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Contents

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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.

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Original Article

Safety and tolerability of deoxycholic acid injections in head and neck areas

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Abstract

Background: DC is used as an injectable drug to reduce unwanted localized adiposity thanks to its adipocitolitic activity. Aim: The aim of our study is to evaluate the safety and tolerability of deoxycholic acid injections in the head and neck areas.
Methods: between January 2010 and January 2020 all the patients were retrospectively treated with DC injections in head and neck area and evaluated. The study population consisted of 46 patients; treated areas were neck/submental fat, buffalo hump deformity, pre-jaw line, lower eyelid, medial cheek and malar fat pad. Session treatments were spaced from a minimum of 3 months, up to 14 months, based on the patient's needs due to the post-operative swelling.
Results: following DC injections all the patients experienced swelling and redness in the injected areas for at least 14 days. No major complications such as skin necrosis, beard loss, mandibular marginal nerve paresis, or others were recorded.
Conclusion: DC injections in the head and neck region look like they could address submental full-ness, buffalo hump deformity, although other areas such as lower eyelid, the pre-jaw line and the cheek can be treated. If properly injected, major complications can be avoided, although the proce-dure should be clearly explained to the patients due to the development of swelling and redness of the injected areas that are difficult to hide compared to DC injections when used for the body.

Keywords

Deoxycholic acid, adipocitolysis, facial aesthetics, head and neck, facial injection

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Introduction

Deoxycholic acid (DC), also known as deoxycholate, is a bile acid, developed by intestinal bacterial fermentation of cholanic acid produced by the liver[1]. The main purpose of deoxycholate is the emulsification of fat into the intestine in order to facilitate its absorption[1]. DC is used as injectable drug to reduce unwanted localized adiposity thanks to its adipocytolitic activity. Once DC is inject-ed into fat tissue, it modifies the fat cell's membranes permeability causing a progressive cellular swelling (ballooning) up to cell's breaking point; the whole process take usually 4 weeks[1,2]. Once the fat cells are broken up, macrophages enter the site and eliminate cytoplasm and cell membranes, while the healing process is carried out by the development of fibrosis. The entire healing process, from DC injections to a complete healing, usually takes from three to six months[1-3].

The Medical use of deoxycholate injections began at the end of the XX century[4,5], but only in 2004, thanks to Rotunda et al., deoxycholate was identified as the "main actor" in adipocitolitic solutions[3]. The Brazilian dermatologist Dr. Rittes has pioneered the description of the effectiveness of DC and phosphatidylcoline (PC) solutions in the non-surgical reduction of localized adiposities, though affirming PC to be solely responsible for adipocitolysis[4-6]. In the same time, a PC-based product was marketed with the brand name Lipostabil (Lipostabil, Sanofi-Aventis, Paris, France), and was indicated for intravenous use in Europe, South America, and South Africa as a treatment for numerous fat-related disorders, including hyperlipidemia, angina pectoris, and diabetic angiopathy[4-6]. In 2004, Rotunda et al. injected DC in a rabbit lipoma, 2 days after the animal was sacrificed and a well de-marcated area of necrosis was histologically identified, for this reason they affirmed the "DC solu-tion, with or without PC, to be able to induce adipocitolysis"[3]. After the study performed by Dr. Duncan in 2008, it was possible to scientifically affirm that the adipocitolitic effectiveness of DC/PC was secondary to DC activity and that the effect of PC was aimed to reduce the morbidity of the procedure by buffering the ablative effects of DC on the tissue[7]. The buffering effect can be explained by the behavior of aqueous mixtures of DC and PC, which spontaneously form deter-gent/phospholipid aggregates called micelles; while unbound DC is capable of ablating the tissue, PC/DC aggregates will not[8-10]. DC injections are mainly performed for non-surgical body reshaping. Further reports have described its application in the head and neck region for HIV+ patients suffering of highly active anti-retro viral therapy (HAART) related lipodystrophy[11-14]. Nowadays, just one DC-based drug is available in the market, with just one indication: sub-mental fullness treatment[15-18]. Nevertheless, several DC-based compounds or DC-based medical devices are also widely used in an off-label fashion[11,19]. During the time, different injective protocols to deliver DC-based solutions have been described[5,7,8,14,20]. The DC target is represented by fat cells, so in every injective protocol it is mandatory to release DC into the fat layer, thus avoiding complications such as skin necrosis. DC has a non-specific selectivity for fat cells, even if Thuangtong et al. in a study published in 2010, which investigated possible mechanisms for the selectivity of DC for fat tissue using in vivo and in vitro models[21]. Other complications described, following DC injections in head and neck areas, are beard loss/beard alopecia and temporary mandibular/marginal nerve paresis with full nerve recovery[22,23]. In the cited paper, the authors report their 10-years experience with the use of DC in head and neck region, evaluating the safety and tolerability of the procedure.

Materials and Methods

All the patients treated with DC injections between January 2010 and January 2020 were retrospec-tively evaluated. A total of 232 patients received DC injections and among them, in 46 cases (41 F; 5 M) the injections were performed in the head and neck areas. The treatments were performed in a private practice setting. Three different DC-based solution were used: Aqualyx, (Marllor Interna-tional, San Giovanni in Marignano, Italy); ATX-101 (Allergan, Dublin, Ireland); Galenica Senese. The Treated areas were: neck/submental fat, buffalo hump deformity, pre-jaw line, lower eyelid, medial cheek and malar fat pad (*Tables 1 and 2*).

Sex	
	N (%)
Male	5 (10.8%)
Female	41 (89.2%)
Age	
	Mean
Age	36.4
Solution	
	N (%)
Aqualyx	10 (21.7%)
ATX-101	17 (37%)
Galenica Senese	19 (41.3%)
Complication	
	N (%)
Edema	46 (100.0%)
Area of injection numbness	12 (26%)
Ecchymosis	12 (26%)
Hardening of the injected tissue	40 (86.9 %)

Table 1 *- Patient's demographics.*

# of patients (%)	Treated area	Solution injected	Mean Volume Injected
39 (84.7%)	Neck/submental fat	8 Aqualyx 12 ATX-101 19 Galenica Senese	Aqualyx: 8 mL ATX-101: 6-8 mL Galenica Senese: 6-8 mL
2 (4.3%)	Buffalo hump	Aqualyx	8 to 16 mL
2 (4.3%)	Jowl fat	ATX-101	0.6 mL per side
1 (2.1%)	Lower eyelid fat bag	ATX-101	0.6 mL per side
1 (2.1%)	Medial cheek fat pad	ATX-101	0.4 mL per side
1 (2.1%)	Malar fat pad	ATX-101	0.4 mL per side

Table 2 *- Injections features.*

Aqualyx is an injectable solution containing a polymer of 3:6-anhydro-l-galactose and D-galactose, buffer systems, 3<, 12< -dihydroxy-5®-24-oico cholanic acid sodium salt, and saline solution, ATX-101 and Gelenica Senese containe DC 10 mg/mL.
The patients excluded from the study were those under 18 years of age, women who were currently pregnant or breast-feeding, and patients with allergies to at least one of the solution's components. Also excluded were patients whose medical history included anaphylactic reactions and/or severe allergies, patients with any acute or chronic skin disease in the affected area, and patients with any severe organic disease.

Injective protocols

Two different injective protocols have been standardized for DC-solution delivery[11,24], although several published papers suggest mesotherapy to inject DC[8]; independently from the technique used, it is mandatory to release DC into the fat layer. The first injective protocol was introduced by Dr Motolese, and was developed for a specific DC-based medical device with a lactose-based delivery system, sold with the brand name Aqualyx, (Marllor International, San Giovanni in Marignano, Italy)[11]. The technique is performed with a 7-cm long, 25-gauge, needle supplied by the manufacturer; the solution must be released into the subcutaneous fat only in a retrograde fashion and in a continuous, streaming manner[11]. This is done in order to have the distribution of the solution be as homogeneous as possible. Almost the entire length of the needle must be inserted into the subcutaneous adipose tissue, parallel to the skin surface, but the injections must not be too superficial (in the skin) or too deep (into the muscles)[11]. Multi-depth injections are required to achieve optimal results. The ray-type distribution pattern is similar to that of liposuction, and the multilevel effect helps to address thick layers of adipose tissue. The technique requires many inward and out-ward movements. Each time the needle is moved outward the solution must be released in a retro-grade fashion. This outward motion is similar to that performed using liposuction cannulae. The released solution must be spread throughout the subcutaneous adipose tissue: this requires a reduction in width, as well as depth, and therefore numerous passes are necessary[11]. The second injective protocol was specifically developed for the administration of the only DC-based drug actually present into the market: ATX-101 (Allergan, Dublin, Ireland), an injectable drug containing deoxycholate, for noninvasive treatment of submental fullness (SMF)[25]. This protocol was also used for Galenica Senese injections. The area to be treated is marked with a surgical pen, and a grid (with points spaced at 1-cm intervals), supplied by the manufacturer, is applied to mark the injection sites. The solution is injected as 0.20-mL aliquots by means of a 12-mm long, 32-gauge needle. The injections have to be performed at 1-cm intervals and at an approximate depth of 7 mm[25]. In order to reduce pain during DC injections, lidocaine was always pre-mixed with the DC solutions. When Aqualyx was used, as recommended by the manufacturer, 0.2 mL of lidocaine 2% was added to each 8 mL vial[26]. When ATX-101 was used, 0.5 mL of lidocaine 2% was added each 2 mL vial[20]. When Galenica Senese was used, 2.5 mL of lidocaine 2% was added each 10 mL vial.

Results

The study population comprised 46 patients (41 women, 5 men). The mean age was 36.4 years (range, 22-64 years). In all the cases, following the injections, the edema of the treated area was recorded, self-resolved within 10 to 28 days (*Figures 1, 2*). Each patient was evaluated 3 months following the injections, and only 9 patients received a single treatment: treated areas were pre-jowl fat (2), eyelid fat bag (1), cheek (1), malar area and 4 cases of neck/submental fat (*Figures 3-6*). The Buffalo hump deformity was treated with 2 treatment sessions in both cases (*Figure 7*); neck/submental fat patients received 3 treatment sessions in 8 cases and 2 treatment sessions in 27 patients (*Figure 8*).
Session treatments were spaced from a minimum of 3 months, up to 14 months, based on patient's needs due to post-operative swelling. No major complications such as skin necrosis, beard loss, mandibular marginal nerve paresis, or others were recorded. Ecchymosis was recorded in 12 patients, all of them received neck injections. DC, when injected into the neck, induced

also a variable hardening of the injected tissue recorded a month after the injections, self-resolved within a few months (3 to 12). The Transitory numbness of the injected area was claimed by 12 patients injected in the submental area. Follow-ups occurred from 14 months to 6 years post treatment. During the follow up, at least 3 months after the last injections, patients were asked to rate the result achieved. Pre-operative and post-operative pictures were shown to the patients and they were asked to complete a VAS (Visual Analog Scale) where 100 represented the best possible aesthetic outcome and 0 was the worst. No patients rated less than 70; the mean VAS score was 78.

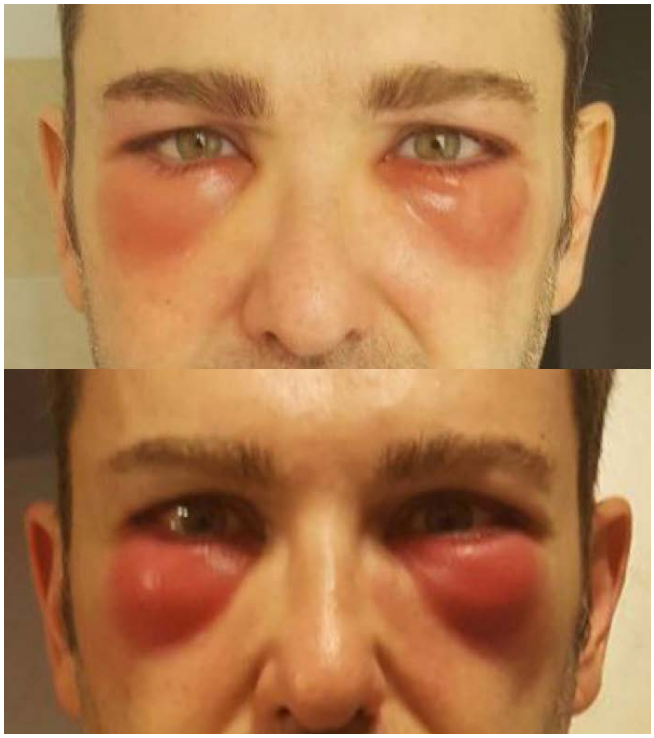

Figure 1 *- Huge swelling in Lower eyelid the day after (lower picture) and 3 days after (upper picture) ATX-101 (0.6 mL per eyelid) injections. The photos are a selfies sent by the patient.*

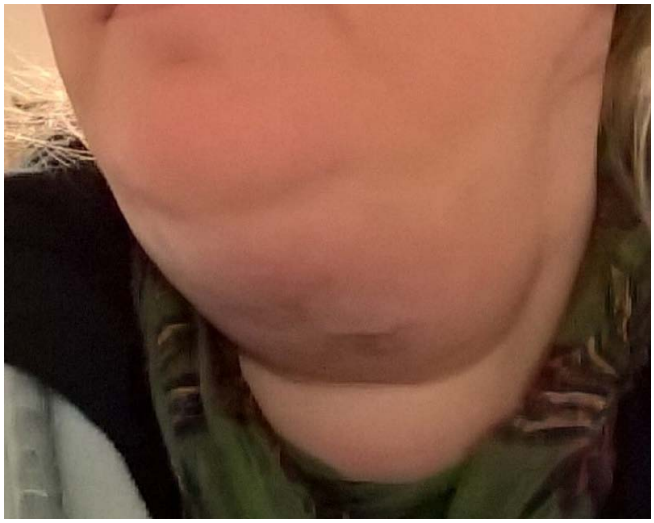

Figure 2 *- A case of huge swelling about 10 hours following the injections of ATX-101 (8mL) in sub mental area. The photo is a selfie sent by the patient.*

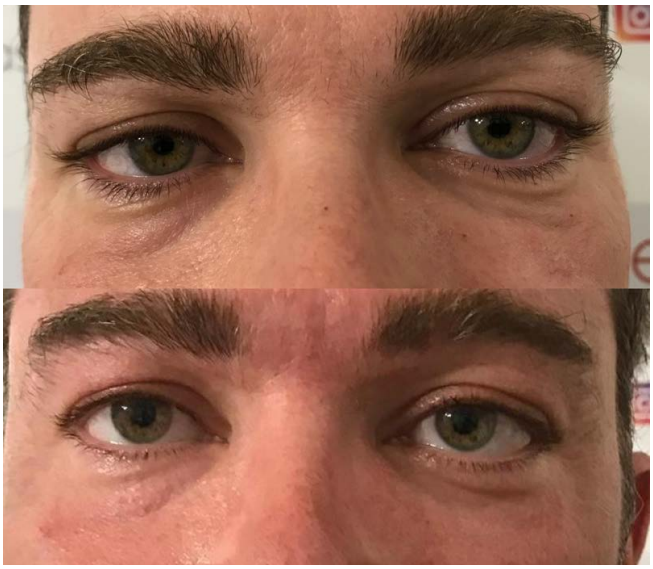

Figure 3 *- Frontal view before (upper picture) and 3 months after (lower picture) ATX-101 injections (0.6 mL per eyelid) of lower eyelid.*

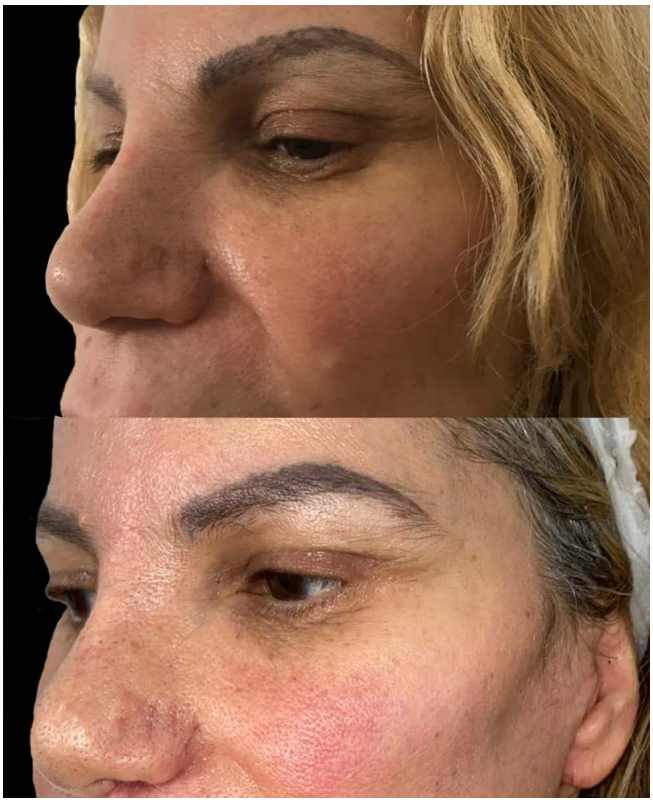

Figure 4 *- Three quarter left view before (upper picture) and 3 months after (lower picture) ATX-101 (0.4 mL per side) injection of malar fat pad.*

Figure 5 *- Right lateral view before (left) and 9 months after (right) ATX-101 (6 mL) injection of sub mental fat pad.*

