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Contents

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

Submission of manuscripts

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: aemj@aestheticmedicinejournal.org. Manuscripts must be written in English, and authors are urged to aim for clarity, brevity, and accuracy of information and language. All manuscripts must include a structured abstract. Authors whose first language is not English should have their manuscripts checked for grammar and stylistic accuracy by a native English speaker.

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Title page
The title page should include:
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The length of the abstract should be no more than 250 words and should include the following hea- dings: Background, Aim, Methods, Results, Conclusions

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Up to six keywords should be listed and separated by a comma (please, verify keywords on MeSH).

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The manuscript should be organised in the following sections:
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· Introduction
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· Results
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· Conflict of interest
· Reference list
· Legends (max 10)

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· Use the table function, not spreadsheets, to make tables

Acknowledgments

The authors declare that they have no conflict of interest.
If potential conflicts of interest do exist, the authors should provide details (see below) for each affected author in a note in a separate DISCLOSURE section of the manuscript document text, before the list of references.

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References must be cited consecutively in the text as superscript numerals and listed on a separate sheet in numerical order at the end of the text. The references must be cited according to the AMERICAN MEDICAL AS- SOCIATION (AMA) CITATION STYLE.
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Journal article - online* *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. *J Hum Nutr Diet.* 2012; 25(1): 43-49. **doi: 10.1111/j.1365-277X.2011.01184.x**
Journal article - online from a library database* *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. *JEMS* **[serial online].** November 2011; 36(11):32-48. **Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed February 2, 2012.**
Newspaper article - in print* *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. *Minneapolis Star Tribune.* May 14, 2004:1B.
Newspaper article - online	Pollack A. FDA approves new cystic fibrosis drug. *New York Times.* January 31, 2012. http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?ref=health Accessed February 1, 2012.
Websites	Outbreak notice: Cholera in Haiti. Centers for Disease Control and Prevention Web site. https://www.cdc.gov Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012.
Entire book - in print	Modlin J, Jenkins P. *Decision Analysis in Planning for a Polio Outbreak in the United States.* San Francisco, CA: Pediatric Academic Societies; 2004.
Book chapter - in print	Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. *Allergens and Allergen Immunotherapy.* 3rd ed. New York, NY: Marcel Dekker; 2004:585-606.

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AMA Manual of Style: A Guide for Authors and Editors. 10th ed. Oxford: Oxford UP.

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Example Article

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. J Acad Nutr Diet. 2012;112(11):1774-1784. doi: 10.1016/j.jand.2012.06.368.

In-Text Citation Example

LARGE 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,[1] it is estimated that SSB account for about 10% of total energy intake in adults[2,3]. High intake of SSB has....

References Section Example

References

1. Duffey KJ. Popkin BM. Shifts in patterns and consumptions of beverages between 1965 and 2002. *Obesity.* 2007:15(11):2739-2747.
2. Nielsen SJ. Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med.* 2004;27(3):205-210.
3. Drewnowski A. Bellisle F. Liquid calories, sugar, and body weight. *Am J Clin Nutr.* 2007;85(3):651-661.

Use commas to separate multiple citation numbers in text, like you see between references 2 and 3. Unpublished works and personal communications should be cited in the text (and not on the reference list).1 Superscript numbers are placed outside periods and commas, and inside colons and semicolons. When citing the same source more than once, give the number of the original reference, then include the page number (in parentheses) where the information was found. See pages 41-44 of the AMA Manual of Style for more information.

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Citing AMA guide website http://libguides.stkate.edu/c.php?g=101857&p. Updated April 2011. Accessed October 24, 2012.

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Editorial

In modern years, aesthetics has become quite important in every aspect of everyday life: following the hundreds of journals, magazines, blogs and websites pointing their attention towards this interesting and fascinating topic, the request for aesthetic medicine has increased manifolds.

Aesthetic Medicine is a new field of medicine, in which different specialists share the aim of constructing and reconstructing the physical equilibrium of the individual. Treatment of physical aesthetic alterations and unaesthetic sequel of illnesses or injuries, together with the prevention of aging, are perhaps two of the most iconic areas of intervention for Aesthetic Medicine.

However, in order to prevent frailty in the elderly, a program of education is similarly important.

Furthermore, the line between health and beauty is extremely thin: psychosomatic disorders resulting from low self-esteem due to aesthetic reasons are frequent and can- not be ignored by a clinician.

It is therefore clear that there is no figure in the field of medicine which is not involved in Aesthetic Medicine: endocrinologists, gynecologists, angiologists, psychologists and psychiatrists, plastic surgeons, dermatologists, dieticians, physiotherapists, orthopedists, physical education instructors, massophysiotherapists, podologists, and rehabilitation therapists are just some of the specialists who are sooner or later going to have to answer their patients' needs for aesthetic interventions.

The involvement of all these specialists fits the description of health as defined by the WHO: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" for which, undeniably, a team of different physicians is required.

The number of patients requiring medical consultation for esthetic reasons is rapidly increasing: in order to be able to provide adequate feedback, medical and paramedical specialists should be trained and, more importantly, should be taught how to work together. Existing Societies of Aesthetic Medicine from different countries share the aim of creating such teams and provide constant updates to the literature: the creation of an international network of specialists from all around the world under the flag of Aesthetic Medicine represents a challenge, but at the same time it is the proof of the widespread interest in this topic.

The first issue of this Journal represents the results of the efforts of the many national Societies and of the Union Internationale de Medecine Esthetique, now together as one; it is our hope that in years to come this Journal might improve our knowledge in this field, and provide adequate scientific advancement in the field of Aesthetic Medicine.

Francesco Romanelli
MD Editor-in-chief
Associate Professor at "Sapienza" University of Rome

Editors' notes

Aesthetic Medicine, the booming medical activity

Aesthetic Medicine was born in France 40 years ago.
The French Society of Aesthetic Medicine was the first of its kind in the world, followed by Italy, Belgium and Spain. Starts were rather difficult as aesthetic procedures in those early years were only surgical.
At that time aesthetic doctors and cosmetic dermatologists had very few real medical procedures to offer to their patients for treating aesthetic problems on face and body.
At the beginning of the '80s, viable medical procedures started to emerge in Europe for aesthetic and cosmetic purposes. Mostly, at that time, they were imported from the United States: those included collagen injections for wrinkles (Zyderm by Dr. Stegman), and chemical peels (phenol by Dr. Baker, TCA by Dr. Oba- gi). But, subsequently, European research on Aesthetic Medicine gained momentum. Hyaluronic acid appeared on the market, as it was discovered that it could be used as a dermal filler for wrinkles. During the '90s, the use of lasers offered aesthetic doctors and cosmetic dermatologists new possibilities.
The "beam revolution" started with CO2 laser for facial resurfacing.
Today, CO2 resurfacing is not used as much anymore, because of the long and difficult postop. CO2 laser was replaced with the gentler Nd-YAG and Erbium lasers and more recently with non invasive photonic devices for facial rejuvenation, including IPL, US and radiofrequency. These new technologies allow today's aesthetic doctors and cosmetic dermatologists to offer their patients procedures with low risk of post- op complications. Then, Botulinum Toxin has "invaded" both sides of the Atlantic Ocean.
Today, Botox injections are the most popular treatment for facial expressive wrinkles.
Botox injections are now so common everywhere that many cosmetic surgeons have given up their bistouries for syringes. Last but not least, development in Aesthetic Medicine is shown by mesotherapy and adipolipolysis.
About lipolysis, new data and recent publications have explained that radiofrequency, ultrasounds and cryolyse could have positive action to dissolve fat and to improve some unaesthetic disorders like cellulite.
These non invasive procedures intend to replace the surgical liposculpture with success.
Nowadays, Aesthetic Medicine has the necessary tools to address all major disorders within the aesthetic field. After 40 years, Aesthetic Medicine is now active in 32 countries in the world (France, Italy, Spain, Belgium, Morocco, Poland, Russia, Switzerland, Kazakhstan, Algeria, Brazil, Argentina, Uruguay, Venezuela, Colombia, Chile, Mexico, U.S.A, Canada, South Korea, Ecuador, China, South Africa, Turkey, Ukraine, Georgia and recently Croatia, Portugal, India, Guatemala, Peru and Bolivia). All 32 national Societies are members of the Union Internationale de Médecine Esth tique (U.I.M.E.). Aesthetic Medicine is taught in 7 countries (France, Italy, Spain, Argentina, Mexico, Venezuela, Kazakhstan) in universities that deliver UIME's diplomas after 3 to 4 years of studies.

What is the future of Aesthetic Medicine?

In the last few decades, patients' desires to look and feel younge, have fueled Aesthetic Medicine and Cosmetic Dermatology: many different procedures have been developed to satisfy the demands.
As life-span have increased, patients today are not only asking about aesthetic procedures, they are also asking for a way to stay in good physical conditions in the last decades of their lives. As a direct result, Anti-Aging Medicine, which covers skin aging and general aging, has recently emerged and expanded very quickly. Anti-Aging Medicine can offer senior patients better nutrition, dietary supplementation with vitamins, minerals, antioxidants, and eventually hormone replacement therapy, but only when needed.
Today, and in the near future, both Aesthetic Medicine and Anti-Aging Medicine will offer to our patients, who now live longer, better wellness with aesthetic treatments for skin aging and anti-aging treatments for general aging. Aesthetic Medicine is booming, but all medical practitioners should be correctly trained, so its future will be bright.

Jean-Jacques Legrand
Former General Secretary and Honorary President of UIME

Aesthetic Medicine: a bioethic act

When in 1977 the Italian Society of Aesthetic Medicine published the first issue of the magazine “La Medicina Estetica” Carlo Alberto Bartoletti, the Founder, wrote an editorial in which traced the pathway of the discipline and of the Scientific Society, still valid and projected into the future.
Today from that Editorial Board arise an International Journal, which wants to be indexed, in order to give to the doctors practicing Aestehetic Medicine all around the world a solid basis of shared knowledge.
In the late ‘60s, what was called in Italy Aesthetic Medicine, moved its first steps thanks to “remise en forme and anti aging projects” imported from the experience the “Institutul de geriatrie Bucuresti”, directed by Dr. Ana Aslan.
For this reason,there is the bioethical imperative that the Discipline should be first prevention, then return to physiology and finally correction.
The worldwide diffusion and the efforts of Industries born on the wave of the phenomenon have often led to choose the fastest route to achieve and maintain the physical aspect in the myth of beauty at all costs, without considering that aesthetic is not synonymous of beauty, but it is a balance between body and mind, and the role of the doctor is to take care of the Person globally and not only focusing on the correction of “a badly accepted blemish”.
Faithful to the teaching of my Master had almost 50 years ago, this new journal will have the task of elevating the human resources, aligning and validating methodologies, but above all affirming the humanitas of the medical art in its purest sense to pursue the good and the graceful for the person who relies on it.

Fulvio Tomaselli, MD
Honorary President of the Italian Society of Aesthetic Medicine

Aesthetic Medicine needs science. All over the world

All Aesthetic Doctors know that science is the basis for safety. Safety is the most important issue in our discipline.
Unfortunately, Aesthetic Medicine is more often surrounded by marketing than by science, despite the hard work done by Scientific Societies all over the World. And, too often doctors working in this field are dealing with sellers that promote products with insufficient scientific studies.
However, they sell it anyway. I think that doctors must learn that the first thing to ask about a medical device is the scientific background regarding that product: patients treated, follow up period, adverse events and, most of all, publications.
With this new International Journal completely dedicated to Aesthetic Medicine, proposed by the Italian Society of Aesthetic Medicine, endorsed by UIME and shared by all the National Societies of Aesthetic Medicine belonging to UIME, World Aesthetic Medicine wants to stimulate scientific production in this discipline to increase safety and quality in aesthetic medical procedures.
Another important goal of the Journal is to catalyze the proposal of new protocols and guidelines in Aesthetic Medicine, with the consensus of the entire Aesthetic Medicine Scientific Community.
What this Journal should achieve in the near future is to improve the number and quality of scientific production in Aesthetic Medicine, in order to allow this discipline to grow in the field of evidence based medicine, not only in the rationale field.
I hope this can be the start of a new era for Aesthetic Medicine, with the commitment of all Scientific Societies all over the world.

