Congresses**

**pag 49**

# Guidelines for Authors

Aesthetic Medicine is a multidisciplinary Journal with the aim of informing readers about the most important developments in the field of Aesthetic Medicine.

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All articles in their final version - completed with name, surname, affiliation, address, phone number and e-mail address of the author (s) - must be sent in word format to the Editorial Committee at the following e-mail address:

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The manuscript should be organised in the following sections:

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- Materials and Methods
- Results
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- Do not use field functions
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- Use the table function, not spreadsheets, to make tables

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Rev. 11/1/2012

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- Periodicals (journals, magazines, and newspapers) should have abbreviated titles; to check for the proper abbreviation, search for the Journal Title through [LocatorPlus](#) at the National Library of Medicine website

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<b>Journal article - in print - more than 6 authors</b>	<b>Fukushima H, Cureoglu S, Schachern P, et al.</b> Cochlear changes in patients with type 1 diabetes mellitus. <i>Otolaryngol Head Neck Surg.</i> 2005; 133: 100-6.
<b>Journal article - online*</b> *if there is no DOI, provide the URL for the specific article	Coppinger T, Jeanes YM, Hardwick J, Reeves S. Body mass, frequency of eating and breakfast consumption in 9-13- year-olds. <i>J Hum Nutr Diet.</i> 2012; 25(1): 43-49. doi: 10.1111/j.1365-277X.2011.01184.x
<b>Journal article - online from a library database*</b> *there is no specific way to cite articles found in library databases according to the AMA so double check with your professor	Calhoun D, Trimarco T, Meek R, Locasto D. Distinguishing diabetes: Differentiate between type 1 & type 2 DM. <i>JEMS [serial online]</i> . November 2011; 36(11):32-48. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed February 2, 2012.
<b>Newspaper article - in print*</b> *if the city name is not part of the newspaper name, it may be added to the official name for clarity * if an article jumps from one page to a later page write the page numbers like D1, D5	Wolf W. State's mail-order drug plan launched. <i>Minneapolis Star Tribune.</i> May 14, 2004:1B.
<b>Newspaper article - online</b>	Pollack A. FDA approves new cystic fibrosis drug. <i>New York Times.</i> January 31, 2012. <a href="http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?ref=health">http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?ref=health</a> Accessed February 1, 2012.
<b>Websites</b>	Outbreak notice: Cholera in Haiti. Centers for Disease Control and Prevention Web site. <a href="https://www.cdc.gov">https://www.cdc.gov</a> Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012.
<b>Entire book - in print</b>	Modlin J, Jenkins P. <i>Decision Analysis in Planning for a Polio Outbreak in the United States.</i> San Francisco, CA: Pediatric Academic Societies; 2004.
<b>Book chapter - in print</b>	Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. <i>Allergens and Allergen Immunotherapy.</i> 3 <sup>rd</sup> ed. New York, NY: Marcel Dekker; 2004:585-606.

To find more AMA style citations, go checkout the [AMA Manual of Style: A Guide for Authors and Editors.](#) 10th ed. Oxford: Oxford UP.

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Rev. 11/1/2012

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Unlike APA or MLA, you will not use the author's last name for the in-text citations. Instead, you will number each instance when you are referencing an article. The order of numbering will be contingent on the order in which you use that reference within your paper. In the example below, the first article referenced is given the number one in superscript. In the References section, you will find the matching article listed as number 1.

<b>Example Article</b>  1. Zoellner J, Krzeski E, Harden S, Cook E, Allen K, Estabrooks PA. Qualitative application of the theory of planned behavior to understand beverage consumption behaviors among adults. <i>J Acad Nutr Diet.</i> 2012;112(11):1774-1784. doi: 10.1016/j.jand.2012.06.368.	
<b>In-Text Citation Example</b>	<p><b>L</b>ARGE INCREASES IN AMERICANS' CONSUMPTION OF sugar-sweetened beverages (SSB) have been a topic of concern. Between 1977 and 2002, the intake of "caloric" beverages doubled in the United States, with most recent data showing that children and adults in the United States consume about 172 and 175 kcal daily, respectively, from SSB.<sup>1</sup> It is estimated that SSB account for about 10% of total energy intake in adults.<sup>2,3</sup> High intake of SSB has....</p>
<b>References Section Example</b>	<p><b>References</b></p> <ol style="list-style-type: none"><li>1. Duffey KJ, Popkin BM. Shifts in patterns and consumptions of beverages between 1965 and 2002. <i>Obesity.</i> 2007;15(11):2739-2747.</li><li>2. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. <i>Am J Prev Med.</i> 2004;27(3):205-210.</li><li>3. Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. <i>Am J Clin Nutr.</i> 2007;85(3):651-661.</li></ol>

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# Forehead contouring with fillers: early experience with 18 consecutive cases

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## Abstract

**Introduction:** forehead contouring is a surgical procedure usually performed to reduce frontal bossing in males. Non-surgical procedures, such as filler injections, in selected cases, could be an alternative to surgical forehead recontouring, improving the aesthetic of the forehead and achieving a more convex appearance of the upper third. Moreover, by reducing the perception of supraorbital bossing, it can also be performed as a procedure to camouflage and deal with the process of forehead aging. Authors describe their early experience in frontal contouring with fillers.

**Material and methods:** this is a retrospective study that takes into account all the forehead contouring procedures performed from January 2014 to January 2019. Eighteen patients, ages ranging from 26 to 56 years old, were treated with hyaluronic acid or calcium hydroxyapatite-based filler injections.

**Results:** a VAS and a Pain scale were submitted to all the patients in order to evaluate the result achieved, and the pain felt in performing the procedure. At the end of every procedure for each case, patients experienced redness and surface irregularities which resolved themselves within 48 hours. No Ecchymosis was recorded. During the follow-up period, in one case, a nodule secondary to the CaHa injections was recognized and surgically excised.

**Conclusion:** although there are several limitations regarding this study, outcomes of the present case series suggest that a non-surgical contouring of the forehead with the use of fillers could be another possible indication for these medical devices, although a filler specifically developed for forehead contouring, has yet to exist. Larger, blinded, and controlled studies are required to support the effectiveness of this technique.

## Keywords

Forehead, filler, hyaluronic acid, calcium hydroxyapatite, non-surgical, contouring

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## Introduction

There is a close relationship between female beauty and femininity of the face, and the prominence of the forehead is one of the most significant aspects for the determination of these feminine features<sup>1-3</sup>. Moreover, there is a clear relationship between gender identity, youthfulness, and beauty with frontal features. Thus, the upper third of the face has a high significance in determining attractiveness<sup>4-6</sup>. In females, forehead contouring is vertically higher, more rounded in the area of the forehead that protrudes creating a smoother gentle arc, supraorbital bossing, and brow ridges are almost inexistent with no special prominence in the glabellar region<sup>7</sup>. These child-like features, give a more youthful, friendly, soft and innocent appearance of the female forehead. However, these characteristics in males differ from this aesthetic ideal: supraorbital ridges are prominent, and the forehead is flat with significantly longer widths and heights<sup>7</sup>.

Nowadays, non-surgical facial treatments performed with fillers are more focused on contouring the face and the body rather than just filling fine lines; several papers focus on how to restore mid-facial and lower third facial features. On the other hand, very little has been written about forehead contouring with fillers<sup>8-11</sup>. Usually, the aesthetic appearance of the forehead is mainly approached with botulinum toxin type A (BoNTA) injections to reduce frontal or glabellar lines; BoNTA can ameliorate the appearance of the facial upper third's wrinkles, achieving a more rested result for the patient, but of course, it cannot contour the forehead<sup>12</sup>. Forehead contouring is usually thought of as a procedure-related only to male-to-female transitioning in order to reduce frontal bossing<sup>1-6</sup>. However, filler injections can improve the aesthetic of the forehead achieving a more convex appearance of the upper third, or it can also be performed as a camouflage procedure to face the aging of the forehead by reducing the perception of supraorbital bossing<sup>13</sup>.

Up to now, a filler tailored to contouring the forehead does not exist, and in medical literature, only a few papers have touched on this topic, excluding the temples and brows.

Authors describe their early experience in frontal contouring with fillers, presenting 18 consecutive patients treated with HA (hyaluronic acid) or CaHa (calcium hydroxyapatite) based fillers.

## Materials and Methods

This was a retrospective study, all forehead contouring procedures performed with fillers by the senior author (RR) were considered. From January 2014 to January 2019, 18 (16 female and 2 male) patients, ages ranging from 26 to 56 years old (mean 33.8 years old), were treated. The Exclusion criteria were the following: pregnancy, lactation, unrealistic patient expectation, and all those diseases that may contraindicate the procedure.

Twelve cases were treated with HA and six with CaHa based fillers. The choice of the filler was not random

made but dictated by the previously developed clinical experience. So far, a specific filler for non-surgical forehead remodeling does not exist. For this reason, and due to the paucity of literature available when the first cases were performed, we decided to use a CaHa based filler. This filler was chosen due to the biocompatibility between the bone and the CaHa itself. In the first 6 cases CaHa was used, but the last case presented a persisting nodule requiring a surgical removal which was recorded. Due to this issue, all the other patients were approached with HA based fillers in order to use hyaluronidase and not surgery in the event of adverse reactions. The amount of HA injected per patient ranged between 3 and 8 mL, and the amount of CaHa between 3 and 6 mL.

All the treatments were performed in one session, and after 15 days from the procedure, a touch-up was performed if required; 6 patients had a touch-up, 2 belonging to the CaHa group, 4 to the HA group, and on average 1 mL of HA or 1.5 mL of CaHa were used.

All the contouring procedures were performed in-office after at least 15 days from a preliminary consultation. The informed consent document was signed by all the patients; in the document it was clearly specified that the pictures taken during the course of the treatment could have been used for scientific purposes such as publications or congress talks. Local anesthesia was never performed. Not all the HA fillers used contained lidocaine, whereas when CaHa fillers were used, they were preliminary mixed with lidocaine 2% (0,5 mL of lidocaine each 1.5 mL of CaHa).

The injections were performed with a cannula or a needle; after a full discussion about the differences between the delivery systems, the choice was based on the patient's preference and past experiences. In fact, patients were more prone to be injected with a cannula if they had already undergone procedures using this delivery system in other facial areas.

The pain perceived by the patients during this procedure was evaluated with a pain scale.

When a 25G cannula was used, the injecting procedure was performed using 3 entry points, all located at the hairline: one in the midline and two lateral ones at the level of the temporal crest. The filler was released retrogradely over the periosteum in a "spaghetti-like" fashion (*Figure 1*).

When a needle was used, the injections were performed perpendicular to the skin, touching the bone and releasing a small bolus of filler (ranging between 0.1 and 0.2 mL) which was then molded with the thumb as soon as the injection was performed (*Figure 2*).

At the end of each procedure, patients were asked to fill out a Pain Scale questionnaire to evaluate the pain perceived during the procedure: 0 was considered no pain, 1 to 3 mild pain, 4 to 6 moderate pain, 7 to 10 severe pain.

During the first follow-up which occurred 15 days after the injections, before performing any touch-ups, patients were asked to evaluate the result with a VAS (Visual Analog Scale) where 100 represented the best possible aesthetic outcome and 0 (was) the worst.

Follow-ups ranged between 1 and 18 months, with the mean being at 3 months. (*Figures 3 a-b; 4 a-f; 5 a-c; 6 a-c; 7 a-f*).



**Figure 1** - A schematic view of the injective protocol performed with the cannula; the procedure was performed using 3 entry points, all located at the hairline: one in the midline and two lateral ones at the level of the temporal crest. The filler was released retrogradely over the periosteum in a "spaghetti-like" fashion.



**Figure 2** - A schematic view of the injective protocol performed with the needle; the injections were performed perpendicular to the skin, touching the bone and releasing a small bolus of filler (ranging between 0.1 and 0.2 mL), after molding with the thumb was performed.



**Figure 3 a-b** - Lateral view of pre (a) and post (b) treatment (1 month apart) of a 27-year-old woman who requested forehead recontouring; the procedure was performed injecting CaHa with needles.



**Figure 4 a-f** - Lateral and frontal views of pre (a; d), post at 1 (b; e) and 8 months (c; f) from the treatment of a 44-year-old woman who requested forehead recontouring; the procedure was performed by injecting HA with needles.



*Figure 5 a-c: Frontal view of pre (a), post 1 (b) and 3 months from the treatment of a 57-year-old woman who requested forehead recontouring; the procedure was performed by injecting CaHa with needles.*



**Figure 6 a - c:** Three quarter view of pre (a), post 1 (b) and 3 months from the treatment of a 27-year-old man who requested forehead recontouring; the procedure was performed by injecting CaHa with the cannula.