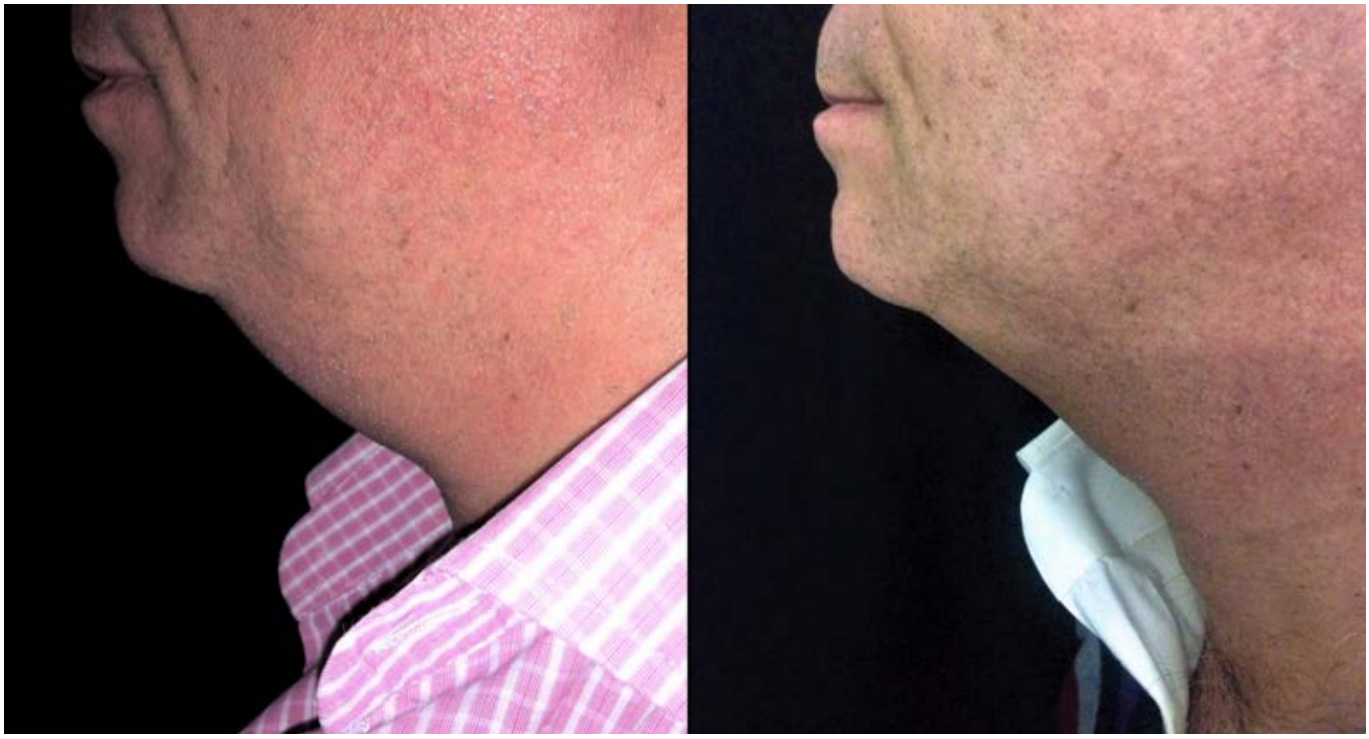

Figure 6 *- Right lateral view before (left) and 6 months after (right) Aqualyx (8 mL) injection of sub mental fat pad.*

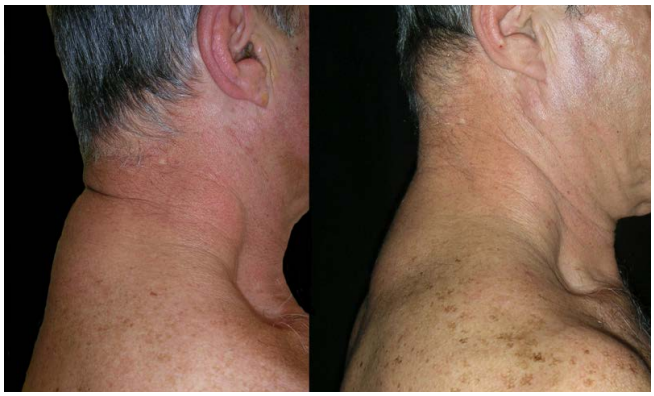

Figure 7 *- Right lateral view before (left) and 4 months after (right) the second session of Aqualyx injections (8 mL per session 3 months spaced) of dorso cervical fat pad.*

Figure 8 *- Left lateral view before (left) and 12 months after (right) 2 sessions of Galenica Senese injection of sub mental fat pad. (8 mL the first session and 4 mL the second one, spaced 6 months from each others).*

Discussion

Non-surgical fat reduction is a rising treatment, indeed the American Society for Aesthetic Plastic Surgery (ASAPS) statistics reports 129,686 procedures performed in 2019 and 140,314 in 2020. 27,28 While nowadays the most performed non-surgical fat reduction therapies are carried out with energy-based devices (EBD)[29], the use of injectables are found to be a viable option[11,14]. Injection lipolysis is more versatile compared to the use of EBD because moving these systems can be cumbersome, and may not be practical for physicians who work in multiple locations[2]. Moreover, the indications for head and neck EBD non-surgical fat reduction are only for the submental and dorso-cervical areas[30]. Labelled injection lipolysis is currently limited to the submental area due to the presence in the market of a specific DC-based drug: ATX-101[15]. However, several DC based compounds or medical devices are widely used, in an off-label fashion, in order to achieve non-surgical fat reduction[11,14,19].

One of the most frightening complications following DC injections is represented by skin necrosis[31]. DC is not selective for fat cells, although possible mechanisms for the selectivity of DC for fat tissue using in vivo and in vitro models have been investigated[10,21]. Therefore, in case of superficial injections into the dermal layer, skin necrosis can be observed: several papers have pointed out the importance of injecting DC in the right way and in the right tissue layer[11,14,32]; in a recent review

regarding properties, AE, and complications in using DC for submental fat reduction, performed by Farina et al., results showed that complications, including, skin necrosis, nerve injury, alopecia, and vascular events, can occur, demanding complex management without specific protocols[33]. About the use of Aqualix or DC-compound, medical literature is lacking about randomized controlled clinical trials or literature reviews, although some retrospective studies stated that major adverse events such as hyperpigmentation, permanent paresthesia/ dysesthesia, skin necrosis, permanent nodules, and skin irregularities, may occur, but are rare and usually related to incorrect injection techniques or overdosing[11,14].

DC injections have been widely performed in order to get body contouring from the beginning of the XX century[1], although one of the first published papers regarding its use was to treat lower eyelid fat bags[4]. Injecting DC into the body has proven to be easier than injecting it in the face; body fat pads are larger and bigger compared to facial and neck fat pads, making it easier to identify exactly the layer that needs to be injected: between the skin and muscular fascia[12,14]. Facial DC injections are less frequent compared to body which is comprehensible due to the complex anatomy of the face, moreover the sensitive and motor nerves of the face can be injured if DC is injected next to their anatomical course[33]. Nerves are covered by phospholipid sheets, and when DC is injected around them it can work on phospholipids reducing the capability of nerve signal transmissions; fortunately this event is transitory, due to the capability of our body to repair the phospholipids sheet[21]. For the reasons mentioned previously, facial DC injections need to be performed by healthcare professionals experienced with this drug.

In our retrospective analysis we evaluated 46 patients who received single or multiple session of DC injections in their head and neck areas and complications were never recorded. Injection techniques were performed strictly following the protocol released by the manufacturer of the injected solution, in the case of DC-compound uses it was administrated as per ATX-101 protocol.

On the other hand, adverse events (AE), such as edema, local pain, bruise, and numbness were often recorded following every injective session. Edemas following DC injections are the clinical manifestation of what occurs in the subcutaneous tissue where the fat cell's membrane permeability is modified causing a progressive cellular swelling up to the cell's breaking point[11,14].

AE following DC injections represent a distressing discomfort for the patients[32], especially when injections are performed in head and neck area: the edema, that could be hidden in case of body injections, but not for the head and neck, often calls for the patient to require some days off from work following the procedure.

During the last 20 years an increase of non-surgical aesthetic procedures has been observed[34]. As reported by the ASAPS in 2016, when analyzing the trends of surgical and non-surgical aesthetic procedures performed in the previous 20 years, while the number of plastic surgery procedures doubled, the number of non-surgical cosmetic procedures increased by 12-fold[34]. Patients are prone to undergo non-surgical procedures for the absence of a surgical intervention and related hospitalization, and they get the chance to undergo the procedure and return to their own social life. Many non-surgical procedures are available for the head and neck area, thanks to the use of hyaluronic acid (HA) fillers, botulinum toxin (BoNTA) and EBD[35-42]; often performed also to restore pathological features induced by illness or surgery[43-45].

These office-based procedures reports are rare AE, and are usually represented by transient redness or bruises, easily camouflaged with make-up[35-42]. DC injections can be performed in an office setting, but AE, especially edema, are always present. Moreover, the patient needs to wait 3 months after the procedure to be able to see the final result, due to the time-lapse necessary to get fat reduction and the tissue healing that induce a variable degree of tightening of the overlying soft tissue. It should be noted that the result achieved is permanent: fat cells, once broken up, cannot be replaced by others[2]. The previously mentioned features of DC injections cause for this procedure to be identified as borderline between surgical and non-surgical, because whereas for surgical operations after DC injections the patient will require some rest, the procedure is performed in an office setting with no need of OR. All these issues must be clearly discussed with the patients prior to the procedure, stressing the possible AE that is always present, and it should be made clear to the patient that could confuse this procedure with other injectable procedures (HA or BoNTA) that wouldn't require said period of rest, allowing the patient to go back immediately to his social life.

Conclusions

DC injections are a well-established procedure to achieve lipolysis in specific areas. DC injections in the head and neck regions mainly address submental fullness and buffalo hump deformities, although other areas such as lower eyelid, the pre-jaw line and cheek can be treated.

In our retrospective study no complications following DC injections such as skin necrosis, nerve injury, alopecia, and vascular events were recorded, confirming that injecting in the right layer (the subcutaneous tissue) with the right injective protocol is safe; although facial DC injections should be performed by healthcare professionals with experience in the use of DC and with a deep knowledge of facial anatomy. On the other hand, AE were always recorded, and especially for head and neck areas that could particularly disturb the patient. This setback may reduce the patient's capability to tolerate the treatment and must be carefully evaluated during the first consultation before performing the procedure.

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Institutional Review Board Statement

Every patient signed an informed consent for the procedures, the use and publication of images and clinical data for scientific research purposes. Data privacy was handled according GDPR.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patients to publish this paper.

Data Availability Statement

Data is available from the corresponding author upon request.

Conflicts of Interest

The authors declared no conflicts of interest.

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Original Article

Clinical study of high-power diode laser in dynamic mode for fine hair removal: effects of pulse duration on efficacy and safety

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Running title: **Dynamic diode laser hair removal on fine hair**

Abstract

Background: Diode laser hair removal is the most commonly used method to permanently remove unwanted hair. The biggest challenge today is the treatment of fine hair. Various studies have shown that using a static modality (single shot with high fluence), better results are obtained.
Objective: this study aims to verify that diode laser hair removal, using a dynamic mode with high power and a short pulse, provides better results than moderate power with a longer pulse, while still being comfortable and safe.
Materials and Methods: subjects (n=14) with skin types II and III and brown and black hair were subjected to diode laser hair removal using the Primelase device (from Cocoon Medical). Left side areas were treated with a high power of 4,800W and a pulse duration of 3 ms, while right-side areas were treated with a power of 1,000W and a pulse duration of 10/14 ms; wavelength of 810 nm and the same fluence dose was used for both sides. Efficacy, pain, side effects and post-treatment satisfaction were evaluated after three sessions.
Results: an overall reduction of hair was observed using high power and shorter pulses (64%, SD 18%) compared to the use of moderate power and longer pulses (55%, SD 18%), with a statistically significant improvement of 16% ($p<0.024$). Greater improvements were found in subjects with skin type II (27%, $p<0.026$) and brown hair (30%, $p<0.0006$, and also in areas with thinner hair (56%, $p<0.07$). An oedema appeared after the treatment was higher for the side treated with 4,800W (48%, $p<0.03$).
Conclusions: the Dynamic mode of the diode laser device using high power and short pulses is more effective than using moderate power and longer pulses. When high power is used in a dynamic mode an improvement in hair reduction and greater satisfaction are obtained, especially on light skin and thinner hair.

Keywords
Photoepilation, hair removal, dynamic mode, thin hair, high-power diode lasers, short pulse duration

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Introduction

Unwanted hair growth is a common cosmetic problem for women and men, for which different types of treatments have been developed such as the use of light for hair removal. Photoepilation has established itself as an effective, safe and long-lasting hair removal option and is one of the most widely used hair removal techniques worldwide.

Photoepilation consists of the laser light being absorbed by a specific chromophore (melanin in the hair) that transforms the energy into heat[1-3]. According to the extended theory of photothermolysis, to achieve a reduction in the follicular structure, it is necessary to damage the germinal structures of the follicle (non-pigmented structures), generating heat from the structures that contain melanin (hair shaft, follicular epithelium and matrix) and diffusing the heat to the areas where the cells are located[4,5]. To achieve the destruction of the germ structures of the follicle it is essential that they are in the anagen phase[6,7].

Among the most common light-based hair removal systems are lasers (diode, Alexandrite, Nd:YAG and Ruby) and Intense Pulsed Light (IPL), which have proven to be sufficiently effective for hair removal[8]. However, thin or residual hair is the biggest challenge for these procedures, because the reduced diameter causes less heating since it cools more easily compared to thicker hair, making it difficult to remove. Therefore, since they are unable to remove thin hair effectively, photoepilation procedures have been found to be limited for the goal of completely removing unwanted hair. To get permanent results, it is necessary to find technologies that allow fine hair to be heated with a high efficiency.

A wavelength of 810 nm is mainly used in diode laser hair removal and its effectiveness depends on the different parameters involved (fluence and pulse duration)[9]. However, few studies tackle the impact of these parameters on its efficacy for thin hair[10-13]. Furthermore, these studies only include the use of diode lasers in the static mode for hair removal, where each zone is treated once by the applicator with a high fluence dose (15-40 J/cm^2) and low frequency (1 to 3Hz). Currently, it is possible to use the so-called dynamic mode, treating each zone multiple times with a low fluence per pass (3-10 J/cm^2) at a higher frequency (usually 10Hz), which reduces side effects and increases subject comfort and safety[5,6,14]. However, there has not been a study of hair removal in the dynamic mode that analyzes fine hair.

In static mode, the use of short pulse durations with high-power diode lasers has been shown to achieve better results in removing fine hair[12]. When the power is increased and the pulse duration decreased, the hair is heated to higher temperatures producing greater thermal damage. This was found to be particularly important for the thinnest hair because it is heated much more effectively with short pulses than with long pulses.

The aim of this clinical study was to analyze the dynamic mode of diode laser hair removal and compare the efficacy of applying high power (4,800W) and short pulses with moderate power (1,000W) and longer pulses. In previous studies, we predicted the efficacy of photoepilation as a function of hair thickness and laser pulse duration using a 3D mathematical simulation model developed in our laboratory[15]. In this study, we present clinical data evaluating the effect of the pulse duration on the efficacy of thin hair removal when using a dynamic mode, without affecting the comfort and safety of the treatment.

Materials and methods

In this small sample-size, single-center and side-by-side study, 14 female subjects were selected who were between 18 and 49 years of age (median 26.5, SD 8.3), with skin types II (4 subjects) and III (10 subjects) according to the Fitzpatrick classification, and black and brown hair colors. Of those subjects, 7 received treatment on the arms, 6 on the legs, and 1 on the buttocks. All subjects had thin hair and had undergone no previous hair removal treatments, no previous waxing treatments or other avulsion hair removal techniques during the last month, and no hormonal treatments. Furthermore, subjects with hypersensitivity to visible and infrared light or those undergoing treatments with visible and infrared photosensitive drugs, subjects with white or very blond hair, and subjects with any infection sensitivity issues or with an oncologic process in the treatment area, were excluded.

A diode laser device (Primelase Excellence, from Cocoon Medical, Barcelona, Spain) was used for the clinical study, operating in dynamic mode at 10Hz. All the subjects underwent a diode laser hair removal treatment with a wavelength of 810 nm and a beam size of 20x9 mm^2. On the left side, subjects received the treatment with the highest peak power of the device (up to 4,800W), while on the right side they received it with moderate peak power (1,000W). Each subject received identical fluence doses and accumulated energy on both sides. The parameters used for subjects with skin type II were: accumulated energy of 3.5 kJ, fluence of 8 J/cm^2, and pulse duration of 3 ms (4,800W) for the left side and 14 ms (1,000W) for the right side. The parameters used for subjects with skin type III were: accumulated energy of 3 kJ, fluence of 6 J/cm^2, and pulse duration of 3 ms (4,800W) for the left side and 10 ms (1,000W) for the right side.

Before carrying out the hair removal sessions, the areas that needed to be treated were shaved and a thin layer of transparent Aqualaser gel (Ultragel) was applied. The diode laser head was placed in contact with the skin while exerting slight pressure. The device emitted laser energy through a cold sapphire crystal window that was also used to cool the skin via continuous-contact cooling. The treatment was performed in a dynamic mode by moving the head of the device horizontally or vertically in a sweeping motion until the target total accumulated energy was reached. In this treatment mode, low fluence values are used, so it is necessary to pass the applicator over the same area multiple times in order to reach the accumulated energy and the temperature necessary to damage the hair follicle. A constant speed was maintained to ensure an even sweep of the entire grid (treated area).