Emanuele Bartoletti, MD
Managing Editor
President of the Italian Society of Aesthetic Medicine
General Secretary of UIME

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aesthetic medicine

Original Article

Comparative efficacy and safety of a resorbable filler (Aliaxin® EV) with and without lidocaine for filling nasolabial folds

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Short Title: Aliaxin® Ev and Lidocaine

Abstract

Background: Hyaluronic acid (HA) is commonly used in aesthetic medicine, often mixed with lidocaine to reduce injection discomfort/pain. However, this approach still raises some concerns relating to the possible impairment of quality and efficacy, and possible allergic reactions.

Aim: This study compared Aliaxin EV, a HA-based filler, with and without lidocaine, in terms of efficacy discomfort/pain sensation.

Methods: Aliaxin EV with and without 0.3% lidocaine were compared in this single blind, single-center study by split-face method. Twenty-six female volunteers aged 40-65 were treated. Study treatments included one baseline visit with product injection, and a final visit after 4 weeks. Efficacy evaluations included WSRS and GAIS scales and skin profilometry by 3D nasolabial fold pictures. Tolerability was clinically assessed by the investigator and rated by volunteers on separate VAS for stinging, itching, tightening, burning, discomfort and pain.

Results: Both preparations induced a very significant reduction in wrinkles severity (WSRS score: -33.3%, $p<0.001$ for both preparations). Aesthetic performance was rated as improved compared to baseline according to the GAIS for all 52 hemifaces. Skin profilometry demonstrated statistically significant reductions versus baseline in average roughness (-36% without and -32% with lidocaine; both $p<0,001$ vs baseline) and wrinkle maximum depth (-41% and -31%; $p<0,001$). Immediately after the injection procedure the differences in VAS for pain/discomfort sensations were significant, but not significant at the 2-hour assessment. Only 3 subjects scored a VAS >5.

Conclusions: Aliaxin EV was effective in reducing nasolabial folds, giving a satisfying aesthetic performance with very well tolerated results, both with and without the addition of lidocaine.

The study was registered on ClinicalTrials.gov public registry with the ID NCT03273556.

Keywords

Hyaluronic acid, lidocaine, nasolabial folds

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Introduction

Age-related facial changes recognize several etiologic factors involving changes of the skin, attrition of the facial septa, and craniofacial resorption, with the significant contribution of external factors, such as body mass index, hormones, alcohol consumption, cigarette smoking, and unprotected sun exposure[1-10].
In developed countries, improving the quality of aging has become a major target, also involving aesthetic dermatology. Over the last decade, minimally invasive procedures have expanded exponentially due to the increasing availability of suitable products and the growing preference of patients for non-surgical methods, with consequent increase in the development of injectable materials for soft-tissue augmentation.
Nasolabial folds may become very marked with aging and can be corrected through dermal filler injections which fill the skin from the inside, restoring the lost facial volume and reducing the depth of these creases.
Multiple injectable materials are available, such as various hyaluronic acid products, calcium hydroxyapatite, and a few others. For deep facial wrinkles, dermal fillers, compared to botulinum toxin, have the unique property of augmenting tissue volume. Hyaluronic acid (HA) is commonly used in aesthetic medicine as a filling material (filler), to reduce both superficial and medium-deep wrinkles, or as a bio-revitalizing product to slow down the skin aging process; in fact, thanks to its natural hydrating and stimulating properties, HA reduces the signs of aging while improving skin turgor and elasticity. HA dermal fillers vary widely in their physical and chemical characteristics and many variables contribute to their overall performance; however, they overall fulfill the request for a safe, quick, and effective procedure, and have a lower risk of allergic reactions compared to previously used collagen fillers[11-13]. The main disadvantage to overcome remains the procedure-associated pain and a limited duration of action[13-17]. In order to reduce the discomfort/pain sensation perceived by the subject during and after the injection procedure, lidocaine is often mixed with injectable dermal fillers[11-17]. Several experiences have been reported on the addition of lidocaine to HA products within the clinical settings with positive outcomes in terms of pain reduction[18,19]. However, this technique still raises some concerns relating to the possible impairment of quality and efficacy, as well as the volume and flow characteristics of the injections. Products containing pre-incorporated, preservative-free lidocaine, which generally preserve volume, concentration, consistency and flow characteristics may seem safer, and associated with less procedural pain[13,17].
There are only a few studies directly comparing pure HA fillers and fillers containing HA and lidocaine, whose results reveal in general no significant differences in the safety, efficacy, and longevity of the two treatments, with less procedural pain associated with lidocaine addition[20]. However, the possibility of a true lidocaine allergy should always be considered since cases, though rare, have been reported, including type I – immediate hypersensitivity reactions and severe angioedema, or type IV – delayed reactions[21-23].
Aliaxin EV Essential Volume (IBSA Farmaceutici Italia SrL) is a resorbable medical device, consisting of a physiological, non-pyrogenic sterile gel that contains cross-linked HA (CLHA) of non-animal origin, produced by bacterial fermentation, used as a filler to correct deep facial cutaneous sagging and to increase facial volume. It is known that chemico-physical and biological characterization of HA-based dermal fillers is of key importance to differentiate between the numerous available products and to optimize their use. The different Aliaxin formulations have been tested for their content in soluble HA, water uptake capacity, rheological behavior, stability to enzymatic degradation, and in vitro capacity to stimulate the production of extracellular matrix components, and the different formulations were found to be equivalent to each other regarding insoluble hydrogel concentration[24-28]. The results obtained support the product claims of different clinical indications, and its classification regarding hydro-, lift- action. Furthermore, the biological outcomes also support the efficacy of the product in restoring skin structure[29]. In the clinical setting, Aliaxin® showed that it can be safely and effectively used, either alone or in combination with a non-cross-linked HA complexed with vitamins, antioxidants, amino acids and minerals, to improve nasolabial fold hydration, trans-epidermal water loss and wrinkle aesthetic appearance[30].
This study was aimed at comparing, in women aged 40-65 years, Aliaxin EV without and with the addition of lidocaine 0.3% (extemporaneous mixture) in terms of filler on nasolabial folds and of discomfort/pain sensation perceived by the subject during and after the injection procedure.

Materials and methods

The investigational product, Aliaxin EV, was compared within subjects with Aliaxin EV with lidocaine 0.3% (split-face method); the two injective products were assigned to the right or left face side of each subject according to a previously defined randomization list.

Ethical and regulatory aspects

This study was performed in agreement with the Declaration of Helsinki. Before the screening, all subjects gave written informed consent.
A final version of the study protocol and appendices were submitted to an Independent Ethic Committee (I.E.C) at DERMING S.r.l., Clinical Research and Bioengineering Institute. The President of I.E.C. was Prof. Demetrio Neri. On 10th March 2017, the clinical trial obtained the I.E.C. approval with protocol number E0817. The study was registered on ClinicalTrials.gov public registry with the ID NCT03273556.

Subjects selection and study design

This was a comparative, randomized, single blind (subjects did not know on which hemiface lidocaine was used), single-center investigator-initiated trial of 4-week duration. The investigator was an experienced dermatologist.
The study was conducted on 27 female volunteers, aged 40-65 years, who met the inclusion/exclusion criteria detailed below.
Inclusion criteria were: a Wrinkle Severity Rating Scale (WSRS) score between 2-4; asking for nasolabial folds

correction; having received lidocaine, at least once before, as local anesthetic; agreeing to maintain their normal habits regarding food, physical activity, make-up use, facial cosmetic and cleansing products, and to arrive at each study visit without make-up; accepting to avoid facial exposure to strong UV irradiation (UV sessions, or sun baths) during the study. Main exclusion criteria were: pregnant or lactating women, smokers, alcohol or drug abusers, women having received skin treatments for aesthetic correction, such as biomaterials implants, face lifting, botox injections, laser, chemical peeling, in the 6 months prior to the study start, or any permanent filler in the past, women with dermatitis, or other clinically relevant skin conditions or any skin lesions in the treated area, women affected with systemic diseases. Use of anticoagulants and antiplatelet drugs, anti-histamines, topical and systemic corticosteroids, narcotics, antidepressants, immunosuppressive drugs (with the exception of contraceptive or hormonal treatments starting more than 1 year ago), or of any drugs able to influence the test results in the investigator's opinion was not permitted during the study period. 3 hours before the visit the volunteers were asked not to drink coffee or alcohol, and no cosmetic product to be applied on the skin test areas in the 2 hours preceding each visit.

Study procedures included 2 visits: one baseline visit (T0), when clinical and instrumental evaluations were performed, followed by the injection procedure and thereafter by skin discomfort/pain subjects' self-assessment (immediately and 2 hours after the procedure); and one final visit after 4 weeks (T4) for clinical and instrumental evaluations.

Injection technique

The investigational aesthetic procedure consisted in injecting a maximum of 0.5 mL of Aliaxin EV per hemiface with and without lidocaine 0.3%. Two injection techniques were used in combination: (I) a single-bolus injection with a 27G x 19 mm needle in the periosteal level of the nasal base; (II) linear retrograde injection with a 27G x 13 mm needle in the deep dermis; the needle was inserted along the length of the skin depression and the product was slowly deposited in the fold during needle extraction.

Assessments

Efficacy evaluation included qualitative (clinical) and quantitative (instrumental) assessments performed at both study visits. Filling activity on the nasolabial folds was rated by the investigator by means of the WSRS (*Table 1*)[31], while the aesthetic performance was assessed by the Global Aesthetic Improvement Scale (GAIS, *Table 2*)[32]. At the end of the study (T4), each volunteer was asked to express a self-assessment on the perceived efficacy of the study treatments on the nasolabial folds in terms of filler results (very marked; marked; medium; slight; absent).

Non-invasive instrumental evaluations included 3D nasolabial fold pictures taken with a Primos compact portable device (GFMesstechnik). The Primos software is able to elaborate 3D representations of skin wrinkles as well as measure the main skin profilometric parameters in vivo or on skin replicas, according to the law DIN EN ISO 4228; moreover, the software directly compares the different images obtained at the study visits before and after treatment. As a measuring method, Primos compact uses a digital stripe projection based on micro-mirrors which allows for fast and highly precise measuring data acquisition (the speed <70 ms for measuring data admission provides perfect results). An assortment of different measuring fields, realized by means of different precise recording optics, was used to ensure a wide spectrum of measuring possibilities with ranges up to micrometers.

Following the injection procedure, the investigator assessed product tolerability noting any immediate local events/reactions (swelling, pain, erythema, bruising) and asking for any other adverse event, local or systemic, occurred during the study. Sensations of stinging, itching, tightening, burning, discomfort and pain were scored by each study subject separately for each hemiface immediately and 2 hours after the injection procedure on a 10 unit visual analogue scale (VAS), where 0 means no sensation and 10 very strong sensation. The VAS scores were expressed separately for each of the two treated sides. The volunteers were also asked to express an overall tolerability self-assessment at the end of the study, as bad, poor, good or excellent.

Rating	Description
Grade 1 (absent)	No visible nasolabial fold; continuous skin line.
Grade 2 (mild)	Shallow but visible nasolabial fold with a slight indentation; minor facial feature.
Grade 3 (moderate)	Moderately deep nasolabial folds; clear facial feature visible at normal appearance but not when stretched.
Grade 4 (severe)	Very long and deep nasolabial folds; prominent facial feature; <2mm visible fold when stretched.
Grade 5 (very severe)	Extremely deep and long nasolabial fold, detrimental to facial appearance; 2-4 mm visible V-shaped fold when stretched.

***Table 1** - Wrinkle Severity Rating Scale[31].*

Rating	Description
1: very much improved	Optimal cosmetic result for the implant in this patient.
2: much improved	Marked improvement in appearance from initial condition, but not completely optimal for this patient. A touch up will slightly improve the result.
3: improved	Obvious improvement in appearance from the initial condition, but a touch-up or re-treatment is indicated.
4: no change	The appearance is essentially the same as the original condition.
5: worse	The appearance is worse than the original condition.