**Figure 7 a - f:** Bottom, three quarter right and left views of pre (a; c; e) and post (b; d; f) treatment (1 month apart) of a 42-year-old woman who requested forehead recontouring; the procedure was performed by injecting HA with the cannula.

## Results

In all the cases, at the end of the injections, patients experienced redness and irregularities of the surface that resolved themselves within 48 hours (*Figure 8*);



*Figure 8:* At the end of all the procedures performed with either cannula or needle, irregularities were recorded, but they self-resolved within 48 hours.

A frontal vein congestion, which also resolved itself within 48 hours, was also recorded in 10 cases. No ecchymosis was recorded. *Table 1* summarizes the fillers used, the delivery technique employed, and the adverse events recorded.

The pain scale evaluation demonstrated that the injective procedure was painful. In fact, no patient reported a pain score lower than 7 (an evaluation between 7 to 10 was considered severe pain). It was also revealed that patients reported more pain when injected with cannulas. In particular, the needle group (10 patients) rated the procedure an overall 7.6, while the cannula group (8 patients) rated it 8.8. Results are labelled in *Table 2*. In 4 cases, a touch-up was required after 15 days from the procedure (in 3 cases, 1 mL of HA, and in the other one, 1.5 mL of CaHa were injected). Patient satisfaction was evaluated with a VAS which was fulfilled by the patients 15 days after the injection; the mean VAS evaluation rate was of 84.1. Results are labeled in *Table 3*. In one case, 3 weeks after the treatment, a nodule secondary to a CaHa injection was recognized (needle injections). After 1 month of weekly washings with saline and lidocaine without seeing any results, it was decided to excise it surgically (*Figure 9*).

Other complications such as infection or skin necrosis were not observed.

Patient	Filler used	Technique of injection	AE
1	CaHa pre-mixed with lidocaine	Needle	-Vein congestion
2	HA with lidocaine	Needle	-Vein congestion
3	HA	Needle	
4	CaHa pre-mixed with lidocaine	Cannula	-Vein congestion
5	CaHa pre-mixed with lidocaine	Cannula	
6	CaHa pre-mixed with lidocaine	Needle	-Vein congestion
7	HA	Cannula	-Vein congestion
8	HA with lidocaine	Cannula	
9	CaHa pre-mixed with lidocaine	Needle	-Vein congestion -Nodule
10	HA with lidocaine	Cannula	
11	HA	Needle	
12	CaHa pre-mixed with lidocaine	Needle	-Vein congestion
13	HA with lidocaine	Needle	
14	HA with lidocaine	Cannula	-Vein congestion
15	HA with lidocaine	Needle	-Vein congestion
16	HA with lidocaine	Needle	-Vein congestion
17	HA with lidocaine	Cannula	
18	HA with lidocaine	Cannula	

*Table 1 - Fillers used, injective protocol and adverse events (AE).*

Patient	Injection	Pain Scale Score
1	Needle	7
2	Needle	7
3	Needle	8
4	Cannula	10
5	Cannula	10
6	Needle	7
7	Cannula	9
8	Cannula	8
9	Needle	7
10	Cannula	8
11	Needle	8
12	Needle	7
13	Needle	9
14	Cannula	7
15	Needle	8
16	Needle	8
17	Cannula	9
18	Cannula	10

**Table 2** - Results of the pain scale questionnaire filled out by the patients at the end of the procedure: 0 was considered no pain, 1 to 3 mild pain, 4 to 6 moderate pain, 7 to 10 severe pain.

Patient	VAS
1	100
2	80
3	90
4	90
5	80
6	80
7	75
8	80
9	80
10	100
11	85
12	85
13	80
14	90
15	80
16	80
17	80
18	80

**Table 3** - Fifteen days following the procedure, patients were asked to evaluate the results with a VAS (Visual Analog Scale) where 100 represented the best possible aesthetic outcome and 0 the worst.



**Figure 9:** A nodule of CaHa excised surgically after forehead recontouring performed with CaHa injected with the needle.

## Discussion

In the last ten years, non-surgical facial aesthetic treatments have largely replaced surgical procedures. This is due to the patients' requests for no downtime but also due to a better knowledge regarding the characteristics of the medical devices sold<sup>14-16</sup>. During the last twenty years, scientific papers have largely improved our knowledge regarding facial anatomy, especially for ligaments, fusion zones, and fat compartments. This can easily explain why nowadays fillers are used not only to fill facial lines but also for several other purposes, such as the correction of the tear trough deformity, chin deficiency, jawline reshaping, etc<sup>17-22</sup>; these are only a few of the plethora of treatments that can be performed with facial fillers, although forehead contouring with fillers is a topic that lacks proper investigation<sup>23-27</sup>.

In order to maintain or create a harmonious face and to restore or improve facial attractiveness, facial plastic surgeons must follow the principles of harmony, proportion, symmetry, and balance, especially in terms of angles and lengths<sup>28</sup>. In females, the forehead curves mildly from the glabella backward toward the hairline, making an arc of approximately 7°, slightly less than in males (10°)<sup>29</sup>. In the clinical assessment of frontal bossing, the nasofrontal angle is more acute in males, measuring approximately 130° degrees compared to a more oblique angle of 134° in females<sup>30</sup>. Moreover, the forehead inclination in the profile view tends to be more vertical in women (6°) and has a relatively greater posterior inclination in men (10°).

Regarding the soft tissue evaluation in frontal eminence, it has been demonstrated that in males, the subcutaneous tissue is thicker (425  $\mu\text{m}$ ) than in females (350  $\mu\text{m}$ )<sup>29</sup>. Thus, the characteristics of females' forehead are in severe contrast to those of males, in whom the forehead protrudes. In fact, women with excessive supraorbital ridge protrusion usually complain about this unpleasant characteristic that exerts a negative impact on their social life. For this reason, they frequently refer to plastic surgeons for its resolution<sup>31</sup>. Moreover, during the aging process, a female facial appearance becomes more masculine. Regarding the relationship between age and attractiveness, Zimm and Kwart respectively described an improvement in attractiveness score after the frontal rejuvenation associated with a decrease in their perceived age<sup>32,33</sup>. Facial manifestations of aging in the forehead area reflect the complex dynamic, synergic, and combined effects of gravity, loss of facial volume, skin textural changes such as decreased elasticity, redistribution of subcutaneous fullness, as well as progressive bone resorption with a gradual loss of underlying support responsible for the descent of the soft tissue<sup>34</sup>. The process of forehead aging is related to a progressive loss of subcutaneous fullness and a consequent accentuation of underlying structures such as the supraorbital rims, bony surface and muscles<sup>35</sup>. In youth, the subcutaneous fullness conceals the muscles of facial expression in the forehead region. During the aging process, this fullness between the muscles and the skin disappears and the tone of the corrugator, procerus and frontalis muscles, presents wrinkles or folds. A skeletonized supraorbital rim with the relative excess of upper eyelid skin, glabellar frown lines and transverse forehead furrows are considered the main features of upper facial third aging<sup>34,35</sup>.

An emerging interest in forehead contouring has been raised in the last few years<sup>23-27</sup>.

In 2020, Hong et al. evaluated the tomography of forehead arteries in order to perform safe filler injections in this area. Sixty-six cadaver heads were dissected, and all the superficial temporal arteries were identified and followed; a total of 319 arteries identified in 48 cadavers passed through the midline; 292 superficial arteries and 27 deep ones were found<sup>13</sup>.

Outcomes of this study confirmed that deep injections over the bones are safe to avoid vascular impairment. Also, Kim, in 2018, stated that deep filler injections are safe for forehead contouring in Asian patients. The author, in a 10 year experience, treated 218 patients with CaHa injections with a personal technique characterized by tumescent solution injections, done in order to cause supraperiosteal hydrodissection, thus avoiding all the vascular structures, followed by subperiosteal filler injections with a cannula. Kim recorded 100% patient satisfaction with no complications<sup>24</sup>.

Some recent papers introduced the role of fat grafting in forehead remodeling. Li and their colleagues evaluated 24 consecutive patients undergoing forehead fat grafting in an overall period of 6 years; stable and satisfactory results were recorded, with an average forehead projection increase of 0.24 U (ratio of horizontal distance from mid-forehead plane to corneal plane/corneal diameter) after one round of fat grafting ( $p = 0.01$ ); although seven patients (29.2%) required more

than a procedure before achieving an optimal result<sup>36</sup>. The role of forehead contouring has also been highlighted in some papers focusing on the "lateral aspect" of the forehead itself, considering forehead contouring as an adjunct to nose and chin remodeling. Oguzhan Demirel released a paper with his early experience treating 15 patients combining forehead fat grafting and rhinoplasty, recording important benefits such as higher patient satisfaction and improvement of facial appearance and personal traits; concluding that forehead contouring with fat graft was an efficient and applicable procedure to be added to rhinoplasty<sup>37</sup>.

Also, Bertossi et al, in 2018, presented their experience proposing a medical algorithm in the management of the profile which focused on the forehead, nose, lips, and chin; the authors concluded that the correction of the aforementioned anatomical areas with filler injections could be a viable non-surgical solution in order to ameliorate facial aesthetics, avoiding scars and the cost of general anesthesia, providing the maximal patient satisfaction<sup>23</sup>.

In the present case series, 18 patients consecutively treated for forehead contouring with fillers were considered. The main indications were:

- to get a more rounded forehead to improve attractiveness in female patients.
- to reduce the perception of supraorbital bossing (male or female patient).
- to deal with forehead aging.

A VAS evaluation demonstrated a high degree of patient satisfaction with a mean score of 84.1. Based on the pain scale questionnaire filled out by each patient, we can state that the procedure is to be considered painful as every score given corresponds to severe pain. Moreover, a difference in patient discomfort (pain) during the procedure was recorded based on the type of delivery system employed: needle injections were rated 7.6, while cannula injections were rated 8.8 on the pain scale. Stable results were recorded during the follow-up. This outcome has been largely described in literature: when an HA filler is injected under or just above the periosteum, a semi-permanent filling effect lasting up to 3 years can be achieved<sup>38</sup>. This issue has been hypothesized for the first time by Mashiko et al.; subperiosteal hyaluronic acid injections seem to be related to periosteal stem cell activation and long-lasting results: published clinical experience confirmed it<sup>38</sup>.

In one case, a complication that required further treatment was recorded. The patient was injected, through a needle, with CaHa based filler; three weeks later, a hard and mobile nodule was recognized. Despite one month of weekly washings with saline and lidocaine, there was no resolution was appreciated. For this reason, surgical removal of the CaHa nodule via tab incision was performed under local anesthesia. The patient complained about the minimal postoperative scar (5 mm) that was visible on the forehead.

Paradoxically, 15 days following the procedure, the patient rated 80, and the result was achieved.

The first case treated in this case series was performed in 2014. Forehead contouring with fillers at that time was a procedure unknown to most people. Moreover, a specific filler for that area, so far, does not exist. The choice to perform forehead treatments with a CaHa

based filler was due to the large experience collected by the senior author (RR) during previous years. Using this filler did not cause any adverse events<sup>39</sup>; moreover, the idea to inject CaHa over the bone was considered safe due to the presence of CaHa itself in the bones. The adverse event recorded in the sixth patient treated induced the senior author to approach other cases with HA in order to treat with hyaluronidase injections, avoiding surgery, and any potential arising complications.

The use of CaHa filler in a diluted or hyper-diluted formulation with lidocaine and saline has been proposed during the last years, for both facial and body treatments, in order to get tightening and no volume enhancement<sup>40,41</sup>, although in an off-label fashion. The use of diluted or hyper-diluted CaHa fillers seems to be related to a low incidence of nodules<sup>42,43</sup>; further studies should be performed to evaluate the safety and stability of forehead contouring with diluted or hyper-diluted CaHa fillers.

Kim, among 218 patients treated for forehead contouring, never recorded such complications when injecting with CaHa; this could be probably related to the tumescent solution injected before the filler which could work as a diluent for the CaHa microspheres<sup>24</sup>. In order to reduce the incidence of nodules following the CaHa filler, a potential hypothesis could be, as suggested for permeant fillers<sup>44</sup>, to perform small droplet injections spaced in different sessions.

The current practice in the case of CaHa nodules consists of washing procedures performed with lidocaine and saline; surgery is indicated in refractory cases<sup>45</sup>. Thanks to the possibility of inducing filler resorption with hyaluronidase injections, this kind of complication could be avoided with the use of HA-based fillers<sup>46,47</sup>. Some studies are trying to understand if sodium thiosulfate may act as a reversal agent for CaHa fillers; however, up to now, the only filler that can be easily and safely reversed is the HA-one<sup>48-51</sup>.