The approximate average speed of movement across each grid was 10 cm/s. The exact parameters were chosen by a board-certified dermatologist using the treatment tables recommended by the manufacturer, in accordance with the skin and hair type of each treated subject. After each treatment session, aloe vera gel was used for a post-treatment massage. The device used has a CE mark. The study was conducted in compliance with the principles set forth in the current version of the Declaration of Helsinki, Good Clinical Practice, and the laws and regulatory requirements for the use of medical devices in Spain.

This study compared hair removal efficacy, the pain experienced by the subjects during the treatment and other post-treatment side effects, adverse effects and the satisfaction of both the subjects and the physician.

The efficacy was compared using hair counts from before and after photographs, and semi-quantitative scales. Images were taken before each session and three months after the third session. Hair counts were performed across an area of 16 cm^2 (4x4 cm template). A Lumix camera (Panasonic DMC-LX100) was used to take the pictures, which were processed with Microsoft© Image using the SAKE filter. For the semi-quantitative assessment, the physician visually assessed the hair reduction and ranked the results: 4 points for very good efficacy with 91-100% hair reduction, 3 points for good efficacy with 61-90% hair reduction, 2 points for moderate efficacy with 31-60% hair reduction, 1 point for low efficacy with 1-30% hair reduction, and 0 points for no effect with 0% hair reduction).

The pain experienced by the subjects during the treatment was evaluated using a scale from 0 (no pain) to 10 (unbearable pain), as were the other post-treatment side effects, such as edema, erythema, and stinging, where a range of 0 (no effect) to 10 (maximum effect) was used. Also, the satisfaction of the subjects and the physician was evaluated on a scale from 0 (not satisfied) to 10 (very satisfied). Adverse effects such as thermal injuries, blisters, crusting, ulcer infections and possible hypo- or hyperpigmentation were also evaluated.

The variables were studied according to descriptive analysis and t-student, using the mean, median, lowest and highest score, outlier, and standard deviation (SD) of the variables. Standard deviation was used to study the dispersion of the data and the variability of individual observations. Also, the improvement when using 4,800W was calculated by subtracting the percentage reduction of 4,800W from the percentage reduction of 1,000W; the result was then divided by the percentage reduction of 1,000W.

A t-student test was used for analysis: two tailed, paired samples. Statistical data for pain and side effects were represented using column and boxplot charts. In the boxplot charts, the median is represented by a straight line inside the box, the mean by an "X" inside the box, the lower and upper horizontal lines are the lowest and the highest scores within the lower and upper limit, and a circle outside the box represents an outlier. The box represents the middle 50% of the scores, without the lowest 25% and highest 25%. Statistical significance was considered to be at $p<0.05$. Microsoft Excel was used for the statistical analysis.

Results

The Analysis of the data from this clinical study revealed, first of all, a significant reduction in hair density for both cases, where an overall greater efficacy for hair reduction with 4,800W (64%, SD 18%) compared to 1,000W (55%, SD 18%) was observed, which corresponds with a statistically significant improvement of 16% ($p<0.024$) (*Figure 1*).

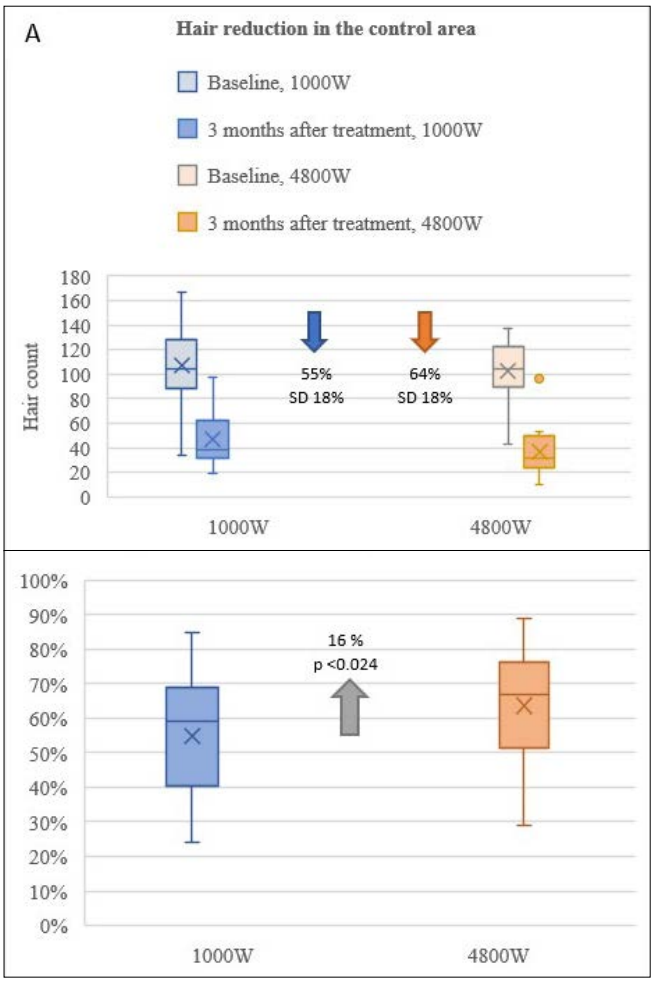


Figure 1 *- (A) Hair count in the control area (4x4 cm) before and after 3 months; (B) Comparison between average percetage of hair reduction and power used.*

In addition, analysis concerning the treated area revealed different improvements in hair reduction results. The area on the back of the upper leg showed the largest improvement (56%), achieving a hair reduction of 70% with 4,800W and 45% with 1,000W. The area on the buttock showed an improvement of 38%, the arms 13%, and the front of the upper leg 6%, but at $p<0.073$ there was no statistical significance.

Additionally, the efficacy of the treatment was compared based on the skin type and hair color of each subject. It was observed that subjects with skin type II presented greater hair reduction and a greater improvement when the highest power was applied. The subject with skin type II had an average hair reduction of 81% (SD 8%) with 4,800W and 64% (SD 8%) using 1,000W (27% improvement, $p<0.026$). The subject with skin type III

presented a reduction of 57% (SD 17%) with 4,800W and 51% (SD 20%) with 1,000W (a 12% improvement but not statistically significant at p<0.216).
An Evaluation according to hair color showed a 30% improvement when applying the highest power in subjects with brown hair, a reduction of 65% (SD 18%) with 4,800W and 50% (SD 17%) with 1,000W, with the difference being statistically significant at p<0.0006. Black hair was also compared but the difference was not statistically significant.
In addition, the visual assessments of the subjects after three months of treatment showed a more noticeable hair removal efficacy when applying 4,800W (64% of subjects with good efficacy) versus the application of 1,000W (36% of subjects with good efficacy) (*Figure 2*).
A mean score of 2.6 was obtained with 4,800W compared to 2.2 with 1,000W, which represented a statistically significant improvement of 18% with p<0.019.
The efficacy analysis was completed with a satisfaction survey of the subjects and physician (*Figure 3*).

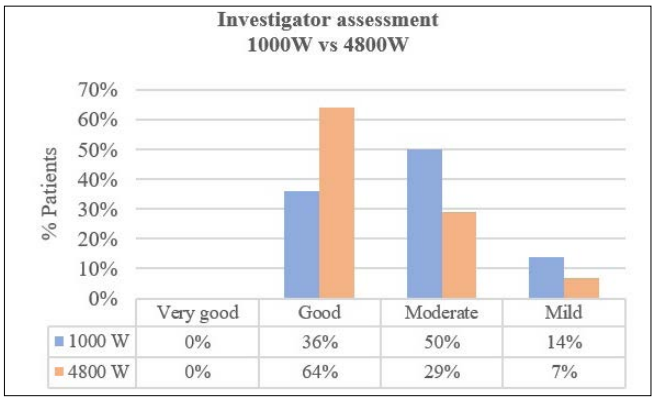


Figure 2 *- Comparative investigator assessment using semi-quantitative scales, with an overall improvement of 18%, statistically significant at p<0.019.*

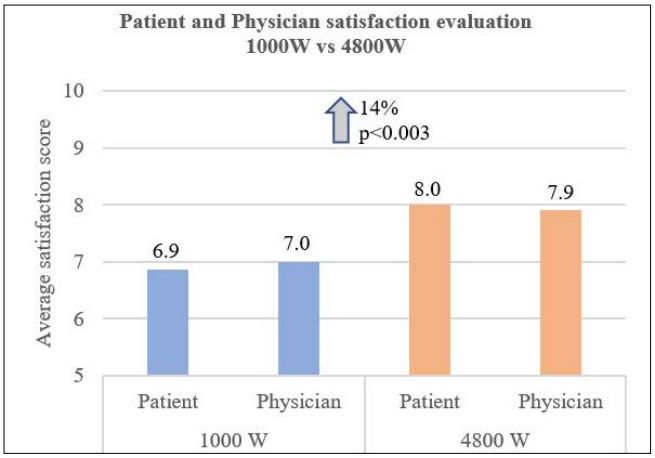


Figure 3 *- Graphical results of the satisfaction survey completed by the patients and physicians (10 is maximum satisfaction and 0 is not satisfied).*

The responses tended to be grouped around 7 points for 1,000W and 8 points for 4,800W (out of 10). There was greater satisfaction for the results obtained with 4,800W, with an improvement of 14% (p<0.003).
Figure 4 shows examples of before and after photographs of different subjects and different areas of application.

The side effect variables were also methodically evaluated during and after each treatment. On the whole, side effects were reported to be generally mild and disappeared in less than 48 hours.

FIGURE 4 - PATIENT 1

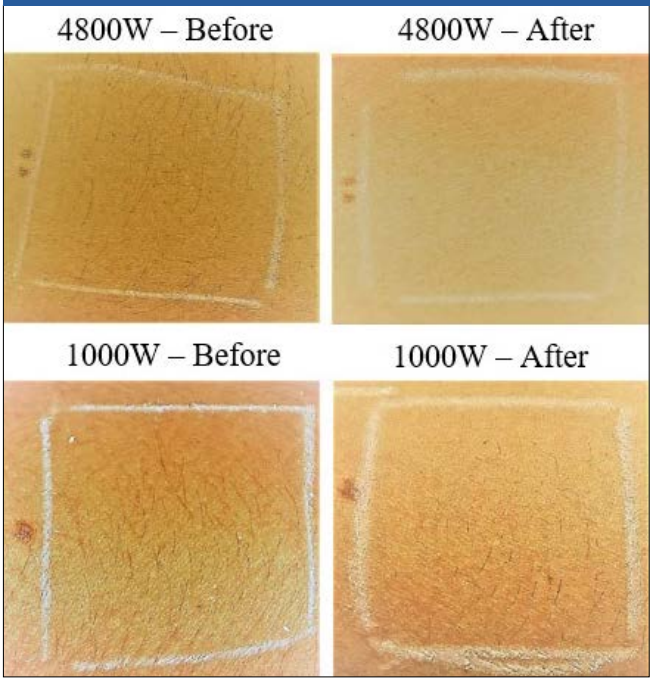


Figure 4 *- Examples of hair removal results: patient 1 (skin type III, brown hair, arms); patient 2 (skin type III, brown hair, arms); patient 5 (skin type III, black hair, arms); patient 6 (skin type III, black hair, front of upper legs); patient 8 (skin type III, brown hair, arms) and patient 9 (skin type II, brown hair, arms).*

FIGURE 4 - PATIENT 2

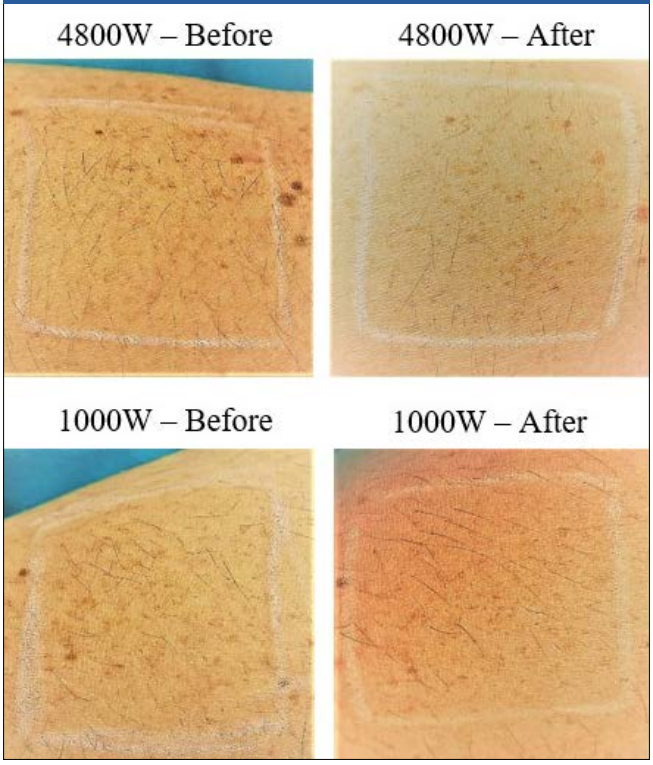


FIGURE 4 - PATIENT 5

FIGURE 4 - PATIENT 8

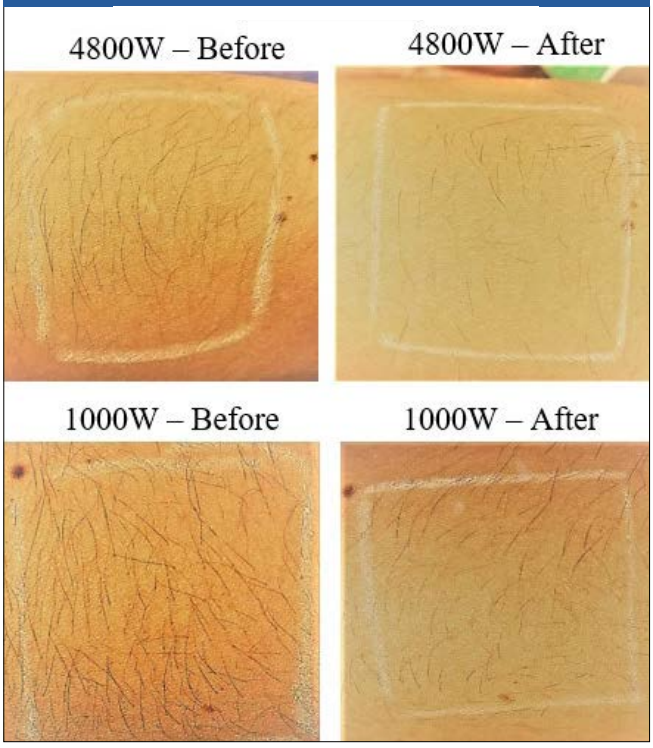


FIGURE 4 - PATIENT 6

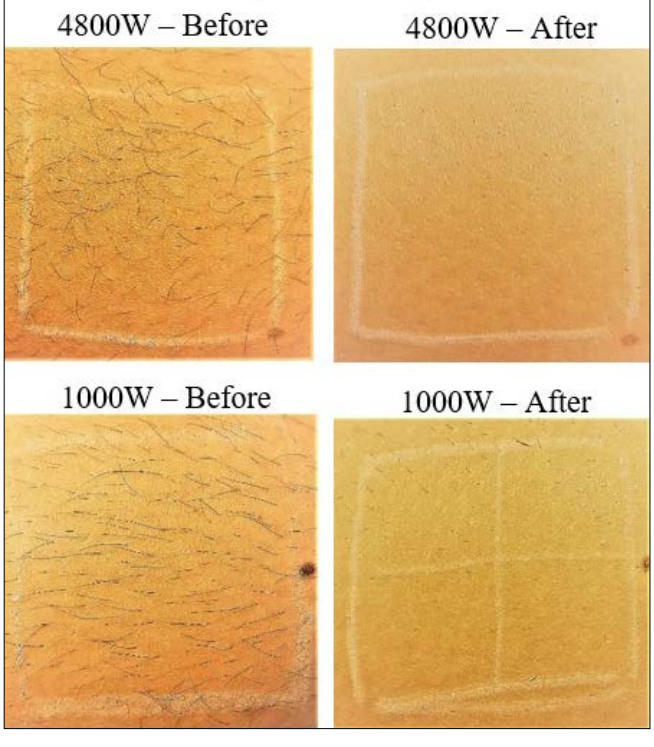
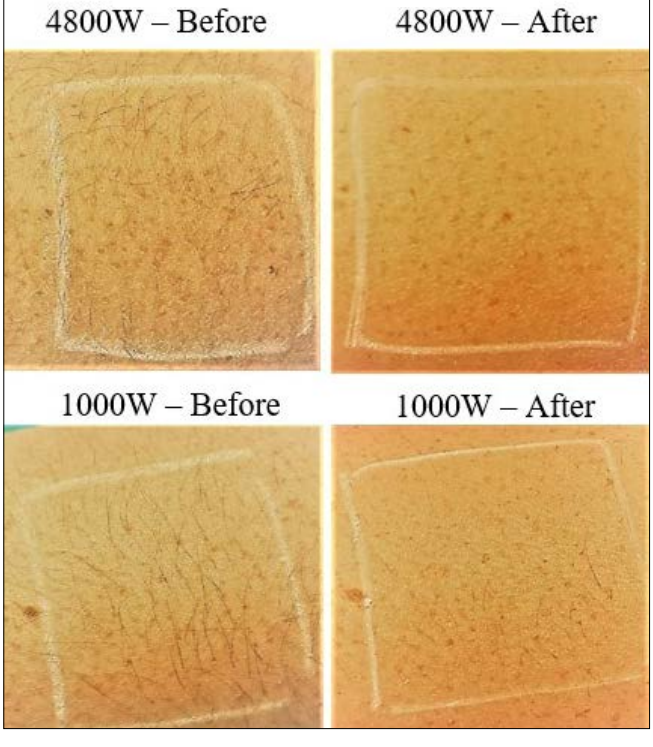


FIGURE 4 - PATIENT 9



Regarding the subjects' comfort during the treatment, the sensation of pain was similar for 4,800W and 1,000W (*Figure 5*). It was observed that subjects tended to feel mild pain with a mean score of 3.1 (SD 2.44) for 4,800W and a mean score of 2.9 (SD 1.86) for 1,000W (on a scale from 0 to 10), with the difference not being statistically significant (p<0.487). For skin type II the pain was greater, with an average of 6.25 (SD 2.21) with 4,800W and 5.25 (SD 0.95) with 1,000W (not a statistically significant difference, p<0.252), compared to skin type III with an average of 1.9 (SD 0.99) with 4,800W and 2 (SD 0.15) with 1,000W (not a statistically significant difference, p<0.726).