***Table 2** - Global Aesthetic Improvement Scale (GAIS)[32].*

Statistical analysis

Efficacy variables expressed in absolute values were compared versus baseline and between the two study products. The data processing was performed by descriptive and inferential analysis: clinical data, VAS and GAIS score by non-parametric test (Wilcoxon test); instrumental data by non- parametric test (Wilcoxon test), when the normality hypothesis was rejected by the Shapiro-Wilk normality test (threshold at 5%), or by parametric test (paired t-test), when the normality hypothesis was confirmed.

Results

Twenty-seven women were included in the study: mean age was 55 years, mean body weight 62.5 kg and mean BMI 27.7. One woman dropped out from the study without a final assessment visit for personal reasons. The statistical analysis was thus performed on the 26 cases who completed the study as per protocol.

Clinical assessment

Both study products induced a very significant reduction in wrinkles severity (mean reduction 33.3%, Wilcoxon test p<0.001 T4 vs T0 for both products) with a decrease ≥1 grade of the WSRS photographic reference scale observed in 100% of the included subjects. The GAIS scores in terms of aesthetic performance, in all 52 hemifaces of the 26 subjects were rated as improved compared to baseline; in particular the investigator rated 8 hemifaces (15% of the subjects) as "improved" (5 with Aliaxin EV alone and 3 with Aliaxin EV plus lidocaine); 26 (50%) as "much improved" (12 and 14 respectively); 18 (35%) (9 and 9 respectively) as "very much improved". There was no significant difference between the two products. The final (T4) GAIS mean value was 1.8 for both treatments. The results of the self-assessment questionnaire on treatment efficacy at T4 are summarized in *Table 3*. All but one volunteer expressed a positive judgment on the global aesthetic performance of the products: 3 reported a slight improvement, 2 a medium improvement and the remaining 21 judged their improvement from marked to very marked; none perceived a difference in overall aesthetic performance between the two treatments.

Instrumental evaluations

Skin profilometry data showed statistically significant reductions versus baseline in average roughness of the analyzed profile (Ra: -36% with Aliaxin EV alone and -32% with the lidocaine combination; Wilcoxon test p<0.001 T4 vs T0 for both products), in wrinkles total height (Rt: -83% and -69% respectively; Wilcoxon test p<0.001 T4 vs T0 for both products), and in wrinkle maximum depth (*Figure 1*; Rv: -41% and -31% respectively; Wilcoxon/ paired t-test p<0.001 T4 vs T0 for both products). No statistically significant difference between the 2 treatments was detectable (Paired t-test T4 Aliaxin vs T4 Aliaxin + lidocaine p>0.05); however, a trend in favor of Aliaxin alone was observed for all parameters. Primos photographic documentation of both hemifaces of subject 21, each treated with a different study product is reported in *Figure 2*.

	Subjects (%)				
	Absent	Slight	Medium	Marked	Very marked
Improvement of nasolabial folds	3.8	11.5	7.7	35	42
Filler effect	3.8	11.5	7.7	35	42
Improvement of skin suppleness	3.8	12	19.2	38	27
Global aesthetic result	3.8	11.5	7.7	42	35

Table 3 *- Efficacy of study treatments: volunteers' self-assessment at study end (T4).*

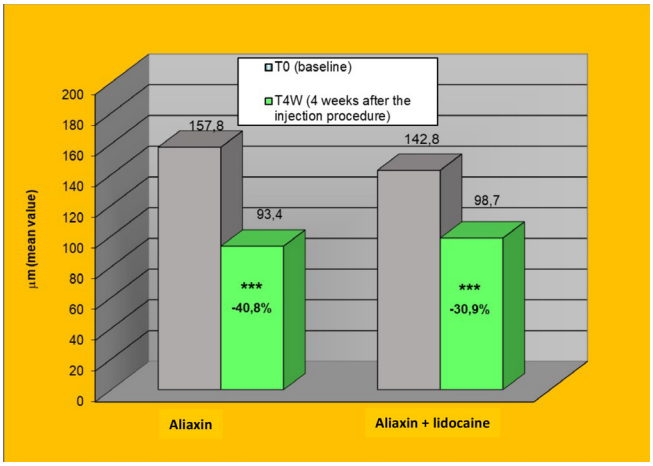

Figure 1 *- Nasolabial fold depth (µm) at profilometry.*

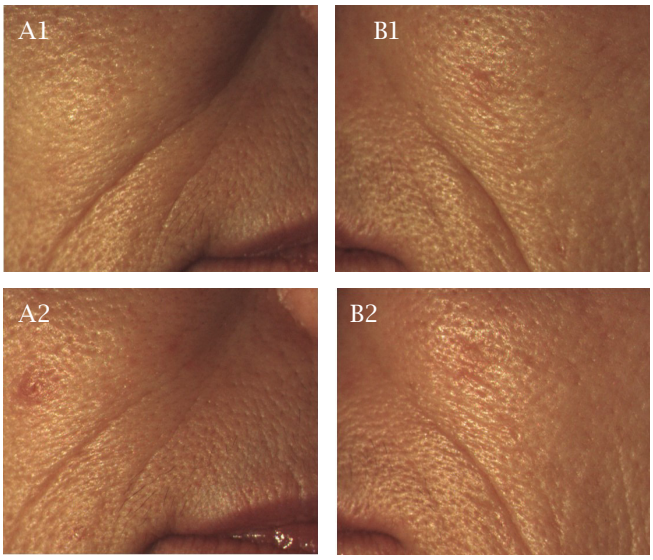

Figure 2 *- Nasolabial folds before and 4 weeks after treatment in the two hemifaces of the same subject (#2).*

A1: *right hemiface at T0;*
A2: *right hemiface at T4, following Aliaxin EV injection (Rv 180 and 113 respectively; Δ -67);*
B1: *left hemiface at T0;*
B2: *left hemiface at T4, following Aliaxin EV + lidocaine injection (Rv 82 and 47 respectively; Δ -35).*

Tolerability

Slight bruising occurred in 10 volunteers at one injection site, which was attributed to the injection procedure and had disappeared at T4; the women reported that the bruises had actually disappeared within 5-10 days. At the volunteers' self-assessment of pain/discomfort sensations, the differences between products were statistically significant immediately after the injection procedure (T0A), losing statistical significance at the 2-hour assessment (T02h). Overall only 3 subjects (12%) scored a VAS magnitude >5. The investigator judged both products overall tolerability good or excellent in 100% of subjects, as did all volunteers. The injection procedure with addition of lidocaine was judged more comfortable by 85% of women, while 15% preferred the procedure with Aliaxin EV alone.

Discussion

An optimal dermal filler should be safe, effective, durable and fully satisfy the patient's aesthetic demand. HA-based injectable products are the most extensively used fillers and may vary greatly in terms of HA concentration, particle size, cross-linking agent used, cross-linking degree, percentage of cross-linked and free unmodified HA. A reliable tool to assess the efficacy of HA-based compounds is the analysis of elastic fibers and collagen in the skin. Indeed, injection of cross-linked HA (CLHA) into dermal-equivalent cultures was shown to induce elongation of fibroblasts and type I collagen synthesis due to up regulation of the transforming growth factor beta (TGF-β) pathway[33]. HA injections also increase the synthesis of neo-collagen I and pro-collagen I and III mRNA compared to baseline[33]. Aliaxin is a recently developed line of HA-based gel medical devices for intradermal treatment, available in prefilled syringes for local injection. All Aliaxin products contain a highly purified cross-linked HA sodium salt, with a mix of molecular weight ranging from 500 to 2000 kDa, and the addition of sodium phosphate and water for injectable preparations. Aliaxin products have a good safety and quality profile, as documented by *in vitro* and *in vivo* tests, and clinical studies[33-36]. Aliaxin EV - Essential Volume is a well-characterized resorbable medical device that, compared to other dermal fillers, showed a particularly high hydro-action with a prolonged aesthetic effect, as well as an easier deliverability due to lower rigidity and viscosity[29]. Its ability to promote restoration of skin structures was demonstrated *in vitro*[29]. The addition of lidocaine to HA products is rather common in clinical practice, with the aim of reducing pain and discomfort associated with the injection procedure, although questions about quality, efficacy, injection characteristics, and safety of the combination have not been fully answered. This is why this study was aimed at comparing Aliaxin EV with and without lidocaine addition in terms of efficacy, safety and tolerability.

In this randomized, split-face study, Aliaxin EV with and without lidocaine showed to be effective in reducing wrinkle depth as measured by the investigator with specific grading scales, by skin profilometry and as judged by volunteers' self-assessment. The two injection techniques used were chosen because the first allows a better performance of the injected product, contributing to the volumetric correction of the compartment without useless dispersion in other anatomical areas, and the second, because it allows a better filling effect of nasolabial folds. The addition of lidocaine to Aliaxin EV reduced pain and stinging and made the injection more comfortable in the judgment of the majority of study subjects, though it has to be remarked that the intensity of such symptoms was rated by very few women higher than half the VAS scale for both products. The overall tolerability of both treatments was judged from good to excellent by the investigator and by all the study subjects. This seems to indicate that the injection procedure was not considered really painful or distressing by the volunteers, even without the addition of lidocaine. Indeed, only 12% of patients scored a significant pain sensation. In our opinion, this suggests refraining from a systematic use of lidocaine, but rather consulting with the patient about his/her pain threshold and evaluate on an individual basis the best anesthetic procedure, also taking into consideration the opportunity of performing a local anesthesia before the procedure instead of using a lidocaine-containing product or an extemporaneous mixture. Though the efficacy of the two products, in terms of nasolabial fold reduction, showed no statistical difference, we think it is worth commenting that the instrumental measurements demonstrated a slight but consistent trend toward a superiority of Aliaxin EV alone for all parameters. Once again, these results do not convince us that the addition of lidocaine to HA dermal fillers impairs their effectiveness. Previous papers published in the literature and a recent metanalysis by Wang[11-16,20] generally report that the addition of lidocaine to HA dermal fillers is safe and inert, and associated with procedural pain reduction. Our results are not in contrast, however, Aliaxin alone showed a somewhat greater efficacy and seemed to not induce clinically significant pain. Moreover, most of the previous studies compared different products[37,38], and only relatively few studies, including a limited number of subjects, directly compared the same product with and without lidocaine[17,39-42]. We feel that the availability of a minimally invasive procedure not conceived as overly painful by women could save the use of an anesthetic with its potential to increase the risk for adverse events, and to impact on product administration and aesthetic outcome[21,22].

Conclusions

In conclusion, Aliaxin EV proved to be effective in reducing nasolabial folds, giving a satisfying aesthetic performance and resulting very well tolerated, both with and without the addition of lidocaine. Further specifically designed studies on larger number of subjects should be required in order to definitely clarify the real impact of the addition of lidocaine to HA dermal fillers.

Notes

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Conflict of interest disclosures

This research was supported by IBSA Farmaceutici Italia Srl. The authors declare that they have no conflict of interest regarding the publication of this paper.

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aesthetic medicine

Original Article

Non-surgical blepharoplasty using fillers: correction of lower eyelid

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Abstract

Background: Injection correction of tear trough with hyaluronic acid fillers usually gives a good aesthetic result. But in some cases, after correcting tear trough with a good immediate result, adverse effects may appear after a while. There is accumulation of the filler below the tear trough, enlargement in the hernia of lower eyelids, and periorbital puffiness. To prevent these adverse effects, it is very important to consider the anatomical features of each patient.
Aim: The report describes the author's classification of the lower eyelid zone and original technique of correction of tear trough and palpebromalar groove, depending on the presence and prominence of orbital fat.
Methods: This study was performed in 118 female patients. Patients were divided into 3 groups, depending on the presence and prominence of orbital fat. The injection correction of the lower eyelid zone was performed using a hyaluronic acid filler.
Results: The result was determined by the patient through a visual assessment of photographs based on the criteria for the presence of tear trough and palpebromalar groove. Patients noted good satisfaction with the results of the correction of the lower eyelid zone. Only six patients were dissatisfied with their results.
Conclusions: Selection of patients and the correction of the lower eyelid zone, taking into account the principles outlined in this report, gives a good aesthetic result with a low risk of adverse effects.