Redness and irregularities, which solved themselves within 48 hours, were always recorded after the procedure, but they could be easily explained by the thickness of the soft tissue of the forehead. In 10 out of 18 cases, frontal vein congestion, which also solved itself within 48 hours, was recorded at the end of the procedure; this can be explained by the thickness of the frontal flap and by the vascular compression secondary to filler injections.

## Conclusions

In the last years, many clinical indications regarding facial filler treatments have arisen, especially in terms of the contouring of facial features. However, due to its novelty, non-surgical forehead contouring with fillers is a topic of rising interest. In the present case series, 18 patients consecutively treated for non-surgical forehead contouring with fillers were evaluated; the procedure was considered painful by patients, although a high overall patient satisfaction rate was recorded. Only one complication using a CaHa filler was recorded, which required a surgical intervention for its resolution.

The present case series has several limitations, such

as the use of needles instead of cannulas or the use of different fillers; nevertheless, due to the paucity of papers concerning this topic, we think that sharing this early experience with physicians involved in facial contouring with injectables could be useful. Larger, blinded, and controlled studies are required to standardize this medical procedure.

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# The art of aesthetic neuromodulation and facial perception

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**Running title:** Aesthetic Neuromodulation

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## Abstract

**Background:** living in a fast-track world, timely identification of the patient's goals, expectations, and current state of self-confidence is imperative, applicable knowledge for the aesthetic injector. The absence of a timely evaluation tool for neuromodulation in the aesthetic industry may instigate an environment of melancholy related to patient outcomes, overall satisfaction, and waste management.

**Aim:** the purpose of this QI project is the development of the Functional Facial Assessment Tool (FAST), a quick tool that aims to educate providers on the aesthetic patient's potential product utilization, goals, and current state of self-confidence.

**Method:** a two-phase patient focused quality improvement (QI) project was implemented to quickly extract vital information on history, product utilization, goals, and confidence level on the pre-survey and gauge goal achievement, confidence progress, and overall patient outcomes on the post-survey.

**Results:** the FAST provided vital information about the clientele. One of the most encouraging discoveries within this project was the improvement seen in self-confidence, rising 44% post-injection.

**Conclusion:** findings of this QI project's success has led to significant advances in the evaluation of patient satisfaction, patient outcomes, and cost efficiency through the utilization of the FAST surveys.

## Keywords

Aesthetic, neuromodulation, botox, quick tool, survey, evaluation

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## Introduction

The beauty industry, fueled by social media standards, is immensely prevalent in the United States today<sup>9</sup>. The concept of being preoccupied with physical perfection and a youthful appearance permeates the demand for botulinum toxin injections. According to the Aesthetic Plastic Surgery National Databank, (APSND) (2019) botulinum toxin type A (BoNT-A) injections were the number one non-surgical aesthetic procedure performed in the United States in 2019<sup>1</sup>. Due to the growing popularity of BoNT-A injections and the current existence of unrealistic beauty expectations, a need has materialized for comprehensive tools that can be utilized by aesthetic injection providers to measure expected satisfaction and patient outcomes. A comprehensive tool of this nature could improve the standard of care in the realm of neuromodulation by creating a plan of care fostering realistic patient expectations and improving perceived patient outcomes.

## Background

### History

Historically, botulism cases associated with improperly stored food date back to the 1700s when the physicians of this period recognized the classic illness symptomology in several clusters of fatal outbreaks<sup>10</sup>. The first case studies regarding botulinum toxicity were published by a German physician, Justinus Andreas Christian Kerner in 1817 and 1820<sup>10</sup>. The term botulism comes from the word “botulus”, Latin, for sausage. Kerner completed several experiments connecting “fat poison” from sour sausages to clinical symptoms such as the drying of the palate, diplopia, nerve conduction interruption, and decreased muscle excitability<sup>10</sup>.

Botox Cosmetic (onabotulinumtoxinA) materialized in 2002 with an FDA approval to treat glabellar lines in adult patients<sup>8</sup>. In 2013 it was approved for the treatment of lateral canthal lines otherwise known as “crow’s feet”<sup>8</sup>. Botox is now a colloquial term used to represent cosmetic neuromodulators in the aesthetic industry<sup>4</sup>. There are three additional neuromodulators that are FDA approved for aesthetic use in the United States in addition to the classic Botox Cosmetic product<sup>4</sup>. Dysport (abobotulinumtoxinA) was approved in 2009, Xeomin (incobotulinumtoxinA) was approved in 2011, and Jeuveau (PrabotulinumtoxinA-xvfv) is the most recently approved product gaining sanction in 2019<sup>4</sup>. All four of these products utilize the same active ingredient BoNT-A with minimal differences in their effects<sup>4</sup>.

### Demographics and Costs

Americans spend upwards of 15 billion dollars annually on aesthetic procedures both surgical and non-surgical to improve their perceived appearance<sup>3</sup>. According to the American Society for Aesthetic Plastic Surgery, (ASAPS) (2016) neuromodulation with botulinum toxin products has held the number one and number two spots for the largest amount of non-surgical aesthetic procedures completed in the nation for the last eight

years<sup>3</sup>. Caucasian females, ages 35 to 50 dominate the market at a rate of approximately 40%<sup>1</sup>. The popularity of these injectable procedures is fueled by the minimal amount of time it takes to complete the procedure, the non-existent downtime, and the results perceived by the patient<sup>1</sup>.

### Clinical Guidelines

BoNT-A injections are governed by the FDA<sup>5</sup>. Aesthetic neuromodulators can be injected by a physician, nurse practitioner (NP), physician’s assistant (PA) or registered nurse (RN) with the proper training. Regulatory requirements are differentiated by each state<sup>11</sup>. Familiarization with personal state standards and regulations is imperative prior to any independent aesthetic practices.

### Existing Tools

Examining the patient’s goals versus their clinical outcome and satisfaction level is crucial information for the thousands of providers across the United States that administer neuromodulation and consumers alike. There are various surveys in existence today both simplistic and comprehensive that evaluate facial appearance satisfaction in the realm of neuromodulation. The Freiburg Questionnaire is a 64-item survey initially developed for the evaluation of the patient’s satisfaction with liposuction and was later translated into a qualified neuromodulation satisfaction survey<sup>12</sup>. The Facial Lines Treatment Satisfaction Questionnaire (FTS) although less lengthy than the others, evaluated patients with neuromodulation alone, or with other aesthetic skin wrinkle treatments which alludes to some inquisition cognoscente of specificity<sup>7</sup>. The FACE-Q two-part survey, also quite comprehensive with 63 questions noted on each portion, reported a satisfaction facial improvement of 28% in participants involved in the study, receiving a neuromodulation in the glabellar lines<sup>6</sup>. Glabellar lines were the only upper facial lines (UFL) evaluated utilizing the FACE-Q tool<sup>6</sup>. The Facial Lines Outcome questionnaire was distributed in an interview style to two groups evaluating the “psychological impacts” associated with UFLs and crow’s feet<sup>14</sup>. This questionnaire is not lengthy and evaluates the patient’s feelings regarding their facial lines before and after neuromodulation<sup>14</sup>. The Functional Facial Assessment Tool (FAST) was created utilizing these pro-tools already in existence in development of a more time conscious model with focus on improving patient outcomes, patient satisfaction, and cost effectiveness.

## Materials and Methods

The promotion of beauty as it exists in the world today in conjunction with mental health considerations such as confidence, reduction of depression, and overall well-being is a pertinent relationship<sup>2</sup>. Aesthetic providers of neuromodulation treatments have opportune access and ability to screen patients both pre and post neuromodulation gaining an invaluable comprehension of vital information as it relates to the patient’s satisfaction, costs, and overall outcomes. The purpose of this quality improvement

(QI) project was to develop and implement the FAST survey into an aesthetic practice bi-modally improving the overall neuromodulation experience and enhancing the patient-provider relationship. By incorporating the FAST survey into practice, the QI project provided a comprehensive, patient-centered approach to quickly delineate the patient's product needs, specific goals for the procedure, current confidence status, and post-evaluation patient outcomes facilitating the shared decision-making process between the patient and provider.

## Design

The QI project was implemented in an upper class privately-owned metropolitan spa. Analysis of the FAST survey data occurred in two phases pre-neuromodulation survey and post-neuromodulation survey. This privately-owned clinic manages approximately 50 patients per month.

## Population Sample

The sample population included female patients ages 25-65 years old that were seen by the privately-owned practice for new and routine neuromodulation appointments. Both new and existing patients receiving neuromodulation were included as well as novice and those with prior injection history. All patients received neuromodulation with either Botox or Dysport. Patients were included in the project despite which area(s) of the face were injected. During a two-month time period, patients were asked to fill out the FAST surveys prior to their appointment. The pre-neuromodulation surveys were sent to the patients via text message one week prior to their injection appointment. The post surveys were sent via text message two weeks post injection. A \$25 coupon incentive to be used by the patient for their next injection appointment for taking the time to complete and return the post neuromodulation survey and participating in the study was included.

## Ethical Considerations

The QI project was reviewed by Creighton University Institutional Review Board and deemed to be a Quality Improvement Project. Once permission to proceed was granted the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule was strictly followed. Participation in this project was voluntary for all selected patients. Collected data was stored in a private and secure location protected from unauthorized personnel. Any patient participating in the project could request education regarding the project's purpose, intents, and results.

## Measurement Methods/Data Collection Procedures

The FAST surveys development stemmed from the PRO tools already in existence and examined in the available knowledge. The survey was created taking different concept attributes from PRO tools and combining them for the common purpose of improving patient satisfaction and cost effectiveness of the business. The FAST survey, as illustrated in Appendices A and B, quickly extracts vital information on history, product utilization, goals, and confidence level on the pre-survey and gauge's goal achievement, confidence progress, and overall patient outcomes on the post-survey. Once received, the FAST pre-survey was assessed examining what area the patient would like to have injected allowing the project lead to estimate the amount of product that would be utilized during that appointment. This was done with each patient, allowing for ordering of the proper product amount, eliminating waste and optimizing cost effectiveness.

The subject's names were associated with their phone number and kept identifiable, so the FAST surveys were able to be compared, and the outcomes analyzed properly. The dates were also tracked by phone number to verify that the two-week time constraints were followed. The practice offered participation in the project to any clients that met the inclusion criteria during the two-month window of implementation.

## Data Analysis

Data from both survey phases was collected and analyzed using descriptive statistics. Continuous variables are expressed as ranges while discrete variables are quantified in percentages. The pre-injection screen and post-injection surveys were analyzed and compared for validity, patient satisfaction data, and waste management purposes.

## Results

### *FAST Pre-injection Screen*

Each client was screened for inclusion and given the opportunity to participate. Thirty-three clients met the inclusion criteria for participation during the 30-day implementation phase. The FAST pre-injection screen had a total of 33 responses with a 100% completion rate. Typically, it took each client 45 seconds to complete the survey.

The first question in the FAST pre-injection screen was, "Have you ever had neurotoxin injections before?" 87% percent responded, "yes" to this question while 12.5% responded "no". One person "skipped" or did not complete this question. The second question asked, "What areas of the face would you like to have injected?" The top answer was forehead at 54.55% followed by crow's feet at 21.21%. Injection of glabellar lines came in at 18.18% followed by a lip flip at 6.06%. Spa lift, gummy smile, and "other" areas did not generate a need with this client group with zero response reflected. The third

question on the pre-injection screen was “What are your goals for the procedure?” The response options included smoothness, with greater than a 50% margin totaling 22 respondents at 66.67%. Lift/refreshed appearance followed at 30.30% with 10 respondents. One client responded “other”, and no one chose symmetry as a primary goal. This question had a 100% completion rate with no skips.

The fourth and fifth questions in the FAST pre-injection screen encompass the concepts of eyebrow movement with neurotoxin injections and overall self-confidence. Question four states, “What is more important to you, elimination of all wrinkles or eyebrow movement?” The dominant answer was exactly parallel with “wrinkles be gone” with 16 respondents at 48.48% and “both if possible” also with 16 respondents at 48.48%. One respondent chose the third answer option “I need my eyebrows to move” making up 3% of the population. There was a 100% completion rate on this question. The final question of the pre-injection screen asked, “How would you rate your current self-confidence?” The response options were displayed as “excellent, good, average, and poor”. “Good” was the most prevalent answer at 63.64%, with 21 respondents choosing this option. Seven respondents (21.21%) reported an “average” confidence level while five (15.15%) of the respondents reported an “excellent” confidence level. None of the respondents reported a poor confidence level. There was 100% compliance with zero skips on question five.