Regarding the side effects after treatment (*Figure 6*), for 4,800W and 1,000W the subjects reported a mean score for stinging immediately after treatment of 2.50 (SD 1.74) and 2.64 (SD 1.70) respectively (not a statistically significant difference, p<0.547), with an average duration of 2 minutes with 1,000W and 3 minutes with 4,800W. For erythema, a higher mean score was observed with 4,800W (2.43, SD 1.6) than with 1,000W (1.93, SD 1.38), which was also not statistically significant (p<0.089). However, an oedema did show a statistically significant higher mean score with 4,800W (2.43, SD 1.6) versus 1,000W (1.64, SD 0.93), an increase of 48% (p<0.035). Although a perifollicular edema is the result of thermal damage, it is a temporary reaction with instantaneous action and, in all cases, there was no persistent dermal damage, disappearing in less than 48 hours.

Regarding complications or adverse effects (burns, blisters, crusting, ulcer infection, and possible hypo- or hyperpigmentation), they were not observed in any of the subjects.

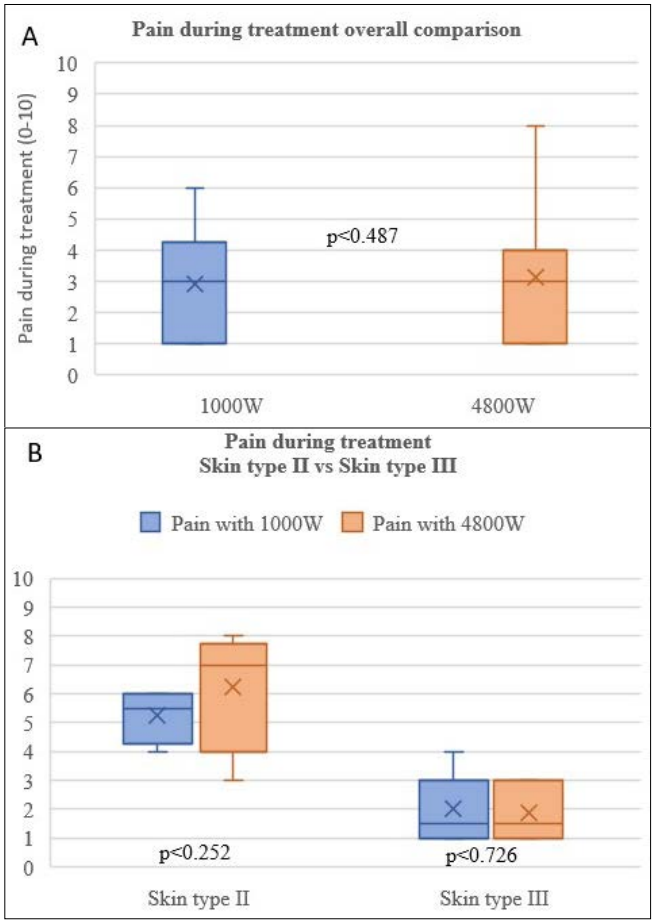


Figure 5 *- Comparison between power and mean pain during treatment. (A) Comparison between 1,000W and 4,800W; (B) Comparison between skin type II and skin type III.*

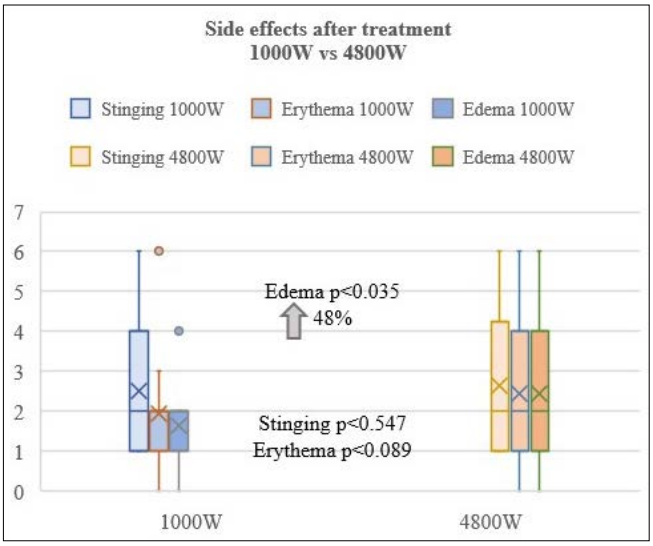


Figure 6 *- Comparison between power and side effects after treatment.*

Discussion

Diode laser hair removal technology is already considered to be one of the most relevant options available on the market. However, the approach of using a dynamic mode with a short pulse duration still represents a paradigm shift for the treatment of fine hair. Consequently, the focus of this study has been to evaluate the application of diode laser hair removal techniques in dynamic mode with different laser powers and, therefore, with different laser pulse durations, with special attention being paid to the removal of fine hair. This study compared therapeutic efficacy, subject and physician satisfaction, and safety. Two cases were studied on each subject to reduce the bias of the sample.

Both laser conditions produced significant hair reduction after treatment, with greater hair reduction being seen with the use of high power and short pulses (4,800W and 3 ms) over moderate power and longer pulses (1,000W and 10/14 ms) using the same fluence dose, meaning that better results are obtained with higher laser irradiance. This is explained by the fact that with shorter pulses, a higher temperature is reached in the hair follicle and therefore greater thermal damage is induced[5,10-12]. A previous in silico model generated by the coauthors of this article[15] had predicted an improvement in efficacy when using shorter pulse durations. This result has been corroborated by the present study.

Regarding subject and physician satisfaction, congruence has been observed between their subjective impressions and the hair counting analysis, since both the subjects and the physician reported a higher degree of satisfaction with the treatment performed using the shortest pulse duration.

A statistically significant overall improvement in efficacy of 16% has been obtained after just 3 sessions of dynamic-mode hair removal when comparing 4,800W with 1,000W. The thermal relaxation time (TRT) and thermal damage time (TDT) of hair are key to understanding the results of this study[15]. In the case of original or untreated hair, the TRT is between 20 ms and 50 ms. Therefore, moderate-power lasers of 1,000W that operate with pulses of 10/14 ms, as used in the present study, can effectively heat this type of hair. However, residual fine hair exhibits a TRT of less than 10 ms. In these cases, high-power lasers in dynamic mode producing pulses of less than 10 ms (such as the 4,800W diode laser operating at 3 ms) allow fine hair to be heated with a high efficacy level and enable the high values of thermal damage required for permanent hair removal to be achieved.

The improvement in efficacy has been found to increase to 27% in subjects with lighter skin and hair (skin type II and brown hair). This is because the difference in pulse duration was greater for the subjects with skin type II (3 ms versus 14 ms) than for those with skin type III (3 ms versus 10 ms), thus producing a greater difference in hair heating and damage. Additionally, we have seen that the group with brown hair (with both skin type II and III) had even better results with the optimum pulse duration of 3 ms, achieving an increased improvement of 30%. This can be explained by the fact that brown hair is thinner and, as explained above, the thinner the hair, the better results there will be with the shortest pulse duration.

Interestingly, the highest improvement of 56% was found on the back of the legs compared to the front of the legs, buttocks, and arms. Again, this is probably due to the presence of thinner hair on this part of the leg, and the fact that the 4,800W device was capable of heating thinner hair with greater efficacy thanks to its pulse duration being shorter than the hair TRT[15].

Importantly, no complications or adverse effects have been observed, and side effects were either transient and mild or, in some cases, moderate. This shows that the application of the dynamic mode with a low fluence dose allows comfortable and safe dynamic-mode hair removal treatments to be performed, without them being significantly affected by the use of higher power and short laser pulses. The sensation of pain in both cases was similar, however, in subjects with skin type II there was a greater difference in the sensation of pain, possibly due to the greater fluence used for this skin type. Pain is closely related to the thermal damage of the hair follicle and was expected to be greater with 4,800W. However, it was found that the sensation of pain was similar in both cases because in the dynamic treatment mode used in study the pain was mild, so the subject could not differentiate between 1,000W and 4,800W. Other side effects such as stinging, perifollicular oedemas, and erythema increased slightly with 4,800W, but only the differences in edema were found to be statistically significant. The Perifollicular oedema is caused by the injury to the hair follicle, due to the thermal damage produced by exposure to the laser. As power increases and pulse duration decreases, thermal damage increases and so does the subsequent skin reaction, hence the increased occurrence of the oedema. The Perifollicular oedema is an immediate and temporary end point of laser hair removal, which usually disappears in less than 48 hours after the treatment.

This study has presented an evaluation of only 3 sessions with an overall hair reduction of 64%, although 5 to 7 sessions are reportedly recommended to obtain a reduction of 70 to 90% for moderate and thick hair in bodily areas[5,7]. The greater efficacy of the diode laser device on residual fine hair when operating at 4,800W suggests that the number of sessions needed to achieve permanent hair removal could be lower. The fact that 4,800W is more efficient on residual hair implies a great advantage, since, with the majority of commercialized diode lasers, residual hair is hard to remove, and the treatment is often painful.

In this study, some of the results obtained were not statistically significant ($p>0.05$). To obtain statistically significant results it would be necessary to evaluate a larger number of cases, carry out more treatment sessions, and have a longer post-treatment assessment period (greater than 6 months) in order to gather more objective data regarding long-term efficacy.

Conclusion

It has been observed that diode laser hair removal in a dynamic mode with a low fluence dose and high frequency is effective in removing unwanted hair, while the use of a high power of 4,800W and short pulses has been shown to produce a statistically significant improvement in its results.
The present clinical study has shown a mean hair reduction of 64% in just 3 sessions and a significant overall improvement of 16% with 4,800W, when compared with a moderate power of 1,000W ($p<0.024$). The satisfaction of the subjects and the researcher were consistent with the efficacy of the results. Additionally, subjects and areas with thinner hair and lighter skin showed greater improvement with 4,800W, as a consequence of greater thermal damage to the hair using the parameters of the high-irradiance laser. Accordingly, fewer sessions were found to be needed to achieve permanent hair removal with a high-power diode laser of 4,800W. Additionally, pain and other side effects remained mild and did not increase significantly with the short pulses, with the exception of the oedema which was greater with the use of 4,800W.
Increased patient comfort and the shorter treatments required to achieve the desired result, position this 4,800W laser equipment operating in dynamic mode as a very promising advance in aesthetic medicine.

Acknowledgments

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Conflict of interest disclosure

Some of the authors of this publication conduct research at Cocoon Medical S.L.U., a company which is developing products related to the research being reported. However, this publication strictly adheres to the objectivity and ethics of an independent research.

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Original Article

The Effectiveness of Hyaluronic Acid Injection with Automated Micro-Needling on the Pliability and Surface Area of Hypertrophic Facial Scars: Clinical study

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Running title: The effect of hyaluronic acid injection with automated micro-needling on hypertrophic facial scars

Abstract
Background: the formation of facial scars is considered the next stage of the wound healing process, which occurs when the facial tissues are exposed to possible damage or surgery. Many treatment methods have been used to treat these scars to try and make them become as close as possible to the healthy skin nearby, but their applications however caused a variety of adverse effects.
Aim: this research studied the changes in pliability and surface area during the treatment of hypertrophic facial scars by hyaluronic acid injection with automated micro-needling according to the Observer Scar Assessment Scale (OSAS).
Methods: this research was a clinical trial. 12 Patients that needed treatment of hypertrophic facial scars were enrolled. 12 scars were treated with hyaluronic acid injections with automated micro-needling. Four treatment sessions were done with an interval of 30 days between each session. Four assessments of pliability and surface area by the Observer were taken during treatment according to the Observer Scar Assessment Scale (OSAS).
Results: there are statistically significant differences in the average assessment of the pliability and surface area among the four studied sessions ($P<0.05$).
Conclusion: within the limitations of this research, we demonstrated that the use of hyaluronic acid injections with automated micro-needling in the treatment of hypertrophic facial scars is considered an effective technique in improving its pliability and surface area with respect to the Observer Scar Assessment Scale (OSAS).

Keywords
Hypertrophic facial scars, hyaluronic acid, automated micro-needling

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Introduction

Scars are a common phenomenon as they develop after a skin injury in patients of all ages[1] and the defective development of these scars has not been understood in depth[2]. Hypertrophic scars on the face are formed following facial wounds and various facial surgeries. The causative factors may be excessive pulling force on the wound, bacteriosis, foreign reactions and an inherited predisposition[3].

Hypertrophic facial scars are characterized by an overgrowth of the collagen fibers within the scar and manifest in the form of tough nodal growths that do not expand and do not extend beyond the edges of the original wound[4]. Although these scars do not pose a health risk, they can be very annoying to patients, as they are painful, raised, rigid and aesthetically unacceptable, which may negatively affect the patient's quality of life[1]. Therefore, these scars were considered one of the most important challenges faced by the surgeon, and required careful treatments later in the event that they may occur[5].

Many treatment methods have been used with the aim of managing these hypertrophic scars to become as close as possible to the healthy skin nearby, such as treatments with corticosteroids[6], cryotherapy[7], radiotherapy[8,9] and laser treatment[10], but all of these methods failed to exclude any unwanted side effects.

Corticosteroids have been adopted with great frequency in treating hypertrophic scars by injecting triamcinolone into the scar tissue[6], but their use was accompanied by the emergence of some side effects such as atrophy, capillary expansion, and pain in the injection area[11], which reduced its use and required searching for alternative treatment methods.

Automated micro-needling has recently spread as a safe and effective dermatological treatment, as the basis for this treatment is the rupture of microscopic needles of old skin collagen structures by forming thousands of microscopic holes[12]. Studies indicate that after pricking the skin, a group of enzymes are released, forming what is known as the metalloproteinase matrix and is responsible for breaking down most of the extracellular matrix proteins during normal tissue growth and transformation[13].

The automated micro-needling technique is accompanied by subsequent healing stages that begin with inflammation, which manifests as visible redness for about 48 hours, and an oedema is considered uncommon[13]. Subsequently, the reproduction phase begins immediately with the introduction of new fibers from the third type collagen into the skin matrix, and the effect on the epidermal stem cells and dermis is still unknown[13]. Then comes the remodeling phase by transforming the formed collagen fibers into a more flexible type 1 collagen[14].

The discovery of the automated micro-needling technique was only a coincidence when it recorded an unexpected improvement in the texture and color of hypopigmented facial scars and their general appearance after subjecting them to the camouflaging tattoo based on needles[15], as these needles work within specific depths and are subject to adjustments, and these depths range from 0.25 mm to 2.5 mm[16].

The dermaroller device, or the so-called skin wheel, was first used in automatic micro-needling, which is a grip equipped with a cylindrical wheel bearing on its surface 192 needles of stainless steel with a diameter 0.25 mm and a length of 1.5 mm[14]. Then the dermapen device, or the so-called skin pen, appeared, as the mechanisms of action of the two devices are similar in terms of relying on microscopic skin needling to stimulate the healing process more regularly and within microscopic areas, which is positively reflected in improving the appearance of the skin, reshaping it and increasing its elasticity[17], but the advantage of the dermapen over the dermaroller is highlighted by the reduction of damage to the skin[18].

This lead to Dermapen receiving approval from the US Food and Drug Administration and the award for the best professional device in skin rejuvenation, as it is used in the treatment of common acne scars, burn scars, tension lines, wrinkles and hair loss[12,17]. Most of the advantages regarding skin treatment with Automated micro-needling with the dermapen are based on the absence of an open wound in patients and there is no risk of photosensitivity in addition to the fact that the device is an inexpensive therapeutic alternative[19], while the disadvantage arises through the possibility of skin bruising in the treatment area during the first two days[12].

Hyaluronic acid is a glycosaminoglycans present in the epidermis with a high molecular weight and its molecules are found on the skin cell envelope and in the cellular space of skin and the vitreous of the eye and in the joints and muscles[20], and has a role in many important vital functions, such as regulating cellular adhesion and cellular movement, managing differentiation, and conferring the mechanical and biological properties of tissues[21]. Initially, hyaluronic acid was isolated from the vitreous in the eyes of cows and was later called Hyalus, and it is present in all living species and does not require an allergy test before injection[22].

There are two types of hyaluronic acid, either it is animal, which is extracted from rooster combs and has a high molecular weight and a low concentration, or it is non-animal as it is extracted by the bacterial fermentation process of streptococcus and has a low molecular weight and a high concentration[23].