Keywords

Tear trough, lower eyelid, injection, filler

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Introduction

Injection correction of tear trough and palpebromalar groove with hyaluronic acid-based fillers has become part of a practice of aesthetic medicine doctor. This procedure can be carried out by a needle or blunt cannula[1].The lower eyelid zone is the most challenging area to treat with hyaluronic acid[1]. Kane described the correction of the tear trough as a difficult problem with multiple causes. He showed the technique of correction of the tear trough and lower lid using injection of the filler by a needle[2]. Lambros stressed that when correcting tear trough, it is important to evaluate the following factors: skin quality, definition of the hollow, the orbital fat, and the color of the overlying skin. Lambros described the microbolus supraperiostal injection technique of the hyaluronic acid by a needle. He noted that the best patients for the treatment are those with young, thick skin and a definite hollow[3].
In some cases, after correcting tear trough with a good immediate aesthetic result, adverse effects may appear after a while. Such delayed adverse effects include: accumulation of the filler below the tear trough (*Figure 1*), enlargement in the hernia of lower eyelids, and periorbital puffiness[4,5].

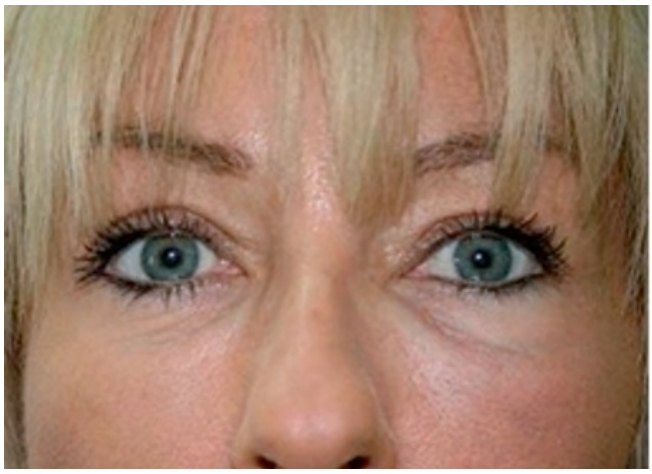

Figure 1 *- Accumulation of the filler below the tear trough.*

To prevent these adverse effects, it is very important to consider the anatomical features of each patient[6].
Hirmand proposed a classification system of the tear trough deformity based on clinical evaluation[7]. Sadick et al. developed the tear trough rating scale by objectively and subjectively evaluating the clinical appearance of the tear trough with regard to depth of the trough, hyperpigmentation, volume of prolapsed fat, and skin rhytidosis[8].
Zhivokova and Krasnoselskikh described the principles of the selection of patients for correction of the periorbital zone by fillers depending on eye prominence, presence and prominence of orbital fat, and location and strength of the orbital ligament[9].
Classification of prominent orbital fat of the lower eyelids is difficult, since the aging of the lower eyelid zone is associated not so much with the increase in fat, but also with the aging of the entire middle third of the face as a whole[10]. However, to facilitate the selection of patients for correction of the periorbital zone by fillers, I apply my original classification of the lower eyelid zone[11]. I identified 3 clinical types of the lower eyelid zone, depending on the presence and prominence of orbital fat:
Type I: no prominent orbital fat *(Figure 2.1)*
Type II: prominent orbital fat in the medial part of the orbit and visualization of the bony orbital
margin in the lateral part (*Figure 2.2*)
Type III: prominent orbital fat visible in both medial and lateral parts of the orbit (*Figure 2.3*).

3 types of aging of the lower eyelid

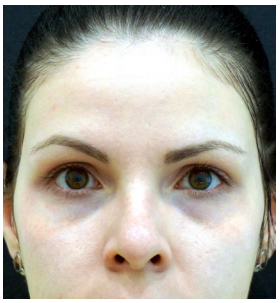

Figure 2.1 *- Type I.*

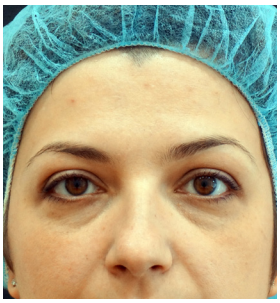

Figure 2.2 *- Type II.*

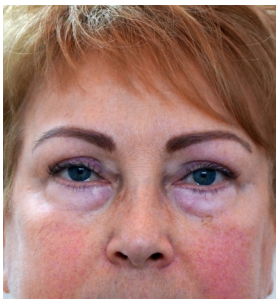

Figure 2.3 *- Type III.*

For patients with the second and especially the third clinical type of the lower eyelid area, I recommend surgical treatment of hernia of the lower eyelid. However, in the presence of contraindications to the operation, injection camouflage of hernias is possible[12].
It should be borne in mind that the target area where the filler will be injected depends on the anatomical features of the periorbital zone, that is, the clinical type of the lower eyelid zone. To reduce the risk of adverse effects, the filler should be injected precisely into the target space, regardless of the instrument used (needle or cannula)[13]. In all cases of augmentation of the periorbital zone by the filler, submuscular (supraperiosteal) level of product placement is used.
Before the procedure, the marking of dangerous areas is necessary to prevent their traumatization: the zone of angular vessels (the inner corner of the eye and the centimeter lateral to it) and a zone of an infraorbital neurovascular fascicle[13]. I recommend to avoid injections into the marked dangerous areas.

Materials and methods

From February 2016 to January 2018 118 female patients were treated, aged between 28 and 56 years old. Patients were divided into 3 groups, depending on the presence and prominence of orbital fat. Treatment was carried out on: 47 type I (37 by needle 10 by blunt cannula), 66 type II (53 by needle 13 by blunt cannula), 5 type III (4 by needle, 1 by blunt cannula). In all cases, a monophasic hyaluronic acid-based filler of average reticulation was used for treatment. Correction of the lower eyelid zone was carried out according to the principles outlined below.

Results

The result was determined by the patient through a visual assessment of photographs based on the criteria for the presence of tear trough and palpebromalar groove. Patients noted good satisfaction with the results of the correction of the lower eyelid zone. Most of the patients in this study were able to resume their normal activities after 1 to 2 days with makeup. In all patients, the aesthetic result lasted for more than one year. Only six patients were dissatisfied with their results because of hypercorrection. For the treatment of this effect, hyaluronidase was used (*Table 1*).

Type of aging of the lower eyelid	Instrument	Total patients	Adverse effects (hypercorrection)	Satisfied patients	Satisfied patients one year after the procedure
Type I	needle	37		37	37
	blunt cannula	10		10	10
Type II	needle	53	2	51	53
	blunt cannula	13	4	11	13
Type III	needle	4		4	4
	blunt cannula	1		1	1

Table 1- *Results and Patient Satisfaction.*

Discussion

Type I correction

The first clinical type is associated with a loss of volume throughout the lower eyelid area[9,11]. More often these are young patients complaining of dark circles under the eyes. When correcting this type, the filler should be injected under the orbicularis oculi muscle into the space bounded from the top (cranial) by septum and from below (caudally) by the orbital ligament (ORL)[14] (*Figure 3.1*). Injection of the filler below the ORL ligament can lead to the accumulation of the filler below the tear trough in the deferred perspective[5]. The marking points between which the injections will be made are: the projection of the bony orbital margin (upper border) and the eyelid-cheek junction (lower border). When correcting with a needle, the filler is injected bolus or microbolus between the upper and lower boundaries under the orbicularis oculi muscle with a preliminary marking of the dangerous zones.

When correcting with cannula, the filler is also injected under the orbicularis oculi muscle between the boundaries described above. The preferred entry point for the cannula at the level of lateral canthus is between the projection of the bony orbital margin and the eyelid-cheek junction (lateral lid entry point). When using the cheek entry point in some cases, the cannula does not pass through the ORL, but pushes it away. As a result, augmentation tear trough using the cannula from the cheek entry point gives a good immediate aesthetic effect, but delayed may result in the accumulation of the filler below the tear trough.

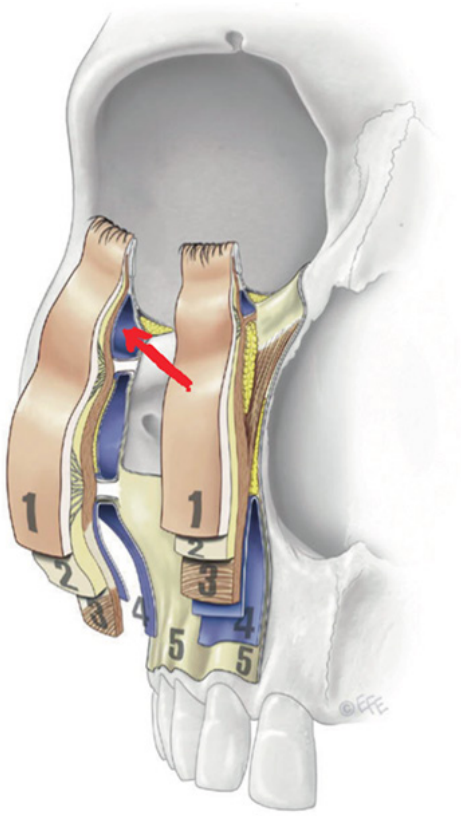

Figure 3.1 *- The anatomy over the skeleton and over bony cavities (1–5), showing the relationship of the soft tissue spaces to bony cavity spaces[9,11]. The arrow shows layout of the filler for type I correction: under the orbicularis oculi muscle into the space bounded from the top (cranial) by septum and from below (caudally) by the orbital ligament (ORL).*

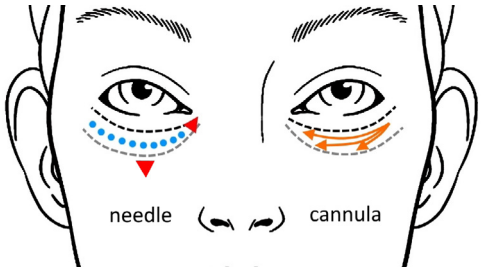

Figure 4.1 *- Scheme of augmentation of the zone of lower eyelid of type I with a needle (left) or a blunt cannula (right). Dangerous areas marked with red. Dashed line - the boundaries of the injection zone: black dotted line - projection of the bony orbital margin, gray dotted line - ORL projection / eyelid-cheek junction. Blue - the location of bolus filler when correcting with a needle. Orange arrows - direction of movement of the cannula.*

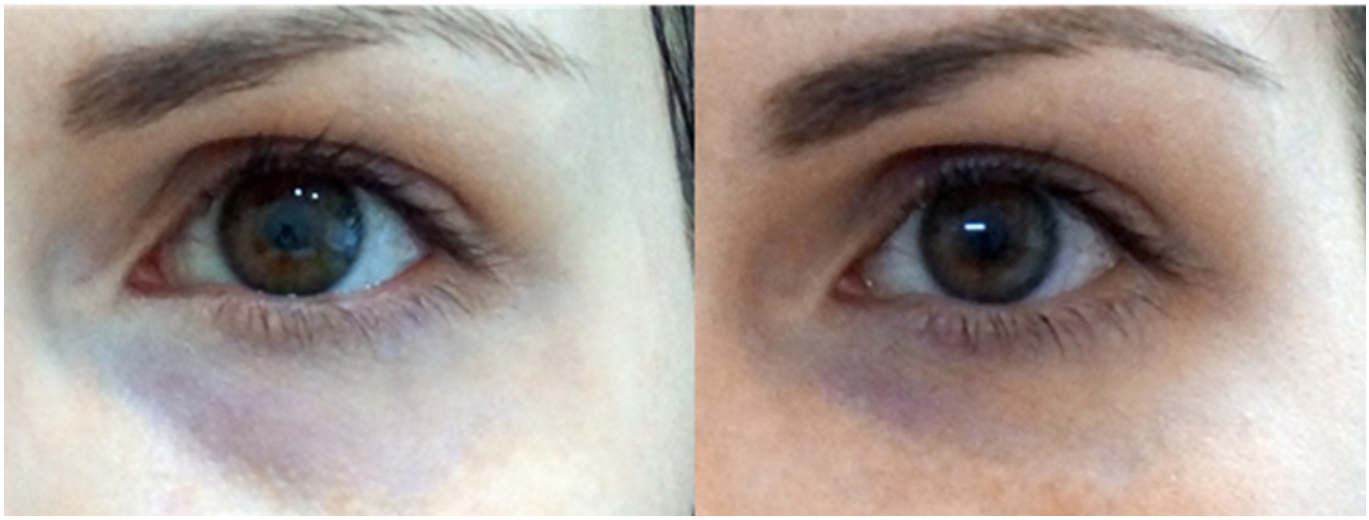

Figure 5.1 *- Type I, photo before augmentation and 2 weeks after.*

Type II correction

This type is manifested by hernia of the lower eyelid, visible in the medial part of the orbit. And simultaneous visualization of the bony orbital margin of the lateral part. Thus, in the medial part of the lower eyelid the excess volume in the form of a hernia, and in the lateral, loss of volume[9,11].