### FAST Post-Injection Evaluation

The FAST pre-injection screen had 33 respondents complete the survey. The FAST post injection evaluation is the second half of this study’s assessment and had 32 respondents to complete the survey, achieving a 99% completion rate. The first question in the post injection evaluation was, “Were you happy with the injection process?” The feedback was positive with 100% of the respondents replying “yes.” The second question asked if the respondent’s goals they depicted in the pre-injection screen were met. Thirty-one out of 32 respondents (96.88%) answered “yes” to this question, one respondent answered “no” (3.13%). Question three of the post-injection evaluation asked, “How would you rate your current self-confidence as it relates to your outward appearance?” “Excellent” and “good” ran parallel as the highest rated answers, both at 43.75%. “Average” followed at 12.5% with the answer option “poor” with zero respondents. All 32 respondents completed this question.

Question four of the post injection evaluation asked the respondents to give a “star rating” for their service. Five stars being the highest rating one could give and one star being the lowest potential rating. All 32 respondents completed this question with approximately 88% of the respondents awarding a five-star review. Three people (9.38%) gave a four-star review, and one respondent (3.13%) gave one star. None of the respondents gave a two or three-star review.

Figure 1 reflects the star rating scale results.

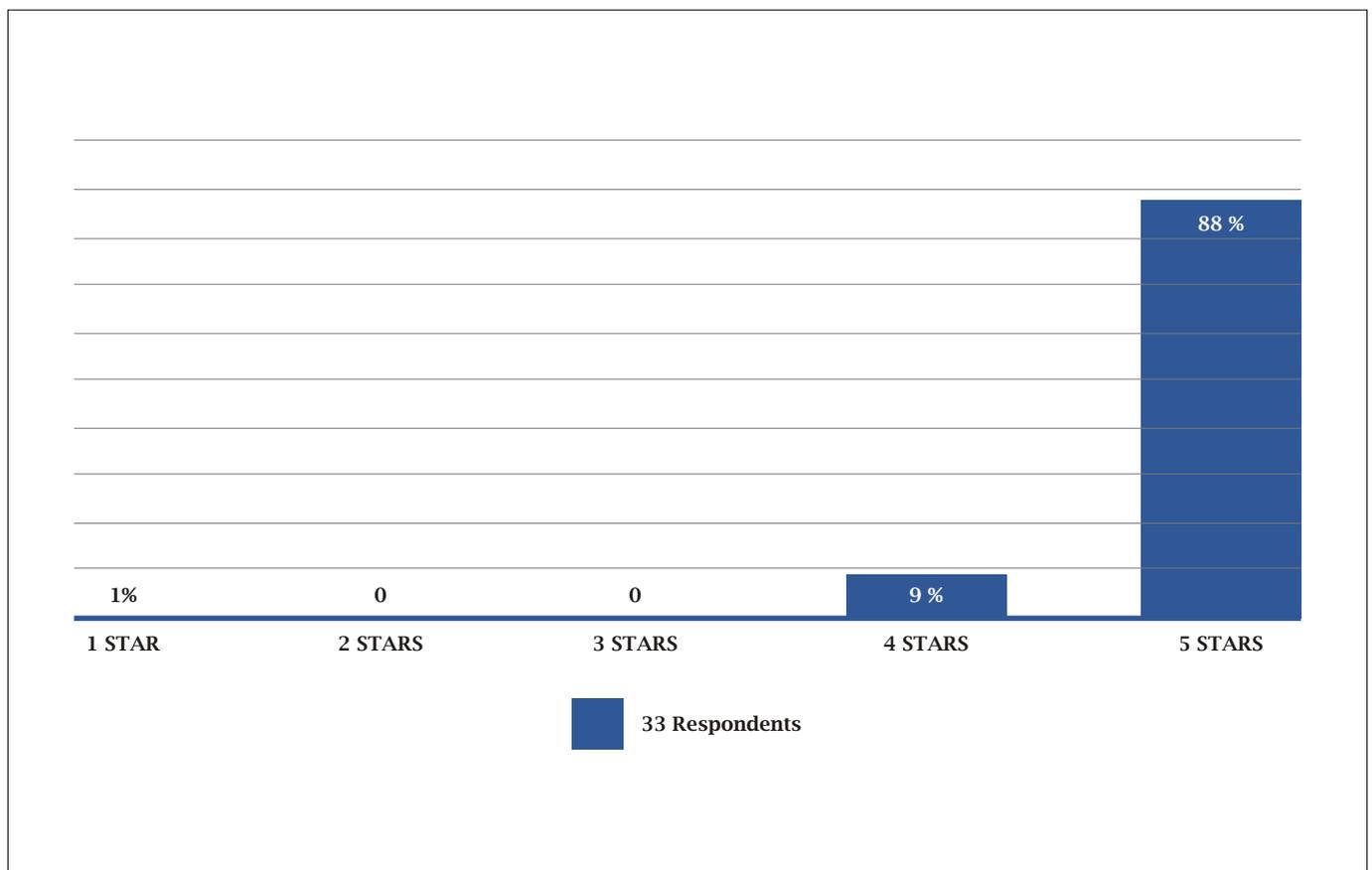


Figure 1 - Star Rating Scale Results.

Question five asked the respondents to leave a comment or suggestion to illustrate any feedback they may have. Twenty-two respondents left comments while ten

skipped this question. The comments left emulated positivity and satisfaction. See *table 1* for a list of comments.

Question Five on the post-injection evaluation -comments/feedback
<p>"I'm always very, very happy with the results I get!"</p> <p>"Amazing experience and flawless results! THANK YOU!"</p> <p>"Love love love my injections! Thank you!!"</p> <p>"I didn't mean to rate that last one for worst!!! It was the best!!!"</p> <p>"Always a pleasant experience and great results"</p> <p>"Haven't been anywhere else so I don't have anything to compare to"</p> <p>"I love it!! definitely recommend"</p> <p>"I am loving how awake my eyes are after getting my injections. My eyebrows have more definition and Ive received a few compliments on how nice my eyebrows look."</p>
<p>"I always love my look!"</p> <p>"Always enjoy conversation! And how quick she is!"</p> <p>"Thank you for being amazing!"</p> <p>"Great service - thank you!"</p>

*Table 1 - The table illustrates various patient comments articulated in Question 5 of the FAST post injection evaluation.*

### Discussion and Conclusion

The absence of a timely evaluation tool surrounding aesthetic neuromodulation patients was identified in a metropolitan aesthetic med spa. Therefore, a two-phase patient focused quality-improvement project was implemented to develop a timely evaluation tool that would distinguish patient's goals, expectations, and current state of self-confidence as it relates to neuromodulation injections. The primary purpose of this QI project was to utilize the knowledge gained to foster a basis for patient-provider communication, improve overall patient satisfaction/outcomes, and optimize waste management. The two-phase survey served this purpose based on the illustrated results. The first question on the FAST pre-injection screen asked patients if they had ever been injected with neurotoxin before. This question informs the injector whether the patient is neurotoxin naïve. In which case the provider could potentially anticipate a conservative amount of product to be injected due to the unknown metabolism of the product in the new patient. Not unlike many medication regimens, when administering neurotoxins, the smallest dose is often utilized first as best practice for a maximal response of the medication with the

most minimal side effects. This gains the provider knowledge on how much product they could anticipate ordering and addresses the aims of waste management and cost efficiency. The second question on the pre-injection screen asks what areas of the face the patient would like injected. Each area of the face that can be injected with neurotoxin has an approximate maximum and minimum amount that can be injected. Providing this information to the aesthetic injector allows them to know the ratio of product that should be ordered based on which areas of the face are being considered. Question two aligns with the first question's aims of waste management and cost efficacy. Questions three and four on the pre-injection screen discussing procedural goals, correlate with question two on the post-injection evaluation determining if those pre-procedural goals were met. The most sought-after goals by the clients surveyed was smoothness (question 3) (67%), lift (question 3) (30%), and elimination of wrinkles (49%) with the option to still be able to move their eyebrows (49%) (question 4). In the post-injection evaluation, an astonishing 97% of respondents reported their goals were met. The common aims of patient satisfaction and improved patient outcomes resonates with this evaluation.

The FAST pre-screen evaluated the respondent's self-confidence in question five. Self-confidence was then re-evaluated in question three on the post evaluation. Perhaps one of the most encouraging discoveries within this project is the improvement seen in self-confidence illustrated from the pre-injection screen to the post-injection evaluation. "Excellent" rated self-confidence started at 15% in the pre-screen phase and elevated to 44% in the post injection survey with an approximate 30% self-confidence improvement rate! With the "excellent" rating rising the "good" and "average" ratings fell, "good" fell by 20%, the "average" rating declined by 8%. The "poor" self-confidence rating had zero responses in both the pre and post evaluations. The aim of improved patient outcomes is defined in this assessment. These results are illustrated below in *figures 2 and 3*.

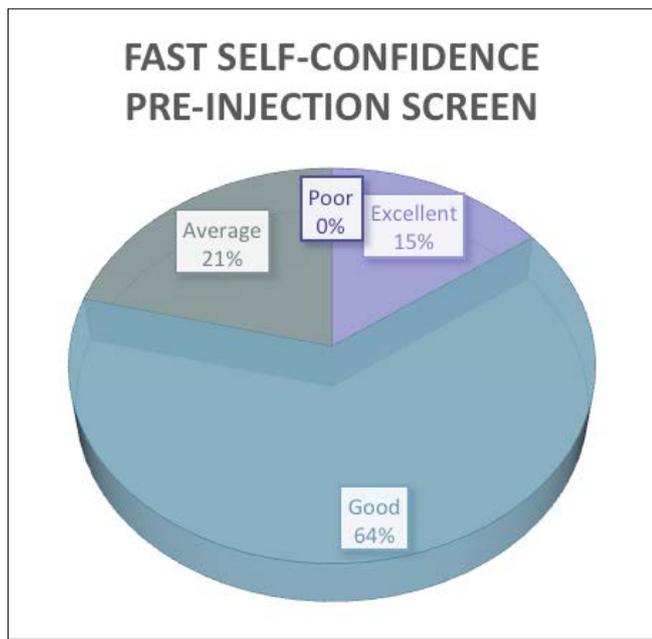


Figure 2 - Self Confidence Rating Results from the FAST Pre-Injection Screen.

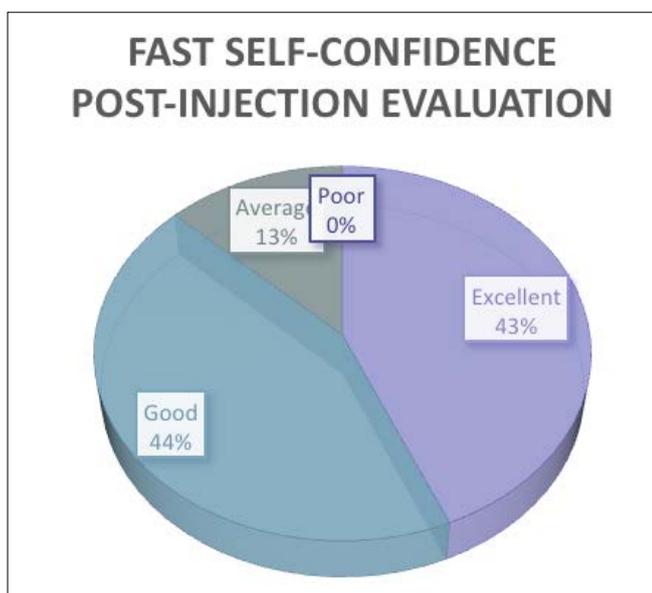


Figure 3 - Self Confidence Rating Results from the FAST Post-Injection Evaluation.

Questions one, four, and five on the FAST post-injection evaluation aim to evaluate patient satisfaction and patient outcomes. The results also revealed a hidden goal and satisfaction piece from the clientele regarding time management and efficiency. In question one 100% of the respondents reported "yes" they were happy with the injection process. Question four asked respondents to give a "star rating" regarding their entire experience with 88% giving a five-star rating and 9% giving a four-star rating.

One respondent gave a one-star rating in question four but made a comment in question five stating, "I didn't mean to rate that last one for worst!!! It was the best!!!". Question five illustrated any comments or suggestions the respondents shared this feedback is listed in *table 1*. Two of the respondents wrote in the comments they were pleased with the efficiency of the process. This brings about a new goal for Faces by Meghann to ensure a quality yet timely injection process.

The aim of this portion focuses on patient satisfaction. The target survey participation rate of 80% during the 30 days of implementation was surpassed demonstrating support for future endeavors.

As implicated in the evidence summary a culmination of the literature supports the ideation that is also demonstrated in the results of this QI project that injection therapy with BoNT-A produces favorable aesthetic outcomes emulating positivity and patient retention.