Hyaluronic acid has been used extensively during the past two decades in eye surgery, wound repair and arthritis treatment, due to its water-soluble properties and its lubricant or sticky properties[24]. With the advancement of biotechnology, this substance has been developed into multiple forms and different molecular sizes with the aim of using it for cosmetic purposes[23], which prompted us to adopt it in this research in conjunction with automated micro-needling in order to treat hypertrophic facial scars.

Materials and methods

This research was a clinical study, and it was done from september 2018 to February 2020 at the clinic of the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Damascus, Damascus, Syria.

12 patients (5 males have 5 scars, 7 females have 7 scars) requiring treatment were included in this research (*Table 1*).

Parameters	Gender		Total
	Male	Female	
Frequency	5	7	12
Percentage	41.7 %	58.3 %	100.0 %

Table 1 *- Gender information of the enrolled patients.*

These facial hypertrophic scars located in the maxillofacial region resulted from oral and maxillofacial surgery operations. The mean patient age was 29 years (*Table 2*). The patients were given written information about the research , and their informed approval was obtained.

Parameters	Number	Mean	Standard deviation
Age (yr)	12	29	5.74

Table 2 *- Age information of the enrolled patients.*

Inclusion Criteria

- Ages of Patients ranging from 18 to 45 years old.
- Patients have had maxillofacial surgeries more than six months ago from the date of the operation and they complain about the presence of subsequent facial hypertrophic scars.
- Patients with a type III or IV Fitzpatrick classification[25], the most common type in the Middle East.
- The patient must be cooperative, mentally capable, and committed to the boycott.

Regarding the scar inclusion criteria[26]:
- The scar is not associated with a local or systemic infection, gangrene, or nonvascular tissue.
- The scar should be at least 6 months old.
- In this research, the length of the scar ranged between 1-3cm, its height was 2mm, and its width ranged between 2-3mm.

Exclusion criteria

- Oncology patients who are subjected to radiotherapy in the face area.
- The presence of diseases that affect the healing process, such as diabetes or immune diseases.
- The presence of bleeding disorders.
- The presence of skin diseases such as psoriasis, vitiligo and skin infections.
- Patients who have had their scars treated with botulinum toxin or fillers in a previous periods between six and eight months prior.
- Lactation or pregnancy.

Materials and tools used in the research

- Clinical examination tools: (gloves-masks-sterile gauze).
- Photography tools: digital camera.
- Sterilization tools: Hexamidine surface disinfectant, concentration 0.1 ml.
- Surface anesthetic: Cosmocaine Plus.
- Automated micro-needling device and its heads. The Dermapen device was used, which is an advanced technological instrument for vertical pricking of the skin through several needles that puncture the skin with an automatic vibratory function. The movement of the needles up and down vertically and the depth of entry of the needles is controlled from 0.25 mm to 2.5 mm and at seven speed levels ranging from 1 to 7 pricks per second, and the depth of entry is adjusted according to the target area by special keys. The device has been calibrated in our study to be a prick depth of 2 mm and at speed levels of 5 pricks per second, according to the instructions of the device manufacturer[27].
- Hyaluronic acid. CytoCare was used from the French company Revitacare, which is a mixture of 32mg/ml non-cross-linked biotechnological hyaluronic acid and CT50 rejuvenating complex[28]. It was filled with insulin syringes and injected into the thread-treated scars.

Surgical procedure

After said scars were clinically examined by direct vision and ensured that they complied with the conditions, an optical image was made of the location of the target scars (*Figure 1*) .

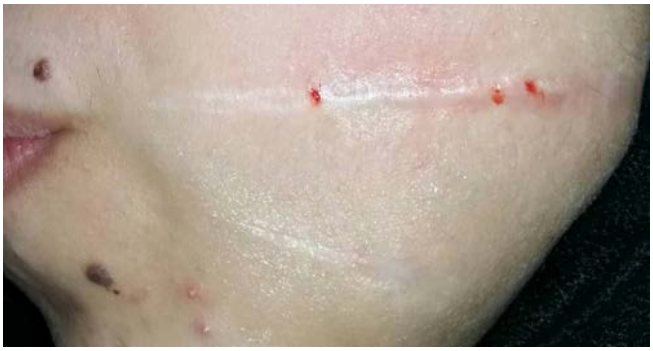

Figure 1 *- An image showing the points of injection.*

The treatment was divided into 4 sessions with an interval of 30 days between each session[29,30], where the work was done in each session as follows: The surface of the scar was cleaned well with 0.01ml hexamidine solution, then the surface anesthetic was applied for 45 minutes[31], and then removed with a sterile gauze. hyaluronic acid was applied by injecting it into the treated scar streakly over the entire length of the scar surface (*Figure 2*). Micro-needling was performed on the treated scar after preparing the first with a new needle head and determining the appropriate speed and depth of puncture. The dermapen was lubricated on the skin at an angle of 90 degrees without applying any pressure in three directions: vertical, horizontal and inclined, and the movement was steady and in one direction (*Figures 3, 4*), the area was wiped with a sterile gauze.

The duration of work in each session was between 5-10 minutes[27]. Patients were asked after each session to not be exposed to the sun for 24 hours, and were allowed to return to work one day after the session.

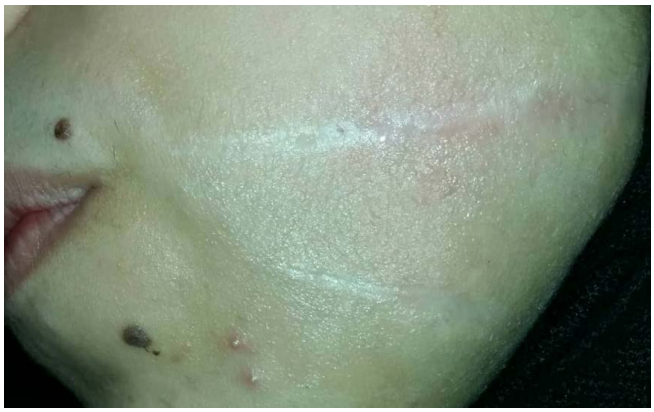

Figure 2 *- An image showing the scar after the second session.*

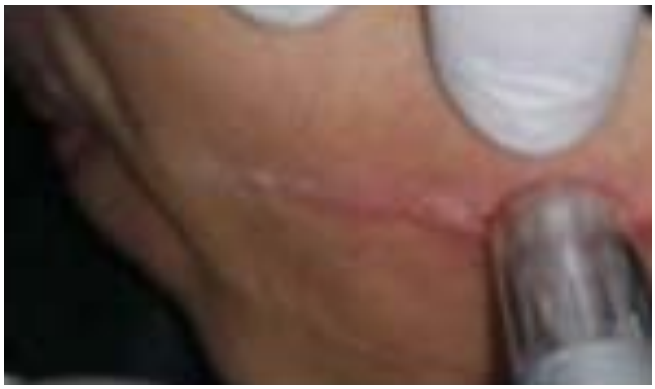

Figure 3 *- An image showing the scar during automated micro-needling.*

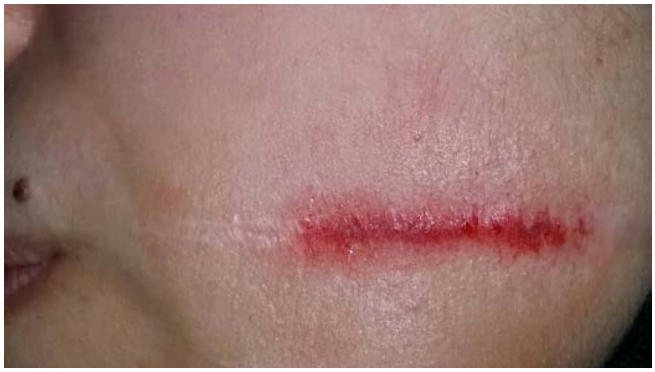

Figure 4 *- An image showing the scar after automated micro-needling directly.*

Study method

The Observer Scar Assessment Scale (OSAS) consists of 6 numerically recorded items that give at the end a total scale number, and the total gives the overall score for the scale[32]. The scale of Observer includes 6 questions about vascularity, pigmentation, thickness, relief, pliability, and surface area, and each of the six items has a scale of 10 degrees, where the score of 10 corresponds to the worst scar that can be imagined or felt, whereas the score of 1 reflects the state of normal skin (*Figure 5*). In this research, pliability was tested by placing the scar between the thumb and forefinger together, while the surface area was tested by comparing the surface area of the scar to the primary wound area. Three external observers who were resident in the Department of Oral and Maxillofacial surgery, Faculty of Dentistry, Damascus University, assessed the pliability and surface area of all studied scars using this scale for all treatment sessions (*Figure 6*).

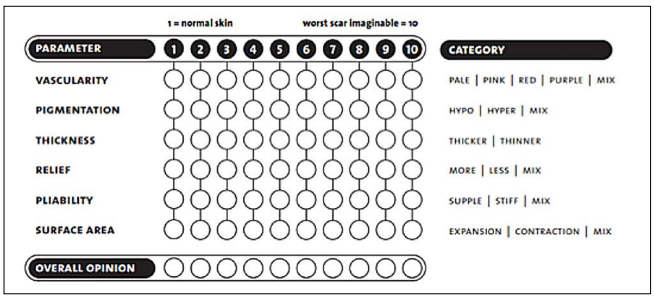

Figure 5 *- An image showing Observer Scar Assessment Scale (OSAS).*

Figure 6 *- An image showing the treated scar after 4 months of treatment.*

Statistical Analysis

The sample size was calculated according to the (G Power 3.1.7) program, considering that the t-test used is: t-test for cross linked or dependent samples and significance level: 5%, study strength: 80%, and effect size: 1.39 after 4months with maximum standard deviations: 7.68, and then the entered information was processed in the program, so the required sample size was 12 cases. The Statistical analysis of the variables of this research - the pliability and surface area was done using a program Statistical Package for the Social Sciences (SPSS) version 20. The t-test was used to evaluate the changes. A dependent t-test was performed to study the significance of the differences in the changes of the pliability and surface are of all treated scars (The P- value ≤ 0.05 was considered statistically significant).

Results

This research evaluated the changes in pliability and surface are (*Tables 3, 4*). The research showed that there are statistically significant differences in the average assessment of the pliability and surface area of treated scars among the four studied sessions (P< 0.05) (*Tables 5, 6*).

Parameters	Studied session	Num	Mean	Standard deviation	Confidence Interval 95 %	
					Lower limit	Upper limit
Pliability	1	12	7.55	1.64	5	9
	2	12	6.72	1.45	5	8
	3	12	5.31	1.15	4	7
	4	12	3.95	0.85	3	5

Table 3 *- Descriptive statistics of the changes in the pliability during the four studied sessions.*

Parameters	Studied session	Num	Mean	Standard deviation	Confidence Interval 95 %	
					Lower limit	Upper limit
surface area	1	12	7.96	1.57	6	10
	2	12	6.93	1.36	5	9
	3	12	5.28	1.04	4	7
	4	12	3.58	0.70	3	4

Table 4 *- Descriptive statistics of the changes in the surface area during the four studied sessions.*

Parameters	T	P- value	Mean Difference	Comparison of scar assessment values between the two stages	Confidence Interval 95 %
					degrees of freedom
pliability	5.423	0.000	- 1.03	B-A	11
	- 14.110	0.000	2.68	C-A	11
	- 23.060	0.000	- 4.38	D-A	11
	- 8.687	0.000	- 1.65	C-B	11
	- 17.637	0.000	- 3.35	D-B	11
	- 8.950	0.000	- 1.70	D-C	11

Table 5 *- T test for dependent samples to study the changes in the pliability during the four studied sessions.*

B-A: In the second session - in the first session.

C-A: In the third session - in the first session.

D-A: In the fourth session - in the first session.

C-B: In the third session - in the second session.

D-B: In the fourth session - in the second session.

D-C: In the fourth session - in the third session.

Parameters	T	P- value	Mean Difference	Comparison of scar assessment values between the two stages	Confidence Interval 95 %
					degrees of freedom
surface area	5.535	0.000	- 0.83	B-A	11
	- 14.937	0.000	2.24	C-A	11
	24.007	0.000	- 3.6	D-A	11
	- 9.402	0.000	- 1.41	C-B	11
	-18.472	0.000	- 2.77	D-B	11
	-9.069	0.000	- 1.36	D-C	11

Table 6 *- T test for dependent samples to study the changes in the surface area during the four studied sessions.*

It can be noted that the value of the significance level is smaller than the value (0.05) when comparing the values of evaluating the pliability and surface area in the assessment of the observer on the Observer Scar Assessment Scale (OSAS) between the stage (the fourth session) and each of the remaining three stages (the third session, the second session, the first session). That is, at the 95% confidence level, there are binary differences of statistical significance in the average evaluation of the pliability and surface area in the assessment of the observer on the Observer Scar Assessment Scale (OSAS) between the stage (the fourth session) and each of the remaining three stages (the third session, the second session, the first session) in the research sample. Since the algebraic sign of the differences between the averages is negative, we found that the values of evaluating the pliability and surface area in the fourth session were smaller than in each of the remaining three sessions, and we found that the values of evaluating the pliability and surface area in the assessment of the observer on the Observer Scar Assessment Scale (OSAS) have decreased with the increase in the number of sessions.

Discussion

A scar is an unavoidable end result of wound healing, Scarring is a natural process of healing after damage to the skin that extends to the reticular dermis. While some scars may be socially acceptable, even admirable, scars of the face can be viewed as disfiguring or ugly[33]. Facial scars can cause significant emotional distress due to their obvious location[34,35]. Hypertrophic scars are characterized by an overgrowth of the collagen fibers within the scar and manifest in the form of tough nodal growths[4].

Many treatments have been used in the management of hypertrophic facial scars, but their applications failed to exclude any side effects. Steroid injections may cause skin depression, atrophy, and pain[11,36,37]. Potential complications of radiation therapy are divided into erythema, hyper-or hypo-pigmentation and carcinogenicity[38,39]. Laser treatment is associated with prolonged erythema, hence the next itch, post inflammatory hyperpigmentation[40,41].

Many scar creams are available, some creams that contain vitamin E. Their use was accompained by the appearance of following allergic reactions[42]. Hyaluronic acid was used in the treatment of atrophic scars as it helps speed up the remolding process[43,44].

In this research, Hyaluronic acid was used in combination with automated micro-needling for the treatment of hypertrophic facial scars in contrast to studies that used micro-needling alone as a skin treatment without applying any materials[13,19], and in contrast to studies that used calcinin with automated micro-needling to speed up the healing process[45].

The treatment was performed in four sessions and the interval between these sessions was of 30 days based on previous studies in this regard[29,30]. From this interval between sessions given sufficient time to effect a change in the properties of the treated scar. The Observer Scar Assessment Scale (OSAS) was also used, and this same scale was adopted in similar studies[32,43] because it gives more realistic values and increasing the statistical values leads to an increase in the credibility of the research results. In contrast to the use of the electronic Viso-scan, which gives values on skin color and scar depth[46], but is completely unable to give values about the other variables of the scar such as pliability and surface area, for example, which were the variables studied in this research.

According to this research, the changes in pliability and surface area on Observer Scar Assessment Scale (OSAS) were found to be statistically significant ($P< 0.05$). These results agree with Aust et al. 2011[12]; Camirand and Doucet (1997)[15]; Ramaut et al (2017)[47], who indicated to the effectiveness of using this technique in treating scars and improving their properties or variables.

Conclusions

Within this research, we find that the use of hyaluronic acid injection with automated micro-needling in the

treatment of hypertrophic facial scars is considered an effective technique in improving its pliability and surface area with respect to the Observer Scar Assessment Scale (OSAS).

Conflict of Interest

Authors declares that there are no conflicts of interest.

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aesthetic medicine

Review

Medical Dermal Filler Procedures Pre-Questionnaire

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Short title: **Questionnaire for Anamnesis**

Abstract

Introduction: dermal filler complications can arise due to unpredictable causes, operator- dependent causes, or at other times are caused by unwanted reactions related to the patient's pre-existing clinical conditions or co-morbidities that favor an unsatisfactory outcome of the aesthetic procedure.
The aim of this study is to formulate, based on a critical review of literary texts and the personal experience of the authors, an anamnestic questionnaire to be completed by patients requiring treatment with dermal filler, in order to facilitate the identification of patients not suitable for the procedure.
Materials and Methods: Medline and PubMed databases were searched on April 25th, 2021 using the terms: "Anamnesis", "Complications", "Medical history" and "Dermal filler". The search covered the 2011-2021 decade.
From the publications found, following the reading of the abstract, those which did not meet the inclusion criteria were eliminated. Out of the ones remaining, the whole article was analyzed in order to highlight the presence of anamnestic indications that contraindicated the aesthetic procedure. Only articles available in English were considered for this review.
Results: the PubMed search showed 478 results for "dermal filler" and "complications", 0 for "dermal filler" and "anamnesis", 26 for "dermal filler" and "medical history". A total of 458 articles were excluded based on analyses of abstracts and full texts. A total of 20 articles were eligible for the study. Active or chronic infections, autoimmune diseases, previous treatments with unknown filler, history of allergies, conditions that cause Koebner response, coagulopathies, and some medical treatments represent known contraindications.
Conclusions: following the review of literary texts, a pre-treatment questionnaire is proposed to help doctors screen out patients who may present contraindications to dermal filler treatments.