The injection of a filler into a prominent orbital fat is dangerous because of the risk of infection complications and adverse effects in the form of long edema of the periorbital zone and increase in the hernia volume; it should be avoided[5].

When correcting this type, the filler should be injected submuscular (*Figure 3.2*), but in the medial part below (caudal) of the tear trough to prevent the filler from getting into the hernia. And in the lateral part - between the projections of the bony orbital margin and the eyelid-cheek junction.

When using the cannula, the medial part is augmented from the cheek entry point, and the lateral one from the lateral lid entry point (*Figure 4.2*).

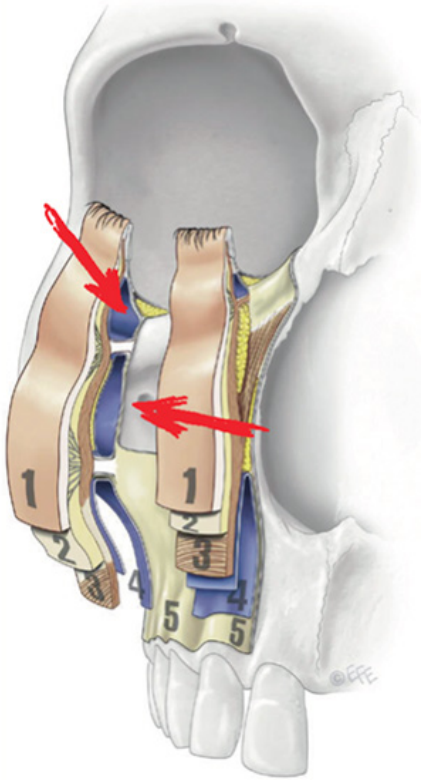

Figure 3.2 *- The anatomy over the skeleton and over bony cavities (1–5), showing the relationship of the soft tissue spaces to bony cavity spaces[9,11]. The arrows show layout of the filler for type II correction: under the orbicularis oculi muscle caudally to the orbital ligament in the medial part and cranial to the orbital ligament in the lateral part.*

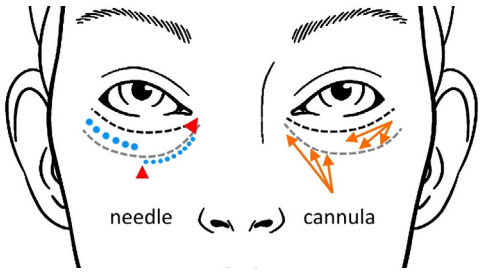

Figure 4.2 *- Scheme of augmentation of the lower eyelid zone of type II with a help of needle (left) or cannula (right). Dangerous areas marked with red. Dashed line - the boundaries of the injection zone: black dotted line - projection of the bony orbital margin, gray dotted line - ORL projection / eyelid-cheek junction. Blue - the location of bolus filler when correcting with a needle. Orange arrows - direction of movement of the cannula.*

Figure 5.2 *- Type II, photo before augmentation and 2 weeks after.*

Type III correction

In this type hernias are visible in the medial and lateral part of the orbit[11]. As I mentioned above, the injection of the filler into the prominent orbital fat is unacceptable. Therefore, when correcting this type, the filler is injected only below (caudal) of the tear trough and palpebromal groove[9,11] (*Figure 3.3*). For the injection, you can use both the needle and the cannula: cheek entry point (*Figure 4.3*). An incomplete correction is recommended to avoid a "pillow face" (*Figure 5.3*).

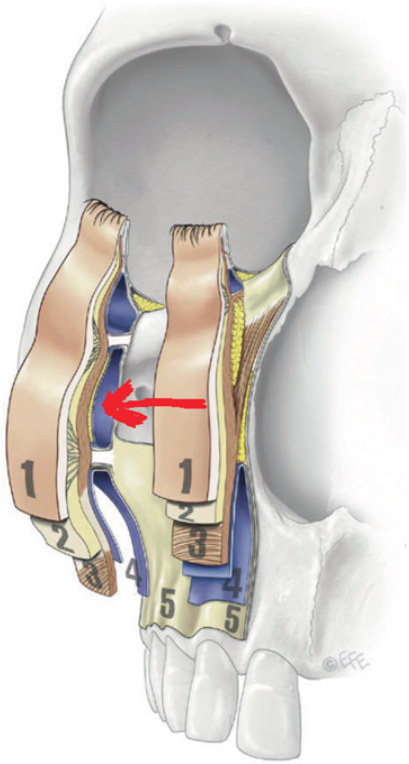

Figure 3.3 *- The anatomy over the skeleton and over bony cavities (1–5), showing the relationship of the soft tissue spaces to bony cavity spaces[9,11]. The arrow shows layout of the filler for type III correction: under the orbicularis oculi muscle caudally to the orbital ligament.*

Conclusions

Observance of the anatomical features of each patient, including the existence and expression of prominent orbital fat, is necessary to obtain the optimal result of injection correction of the periorbital zone. Correction of the lower eyelid zone, taking into account the principles outlined in this article, gives a good aesthetic result with a low risk of adverse effects. If the level and target zone of augmentation are observed, post-procedure puffiness is minimal or absent, and a good aesthetic result lasts more than a year.

Disclosure

The author declares that she has no conflict of interest and has not received any contribution for this publication.

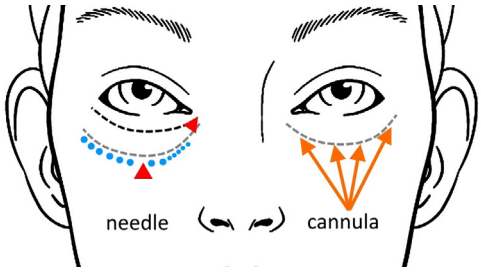

Figure 4.3 *- Type III augmentation scheme by needle (left) or cannula (right). Dangerous areas marked with red. Dashed line - the boundaries of the injection zone: black dotted line - projection of the bony orbital margin, gray dotted line - ORL projection / eyelid-cheek junction. Blue - the location of bolus filler when correcting with a needle. Orange arrows - direction of movement of the cannula.*

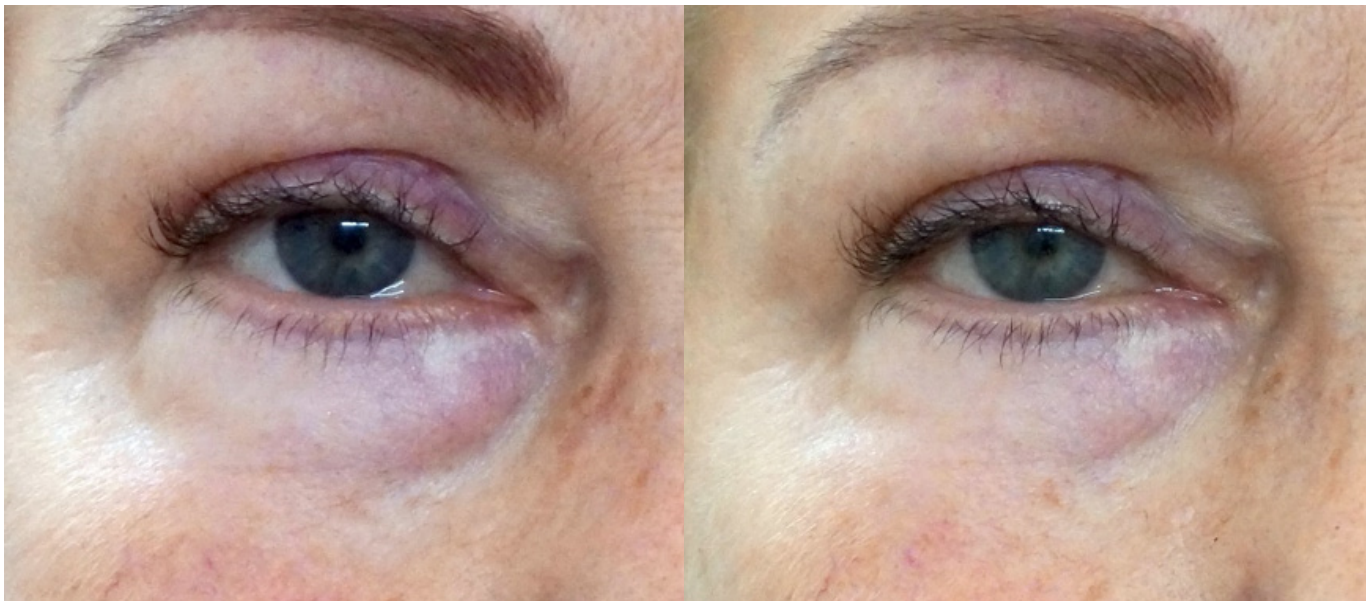

Figure 5.3 *- Type 3 augmentation. Photo before augmentation and 2 weeks after.*

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aesthetic medicine

Mini-review

Influence of histamine on keratinocytes differentiation and its modifications in the follicular cycle

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Abstract
Several leukocyte populations normally reside in mouse skin and they are frequently identified within or around hair follicles. Some of these leukocytes release significant amounts of histamine. In particular, the number and granulation status of the mast cells and the histamine content change dramatically during the murine hair cycle, i.e. rising during each telogen, to reach a peak within the first days of anagen, followed by a decline. Keratinocytes are the major cellular component forming both the interfollicular and intrafollicular epidermis. A role of endogenous histamine in the modulation of keratinocyte maturation has been suggested but only in patients with atopic dermatitis. This data may suggest a role of histamine in some forms of hair loss, which today we call more generally androgenetic alopecia.

Keywords
Histamine, androgenetic alopecia, histaminergic alopecia, follicular cycle, cetirizine, mast cells

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Introduction

Androgenetic alopecia is a common form of scalp hair loss that affects up to 50% of males between 18 and 40 years old[1,2]. It is a disorder that also affects the female sex and is characterized by a polymorphic clinical presentation. Even though this condition is a paraphysiological condition, the loss of hair leads to stressful events for the patients with considerable psychosocial consequences[3]. Genetic and hormone factors play a major role in the pathogenesis of the disease but, given the variety of phenotypes, other etiological factors could divide the disorder into different subgroups. Hair follicle is a skin appendage and exhibits hair cycle that is divided into three phases: anagen, catagen and telogen[4]. The relative duration of these phases varies with a lot of physiologic and pathologic factors as well as hormone factors[5], body site, age and nutritional status[6,7]. Many biochemical substances have been investigated pathologically for studying hair growth and its cycle[8,9], but the regulatory mechanism of the hair cycle has not yet been fully understood.

Two leukocyte populations reside in the epidermal compartment of normal skin in adult mice: Langerhans cells, which are a skin-specific member of the dendritic cell family of antigen- presenting cells[10], and dendritic epidermal T cells, which are tissue resident γδ T cells[11]. The dermal compartment also contains several resident leukocyte populations, including dermal dendritic cells, macrophages, and mast cells. Keratinocytes are the major cellular component forming the interfollicular epidermis and the intrafollicular epidermis known as the outer root sheath. Interestingly, Langerhans cells and dendritic epidermal T cells are frequently identified in the outer root sheath of hair follicles[11-15], and macrophages and mast cells often show perifollicular distributions in the dermal extracellular matrix[12,16,17]. Mast cells release a number of important signalling molecules, among which histamine has particularly potent pro-inflammatory activities[18].