The literature also reinforces the clinical practice recommendation highlighting the importance of a regular evaluation with PRO based tools as a best practice method in aesthetics to emphasize quality of care<sup>13</sup>. The research surrounding mental health supports the notion of findings in this QI project illustrating improvement in self-confidence post neuromodulation which relates to an overall improvement in mental health capacity.

This concept is also perpetrated in the literature review with various studies showing improvement in depression scores, mood, confidence, and overall psychological state. Further research is required to fully delineate clinical practice guidelines and fulfill further knowledge deficits based in mental health. Findings of this QI projects success has led to significant advances in evaluation of patient satisfaction, patient outcomes, and cost efficiency through utilization of the FAST two phase pre and post neuromodulation evaluation tool for this independent practice.

Policy change requiring bi-annual evaluations will be implemented using the FAST.

Initial application of the FAST bi-annually instead of creating a daily policy utilization requirement will likely increase the sustainability of the tool eliminating overwhelming "busy-work" for staff and "survey-fatigue" for clients thus preserving the authenticity of the responses rendered. Allowing for intermittent application when obstacles arise will potentiate problem-solving strategies and reinforce the cornerstone of any flourishing medical practice, the patient provider relationship.

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### **Conflict of Interest**

I have no conflicts of interest to disclose.

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# Facial aging in patients with schizophrenia

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**Running head: Facial aging in schizophrenia**

## Abstract

**Background:** schizophrenia has long been associated with accelerated physical aging, along with increased and premature medical comorbidities and mortality. Several anatomical and functional abnormalities have a higher prevalence among people with schizophrenia.

**Aim:** to assess facial aging of patients with schizophrenia compared to an age-matched control group, without schizophrenia.

**Methods:** wrinkle depth using Lemperle's classification and a subjective age estimation were independently evaluated by two investigators and the two groups were compared. Data regarding BMI, sun exposure habits, the use of sunscreens, and current medications were recorded.

**Results:** seventy-four participants were enrolled, including 37 patients in each group. Age, sex, BMI and smoking status did not differ significantly between the groups. Patients with schizophrenia took significantly more medications, had more sun exposure and used less sunscreen than the controls did. They had significantly deeper periorbital, nasolabial, chin, and cheek wrinkles and their ages were estimated to be older than the controls'.

**Conclusions:** patients with schizophrenia had increased facial aging, evidenced by deeper facial wrinkles and were estimated to be significantly older than the controls. Probable causes include an unhealthy lifestyle, an increased facial muscle tone due to the chronic use of antipsychotic drugs and a genetic diathesis related to the aging process.

## Keywords

Wrinkle assessment, schizophrenia, aging, sunlight

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## Introduction

Although descriptions of people who might have had a schizophrenia-like illness can be found throughout history, the first comprehensive descriptions date from the beginning of the 19<sup>th</sup> century<sup>1</sup>. These historical descriptions and the modern concept of schizophrenia formalized by Emil Kraepelin<sup>2</sup> emphasize the accelerated aging that accompanies the disease, naming it dementia praecox. Schizophrenic patients have a higher risk of aging associated with their significantly higher somatic morbidity, especially cardiovascular disease, diabetes, stroke, obesity and hyperlipidemia<sup>3-5</sup>. In addition, medications taken and lifestyle behaviors, particularly smoking, dietary habits and decreased sun safety<sup>6,7</sup> might be factors contributing to this tendency. The increased oxidative stress-induced cellular damage of macromolecules, chronic inflammation and altered gene expression might play a role in common pathways of accelerated aging in schizophrenia<sup>8,9</sup>.

This study evaluated and compared the facial wrinkles of schizophrenic patients to those of healthy, age matched controls using Lemperle's classification<sup>10</sup>.

## Material and methods

The study was approved by the local Institutional Review Board. All participants gave voluntary informed consent in writing after receiving a detailed explanation of the study from the primary investigators. We could not use photographic documentation due to the mental state and the vulnerability of the patients.

Patients with schizophrenia in a hospital-based setting who met the inclusion criteria of: A) 25 to 55 years of age; B) schizophrenia diagnosed according to DSM-IV criteria; C) stable body weight and BMI in the normal range in the last year; and D) the ability to sign an informed consent form, were enrolled in the study group. Exclusion criteria were: A) known skin disease; B) previous facial rejuvenation procedures such as resurfacing (peeling, laser), botulinum toxin injections, filler injections or rhytidectomy; C) pregnancy; and D) known malignancy. A matched control group of people without schizophrenia, with similar age, sex, body mass index, smoking habits and Fitzpatrick's skin type was recruited, as described above<sup>11</sup>.

Data collected for each participant included demographics, height, weight, physical co-morbidity, concurrent medications, sun exposure habits and the use of sunscreen. Physical co-morbidities were categorized into the following groups: metabolic disorders, cardiovascular, gastrointestinal, neurologic, and others. Medications were classified into the following groups: anti-hypertensives and anti-aggregates, anti-hyperlipidemics, anticonvulsants and mood-stabilizers, hormones, antipsychotics, and others. Sun exposure was graded as 0 = no exposure, 1 = little exposure (mainly during weekends and holidays) and 2 = daily exposure.

For the clinical evaluation of facial wrinkles, we used the Lemperle wrinkle assessment scale<sup>10</sup>. This classification

includes 12 anatomic landmarks. Horizontal forehead lines were evaluated at their intersection with the vertical pupillary line. Glabellar frown lines were estimated at the level of the upper border of the eyebrows. Periorbital lines were estimated 1.5 cm lateral to the lateral canthus. Preauricular lines were evaluated at the level of the lower groove of the tragus. Nasolabial folds were evaluated midway between the alar rim and the corner of the mouth. Cheek lines were also measured at the level of the corner of the mouth. The marionette lines were measured 5 mm below the oral commissure of the mouth. Radial lip lines were measured 2 mm above or below the vermilion border. Marionette lines were measured midway between the corner of the mouth and the border of the lower jaw. The labiomental crease and neck folds were measured in the midline.

The facial wrinkle depth was independently evaluated by two of the investigators, one board certified in dermatology (YW) and the other in plastic surgery (TF). In addition, each investigator independently estimated the subjects' ages. The investigators were blinded to the subjects' demographic and clinical parameters, as well as to each other's ratings.

All the data was stored on an Excel electronic data base. The relevant statistical analyses were performed. A Chi-square test was used to compare categorical variables.

## Results

Overall, 74 subjects were enrolled, including 37 patients with schizophrenia (24 men and 13 women, with a mean age of  $42.7 \pm 9.7$  years and mean BMI of  $22.2 \pm 6.1$ ). They were compared to the control group, which consisted of 20 men and 17 women, mean age  $42.4 \pm 9.2$  years and BMI  $22.2 \pm 4.6$ .

Patients with schizophrenia had significantly more sun exposure and used significantly less sunscreen protection compared to the control group (*Table 1*). In addition, they took significantly more types of medications (excluding psychotropics) and significantly more photosensitizing medications.

Nasolabial, chin, cheek and periorbital wrinkles were significantly more noticeable in the patients with schizophrenia, as compared to the control group (*Table 2*). There was no significant difference in forehead wrinkles.

The calculated correlation ratios ( $r^2$ ) for the estimated and true ages of the schizophrenic patients and the controls were 0.76 and 0.91, respectively. Age assessments in the control group were significantly closer to actual ages, as compared to the schizophrenic patient group ( $P = 0.0001$ ).

Variable	Patients (n = 37)	Controls (n = 37)	P-value
<b>Sun exposure</b>			0.0001
None	1	7	
Little	6	23	
Daily	30	7	
<b>Sunscreen use</b>			0.0001
Yes	2	20	
No	35	17	
Medications (excluding psychotropics)	7	0	0.02
Photosensitizing medications	37	2	0.02

Table 1 - Variables differentiating schizophrenic patients and controls regarding sun exposure behavior and medications.

Wrinkle Depth (percent of patients)							
Type of Wrinkle	0	1	2	3	4	5	P-value
Chin - 0	5.88	29.41	20.59	20.59	17.65	5.88	<0.0001
Chin - 1	36.84	52.63	10.53	0	0	0	
Neck - 0	2.70	35.14	21.62	13.51	27.03	0	0.0432
Neck - 1	11.76	35.29	35.29	11.76	2.94	2.94	
Cheek - 0	40.00	45.71	5.71	8.57	0	0	0.0169
Cheek - 1	78.95	15.79	5.26	0	0	0	
Forehead - 0	10.81	43.24	13.51	13.51	16.22	2.70	0.2531
Forehead - 1	11.11	55.56	22.22	11.11	0	0	
Glabella - 0	29.73	29.73	18.92	8.11	10.81	2.70	0.4285
Glabella - 1	33.33	24.24	30.30	9.09	3.03	0	
Mouth corner - 0	8.70	39.13	30.43	17.39	0	4.35	0.0198
Mouth corner - 1	42.86	28.57	28.57	0	0	0	
Perioral - 0	41.18	47.06	8.82	2.94	0	0	0.1991
Perioral - 1	36.36	36.36	13.64	13.64	0	0	
Periorbital - 0	13.89	47.22	22.22	0	16.67	0	0.0036
Periorbital - 1	15.15	30.30	30.30	21.21	3.03	0	
Preauricular - 0	29.73	35.14	18.92	10.81	2.70	2.70	0.0774
Preauricular - 1	44.44	38.89	16.67	0	0	0	
Nasolabial fold - 0	5.41	29.73	24.32	18.92	13.51	8.11	0.0003
Nasolabial fold - 1	17.65	20.59	58.82	2.94	0	0	

Table 2 - Wrinkle assessment scores of schizophrenic patients (0) and controls (1).

## Discussion

Schizophrenia has been historically termed dementia praecox, reflecting the disease's accelerated aging of the nervous system<sup>12</sup>. Several dental and hair changes have been anecdotally reported to reflect an aged appearance among patients with schizophrenia<sup>13,14</sup>. The common embryonic origin of the cutaneous and nervous epithelium may lend itself to parallel aging processes.

Many extrinsic and intrinsic factors influence the facial aging process. Intrinsic factors include the

internal aging process of tissues, which is determined genetically. Important as well, are extrinsic factors, such as ultraviolet radiation exposure, smoking, significant weight loss, and an unhealthy lifestyle.

The Lemperle wrinkle assessment scale is a simple clinical tool for assessing changes resulting from the injection of filler materials. By correlating the grade of the wrinkle in the reference photographs with the wrinkle in a patient's face, a classification of 0 to 5 is assigned. The scale was found to have robust psychometric properties. Mimetic wrinkles, commonly referred to as lines or furrows, are the visible effects

of a deep dermal creasing caused by repeated facial movements and expressions. They are perpendicular to the direction of the underlying facial muscles. In the nasolabial fold, the dermis is attached to the muscles along the nasolabial crease, with the bulge of the fold created mostly by fat<sup>15</sup>. The nasolabial folds are exaggerated by smiling, which is a repeated contraction of the upper lip elevators, mainly the zygomaticus muscles. Radial lip and marionette lines are caused by the concomitant movement of mimetic muscles during chewing and lip tightening. It is well-known that mimetic wrinkles respond to the decreased muscle tone induced by therapeutic measures, such as the injection of botulinum toxin to the muscle or a direct muscle resection. In contrast, patients with long-standing unilateral facial nerve paralysis will develop a descent of the hemifacial cheek soft tissues and flattening of the nasolabial crease, as compared with the contralateral healthy cheek.

Based on the subjective clinical observation of the “older appearance” of the schizophrenic patients, the present study was designed to assess facial aging. We evaluated wrinkle depth using a dependable and reproducible technique, but found it unreliable for precisely evaluating other facial anatomical changes that occur with aging, such as progressive fat atrophy and folds. Therefore, we added subjective general age estimations by a plastic surgeon and a dermatologist.

Our results showed an overall significant deepening of facial wrinkles in the schizophrenia group in both sexes, as compared to the control group. The correlation ratio between the estimated and true ages was lower for the patients with schizophrenia than for the healthy individuals, with the patient group considered older than they were.

Deeper facial wrinkles can be explained by accelerated photo-aging. Ultraviolet radiation from sun exposure is another factor that can influence aging. We previously reported that hospitalized schizophrenic patients have higher ultraviolet radiation exposure and use less sun protection<sup>16</sup>. This increased sun exposure contributes to changes involving all skin layers, including actinic keratosis (damage to the epidermis), solar elastosis (damage to the dermal connective tissue, wrinkles (damage to the dermis), telangiectasia (damage to the blood vessels), solar comedones (damage to the sebaceous glands), as well as lentiginosities and other pigmentary changes, which contribute to the older appearance of these patients.