Keywords

Questionnaire, dermal filler, complications, medical history, autoimmune diseases, chronic inflammatory diseases

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Introduction

Over the past 10 years, the popularity of non-surgical rejuvenation procedures using dermal fillers has progressively grown. In 2018, non-surgical aesthetic procedures emerged from a survey of AICPE (Italian Association of Aesthetic Plastic Surgery) members who were 688,690, representing 68.2% of all aesthetic procedures, with more than 250,000 fillers injected, with a growing trend of 7% per year[1]. Considering the small sample included in the questionnaire, it is important to assume that the actual figures were much higher.

The popularity of dermal fillers is due to their efficacy, ease of administration, low cost and safety profile involving few complications or contraindications. Complications can be classified as operator dependent or idiopathic or related to the type of filler chosen for implantation (permanent/temporary). Operator-dependent complications cause infections, skin necrosis, material dislocation, hyper-or hypocorrections[2-4] and can be prevented by specialized training of the physician administering the treatment, careful asepsis/antisepsis of the skin, anatomical knowledge of the treatment area[5], or by avoiding some categories of permanent fillers or liquid silicone, which is forbidden in Italy by DM 3.09.1993[6].

In some cases, however, in spite of all of the precautions, there can be adverse effects related to pharmacological or phytotherapeutic treatments, or to the clinical history of the patient. The anamnesis, in medicine, is the collection from the direct voice of the patient of all the information that can help the doctor with the diagnosis of a certain pathology, and that allows to create a basis for the construction of a solid doctor-patient relationship by establishing a mutual link.

The anamnesis is part of the initial evaluation of the doctor with the patient and an accurate collection of data assists not only to make a diagnosis but, especially in Aesthetic Medicine, is useful to prevent complications related to the same practices.

However, many physicians have lost interest in carefully analyzing a patient's medical history[7].

The purpose of this study is to provide the aesthetic physician, dermatologist, or plastic surgeon with a questionnaire, that should be submitted to the patient during the anamnesis, that can identify the presence of contraindications to the use of dermal fillers.

Materials and Methods

A review of scientific literature by searching PubMed/MEDLINE electronic bibliographic database (https://pubmed.ncbi.nlm.nih.gov/) was performed on April, 25th 2021. All eligible articles written in English and pertaining dermal filler complications in the time span of 2011-2021 were searched by identifying pertinent index terms (Medical Subject Heading [MeSH]). The search terms we used were "Anamnesis" or "Complications" or "Medical history" and "Dermal filler".

Eligibility Criteria:

1) Any case report or literature fact on dermal filler complications which was published in the English language only from 2011 to 2021.

2) Only descriptions of anamnestic factors related to dermal fillers complications were considered.

Out of the 462 articles that were available, two independent reviewers selected the studies for the systematic reviewing through each phasing of review-screening, eligibility criteria and inclusion criteria. The abstracts searched were further screened for compliance with inclusion criteria and full text analyses were performed, selecting a total of 20 articles (*Table 1*).

Results

Primary endpoints: only 20 publications provided indications regarding the collection of specific medical history regarding dermal fillers treatments. Only 5 papers published a table of pathological conditions that contraindicated in an absolute or relative way (in the opinion of the physician) the treatment with filler. Chronic inflammatory diseases, autoimmune diseases, blood diseases, previous treatments with unknown or permanent fillers, the assumption of antiplatelet or anticoagulant therapies or allergies to known components of the fillers are the most cited elements.

Discussion

From the analysis of the literature, only a few works highlight the need to perform a thorough medical history form before subjecting patients to dermal filler, verifying the absence of contraindications to aesthetic treatment, through the search for skin diseases, allergies, systemic diseases or pharmacological treatments. Heydenrych et al. reported the importance of a patient medical history questionnaire to rule out the presence of clinical conditions that contraindicate a specific treatment, without providing the questions needed[8].

The literature review revealed clinical conditions that represent absolute or relative contraindications to the dermal filler treatment, which can be detected by asking the patient specific questions summarized in *Table 2*.

Blood diseases or the intake of anticoagulants represent a relative contraindication because of the recurring presence of bruising or bleeding[9].

Local or systemic infections represent an absolute contraindication to filler treatments because of the risk of septic complications in implantation[8].

A relative local contraindication is represented by the presence of previous treatments with unknown fillers with different and often irreconcilable physical properties between the various products, which can also be detected by ultrasound[10] or MRI scan[11].

Allergic or anaphylactic reactions in patients with multiple allergies represent a contraindication to the use of devices containing the allergens in the filler or excipients, which can be verified by reading the package insert[12]. Hypersensitivity reactions can be classified as acute or delayed, depending on the time of onset.

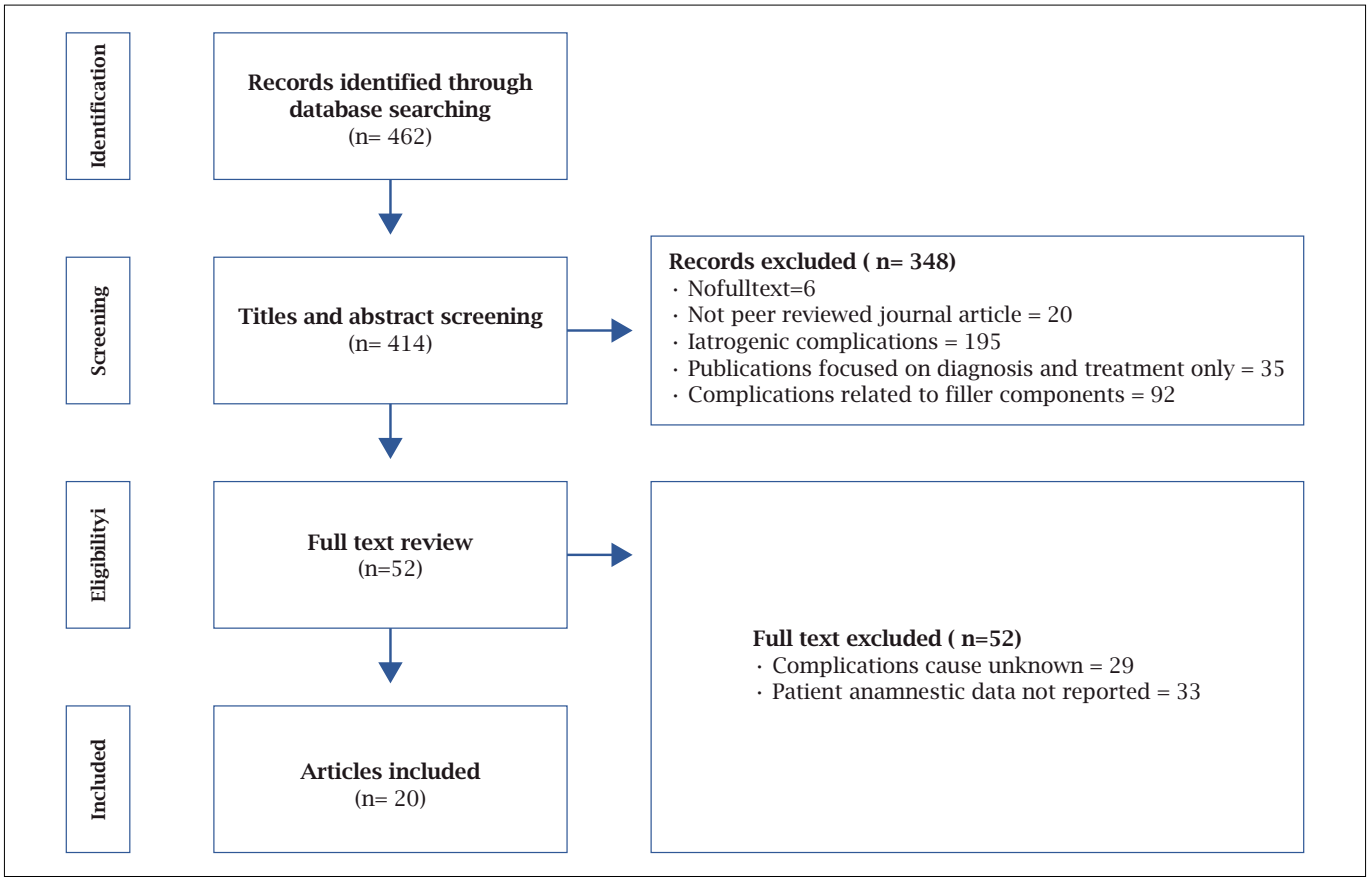

Table 1 *- Flowchart of literature review.*

Medical history questionnaire to screen for contraindications to filler use.

- Do you suffer from recurrent skin infections (such as herpes simplex, acne, folliculitis or rosacea)?
- Have you recently or currently suffered from a dental condition (such as abscess, periodontitis, otitis, sore throat or sinusitis)?
- Have you recently or currently suffered from flu syndromes, fever, gastroenteritis or urinary infection?
- Have you ever suffered allergies with severe manifestations of illness (anaphylactic shock, edema of the glottis or chronic urticaria)?
- Have you ever experienced allergies to lidocaine, PEG or other components of a filler?
- Have you been diagnosed with an autoimmune disease (active Hashimoto's thyroiditis, mixed connective tissue disease, undifferentiated connective tissue disease, active morphea or active SLE)?
- Do you suffer from coagulation disorders (hemophilia, thalassemia, hemoglobinopathies) or are you taking anticoagulants?
- Have you been diagnosed with Crohn's disease, ulcerative rectocolitis, psoriatic arthritis, acquired immunodeficiency or autoimmune diseases such as dermatomyositis, polymyositis, SLE, or rheumatoid arthritis?
- Have you ever undergone a transplantation? (heart, liver, bone marrow or kidney)
- Have you ever undergone any treatment with permanent fillers? In which areas?
- Have you ever experienced complications or adverse effects after filler use?

Table 2 *- Medical history questionnaire to screen for contraindications to filler use.*

Type I hypersensitivity reactions occur within minutes to hours after injections due to an immunoglobulin E (IgE)-mediated immune response to the dermal filler. They may manifest as angioedema or anaphylactic reactions that occur after initial or repeated exposure. Late-onset inflammatory reactions are rare complications that can occur following injection of HA dermal fillers[13] due to infectious or immune-mediated causes. Delayed type IV hypersensitivity after HA implantation is the most likely explanation for late-onset events; it is impossible to predict and can occur both in patients who have been given the injection previously and in patients giving the injection for the first time. Although serious adverse events may occur with any Hyaluronic Acid filler, frequency rates appear to vary among products that may exhibit different cross-linking technology[14].
With regard to hyaluronidase, which is used to treat complications of granulomatous or ischemic nature, it can be administered to patients allergic to hymenoptera venom of which it is a component, since no cross-allergy with hymenoptera venom has emerged[15]. Patients with allergies and autoimmune-type immune system diseases seem to be more predisposed to develop reactions to fillers, and for this reason the list below is an important reminder to compile an accurate anamnesis[12]. Atopic dermatitis (AD) or atopic eczema is an itchy dermatitis of multifactorial etiology, with a chronic-recurrent course and typical distribution of lesions according to age. The fundamental characteristic of patients with AD is the presence of a defective epidermal barrier associated with an inflammatory skin hyper-reactivity to different environmental stimuli[16], developing both IgE-mediated and cell-mediated allergies.
One of the components of hyaluronic acid cross linking is an epoxy resin derivative with linear macromolecules obtained by the condensation of epichlorohydrin and polyphenols, especially Bisphenol A[17]: these components can cause allergic contact dermatitis, with symptoms varying from erythema to vesicles and ulcerations, often at the site of contact with the allergen, but can appear on any exposed skin area with a delayed cell-mediated mechanism[18].

- Alawami AZ, Tannous Z. Late onset hypersensitivity reaction to hyaluronic acid dermal fillers manifesting as cutaneous and visceral angioedema. *J Cosmet Dermatol.* 2021;20:1483-1485
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Urticaria / angioedema represents an absolute contraindication to treatment with fillers because of the reactivity of skin and mucus membranes that characterizes this pathology. It can be acute or chronic, in which case it can last for years and is divided into spontaneous and physical urticaria[19].
Fillers can also cause a recrudescence of the pathology in patients suffering from multiple chemical sensitivity (MCS), whose most frequent symptoms are those of allergic type such as difficulty in breathing, nausea, migraine, contact dermatitis, dizziness, hypersensitivity to odors and manifestations, sometimes even serious, at the neurological level such as split personality and amnesia[20].
Treatment with fillers has long been avoided in patients with systemic Lupus erythematosus, similar to other autoimmune or connective tissue disorders, because of the theoretical risk of exacerbation or reactivation of the disease caused by tissue stimulation[21]. Despite the theoretical risk of disease, the reactivation after tissue stimulation, there are no reports in literature on lupus reactivation after injectable treatment, the recommendation to not treat patients with active disease remains. However, more controlled studies are needed to understand the tissue effects of injectables in this patient population.
Psoriatic patients present a relative contraindication due to the possible occurrence of Koebner's phenomenon at the site of filler administration, which consists of the appearance of psoriatic patches at sites of physical trauma such as scratching, burns, and surgical scars. The size of the individual patches is highly variable[22].
Koebner's phenomenon may also occur in patients with vitiligo as a result of the skin's reaction to the continuous lesion created by the filler needle[23].
Morphea is a form of cutaneous scleroderma due to an autoimmune reaction, which causes the localized overproduction of collagen. Despite the theoretical risk of disease reactivation following needle trauma, no data regarding this issue has been reported in the literature[21].

Conclusions

Dermal filler procedures are very popular and can be offered to a wide range of patients.
Through the anamnesis it is possible to identify patients who for comorbidity, or for previous treatments or concomitant medical therapies are not suitable for treatment with fillers. The patient questionnaire which must be submitted during the collection of each individual's medical history, based on the evidence reported in the literature and the personal experience of the authors, is a quick and valid tool to help the doctor in carrying out the pre-treatment screening.

Aknowledgments

The Authors declare that they have no conflict of interest.

Disclosure

The Authors did not receive any funds and certify that there is no actual or potential conflict of interest in relation to this article.

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aesthetic medicine

Review

Local anesthetic and lip filler: golden egg or poisoned chalice?

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Short title: **Review: anesthetic and lip filler**

Abstract

Background: the use of local anesthetics to reduce patient-perceived pain is now widespread practice. This practice leads to the reduction of the sensitivity of an area for a variable long time, which presumably results in an alteration of the symptoms and, possibly, the symptoms that occur following certain complications.
Objectives: to determine whether 1) the use of lidocaine affects the safety of lip hyaluronic acid filler treatments and 2) adverse events increase in relation to the use of local anesthetics in the nerve block.
Methods: there was a review of the scientific literature on the use of hyaluronic acid fillers, related adverse events, and the use of local anesthetics, particularly lidocaine.
Conclusions: in most cases, it is not possible to distinguish in the collected data the experience of the personnel who performed the treatment and when an anesthetic was used. Although the available literature does not report any increase of adverse events in relation to use of local anesthetics, it would be useful to make examinations about the data collection of adverse events, the number of patients treated by the aesthetic medical doctor and the use of lidocaine or other factors that might confound the interpretation of the data.

Keywords
Anesthetic, hyaluronic acid, dermal fillers, pain management

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Introduction

The ability to perceive painful stimuli is essential for the survival of organisms, yet the definition of pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1].
Besides other factors that may determine the pre-procedure, the procedure and the post-procedure phase, pain control remains an important key factor in determining the patient's experience and opinion of the medical doctor, the staff and the success of the procedure itself. Unfortunately, this is not always possible and pain affects clinical practice. According to some studies, in fact, there is a relationship between patient satisfaction and pain control[2,3,4].
In studying the effect of pain control on surgical inpatients, Hanna et al, reported that pain control was a greater predictor of satisfaction than courtesy and respect from the healthcare staff[5]; on the other hand, there are only a few studies in the medical aesthetic field: Weiss and Lavin reported that 69% of patients experience mild to moderate pain during botulinum toxin treatments, and 29% of all patients experience anxiety before treatment, and for 31% of patients, fear of pain which leads them to not schedule a new appointment[6]; and finally, Dayan, studying specifically a small group of patients in the field of medical aesthetics has obtained results not as decisive as the previous ones, leading him, on the contrary, to ask how capable we are to recognize the thoughts, fears, anxiety of patients[4].
Pain is an inherent limitation of aesthetic procedures that can be an obstacle to the final result; fear of the needle or painful procedures is a key factor in the patient's final evaluation not only of the procedure itself, but also of the physician and staff[7].
Furthermore, the level of pain felt by the patient during the procedure is determining for the patient's willingness to continue therapy. Having taken this into consideration, it is interesting to point out the possible coincidental correlation between the events, but in the year of approval of hyaluronic acid fillers with lidocaine there was a rapid increase in product-related procedures[4].