Discussion

Many authors[19-22] have observed that both the mast cell population and the total histamine content reveal quantitative fluctuations during each cycle. Botchkarev et al.[24] for example, have reported pathologically that the number and granulation status of the mast cells change dramatically during the murine hair cycle and the mast cells product antagonists and the mast cell secretagogues significantly alter hair cycling in mice. Moretti et al.[23] demonstrated the fluctuations of the skin mast cell population and histamine content which occur during the hair cycles of rats. The mast cell population revealed a rise during each telogen, to reach a peak within the first days of anagen, followed by a decline. Histamine fluctuations were also fairly regular, hence the amine content steadily increased over, approximately, the first 7-11 days of each anagen, continuously decreased during telogen and then increased again. There was a steep rise of histamine in the first month, already observed by Hardwick[25] and Parratt[26] and referred by the last author to a temporary influence on the skin of unknown factors, perhaps extracutaneous and "related to the stress involved in weaning". During subsequent cycles, the pattern of each fluctuation was remarkably similar and the mast cells and the amine's quantitative changes, instead, probably depended on the hair cycle. With the aging of the animals, both mast cell and histamine fluctuations manifested a progressive tendency to level out and disappear. On this ground the continuous decline of the amine while the rats are growing older could indicate a progressive hair's mantle involution. A close relationship between hair's mantle involution and aging has been noted, in fact, by some authors[27,28]. There is no doubt, on the other hand, that the flattening out of all observed fluctuations is a function of aging. This is in agreement with the fall of skin histamine typical of that process in many species[25, 29-32]. Thus, the follicle would produce the histamine which would cause the involution of the follicle itself.

Kumamoto et al.[33] stated that hair follicles might also serve as local reservoirs of precursors for one or more of the skin resident leukocyte populations. To test this concept, they isolated vibrissal follicles from adult mice and cultured them in the presence of stem cell factor, interleukin 3, interleukin 7, granulocyte-macrophage colony-stimulating factor and Flt3 ligand, which are known to promote the growth and differentiation of Langerhans cells, dendritic epidermal T cells, macrophages, and mast cells[34-43]. They reported that relatively large numbers of CD45+/lineage- negative (Lin-)/c-kit+/ FcЄRI+ leukocytes with characteristic features of mast cells emerge from the hair follicles under these culture conditions. Unfractionated hair follicle cultures (containing 40%-70% CD45+ cells) released significant amounts of histamine on ligation of surface IgE receptors, as well as in response to substance P or compound 48/80. They have demonstrated in this study that relatively large numbers of CD45+/Lin-/c-kit+ leukocytes can be readily propagated ex vivo from hair follicle specimens in the presence of 5 added growth factors (stem cell factor, interleukin 3, interleukin 7, granulocyte-macrophage colony-stimulating factor and Flt3 ligand). These hair follicle derived leukocytes exhibited characteristic features of mast cells, including inclusion of metachromatic granules, surface expression of FcЄRI, proliferative responsiveness to stem cell factor, and histamine release on ligation of surface IgE.

Mast cells are present in normal skin, and increased numbers of mast cells are regularly observed in the skin of patients with atopic dermatitis even before the onset of inflammation[44,45]. Unfortunately, in literature, there are no studies that show the histamine activity on follicular keratinocytes but, although with proper precautions and expanding the search area, we can introduce the topic referring to studies conducted on patients with atopic dermatitis. Mast cells release a number of important signaling molecules, among which histamine has particularly potent pro-inflammatory activities18. After mast cell degranulation, histamine concentrations within the tissue can rise to 10– 1000 μM[46], and increased histamine levels have been reported for lesioned and nonlesioned skin of patients with atopic dermatitis[47]. A role of endogenous histamine in the modulation of keratinocyte maturation has been suggested by Ashida et al.[48] based on the observation that antihistamines have a beneficial effect on skin barrier recovery after tape

striping in normal mouse skin. Gschwandtner et al.[49] addressed the impact of histamine on the differentiation of human keratinocytes and their findings show that histamine prevents the expression of late differentiation antigens in keratinocytes and strongly decreases the expression of tight junction and desmosomal proteins, leading to the formation of a defective skin barrier. To investigate which of the four known histamine receptors (H1R–H4R) is targeted by histamine to induce its effect on keratinocytes, selective agonists and antagonists for the different receptors were applied to keratinocytes in the presence or absence of histamine. The expression of differentiation proteins was inhibited by the histamine receptor-1 (H1R) agonist 2-pyridylethylamine, while agonists of the other three histamine receptors did not change the expression of keratinocyte differentiation markers. Accordingly, preincubation of keratinocytes with the H1R antagonist, cetirizine, suppressed the histamine effect.

Cetirizine is a safe and selective, second-generation histamine H1 receptor antagonist, widely used in daily practice. Charlesworth et al.[50] showed that cetirizine causes a significant reduction in both the inflammatory cell infiltrate and PGD2 production and these effects are not related to its anti-H1 activity. Studies on H1 receptor binding have demonstrated that compared with many other commonly used second-generation H1 antihistamines, cetirizine has a relatively higher and more favorable affinity and selectivity for H1 receptors, which confers a more potent, faster onset and longer duration of action. Studies investigating the anti-inflammatory/anti-allergic effects of cetirizine have indicated that it may exhibit anti-inflammatory properties independent of its H1 effects[51]. Rossi et al.[3] carried out a pilot study to evaluate the efficacy of topical cetirizine in patients with AGA. This study arises from the assumption that prostaglandins would have an important role in the hair growth. Their action is variable depending on the class they belong to: PGE and PGF2α play a generally positive role on the hair growth, while PGD2 an inhibitory role on the hair growth[52]. In this report the efficacy and tolerability of a galenic lotion based on cetirizine 1% once a day on the scalp in a sample of 85 patients was evaluated. On the basis of hypertrichosis observed in patients treated with analogues of prostaglandin PGF2α, the supposed mechanism of action concerns the probable ability of Cetirizine to influence the prostaglandin activity. Nevertheless, it is undeniable that cetirizine is an antihistamine drug.

The data available in literature, therefore, lead us to think that histamine can play a central role in the regulation of the hair cycle. Histamine can be responsible for the onset of some pathological models that we now call “androgenetic” but which may actually have different etiology. These disorders could be managed differently from classical androgenetic alopecia, for example using an oral antihistamine drug, such as cetirizine, at an early stage. Thus, in order to prevent thinning. They are well known:

- The perifollicular inflammation that accompanies hair miniaturization in androgenetic alopecia;
- The active phases of the disease in which the patient reports scalp pain and itching, accompanied by an intense hair fall;
- And the “fibrous streamers” located below the follicles in advanced miniaturization, along which it is possible to observe the “Arao-Perkins bodies”, a small residue of anagen follicles of previous cycles.

All these considerations would seem to suggest the presence of a chronic inflammatory disease that presents episodes of remission and exacerbation and that it should be treated as such. Our knowledge is still very limited and further studies are required to explore the topic.

Conclusions

In the literature, different articles show that several leukocyte populations normally reside in mouse skin and they are frequently identified within or around hair follicles. These hair follicle derived leukocytes exhibited characteristic features of mast cells. Mast cells release a number of important signaling molecules, among which histamine has particularly potent pro-inflammatory activities. Both the mast cell population and the total histamine content revealed quantitative fluctuations during each cycle. Histamine prevents the expression of late differentiation antigens in keratinocytes and strongly decreases the expression of tight junction and desmosomal proteins, leading to the formation of a defective skin barrier thus, the follicle would produce the histamine which would cause the involution of the follicle itself. Preincubation of keratinocytes with the H1R antagonist, cetirizine, infact, suppressed the histamine effect. Cetirizine is a safe and selective, second-generation histamine H1 receptor antagonist, widely used in daily practice. Studies investigating the anti-inflammatory/anti-allergic effects of cetirizine have indicated that it may exhibit anti-inflammatory properties independent of its H1 effects. The data available, therefore, leads us to think that histamine can play a central role in the regulation of the hair cycle. Histamine can be responsible for the onset of some pathological models that we now call “androgenetic” but which may actually have a different etiology. These disorders could be managed differently from classical androgenetic alopecia, for example using an oral antihistamine drug, such as cetirizine, at an early stage in order to prevent thinning.

Three major pitfalls of this review must be noted. Firstly, there are currently no studies that refer to the influence of histamine on follicular keratinocytes. The author was inspired by work on patients suffering from other diseases, trying to broaden the field of research. Secondly, to date, histamine has been considered as a factor that positively influences hair growth. According to the author, the opposite is true. Lastly, most of the studies in the literature refer to experiments on mice. The data available are still too few. Perhaps in the future, we will be able to talk about “histaminergic alopecia” but further studies are needed to clarify this important issue.

Conflict of interest disclosure

The author declares no conflict of interests or funding.

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aesthetic medicine

Case Report

Abdominal CT-scan 3 months after a cryolipolysis session: a Case Report

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Abstract

Cryolipolysis is a unique non-invasive method for the selective reduction of fat cells with controlled localized cooling. We report a case of a 58-year-old woman without any significant medical history, who received an abdominal cryolipolysis session. Three months after this treatment, she presented a belly pain and a CT-scan was performed. It discovered a hyperdensity of subcutaneous fat limited to the cryolipolysis treated area. The pain disappeared spontaneously and the results at four months were satisfying.

Keywords

Cryolipolysis, non-invasive method, fat reduction

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Introduction

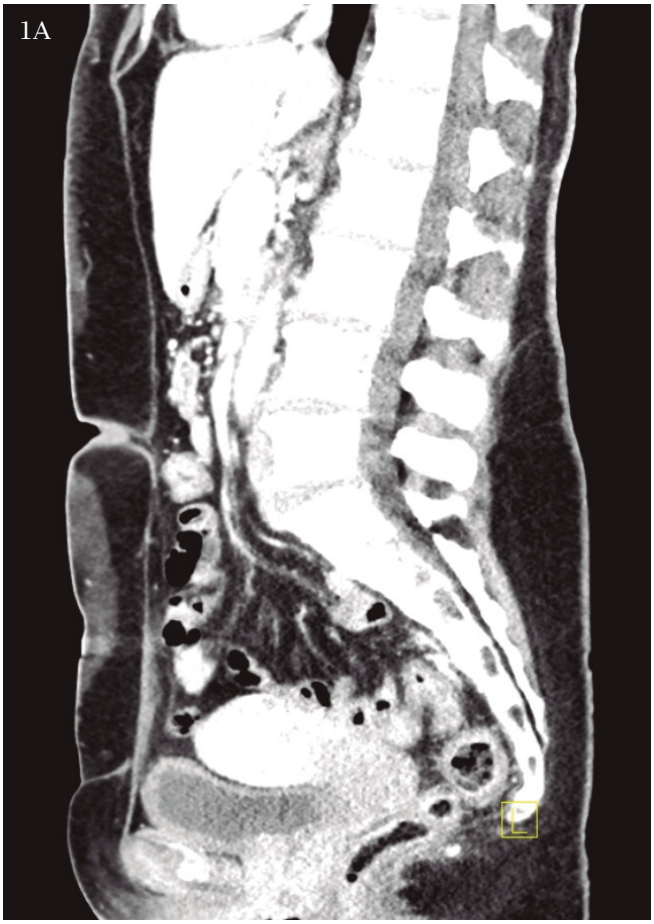
Cryolipolysis was first described by Rox Anderson and Dieter Manstein in 2008[1]. It is a *unique non invasive method for the selective reduction of fat cells* with controlled, localized cooling. It can selectively damage subcutaneous fat without causing damage to the overlying skin[1]. Three days after a cryolipolysis session, histological analysis reveals an apoptosis of the adipocytes and a phagocytosis of fat by macrophages, that is present 14-30-days post-treatment. Histopathologic evidence of *inflammation becomes apparent at 10 days and declines 90 days after treatment*[2].