In addition, periorbital wrinkles are believed to stem partially from the repeated mimetic contraction of the orbital muscles, primarily the orbicularis oculi, as a defense from solar radiation, when the eyes are not protected by sunglasses.

Schizophrenic patients used more psychotropic drugs than the healthy controls did. Because of an increased physical co-morbidity, patients with schizophrenia are treated with a myriad of systemic drugs. Many of these agents from different classes, such as anti-hypertensives and anti-hyperlipidemics, are potentially photosensitizing<sup>17-21</sup>. It is also well-recognized that higher facial muscle tonus is a side-effect of antipsychotic drugs. This might be a possible pathogenesis of the deeper nasolabial crease in these

patients. The deepening of these facial creases and furrows might be a consequence of higher facial mimetic muscle tonus over a long period.

Cigarette smoking is another potentially exacerbating factor in skin aging, with a direct correlation between the number of packs smoked a year and aged appearance. Also not investigated in our study, previous studies have shown that schizophrenic patients have a higher rate of smoking than the general population and more difficulty with smoking cessation<sup>22,23</sup>.

## Conclusion

In summary, we found deeper facial wrinkles and increased facial aging in patients with schizophrenia compared to controls, as evidenced by the subjectively older facial appearance.

The accelerated aging presumed to be associated with schizophrenia may have a multifactorial pathogenesis. Factors such as antipsychotic drugs, which increase facial muscle tonus and photosensitizing drugs, which increase damage from sun exposure, as well as lifestyle factors such as increased cigarette smoking and sun exposure are contributing factors.

Further studies that assess additional features associated with accelerated aging might contribute to a better understanding of the mechanisms involved in aging and schizophrenia. Patients with schizophrenia should be made aware of the negative consequences of sun exposure and smoking to help minimize the effects of accelerated aging associated with their condition.

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## Conflict of interest

None to declare.

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Case report

# Clinical and histochemical response to an automated microneedling therapy in the treatment of traumatic scars

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Running short title: Microneedling for Scars

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## Abstract

**Background:** post traumatic skin injuries tend to pose as a challenge. Patients may have erythematous, hypertrophic, or atrophic scars. Microneedling therapy is minimally invasive non-surgical and non-ablative procedure used for skin rejuvenation that relies on the principle of neocollagenesis.

**Aim:** our aim was to assess the clinical and histochemical response to an automated microneedling therapy in the treatment of traumatic scars.

**Methods:** this prospective study included twenty patients with traumatic scars. All patients received 4 monthly sessions of said automated microneedling therapy. The outcome assessment included a modified Vancouver Scar Scale, digital photographic documentation and a representation of the patient's satisfaction. A Histochemical evaluation was obtained by a quantitative morphometric assessment for collagen and elastic fibers using an image analyzer performed before and 3 months after treatment for Masson's trichrome and Orcein stained sections respectively.

**Results:** there was a statistically significant improvement in scar vascularity ( $p= 0.018$ ), scar pigmentation ( $p= 0.008$ ), and scar pliability ( $p= 0.002$ ) and the sum of mVSS ( $P=0.000002$ ). Histochemically, there was a significant increase in the amount of collagen, ( $p= 0.023$ ), and elastin ( $p= 0.003$ ) as quantified by an image analyzer. There was no significant correlation ( $r: 0.158$  and  $-0.259$ ;  $p$ -values:  $0.55$  and  $0.34$ ) between the micro-needling therapy and the scar type (atrophic versus hypertrophic). The Treatment was associated with a satisfactory outcome and, except for a temporary erythema, no adverse effects were noted in any patient.

**Conclusions:** the Microneedling therapy for post traumatic scars showed clinical improvement associated with a significant increase in the amount of collagen and elastin. Microneedling seems to be a promising form of treatment, and is a safe, effective and affordable treatment option for the patient.

## Key words

Automated Microneedling, histochemical, traumatic scars

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## Introduction

Post traumatic skin injuries are challenging to deal with. Patients may seek care either immediately after their injury or up to many months later. Patients who seek expert care long after the acute phases of wound healing may have erythematous, hypertrophic, or atrophic scars<sup>1</sup>.

The Microneedling therapy is a minimally invasive non-surgical and non-ablative procedure used for skin rejuvenation. This procedure involves the use of a microneedling device to create a more controlled skin "injury". There are various skin needling devices including the Dermaroller and automated microneedling devices (Dermapen). Microneedling relies on the principle of neocollagenesis and neovascularization which occur as a result of the release of growth factors following the needle piercing of the stratum corneum. These growth factors are believed to be responsible for the beneficial effects of the procedure in the treatment of scars<sup>2</sup>. In this prospective study we aimed at evaluating the clinical and histochemical response to the automated microneedling therapy in the treatment of traumatic scars.

## Patients and methods

Twenty patients with post traumatic scars were prospectively recruited in this study. Patients with Fitzpatrick skin types V and VI, unrealistic expectations, isotretinoin therapy or cosmetic interventions in the treatment area up to 12 months prior were excluded from the study.

All patients were provided an informed signed consent and the study was approved by the Dermatology Research Ethics Committee.

### Treatment procedure

All patients received 4 automated microneedling sessions (4 weeks apart), using an electric Derma stamp pen, Ostar Beauty -OB-DG 01-12 pins-0.25: 2.00 mm depth of penetration. It was adjusted at a 1.5 mm depth and speed level 4. It contains 12 stainless steel needles, where each needle has a 33-gauge diameter, with a 250 µm diameter at entry point. A 25% Lidocaine cream was applied under occlusion 60 minutes before and wiped off just before the session. Sterile saline was used to help the gliding action of the tip of the pen over the skin. All patients were recommended a topical antibiotic cream and a broad-spectrum sunscreen after each micro needling session. All patients were followed up for 3 months after last treatment session.

### Assessment of outcome

Assessment of outcome was done at baseline and three months after the last treatment session by two blinded investigators. The criteria were:

- The Functional outcomes for scar vascularity, pigmentation and pliability according the modified Vancouver Scar Scale<sup>3</sup>.
- A Digital photographic documentation using Sony Cyber, shot on a digital still camera (DSC-W300, Japan);

improvements in scars were assessed independently by comparing clinical photographs obtained before and at the follow up visit (3 months) after the treatment under identical conditions of lighting and positioning.

- The Patient's satisfaction after 3 months of microneedling therapy was graded into slightly better, fair, good, and excellent corresponding numerically to less than 25%, 25% to 50%, 51% to 75%, 76% to 100% improvement respectively.

### Histochemical Evaluation

Two skin biopsies were taken from each patient; one was taken from the scar before the treatment and the 2nd at 3 months after the treatment. Sections of the skin were prepared for the histochemical staining of collagen fibers using the Masson's trichrome stain and elastic fibers using the Orcein stain<sup>4</sup>.

### Image analysis (quantitative morphometric study)

This was performed at the histology department, faculty of medicine, using the Leica Qwin 500 Image Analyzer (Leica Imaging Systems Ltd, Cambridge, UK). It consists of a Leica DM-LB microscope with a JVC color video camera attached to a computer system (Leica Q 500IW). A Morphometric analysis was carried out on both the Masson-stained and Orcein-stained slides. The positioning of the illumination was adjusted in respect to what was visible on the video monitor. Morphometric measurements were performed on a real-time image from the microscope that was visualized on the video monitor. Then the area stained with Masson/Orcein was measured in five fields using a x400 magnification. Results automatically appeared on the monitor in the form of the mean ± the SD<sup>5</sup>.

### Statistical analysis

All analyses were done using IBM, SPSS version 24.

## Results

The age of the patients in the study group ranged between 17 and 43 years old (mean ± SD 27.27± 9.65). Males represented 65% (13 patients) and females represented 35% (7 patients). Fourteen patients (70%) had Fitzpatrick skin type III and the remaining 6 patients (30%) had Fitzpatrick skin type IV. The duration of their Scars ranged between 1 and 5 years (mean ± SD: 3.13± 1.4 years). Thirteen patients (65%) had atrophic scars and 7 patients (35%) had hypertrophic scars. The length of their Scars ranged between 15 and 154 mm (mean ± SD: 54.13±42.7 mm) and the scar width ranged between 1 and 5 mm (mean ± SD: 2.73±1.1mm).

### Modified Vancouver Scar Scale (mVSS)

As shown in table 1, there was a statistically significant improvement in scar vascularity (p= 0.018), scar pigmentation (p= 0.008), and scar pliability (p= 0.002) after each treatment.

This was reflected as a significant improvement in the sum of mVSS after the treatment with automated microneedling (mean ± SD: 1.2± 1.5 compared to 5± 1.5 before treatment, P=0.000002).

Modified VSS (before) and (3 months) after the microneedling therapy									
Scale	Vascularity			Pigmentation			Pliability		
	Pre	Post	P value	Pre	Post	P value	Pre	Post	P value
0	6	14	0.018	7	14	0.008	0	7	0.002
1	11	5		3	2		0	12	
2	3	1		10	4		7	1	
3	0	0		0	0		9	0	
4	0	0		0	0		4	0	

Table 1 - Modified VSS (before) and (3 months) after the microneedling therapy.

### Histochemical Analysis

There was a statistically significant increase in the amount of collagen as assessed by the Masson stain, (Figure 1) and quantified as the area percentage by the image analyzer after the treatment with automated microneedling ( $13.6 \pm 8$  versus  $15 \pm 7.3$ ,  $p: 0.024$ , figure

2). There was also a statistically significant increase in the amount of elastin as assessed by the Orcein stain, (Figure 3) and quantified as area percentage by the image analyzer after the treatment with automated microneedling ( $3.8 \pm 2.7$  versus  $5 \pm 3.1$ ,  $p: 0.0003$ , figure 4).

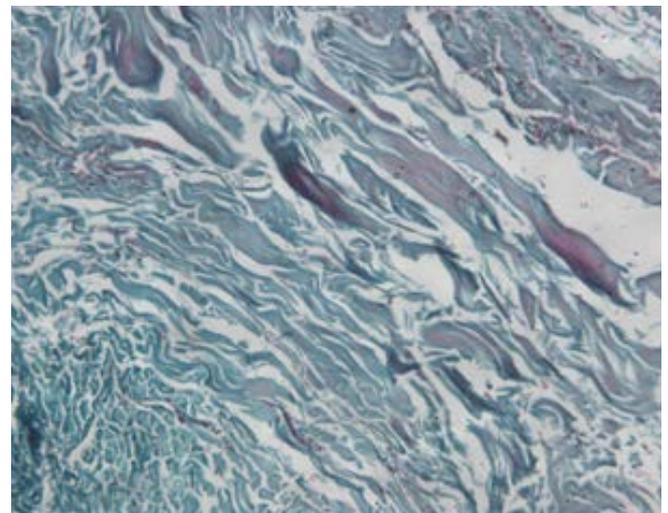
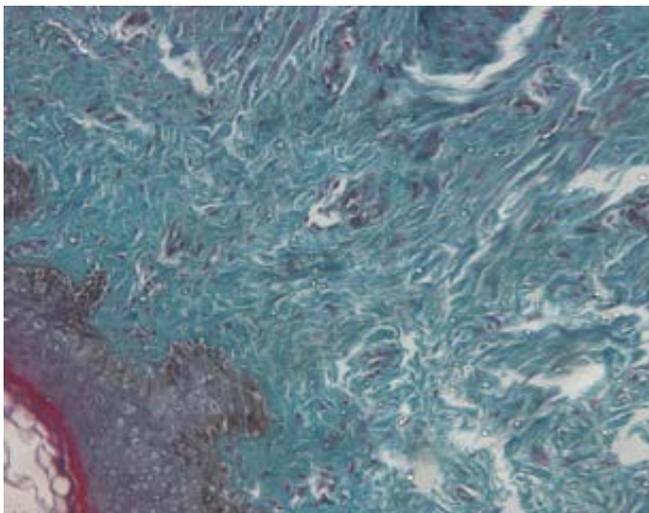


Figure 1 - Collagen content before and after 4 monthly microneedling therapy, Masson stain, x 400.

As the study population included atrophic and hypertrophic scars with different histopathological features, and aimed to study the effect of automated microneedling on histopathological changes, we chose to consider the correlation between scar type (atrophic/hypertrophic) and stained areas.

There was no statistically significant correlation ( $r: 0.158$  and  $-0.259$ ;  $p$ -values:  $0.55$  and  $0.34$ ) between atrophic versus hypertrophic scars treated with the microneedling therapy regarding a change in Masson or Orcein stained areas respectively.

### Photographic Assessment

There was an improvement in the clinical appearance of scars as shown in table 2, figures 5 and 6.

### Patient Satisfaction

The Automated micro-needling therapy was associated with a satisfactory outcome as assessed after 3 months of treatment, (Table 2). All patients tolerated the procedure well, and except for a temporary erythema, no adverse effects were noted in any patient.