Notes on the phisiology of pain

Sensations of pain and temperature come from the myelinated dendrites of sensory neurons that are located in the skin, both in the presence and absence of hair follicles, even in deep tissues. Pain encompasses an initially rapid sensation (rapid pain) with sharp and well-defined sensitivity, to be then replaced by an unpleasant and dull sensation (late pain), a dynamic that seems to be related to the different signal on nerve fibres.
Tissue injury leads to the release of bradykinin and prostaglandins with direct action on nociceptors (both as sensitizers and as activators), which release substance P and calcitonin gene-related peptide (CGRP); while substance P alone acts on mast cells causing degranulation and histamine release, the combination of substance P and CGRP acts on blood vessels, dilating them and causing an oedema and a subsequent further release of bradykinin. Finally, the same platelets, called upon by tissue damage, release serotonin, which in turn activates nociceptors[8]. When stimulated, nociceptors (pain receptors) transmit impulses on a system composed of two types of fibres (*Table 1*)[9]:
Information from nociceptors travels on the same fibres: cold occupies transmission on both types, hot only on C fibres. Finally, there are chemically sensitive nociceptors (to bradykinin, histamine, high acidity, environmental irritants, etc.) and polymodal nociceptors that are stimulated by stimuli of a mixed nature.
It is important to remember that cold is an excellent local anesthetic only if the temperature to which the receptors are subjected falls below 10°C, only at this point, in fact, the discharge frequency of the receptors is essentially zero, making these receptors inactive. Specifically, when the temperature reaches 10°C, nerve conduction velocity drops by 33%, resulting in a higher pain threshold[10].
The use of vibration to induce anaesthesia[11], which is in fact comparable to rubbing and local pressure, is one of the main techniques[12].
This technique has its roots in the "gate control" theory[13], the mechanical stimulus then activates mechanoreceptors that lead to the stimulation of Ab fibres so they block the rise of pain signals to the brain.

Fibre type	Subtype	Diameter	Cladding	Conduction v. (m/s)
A(delta)		2-5 micrometres	Myelinated	12-30
	Type 1 (HTM)	respond to mechanical and chemical stimuli, but have a relatively high threshold value		
	Type 2	much lower threshold value for heat, but higher for mechanical stimulus		
C fibres		0.4-1.2 micrometres	Unmyelinated	0.5-2

Table 1 *- Types of fibres involved in the nociceptive system.*

Materials and methods

We identified the study population as patients of aesthetic physicians, dermatologists, and plastic surgeons. The topic of interest was the anaesthetic method used during practice and related adverse reactions and, when applicable, pain control.
An evaluation through the PubMed database of the scientific literature was carried out using the keywords "local anaesthetic", "filler", "adverse reaction", "pain", at a first stage individually and at a second stage combined in multiple conjunctions (*click here to see Table 2*).
The studies were selected whether they were relevant to the research's topic according to their titles and abstracts, using a "most updated" criteria when choosing between two similar papers. When pertinent, we selected the field of interest for the research, i.e. the perioral area.
Letters, studies with missing data and those in languages other than English were excluded from this study. After investigating full texts, the information was summarized and synthetized.

Discussion

There are numerous types of anesthesia used in the field of aesthetic surgeries, with topical and local anesthesia being the most frequently used methods. The chemical structures of topical anesthetics are similar to each other: they contain a lipophilic aromatic group, intermediate chain, and a hydrophilic amino group. The chemical group of the intermediate chain determines the classification amino amides (lidocaine, bupivacaine, articaine, mepivacaine, prilocaine, levobupivacaine, etc.) or amino esters (procaine, benzocaine, chlorprocaine, tetracaine, etc.). Epinephrine or other adrenergic agonist agents may be added in order to bring about local vasoconstriction, decreasing systemic absorption and prolonging the anesthetic effect[14].
The anesthetic binds to voltage-gated sodium channels (*Figure 1*) present on nerve endings and blocks sodium from entering; this results in inhibition of cellular depolarization and prevents nerve impulse propagation. Anesthetics primarily prevent the conduction of myelinated autonomic B fibres, and later the unmyelinated C fibres, ending with the 'the A fibres[16].
A peripheral nerve block has been shown to be successful only when it succeeds in blocking more than 70% of voltage-gated sodium channel's transmembranes. On three successive nodes of Ranvier. Internodal distance in mammals is between 200 microns and 2000 microns. For this reason, local anesthetic dosing must occur in sufficient volume to cover at least 6 millimetres of the nerve with enough molecules to block at least 70% of the sodium channels[17].

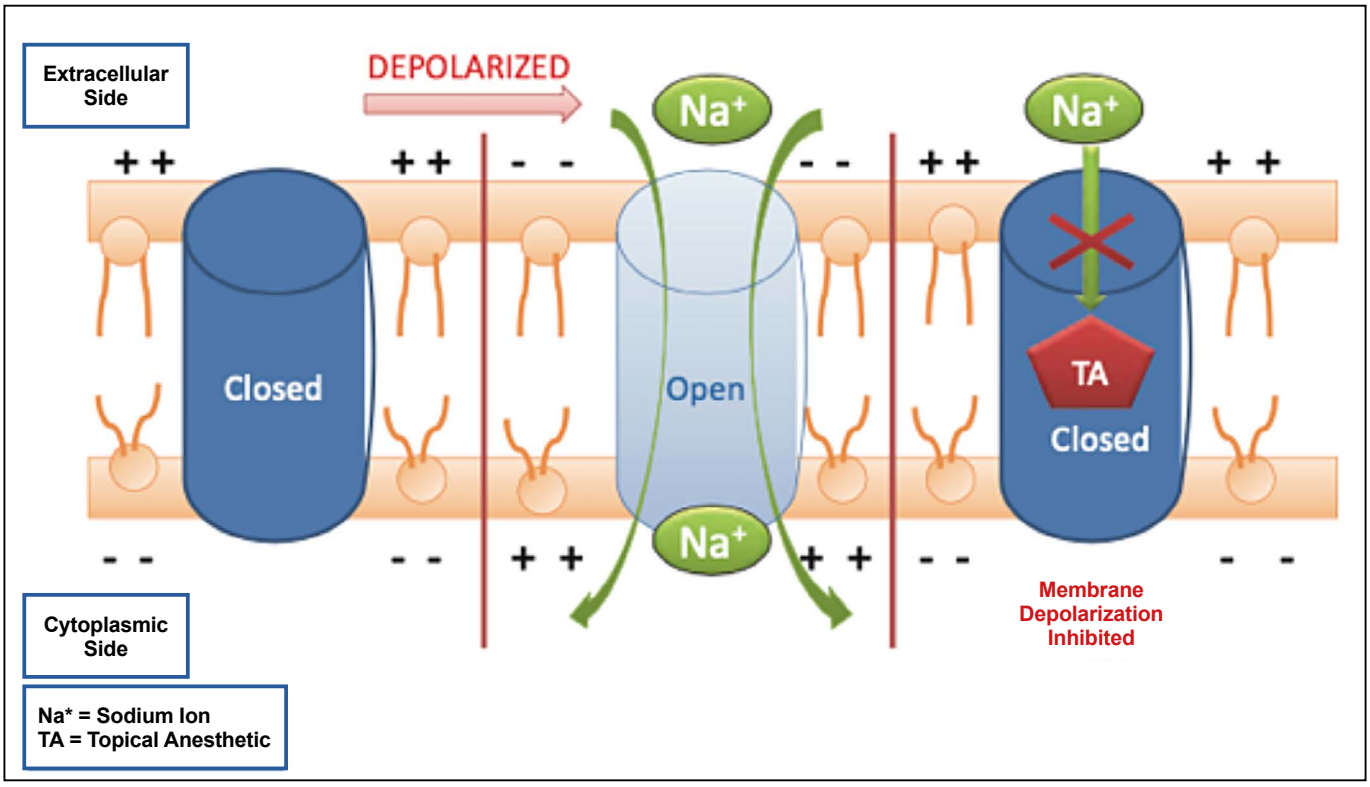

Figure 1 *- Cell membrane depolarization and its inhibition after the use of topical anesthetics[15].*

Topical anesthetics

The efficacy of topical anesthetics in reducing pain has been repeatedly confirmed, but the time required to achieve optimal anesthesia is sometimes excessively long (from 30 to 60 minutes of application depending on the anesthetic used[15,18,19]). It is also important to know that whilst gently cleansing the area that needs to be treated before application, which is essential, benzoyl peroxide should be avoided as it may diminish the effect of the anesthetic[20] and that the application thickness should be of at least 3 mm[15].
However, topical anesthetics are not entirely free from complications, which, although generally local (redness, irritation, etc.) and momentary, depend on the mode of use of the substance, which when used improperly can lead to cardiotoxicity and neurotoxicity[21,22,23].
Unfortunately, the use of topical local anesthetics seems to have a mild effect during the most painful cosmetic procedures. Similarly, the use of painkillers or anti-inflammatories in conjunction with the topical local anesthetic has not demonstrated much pain resolving efficacy[7].

Injectable anesthetics: locoregional anesthesia

The locoregional anesthesia involves the localization of a nerve branch that needs to be made inactive, it is necessary to inject it right in the immediate proximity of the nerve: "regional anesthesia always works – provided you put the right dose of the right drug in the right place"[24].
Loco-regional blocks are fast, reliable, secure and the learning curve is quick. Indeed, some authors consider the use of this technique essential for procedures involving the vermilion border and lips[25,26].
Some of the most commonly used nerve blocks in aesthetic medicine involve branches of the trigeminal nerve: the V nerve (*Figure 2*) is a predominantly somatic nerve, providing sensation to most of the face, and is to a lesser extent motor. The infraorbital (*Figure 3*) emerges from the largest branch of the maxillary nerve (V2) at the cutaneous level of the face through the infraorbital foramen directed downward and medially along a vertical line between the pupil and the medial canthus, approximately 6 mm (in females) 7 mm (in males) below the lower margin of the orbital rim.
The intraoral access involves the insertion of the needle at the level of the gingival fornix between the third and fourth tooth from the facial midline, inserting the needle along its entire length in the direction of the foramen previously identified; for a greater anesthesia it is possible to repeat the operation by inserting the needle between the second and third tooth. Usually, a dose of 1-1.5 ml of anesthetics around the foramen area is sufficient. The anesthetized site covers an area extending from the lower orbital margin to the upper lip, including the wing of the nose and the medial part of the maxilla. The time of action of the local anesthetic is generally between 5 and 10 minutes[28].
The mental nerve (*Figure 4*) emerges from the namesake hole venting from the inferior alveolar nerve, from here it will mostly cause an ipsilateral innervation of the lower lip.

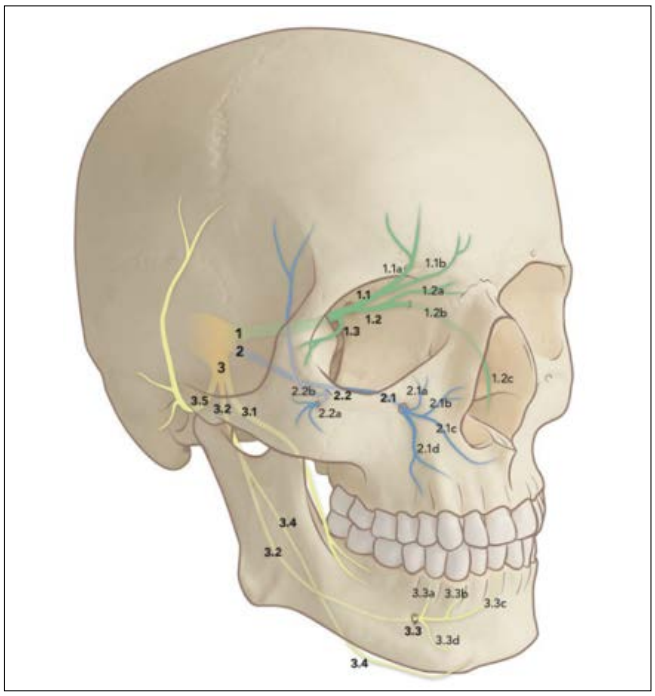

Figure 2 *- Illustration of the trajectories of the cutaneous branches of the V cranial nerve (1 green = ophthalmic branch, 2 blue = maxillary branch, 3 yellow = mandibular branch) 27. By gracious permission of Prof. Thomas Von Arx.*

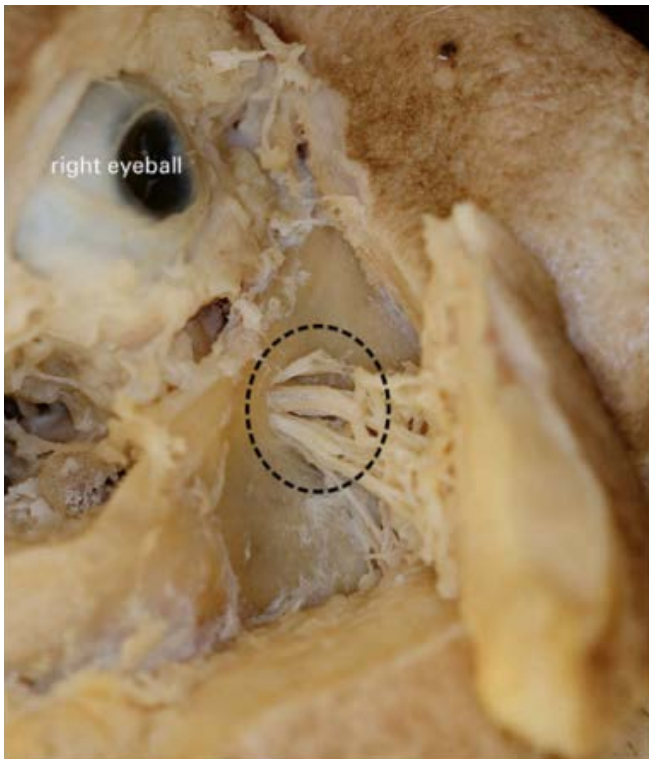

Figure 3 *- Cadaveric dissection of the infraorbital nerve destroy (circled in black) 27. By gracious permission of Prof. Thomas Von Arx.*

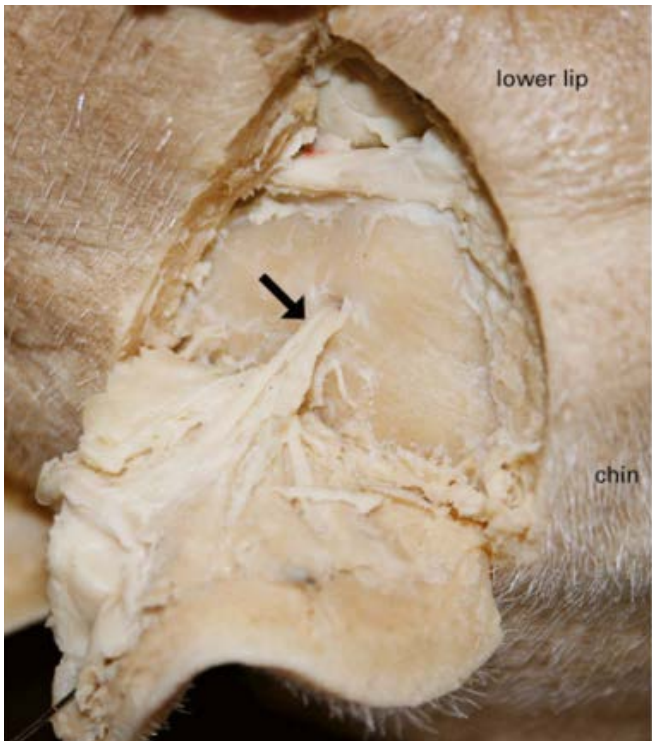

Figure 4 *- Cadaveric dissection of the right mental nerve (arrow)[27]. By gracious permission of Prof. Thomas Von Arx.*

The mental hole is identified at the level of the mandible, along the hemi-pupillary line.
Intraoral access is located in the space between the fourth and fifth teeth from the midline of the face at the level of the gingival sulcus. The mental nerve can be reached by an intra-oral approach, and by advancing 5-6 mm the mental foramen area will be reached.

Slowly injecting the anesthetic will reduce pain. Occasionally, 0.5 mL of the anesthetic at the level of the frenulum is needed to provide total anesthesia of the entire lip[28,29].
In order to increase patient comfort, a local anesthetic may be applied to the maxillary and mandibular anterior vestibular area[30]. In any case, whether the access is percutaneous or intraoral, it should be mentioned that in vivo anatomical structures occupy well-defined three-dimensional spaces, if the anesthetic is placed in a different plane from that in which the nerve lies, then it may take longer to achieve the result[31].

Adverse reactions of local anesthetic

It is important to consider all those local reactions (*Table 3*) that include pain, bleeding, bruising, oedema, nerve impairment from a direct injury, and infection; these are the immediate reactions such as adverse drug reactions, overdose, allergies[32].
Local Anesthetic Systemic Toxicity (LAST) occurs when the plasma anesthetic concentration exceeds recommended limits (e.g.: lidocaine in adults 4.5mg/kg - maximum dose 300-350 mg). Symptoms are primarily nerve-related with perioral paresthesia, facial paresthesia, dysarthria, a metallic taste, diplopia, tinnitus, and convulsions; tachycardia and an elevated blood pressure may be associated. Cardiovascular toxicity occurs at higher plasma concentrations with bradycardia, QT prolongation, hypotension, up to asystole. However, acute secondary toxicity from local anesthetics is rare (0.025-0.075%) when used at the recommended dosages, also considering that the required dosages for aesthetic medicine are much lower than the toxic ones[33,34,35].

Complications	Notes
Bleeding and hematoma	Attention to the case history of patients with altered INR or t hrombocytopenia. Nerve blocks should not be used if low- molecular-weight heparins have been administered in the previous 12 hours, and these should not be administered until 4 hours later.
Incomplete anesthesia	Additional infiltrations of local anesthetics may be necessary, depending on the calibre of the nerve it may be useful to wait even several minutes (10-15) to obtain a complete block.
Pain/paresthesia	If these symptoms are due to needle insertion, the needle should be retracted and repositioned to avoid intraneural placement.
Intravascular injection	It is good practice to proceed with aspiration every 5 ml of local anesthetic.
Nerve injury	It is an uncommon complication (1.5/10,000), in most cases transient and subclinical. Watch for the case history of patients with diabetes or neurological conditions.
Systemic toxicity	Toxicity depends on the peak plasma concentration[36,37,38].