Clinically, cryolipolysis results in localized panniculitis and modulation of fat. The decrease of fat thickness occurs gradually over the first 3 months following the treatment, and is most pronounced in patients with limited, discrete fat bulges. Erythema of the skin, bruising, and temporary numbness at the treatment site are commonly observed[3]. Paradoxical adipose hyperplasia[4] and skin necrosis[5] are rare side effects of cryolipolysis[6]. *The aim of this case report is to share CT-scan pictures of a patient revealing subcutaneous fat hyperdensity 3 months after a cryolipolysis session.*

Case Report

A 58-year-old woman with no known medical or surgical history came to our clinic with complaints of abdominal fat. After reviewing available options, we decided to perform a cryolipolysis session. The cryolipolysis device was a Cristal® (Deleo, France). An aspirated and refrigerated handpiece set named Ruby by the Deleo company was used at -7°C and with a vacuum level 4 on the sub-umbilical area. A non aspirated and refrigerated handpiece set named Ametysth was used at -7°C without vacuum on the supra-umbilical area. The session was performed in August 2017 lasting 60 minutes by a French plastic surgeon (L.L.). The 2 areas (sub and supra-umbilical) were treated simultaneously. The size of the treated area was around 450cm2. No issues were noted during or immediately after the procedure. *Three months after treatment, the patient visited a gastroenterologist for belly pain* without any other symptoms. The blood test was normal (CBC, ALT, AST, GGT, and PROTEIN C). *An abdominal CT-scan was performed as suggested by the gastroenterologist and discovered a hyperdensity of the subcutaneous fat limited to the cryolipolysis treated areas* (*Figure 1A - 1B*).

No organic cause was noticed and the belly pain disappeared spontaneously without any treatment within a month. Four months after the procedure, the patient had a 1kg weight loss (66kg to 65kg), a sub-umbilical circumference loss of 4cm (105cm to 101cm) and a supra- umbilical circumference loss of 3cm (77cm to 74cm) (*Figure 2A - 2B*). The pinch test decreased from 52mm to 40mm on the sub-umbilical area and from 52mm to 48mm on the supra-umbilical area.



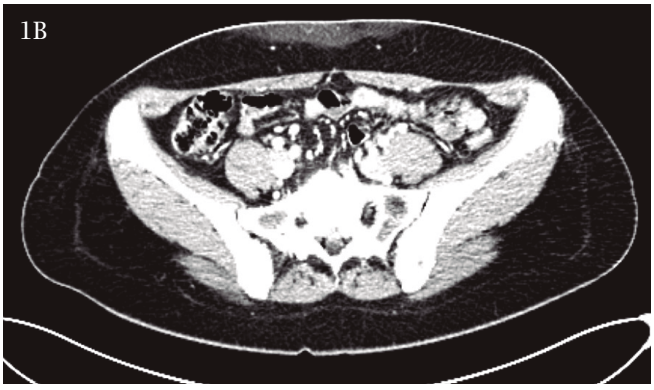


Figure 1 *- Abdominal CT scan (A) sagittal and (B) transverse views: hypersignal in supra and sub-umbilical areas, 3 months after a cryolipolysis session.*

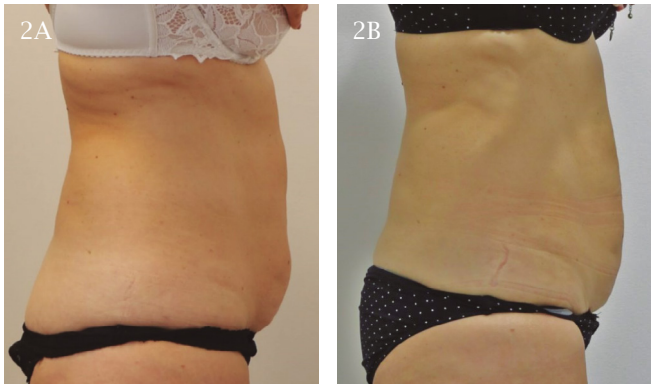


Figure 2 *- Photographs of this 58-year-old woman (A) before and (B) 3 months post- cryolipolysis.*

Discussion

Cryolipolysis is a safe and effective procedure for the reduction of fat in isolated pockets of excess adipose tissue[7]. Biologically, no changes in lipid levels or liver function tests have been linked[8]. In our case, the CT-scan was performed 3 months after treatment. *To date, no case describes the radiological signs of cryolipolysis on CT-scan.* The hyperdensity of the subcutaneous fat found in imaging confirms the inflammatory reaction of cryolipolysis but also proves its safety on the overlying tissues. It has been shown histologically in previous studies that inflammation and loss of adipose tissue are well correlated[2], and the maximum lobular panniculitis is approximately 4 weeks after cold exposure and resolves about 3 months after. *About this patient, this would seem to support the conclusion that the sequelae of cryolipolysis was responsible for the pain.* The inflammatory reaction is still present even after 3 months, suggesting that some people are more sensitive than others. The reaction of cold exposure seems to be more important and having a prolonged effect in time. The CT- scan had also shown that the *tissue's inflammation was deeper on the area treated with a handpiece using vacuum compared to a no-vacuum handpiece* (maximum supra-umbilical fat hypersignal depth: 0.8cm versus maximum sub-umbilical fat hypersignal depth: 1.6cm). This suggests that, when the skin laxity allows it, the handpieces with vacuum are more efficient than the handpieces without.

Conclusion

Cryolipolysis induces inflammation related to cold exposure. At the time of maximum effectiveness, the subcutaneous fat becomes a panniculitis. This phenomenon is observed on CT scan by a hyperdensity area. The physiology and efficacy of cryolipolysis have been largely described in the literature. *But for the first time, a case report correlates known clinical and histological data with radiological evidence of inflammation related to the destruction of adipocytes.*

Disclosure

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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aesthetic medicine

Case Report

Gummy smile: dental, gingival and facial approach

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Short title: Gummy smile: multidisciplinary approach

Abstract
The pursuit of aesthetic excellence has become a major goal in the dental and facial treatments. The beauty of the smile is not only constituted by the shape, position and size of the teeth, but also based on the characteristics of the gingival tissue and conformation of the lips, which should be as harmonious as teeth. Gummy smile is one of the complaints of the patients, since such a situation can influence self-esteem and social relationships. The development of new further conservative techniques may provide a better therapeutic option than surgical procedures, such as the application of botulinum toxin, in the treatment of gummy smile. The purpose of this article is to present a case study of a patient who showed dentogingival discrepancy and gummy smile, treated by gingivoplasty and by application of botulinum toxin. The gingivoplasty promoted the improvement of dental architecture and the application of botulinum toxin caused the dehiscence of the upper lip, optimizing smile harmony and achieving improved self-esteem and quality of life. The application of botulinum toxin is an alternative less invasive, faster, safer, more effective and it produces harmonics and pleasing results, when combined with gingivoplasty.

Keywords
Gingival overgrowth, botulinum toxins type A, gingivoplasty, gummy smile, dental

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Introduction

Currently, the demand for cosmetic procedures has grown exponentially. Dental procedures, as well as medical ones, besides working to obtain the principle of health promotion, accompany this trend by the search for aesthetics and welfare[1-3].

Facial aesthetic harmony correlates directly with the smile which, in turn, is formed by the union of three components: teeth, gum and lips[1-4].

The smile becomes aesthetically pleasing when these elements are disposed in suitable proportion, and exposure of the gingival tissue is limited to 3 mm. When the gingival exposure is greater than 3 mm, it is characterized the non-aesthetic condition called gummy smile, which affects some patients psychologically[1,5-8]. The gummy smile is often found in women[9].

The predominance of females can be explained by the fact that male patients present a lower smile line[4,5].

Several therapeutic modalities have been proposed for the correction of gummy smile, among them: gingivectomy or gingivoplasty[1,3,5,6,8], myectomy[6,8] and orthognathic surgery[6,8,9]; and the last two procedures are more invasive and associated with high morbidity[7].

In contrast, the use of botulinum toxin can be considered as a therapeutic option to surgery, because it is a more conservative method, more effective, faster and safer[1,5,10].

Currently, botulinum toxin has been shown effective in the treatment of gummy smile in patients with hyperfunction of the muscles involved in smiling, as well as in patients with other stomatological disorders such as bruxism, clenching and orofacial pain[1,6,9].

The purpose of this article is to present the therapeutic association between gingivoplasty and the application of botulinum toxin in managing gummy smile.

Case Report

Caucasian female, 26-years-old, attended the private clinic with complaints of gummy smile (*Figure 1*).

Clinically, the patient had an anatomic discrepancy between the length of the upper anterior teeth, and evident gingival exposure greater than 3 mm, featuring the gummy smile (*Figure 2*). Initially, gingivoplasty was proposed. Subsequently, after the clinical results, the application of botulinum toxin was suggested for the correction of gummy smile. However, the patient was oriented about the recurrence of gingival smile after 6 months of application, because of temporary results.

Under local infiltrative anesthesia, the gingivoplasty was performed with the electrocautery (BE 3000™, KVN, São Paulo, Brazil)[3]. The length of the teeth was increased, characterizing the dental zenith (*Figure 3*). The patient reported no complaints or complications after surgery.

After 30 days, satisfactory tissue repair (*Figure 4*) and the persistence of complaint of gummy smile reported by the patient (*Figure 5*) were observed. In the same consultation, botulinum toxin was applied. Prior to application of botulinum toxin, the surface of the skin was disinfected with ethyl alcohol 70% and the oils from the area were removed, in order to avoid local infection. The points of application were marked, beside each nostril. Then, local anesthetic (Emla™, Astra, São

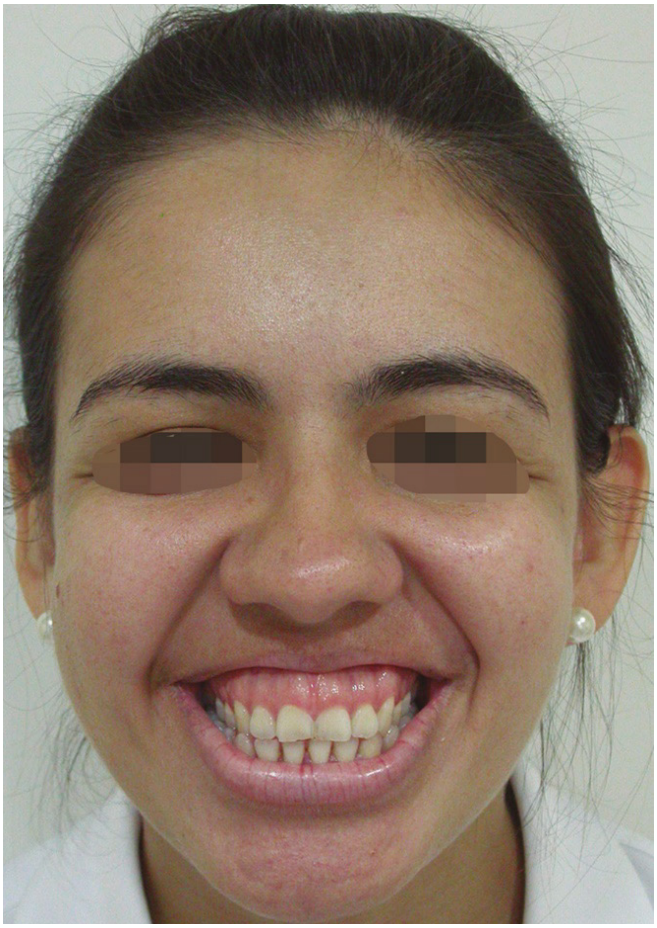

Figure 1 *- Exposure of evident gum, featuring the gummy smile.*

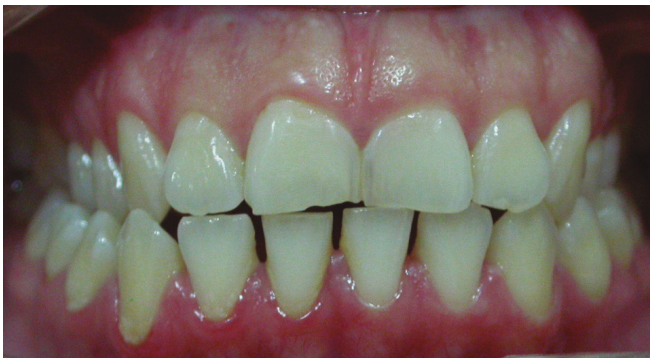

Figure 2 *- Initial clinical appearance showing an anatomical discrepancy between the length of teeth 11, 12, 13, 21, 22 and 23.*

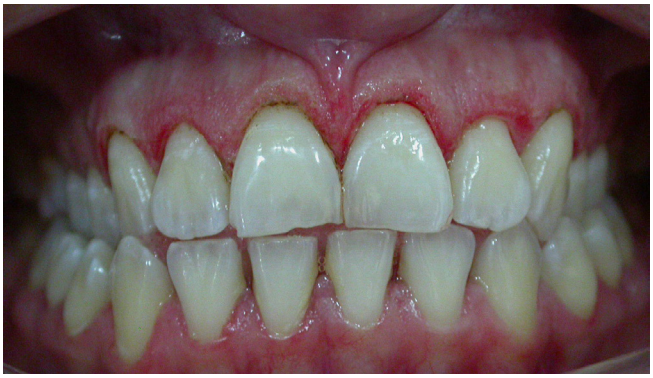

Figure 3 *- Immediate post-surgical: gingivoplasty on teeth 11, 12, 13, 21, 22 and 23.*

Paulo, Brazil) was applied with the aim of promoting comfort during the procedure. Botulinum toxin type A (Botox™ 200 units, Allergan Pharmaceuticals, Westport, Ireland) was diluted in 2 ml of saline, according to the manufacturer's instructions, and injected 2 units in the recommended site, laterally to each nostril. After application, the patient was advised not to bow their head during the first four hours and not to engage in physical activity during the first 24 hours after the procedure.
After 10 days, the patient was examined. She presented a uniform dehiscence of the upper lip (*Figure 6*). Side effects or complaints were not reported.