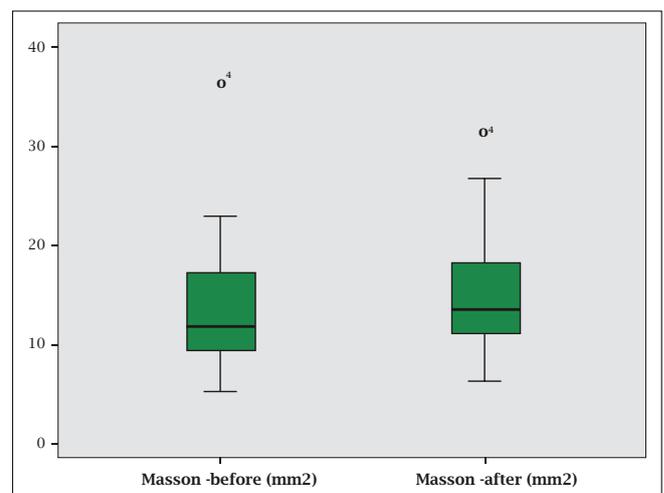


Figure 2 - Collagen content (Masson stain area) before and after 4 monthly microneedling therapy.

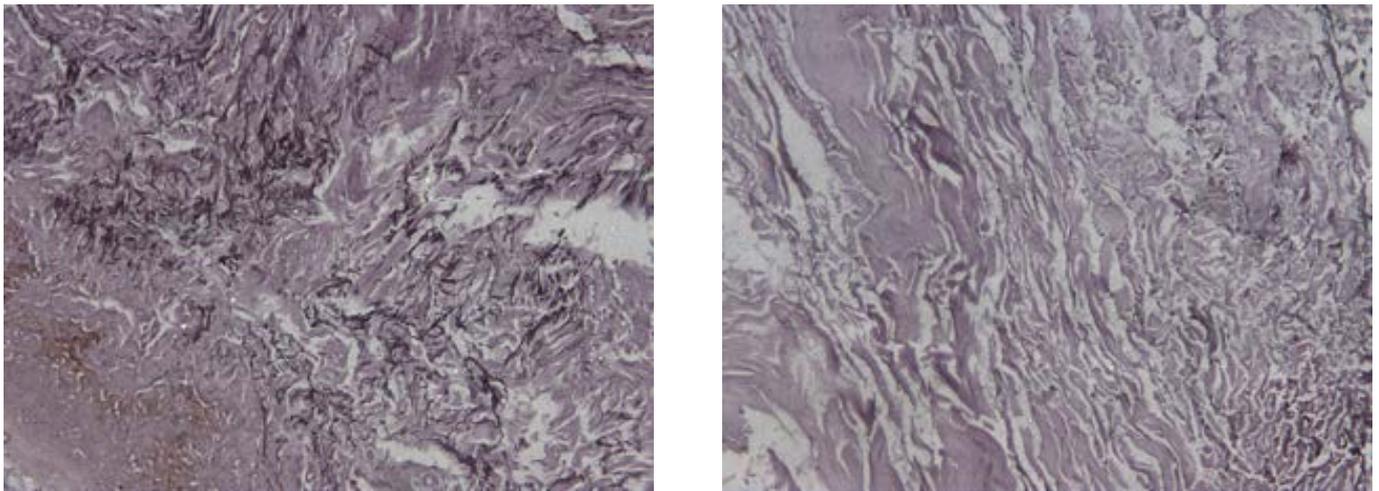


Figure 3 - Elastin content before and after 4 monthly microneedling therapy, Orcein stain, x 400.

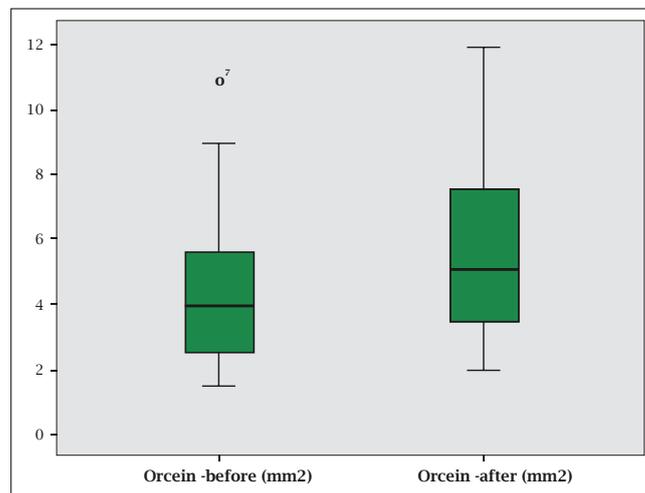


Figure 4 - Collagen content (Masson stain area) before and after 4 monthly microneedling therapy.

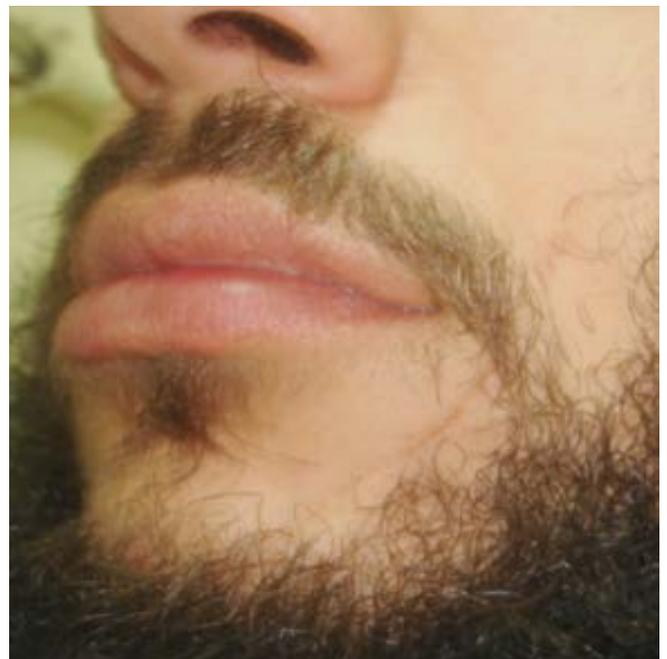
	Photographic outcome				Total
	SB	Fair	Good	Excellent	
Count (%)	3 (15%)	2 (10%)	9 (45%)	6 (30%)	20 (100%)
	Patient satisfaction				Total
	Count (%)	2 (10%)	2 (10%)	8 (40%)	

SB: Slightly better

Table 2 - Photographic outcome and patient satisfaction after the microneedling therapy.



*Figure 5 - Atrophic scar, before and 3 months after treatment with microneedling.*



*Figure 6 - Atrophic scar, before and 3 months after treatment with microneedling.*

## Discussion

In the current prospective study, twenty patients with traumatic scars were subjected to an automated microneedling therapy using a dermapen device. There was a statistically significant improvement in scar vascularity, pigmentation, pliability and the sum of modified VSS post treatment. This was associated with a significant improvement in the photographic outcome and patient satisfaction.

Compared with ablative procedures, microneedling keeps the epidermis partially intact, and the retained skin barrier hastens its recovery and limits the risks of infection and scarring<sup>6</sup>. In addition, microneedling does not target specific chromophores in the skin or use thermal energy, and therefore has a minimal effect on its pigmentation<sup>7</sup>.

Few previous studies evaluated the role of microneedling therapy in treatment of traumatic scars. Vijaya Y et al., evaluated microneedling therapy using dermaroller for 14 patient with facial scars mostly of traumatic and postoperative origin and reported a satisfactory clinical improvement in the scar level and color with an added advantage of minimal downtime<sup>8</sup>. Bandral et al., evaluated the role of microneedling using a dermaroller in the treatment of 50 patients with facial scars of different etiologies, including 27 patients with traumatic scars and reported a 64% clinical success rate<sup>9</sup>.

In a large prospective study, Alster et al., evaluated 120 patients with facial and non-facial scars from a variety of etiologic sources (acne, trauma, surgery) treated using a mechanical microneedling device, with which a clinical improvement was achieved in most patients. Moreover, no significant clinical differences were observed in the treatment responses of facial versus non-facial scars nor between responses of atrophic acne scars and traumatic or surgical scars<sup>10</sup>. In a recently published systematic review involving 1845 patients from 58 studies, the microneedling therapy proved to be a well-tolerated, minimally invasive procedure with a high level of patient satisfaction for the treatment of different types of scars<sup>11</sup>.

Histochemically, this study revealed a statistically significant increase in collagen and elastin contents, as quantified by an image analyzer. In a pilot study, El-Domyati et al., reported a 51%–60% improvement in scar appearance, 40%–50% improvement in skin texture, 80%–85% overall satisfaction, and a significant increase in the production of collagen types I, III, and VII following six treatment sessions using microneedling in 10 patients with atrophic post acne facial scars<sup>12</sup>. In post burn scars, Zayed et al., reported a significant increase in the deposition of elastin, but an insignificant increase in the deposition of collagen after the microneedling therapy<sup>13</sup>. On the other hand, Aust et al., reported a considerable increase in collagen deposition in atrophic burn scars 6 months following the microneedling treatment sessions<sup>14</sup>.

A Few studies in literature compared the efficacy of microneedling versus other modalities like lasers, resurfacing in different clinical subsets. Soliman et al., reported a 55% moderate-excellent improvement of striae in the dermaroller-treated side versus 76% with

a fractional CO2 laser-treated side concluding that, the fractional CO2 laser is more effective in treating striae, with acceptable side effects, however microneedling can be considered an effective, safe and cheap method<sup>15</sup>.

In a split-face study, Osman et al., reported a significantly higher efficacy with the ablative fractional Er:YAG laser than with microneedling in the treatment of atrophic acne scars, with a significantly shorted total downtime in the microneedling-treated sides<sup>16</sup>. On the other hand, Cachafeiro et al., reported no statistically significant difference between the efficacy of a 1,340 nm non-ablative fractional erbium laser and microneedling in the treatment of post acne scars<sup>17</sup>.

Previous articles suggest that microneedling improves the appearance of scars. However, a noticeable difference in treatment regimen was observed in a recently published systematic review. A Microneedling procedure was performed between 3 and 8 times with intervals ranging from 2 to 4 weeks, highlighting the lack of standard treatment protocol<sup>18</sup>.

During the 3-month follow-up in our study, there were no reported cases of hypopigmentation or permanent hyperpigmentation. Moreover, treatment sessions were well tolerated by the patients. A Treatment with microneedling may reduce the risk of hyperpigmentation through the downregulation of a melanocyte-stimulating hormone during the postinflammatory response<sup>19</sup>.

To the best of our knowledge, this is the first prospective study assessing an automatic microneedling therapy for post traumatic scars with a clinical and histopathological analysis of all the study population. The Current studies clearly demonstrated that the microneedling therapy is a safe, efficacious more affordable alternative treatment option for these patients. Microneedling seem to be a promising treatment modality for post traumatic scars. Multiple adjunctive therapies are available and scar treatment should be individualized based on the patient and scar characteristics. The best results will likely be achieved through a multi-specialty collaboration, the use of innovative technology, and a combination of therapeutic modalities. Finally, further studies need to be carried out on a larger sample size with the consideration of scar subtypes and the skin types of individuals for more conclusive results.

## Conclusions

The Microneedling therapy for post traumatic scars showed clinical improvements associated with a significant increase in collagen and elastin content. Microneedling seems to be a promising treatment modality being a safe, efficacious and an affordable treatment option for these patients.

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### Conflict of interest

The authors declare no conflict of interest.

### Author's contributions

HAS and SE were the principal investigators and carried out the study design, supervision and data auditing. NAS and SBM were involved in patient assessment, performing microneedling sessions. ES and RFH were responsible for the recruitment of patients, database entry, and follow-up of patients. SSES performed the histochemical and quantitative morphometric analysis. NAS and ES wrote the manuscript. All authors have read and approved the manuscript.

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Case report

# Evaluation of the beneficial impact of atopic dermatitis treatment with high- and low-molecular-weight hyaluronic acid hybrid stable cooperative complexes: a case report

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## Abstract

**Background:** in the general population up to 10% of adults and 20% of children are affected by atopic dermatitis (AD). This is presented as an inflammatory skin alteration that can chronify with a pattern of skin lesions with pruritus. The primary pathogenic mechanism of AD is thought to be an immune malfunction. The mainstream therapy is composed of steroids applied topically and an oral immunosuppressant: both treatments may generate side effects in the long-term. High and low molecular weight hyaluronic acid hybrid stable cooperative complexes (HCC) are considered different ways to cure, prevent and manage AD.