Table 3 *- Complications of nerve blocks, adapted from T. Davies et al.[29].*

Use of adrenaline

If employed, adrenaline should be used at a concentration of 5 micrograms/millilitre or a solution concentration of 1:200,000 39. It should never be used for the treatment of tissues with terminal arteries: nose, fingers, penis where the intense vasoconstriction could lead to ischemic or necrotic complications.

Alteration of lip symmetry

Some authors have reported a higher incidence of lip ptosis after nerve blockage. Altered skin structures may result in the need for a second appointment for the correction of any asymmetries, due to altered tissue and anatomical landmarks resulting in improper filler placement[40].

What is the relationship between hyaluronic acid with lidocaine and adverse events?

Many studies have compared the efficacy, tolerability, and safety of hyaluronic acid fillers with or without lidocaine. According to the available literature, the use of hyaluronic acid fillers with lidocaine is effective in decreasing the pain experienced by patients during the operation[41-45].
Products based on hyaluronic acid with lidocaine maintain the same characteristics of flow, consistency, volume, concentration, duration, and effectiveness of action as those without[40]; in other words, the ideal characteristics of a filler[46] are preserved and the presence of anesthetic agents can only implement them making the procedure less painful on the patient.
Filler complications can be divided into mild, moderate, and severe as presented in the 2019 Consensus report[47]. A point of interest for past works have been serious complications, particularly vascular complications, and their possible different incidence in case a hyaluronic acid-based filler with or without lidocaine is chosen.
Serious complications are rare and are expected to account for 0.001% of the total[48], generally due to vascular compression or intravascular injection of filler or vascular spasms[49]. Despite the low incidence, the consequences of such an eventuality can be devastating[50] both in terms of patient clinical outcomes and in legal terms: an analysis of the Thomson Reuters Westlaw Edge database reported 2813 adverse events in the period 2008-2017, 17.9% of which related to labial area procedures, including 11 lawsuits related to malpractice with an average settlement of $600,000[51].
Therefore, as reported several times in the literature, the knowledge of the anatomy of the face and the experience necessary to identify the correct tissue plane in which the filler should be injected is of fundamental importance for the success of the operation[49]. Finally, it is interesting to note that some fillers appear to be able to cause more severe vascular damage than others, probably because of their ability to stimulate inflammatory processes and the platelet cascade[52].

Intravascular injection: do symptoms change with the presence of lidocaine?

Intravascular injections result in early symptoms: pain, associated with rapidly white skin that loses its tone, cold. As previously described by DeLorenzi[52], pain may be absent in presence of anesthetics, but this does not affect the other symptoms of intravascular injection of hyaluronic acid. Paleness is an immediate consequence of the intravascular injection, but it is not always constant, it can last even a few minutes and can be confused with the effect of epinephrine if used. However, livedo reticularis is more commonly observed. Therefore, the use of local anesthetics may alter the symptomatic manifestation of intravascular filler injections in terms of pain. However, it does not seem to do so for the remaining symptomatology [52,53].

Conclusions

The number of aesthetic procedures is continually growing, 2018 reported a 13.1%[54] increase in procedures concerning hyaluronic acid. Reducing the patient's pain during aesthetic medical treatments should certainly be one of the main objectives of the doctor: a painful procedure invalidates not only the possibility of future treatments at the same office, but also the immediate evaluation of the aesthetic result.
Anesthesiological procedures are many: some do not even require the use of instrumentation, sometimes it is sufficient to reassure the patient to be able to manage the pain and anxiety related to the aesthetic treatment and some authors have described the "Talkaesthesia" technique[55].
Topical anesthetic agents still play a fundamental role. Unfortunately, they require some procedural precautions in order to carry out their action efficiently: correct application time, thickness of the layer of product applied, sometimes occlusion of the surface that needs to be treated; in any case, they retain their role of great interest for the simplicity of use and the rapid resumption of social activities.
On the other hand, there is a unanimous consideration regarding the use of infiltrative anesthetics, which is the practice whereby the agent is diffused into the area by imbibing the tissues. This inevitably alters the anatomy of the area that needs to be treated and may be a reason to avoid its practice in aesthetic medicine.
Diepenbrock et al.40 In their prospective randomized study, they demonstrated that 77% of patients undergoing treatment with hyaluronic acid-based fillers of the nasolabial folds, upper lip, and/or lower lip found nerve blockage to be most effective in reducing treatment pain. It is important to note, however, that in his study nearly a quarter of patients who found nerve blockage to be the treatment that provides the least pain would choose topical anesthesia for subsequent aesthetic treatments. This first-of-its-kind study allows us to remember a fundamental point: the experience of pain involves other variables in personal preference for anesthesia before aesthetic treatments. Some patients have reported that they do not want to incur

post-treatment paresthesia, others may be afraid of the injection perhaps recalling bad previous experiences, and still others may associate intra-oral access with the sensation of dental anesthesia.

This literature review examines the most recent knowledge currently available with the purpose of evaluating the safety of local anesthetic use during the lip hyaluronic acid filler treatment.

The purpose of the use of anesthetics, painkillers, anti-inflammatories in medical aesthetic practices is certainly the reduction of the pain component: on the one hand it aims to eliminate it completely, on the other hand it is the fear of not being able to recognize early signs of catastrophic events.

As far as reported in the literature, the use of lidocaine as a local anesthetic is not among the risk factors for vascular complications. In other words, there are no reported cases of mild, moderate, or severe complications (as classified by Trocchi et al.) whose diagnosis was delayed because of lidocaine use.

On the other hand, it is reported that the anesthetic practice of nerve blockage (e.g., infraorbital n.) can result in the ptosis of innervated structures. Therefore, it is fair to ask whether the iatrogenic anatomical alteration may result in greater difficulty in identifying the correct anatomic plane of infiltration, leading to decreased safety, also because of the anatomical variations in the pattern of labial arteries (*Figure 5*)[56].

It is crucial to remember that the external diameter of the ALS varies from 0.3 to 3 mm, which makes it a perfect size to be eventually penetrated by a 27-30G needle (i.e. with an external diameter of 0.4-0.3 mm respectively), and that, therefore, it is pressing to know the possible increase in clinical risks following the anesthetic procedure. To date, there are no studies considering the incidence of adverse events in the presence or absence of nerve block. To the best of the author's knowledge, no cases of vascular adverse reactions related to the use of local anesthetics for nerve blockage have been reported, however, in the author's opinion, the available data is not completely adequate to fully answer the questions of this review. Ultimately, the practice of nerve blocking in clinical medical aesthetic operations has been widely described and widespread for many years now[25,55,59]. This, however, should not cause the doctor to underestimate the use of this technique: they must know that, although not frequent, adverse reactions to local anesthetics exist, so it plays a key role in the patient's history, identification of the right drug, knowledge of the same and the procedures required to resolve any complications[60]. On the other hand, it is necessary to consider that studies regarding adverse events in medical aesthetic practices consider aggregate data and do not lend themselves to an interpretation related to the expertise of the surgeon. Therefore, in collecting the adverse event data, it would be important to investigate the number of patients treated by the aesthetic physician, his or her training and the use of lidocaine, or other factors that might confound the interpretation of the data.

Disclosure

Nothing to disclose.

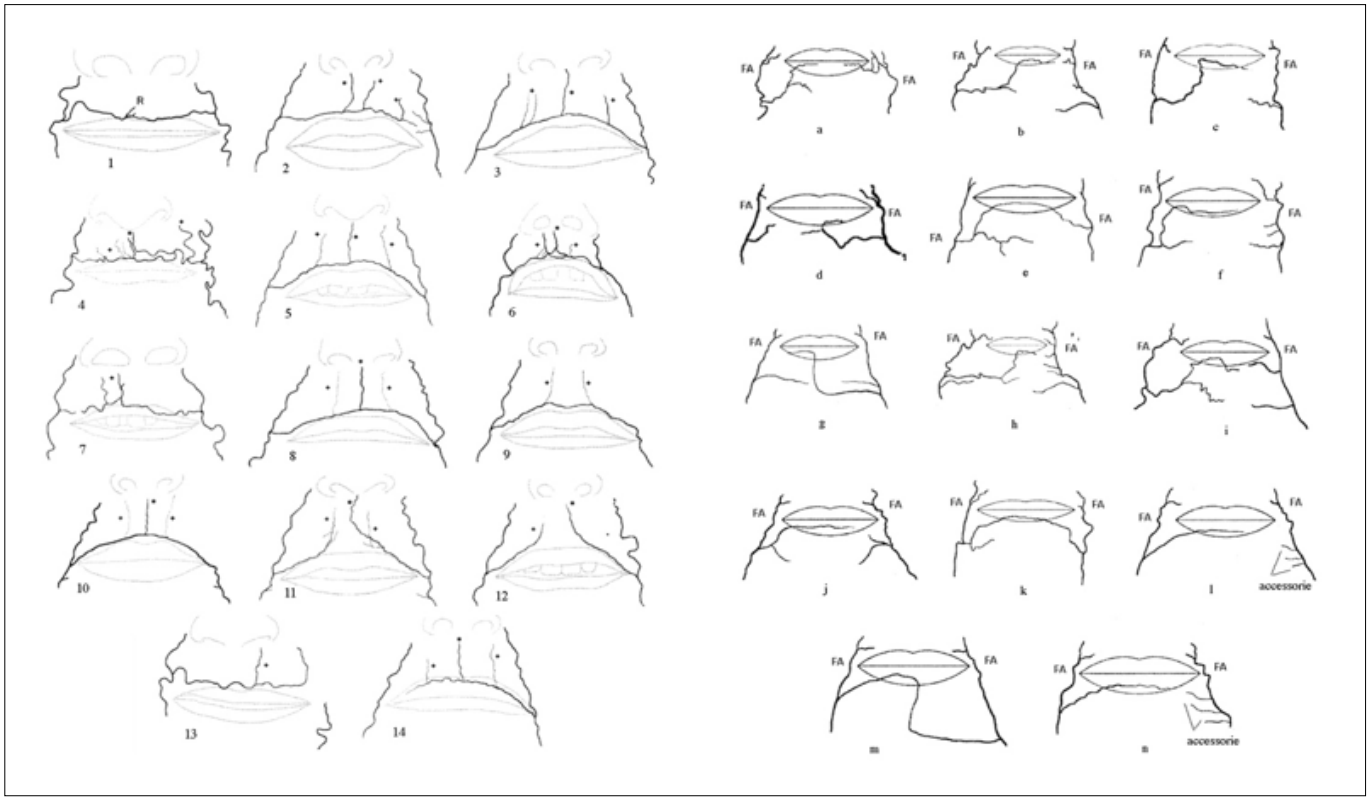

Figure 5 *- Anatomical representation of the variations in the pattern of labial arteries. 1-14 Superior labial artery; a-n inferior labial artery. Adapted from Edizer and Magden[57,58].*

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aesthetic medicine

Letter to the Editor

Can a code of ethics facilitate the development of mesotherapy in the aesthetic field?

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Mesotherapy is an increasingly widespread technique all over the world. For several decades, it has been successfully applied in many clinical conditions[1].
The Italian Society of Mesotherapy (SIM) has started a process of scientific evaluation of intradermal therapy, from which rules of good clinical practice have emerged[2]. From these recommendations, a group of researchers also extrapolated a preclinical and clinical development plan in order to correctly target future research investments. This decision-making process was carried out after defining two basic rules: only scientifically valid evidence can be considered, and only reviewers with no conflicts of interest can validate final decisions. To achieve this goal, it was necessary to draw up a code of ethics to guarantee the process of approval, publication, and dissemination of the recommendations (teaching). Unfortunately, fewer clinical studies have been conducted in the aesthetic field, and this has caused some controversy over whether business prevails in the aesthetic field[3,4].
For this reason, we further wished to evaluate whether the ethical code used in mesotherapy had been approved by experts in aesthetics as well as by other doctors who are experts in different clinical areas; in addition, we asked whether the same code could help the scientific development of mesotherapy in the aesthetic field.
A SIM steering committee coordinated the multidisciplinary validation process by proposing the first draft of a code of ethics on mesotherapy. The first round of reviews was carried out by a group of multidisciplinary experts (aesthetic and non-aesthetic doctors). A group of international experts was involved in the second round. A third round of validation was conducted by an external scientific board. Finally, the approved document was submitted to the Ethics Committee. The code of ethics on mesotherapy is now approved and available[5].
During the approval process of the code of ethics, no criticisms were raised by either specialists in various medical areas or doctors involved in the aesthetic field. This fact allows us to claim that not all doctors who deal with aesthetics are oriented towards business areas[3,4].
Our code of ethics emerged from the scientific, moral and ethical mission that guides a scientific society and the professionals who are part of it. We believe that it is useful to create a standard of care in every field of application of intradermal therapy, whether for prevention, treatment or rehabilitation.
We observed that even when mesotherapy technique was considered for aesthetic purposes, a code of ethics was necessary to evaluate the medical literature, to create scientific documents, to design scientific research, and to design teaching and congress activities, in addition to aiding in clinical practice. In fact, the application of the mesotherapy code of ethics has allowed us to award low grades to some areas and higher ones to others. Thanks to the scientific integrity imposed by the ethical code, we have identified weaknesses and consequently areas that require more investment in research.
This code of ethics must not be interpreted as a rule that replaces the law; nor does its content constitute an alibi as a remedy to the provisions issued by the Institutions. Often some experts proclaim themselves as such and express recommendations, but opinions are invalid forms of proof[6]. Our code represents a guide to scientific integrity for researchers, clinicians and trainers. Scientific integrity is the crucial condition for designing a clinical study and designing algorithms which are evidence-based. Clinical trial results should not be overestimated to persuade a patient to undergo treatment. Beliefs should also be excluded from scientific meetings (or at least classified as such and not be put forth as recommendations). In both publications and medical conferences, areas with a lack of scientific evidence should be appropriately identified. Just as doctors constantly update procedures, trainers must also adapt lessons to scientific evidence. Whenever a mesotherapy treatment is proposed, the benefit-risk ratio must be declared. Therefore, in every field of application of mesotherapy, good clinical practice requires involving the patient in order to obtain his or her valid and informed consent, regardless of his or her cultural or religious background[7-10].
Another aspect drew our attention. It has been found that the medical record is an essential element even when mesotherapy is applied for aesthetic purposes. The detailed compilation of the diagnostic-therapeutic path is a crucial part of the doctor's duty, regardless of the treatment setting. Therefore, it has been seen that the medical record is just as important when mesotherapy is applied only for aesthetic purposes, both to evaluate positive effects and to assess adverse events retrospectively.
Finally, we wish to bring up an important component which is the 'conflict of interest'. Any conflict, even potential, must be declared before accepting any role involving the production of scientific documents or teaching. Announcing a recommendation to save one's 'business' without robust data puts the patient at risk and undermines the credibility of the entire scientific society in question. In this regard, relations with any commercial entity must be declared openly if they cannot be avoided altogether[11].
When a doctor proposes mesotherapy for aesthetic purposes, in addition to informing the patient about the risk-benefit ratio of the mesotherapy technique, he or she must also provide the patient with information about any alternative techniques with equal (or greater) effectiveness before obtaining the latter's valid informed consent[7].
We conclude by summing up with three 'take-home' messages:

1. experts must evaluate clinical data with scientific integrity and without conflicts of interest; self referencing is based on belief and not evidence;
2. a doctor who decides to work in the aesthetic field must consider the person as a 'patient', not as a 'client'.
3. if every teacher also takes ethical aspects into account in his or her lessons, the next generation of doctors can only be better than ours.

Therefore, in Italy, the application of mesotherapy in the aesthetic field, according to current recommendations based on our code of ethics, meets the requirements.

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The Code of Ethics on Mesotherapy is dedicated to Carlo Alberto Bartoletti and Sergio Maggiori, who for many decades have recommended that we act as physicians.

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Courses and Congresses 2021

16 - 18 July - Rome (Italy)
42nd SIME Congress
Italian Society of Aesthetic Medicine
Rome Cavalieri Congress Center
President: E. Bartoletti
E-mail: congresso@lamedicinaestetica.it
Web: www.lamedicinaestetica.it

3 - 4 September - Paris (France)
41st Congress of Aesthetic Medicine and Dermatological Surgery
French Society of Aesthetic Medicine
Palais des Congrès de Paris
President: J.J. Legrand
Email: info@sfme.info
Web: www.sfme.info

8 - 9 October - Montreux (Switzerland)
17th Congress of the Swiss Society of Aesthetic Medicine
Hotel Suisse Majestic, Montreux
President: V. Parzin
Email: info@ssme.ch
Web: www.ssme.ch

Courses and Congresses 2022

27 - 29 January - Paris (France)
IMCAS World Congress 2022
Palais des Congrès
President: B. Ascher
Web: www.imcas.com/en/attend/imcas-world-congress-2022

17 - 19 March - Mexico City (Mexico)
23rd World Congress of Aesthetic Medicine - UIME
Mexican Scientific Society of Aesthetic Medicine
Pepsi Center, WTC Mexico City
President: B. Miller
Email: inscripciones@congressmcme.com
Web: https://congressmcme.com/2022/

13 - 14 - 15 May - Rome (Italy)
43rd SIME Congress
Italian Society of Aesthetic Medicine
Rome Cavalieri Congress Center
President: E. Bartoletti
E-mail: congresso@lamedicinaestetica.it
Web: www.lamedicinaestetica.it

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