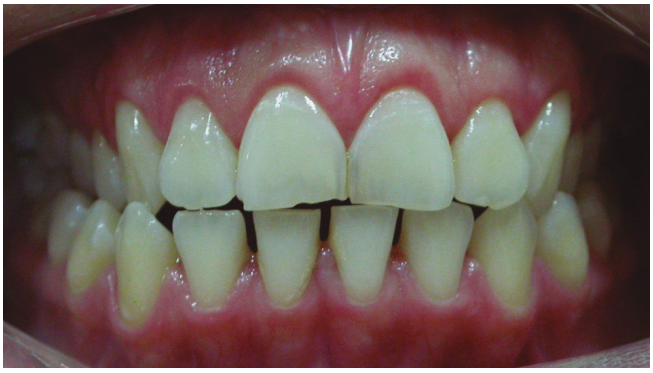

***Figure 4** - Post-surgical (30 days): observed satisfactory tissue repair.*

Discussion

Several etiologies have been suggested to gummy smile, as vertical maxillary excess[4-6,8,9], delayed passive eruption[4,6,7,9], hyperfunction of the muscles involved in smiling[1,6,7,9] and reduced length of the clinical crown of the teeth[1-3,7], which can occur separately or together, and determine the type of treatment to be used.
In gummy smile caused by overactive muscle, botulinum toxin was indicated. It is the first treatment of choice for the ease and security of applications, fast effect, besides being a more conservative approach when compared to surgical procedures (myectomy or Le Fort I osteotomy)[1,4-11].
The activity of the smile is determined by several facial muscles, such as the elevator of the upper lip and wing of the nose, the zygomatic major and minor, the angle of the mouth, orbicularis oris and risorius[1,4-6,8-10]. Among them, the first three ones play higher function and determine the amount of lip elevation and, therefore, should be the muscles affected by the injection of the toxin. The fibers of these muscles converge to the same area, and they form a triangle, which suggests that the point of adequate election comprehend the three muscles in a single injection. The toxin, when injected, can spread in an area of 10 to 30 mm, which allows the effective extent[1,4,5]. The proposed site of injection was laterally to the wing of the nose[1,4,8-10]. After being injected into predetermined locations, the toxin decreases the contraction of the muscles responsible for the elevation of the upper lip, and this reduces gum exposure[1,4-11].
In this report, the result was satisfactory to the harmony of the smile of the patient by association of treatments - gingivoplasty and application of botulinum toxin type A. The institution of isolated treatments could not culminate in the excellence of the earned results. Initially, the creation of the new dental zenith during the course of gingivoplasty promoted the new dental architecture (*Figures 2 and 4*), favoring harmony gingival-dental-facial for the patient (*Figures 1 and 5*). Subsequently, the application of botulinum toxin type A softened the gummy smile, by the uniform dehiscence itself of the upper lip, still promoting smoothness to facial lines of the smile, as can be seen in the nasolabial folds, adjacent to the nostrils, comparing *Figures 1 and 6*.

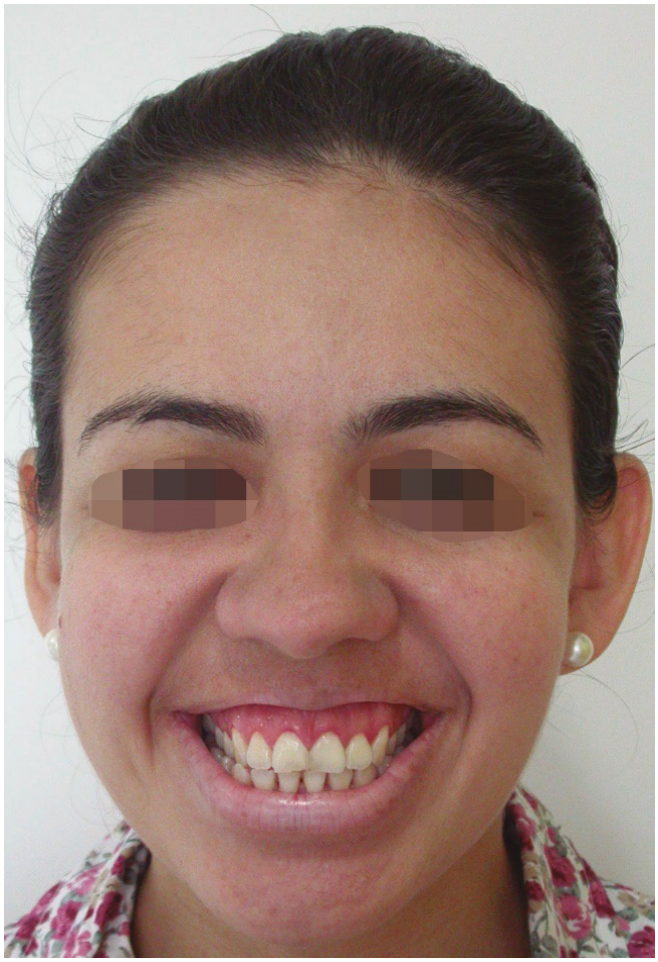

***Figure 5** - Improved dentogingival relationship with persistence of complaint of gummy smile.*

Conclusion

The application of botulinum toxin is an alternative; it is less invasive, faster, safer, more effective and it produces harmonics and pleasing results when applied in target muscles, respecting the appropriate dose and type of smile. It is therefore, a useful adjunct in the aesthetic improvement of the smile and provides better results when combined with gingivoplasty.

Conflict of Interest

I declare there is no conflict of interest or funding sources.

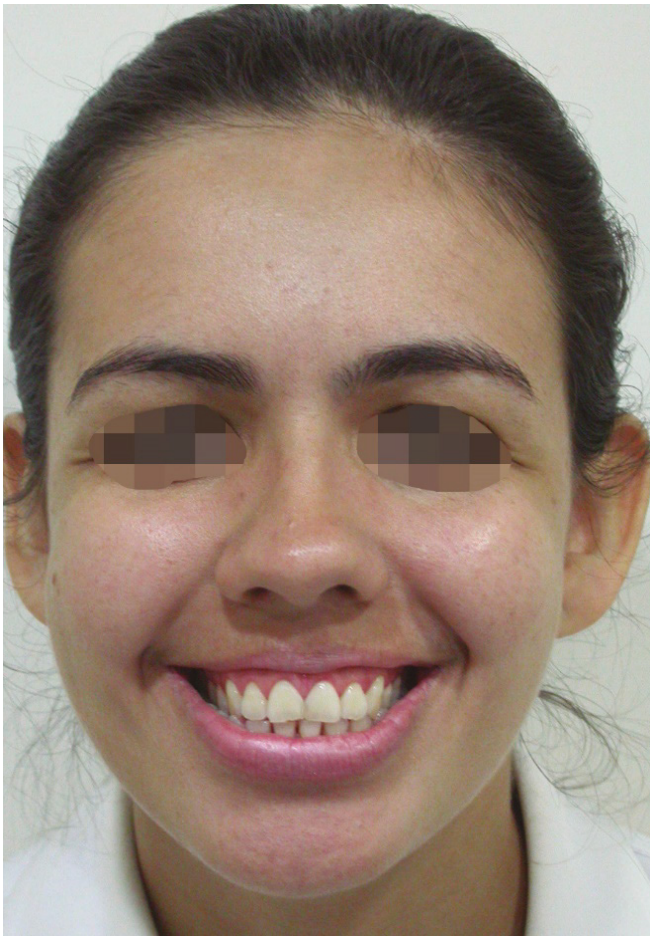

Figure 6 *- Aesthetic results after 10 days of application of botulinum toxin.*

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Courses and Congresses

2018

26 - 27 October - Toronto (Canada)
CAAM 15th Annual Conference
Canadian Association of Aesthetic Medicine
Hilton Toronto / Markham Suites Conference Centre
President: R. Van Aardt
Web: www.caam.ca/annual-conference

9 - 10 November - Santiago (Chile)
XII Chilean Congress of Aesthetic Medicine
Chilean Association of Aesthetic Medicine
Hotel International - Las Condes, Santiago - Chile
President: G. Marzullo
Email: ecco@eccochile.cl
Web: www.sochme.cl/congesomedicinaestetica

9 - 11 November - Miami (Florida - USA)
15th Annual AAAM Congress
American Academy of Aesthetic Medecine
JW Marriott, Miami
President: M. Delune
Email: delegate@aaamed.org
Web: www.aaamed.org

7 - 9 December - Cascais, Lisbona (Portugal)
3rd National Congress of Aesthetic Medicine
Portuguese Society of Aesthetic Medicine
Hotel The Otaivos, Cascais
Presidente: J.P. Vale
Email: congressonacional@spme.pt
Web: www.spme2018.com

2019

21-23 February - Malaga (Spain)
34th National Congress SEME
Spanish Society of Aesthetic Medicine
Palacio de Ferias y Congresos
President: P. Vega
Email: seme2019@pacifico-meetings.com
Web: www.seme2019.org

26 - 27 April - Brussels (Belgium)
Congress SBME - BVEG 2019
Belgian Society of Aesthetic Medicine
Radisson Blu Royal Hotel
President: J. Hebrant
Web: www.radissonblu.com

17 - 19 May - Rome (Italy)
40th SIME Congress
Italian Society of Aesthetic Medicine
Rome Cavalieri Congress Center
President: E. Bartoletti
E-mail: congresso@lamedicinaestetica.it
Web: www.lamedicinaestetica.it

14 - 15 June - Basel (switzerland)
16th Congress of the Swiss Society of Aesthetic Medicine
7th Congress of the Swiss Society of Aesthetic Surgery
Safran Zunft, Basel
President: S. Le Huu
Email: info@ssme.ch
Web: www.ssme.ch

13 - 14 September - Paris (France)
40th National Congress SFME
French Society of Aesthetic Medicine
Palais des Congrès de Paris
President: J.J. Legrand
Email: congres@sfme.info
Website: www.sfme.info

8 - 10 November - Long Beach California (USA)
16th AAAM Congress
American Academy of Aesthetic Medicine - AAAM
President: M. Delune
Email: delegate@aaamedorg
Website: www.aaamed.org

24 November - Montevideo (Uruguay)
XVIII Congress of the Aesthetic Medicine Society of Uruguay
President: A. Elbaum
Email: medicinaesteticacongreso@gmail.com
Website: www.sume.com.uy

2020

15 - 17 October - Quito (Ecuador)
XIII Pan American Congress of Aesthetic Medicine - UIME
Organised by: Ecuatorian Society of Aesthetic Medicine
President: V. Tinoco Kirby
Email: medesteticapanam2020@gmail.com
Web: www.seem.com.ec

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