**Purpose:** to report a two year follow up assessment of a therapy where an injection of HCC in a female person with AD was performed.

**Materials and methods:** product treatment sessions have been done according to the HCC protocol of injection, i.e. 0,2mL per point on 10 points for the full face following the technique described as Bio Aesthetic Points (*Figure 1*).

The suggested protocol included 2 treatments that were performed one month apart from each other, then there were programmed follow-up sessions every 2 months. The follow-up sessions, as well as assessing the patient skin status, were performed as a maintenance treatment.

**Results:** the injection of HCC created a steady beneficial impact with a visible improvement in two aspects: curing the inflammatory lesions and keeping the skin barrier in the adult affected by AD. There were not observed adverse events.

**Conclusions:** even though these results need to be corroborated, there is strong evidence that the HCC treatment may be used as an additional therapy for the treatment of AD.

## Keywords

Atopic dermatitis, hyaluronic acid, stable hybrid cooperative complexes

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## Introduction

In the general population up to 10% of adults and 20% of children are affected by atopic dermatitis (AD). This is presented as an inflammatory skin alteration that can chronify with a pattern of skin lesions with pruritus. It is well known that the quality of life of patients affected by inflammatory skin alterations is lowered<sup>1,2</sup>. Research on this field has shown that AD is manifested with a complexity of different factors combining specific genes and the environment. Both contributing to the manifestation of this disease<sup>3,4</sup>.

Traditionally, the primary pathogenic mechanism of AD is thought to be caused by an alteration of the immune system due to a malfunction of Th1/Th2, synthesis of IgE and others, provoking pruritus and skin dermatitis but also an alteration of the epidermal barrier<sup>5-7</sup>. An Epidermal barrier dysfunction is the key abnormality in the pathophysiology of atopic dermatitis not a consequence of the atopic dermatitis.

During childhood the environment and its factors have a primary relevance on the pathogenesis of AD<sup>8</sup>. Some of them such as food allergies<sup>9</sup> or infections generated by microorganisms can aggravate the disease<sup>10</sup>.

The diagnosis is clinical even though other checks, including the biopsy of the skin, can be done to discard different illnesses<sup>11,12</sup>.

Several sets of criteria have been proposed for the diagnosis of AD, including recently also new simplified models, in order to further define and update current diagnostic criteria<sup>13,14</sup>.

The most commonly used drugs for this treatment are systemic immunosuppressants and steroids and are applied topically. Unfortunately, however, they can become toxic in the long run. Nowadays systemic drugs (azathioprine, cyclosporine) and phototherapy have been used as therapeutic procedures for refractory and severe AD<sup>4,15</sup>. Alternative therapies are gamma-interferon and mycophenolate<sup>16</sup>.

Recently we can find a focus increase on the use of different biological agents even though these treatments are linked to an increase in the number of paradoxical adverse events, including the acceleration of AD<sup>17</sup>.

Hyaluronic acid's (HA) antioxidant capacity and anti-inflammatory properties have been described recently linked to its specific molecular weight<sup>18</sup>.

Low and medium molecular weight HA boosts hydration and activates CD44 receptors. The normal functions of HA binding with CD44 induce wound healing, angiogenesis and immune modulation<sup>19</sup>.

These activities are linked depending on the specific HA molecular weight. From 1800 kDa down to 50 kDa, CD44 was the recognized receptor and pro-inflammatory biomarkers were only slightly up-regulated during wound healing in the presence of HA, the lower the fragment size (<50kDa), the higher is the up-regulation of the inflammatory cytokines<sup>20</sup>.

However, CD44 is found to be highly expressed in pathologic skin processes. The concentration is found to be negatively correlated with the distribution of HA<sup>21</sup>. The synthesis of HA is regulated by hyaluronan synthases (HAS). Regarding AD during inflammation, changes on the regulation of HAS can also be observed: HAS1 is downregulated while HAS3 is upregulated<sup>22</sup>.

Regarding high molecular weight HA, it provides lift, scaffold action and it is the main extra cellular matrix component, playing a crucial role in the structural maintenance thanks to the interaction within collagen, elastin, glycoproteins and proteoglycans. Low molecular weight HA: induces a deep cellular trophic and hydrating action<sup>23,24</sup>.

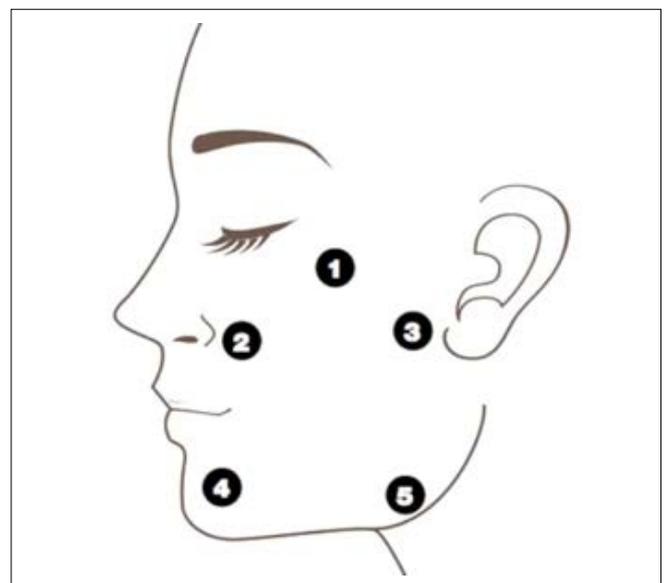
The combination of high molecular weight HA together with low molecular weight HA re-establishes an optimal extracellular microenvironment. Hyaluronic acid stable hybrid cooperative complexes (HCC) induce wound-healing activity<sup>25</sup>. The slow long-lasting release of HA does not cause any further stress to the tissue and helps to prolong the action of HA. Higher biological activity of HCC than natural H-HA and L-HA was reported in fibroblasts (HDF cells). In addition, HCC showed a much lower activation of the TGF- $\beta$  expression and therefore less inflammation. The mix of these properties can result into the down regulation of the skin inflammatory reaction in AD<sup>25</sup>.

The evaluation of the beneficial impact of the treatment of AD with HCC in an adult patient is described in this case report.

## Case description

A 42 year old female affected by AD since youth, mostly present on the facial area, creating a psychosocial impairment, not properly managed with systemic immunosuppressant or topical corticosteroids and without other illness, was selected for a HCC skin tightening procedure in our clinic.

Three treatment sessions were suggested in the first year, with the first two programmed monthly, while the follow-up sessions were programmed bimonthly. Two milliliters HCC were used per session. The injectable method used was the Bio Aesthetic Points (BAP) technique (*Figure 1*)<sup>26</sup> with a 29G needle, 5 boluses subdermal per hemiface with 0,2ml per bolus.



*Figure 1 - Schematic representation of the Bio Aesthetic Points technique injections. Adapted from<sup>26</sup>.*



**Figure 2** - Representative images of AD before HCC injection (A) (baseline), one month after 2nd treatment (B), one year after 1st treatment (C) and two years after 1st treatment (D), a progressive reduction on erythema and scaling with an improvement of skin texture have been observed (B, C and D).

The BAP technique was used to avoid danger zones and to promote a better diffusion of the product into the tissue<sup>26</sup>. Contraindications, such as an active infection of the skin, pregnancy and anyone younger than 18 years old, were not present.

No adverse events occurred, except for a visible bruise on the lower malar mound region that healed within 2 days.

The treatment was able to produce a significant improvement of both the pruritus and eczema, in a time-dependent manner already observable after 1 month of therapy (Figure 2). In addition, a progressive reduction on the erythema with an improvement of skin texture have been observed (B, C and D). Two years after the first treatment, the patient was very satisfied with the overall outcome and with no evidence of relapse.

## Discussion

AD is the most frequent inflammatory skin disease, associated with a significant morbidity, including dry skin, eczematous lesions, chronic itching and generally a relapsing clinical history, that greatly impacts the patient's quality of life<sup>4</sup>. Knowing the different features of AD, finding a therapeutic option whilst avoiding complications like sleep loss, skin infections, psychosocial problems or hospitalization, can be complex<sup>27</sup>.

This case report suggests that subcutaneous injections of HCC ameliorate the signs and symptoms of AD and that possibly their immunomodulatory effects can alleviate the inflammatory/allergic response. In fact, the treatment produced a long-standing therapeutic effect with significant improvements of the AD clinical signs and reduction in pruritus. In addition, treatment compliance was very good with a high level of satisfaction from the patient.

## Conclusion

This report demonstrates that an injectable treatment with HCC is beneficial to conserve the skin barrier and reduce inflammation. This outcome suggests that the wound healing and reduction on inflammation capacity of HCC, as recently published evidence support<sup>23,24,28</sup>, may help to reduce the symptoms of AD. This data needs to be corroborated, but suggests that HCC has a therapeutic and preventive benefit in the handling of AD. The molecular mechanisms underlying the observed effect need to be investigated further.

## Ethics and consent

The patient gave signed informed consent for the publication of her case and images. No Approval from the institutional review board is needed.

## Disclosure

The author declares no conflicts of interest.

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## Courses and Congresses 2022

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**22 - 23 April - Brussels (Belgium)**  
**National Congress of the Belgian Society of Aesthetic Medicine**

Hotel Du Congres - Radisson Collection Hotel  
President: J. Hebrant  
Web: [sbmebveg.be](http://sbmebveg.be)

**13 - 15 May - Rome (Italy)**  
**43rd SIME Congress**  
**Italian Society of Aesthetic Medicine**

Rome Cavalieri Congress Center  
President: E. Bartoletti  
E-mail: [congresso@lamedicinaestetica.it](mailto:congresso@lamedicinaestetica.it)  
Web: [www.lamedicinaestetica.it](http://www.lamedicinaestetica.it)

**3 - 5 June - Paris (France)**  
**IMCAS World Congress 2022**

Palais des Congrès  
President: B. Ascher  
Web: [www.imcas.com/en/attend/imcas-world-congress-2022](http://www.imcas.com/en/attend/imcas-world-congress-2022)

**17 - 18 June - Opatija (Croatia)**  
**3rd Croatian Congress of Aesthetic and Antiaging Medicine**

**Croatian Association of Aesthetic Medicine - HUEM**  
Hotel Milenij  
President: E. Bunar  
Web: [www.huem.eu/congress](http://www.huem.eu/congress)

**23 - 25 June - Mexico City (Mexico)**  
**23rd World Congress of Aesthetic Medicine - UIME**  
**Mexican Scientific Society of Aesthetic Medicine**

Pepsi Center, WTC Mexico City  
President: B. Miller  
Email: [inscripciones@congressmcm.com](mailto:inscripciones@congressmcm.com)  
Web: <https://congressmcm.com/2022/>

**8 - 10 September - Pretoria (South Africa)**  
**17th Aesthetic Medicine Congress of South Africa**  
**AMCSA 2022**

CSIR International Convention Centre  
President: A. Clark  
Email: [info@aesthmed.co.za](mailto:info@aesthmed.co.za)  
Web: <https://aesthmed.co.za/>

**9 - 10 September - Paris (France)**  
**42nd Congress of Aesthetic Medicine and Dermatological Surgery**  
**French Society of Aesthetic Medicine**

Palais des Congrès de Paris  
President: JJ. Legrand  
Email: [info@sfme.org](mailto:info@sfme.org)  
Web: [www.sfme.org](http://www.sfme.org)

**29 September - 1 October - Lima (Peru)**  
**3rd Scientific Congress of Aesthetic Medicine**  
**Scientific Association of Aesthetic Medicine of Peru - ASOCIME**

Hotel Sol de Oro  
President: I. Ogata  
Email: [informes3@grupomilenium.pe](mailto:informes3@grupomilenium.pe)  
Web: <https://www.facebook.com/Asocime/>

**21 - 22 October - Toronto (Canada)**  
**CAAM 19th Annual Conference**  
**Canadian Academy Aesthetic Medicine**

The Westin Harbour Castle  
President: J. Carroll  
Email: [info@caam.ca](mailto:info@caam.ca)  
Web: <https://www.caam.ca/conference-education->

**11 - 12 November - Long Beach (California - USA)**  
**18th AAAMC**  
**American Academy of Aesthetic Medicine Congress**

Hilton Long Beach Hotel  
President: M. Delune  
Email: [enquiries@aaamed.org](mailto:enquiries@aaamed.org)  
Web: <http://www.aaamed.org/congress/>

**25-27 November - Warsaw (Poland)**  
**20th International Congress of Aesthetic and Anti-Aging Medicine**  
**Polish Society of Aesthetic and Anti-aging Medicine - PTMEiAA**

Hotel Hilton Warsaw  
President: A. Ignaciuk  
Web: <https://www.ptmeiaa.pl/>



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