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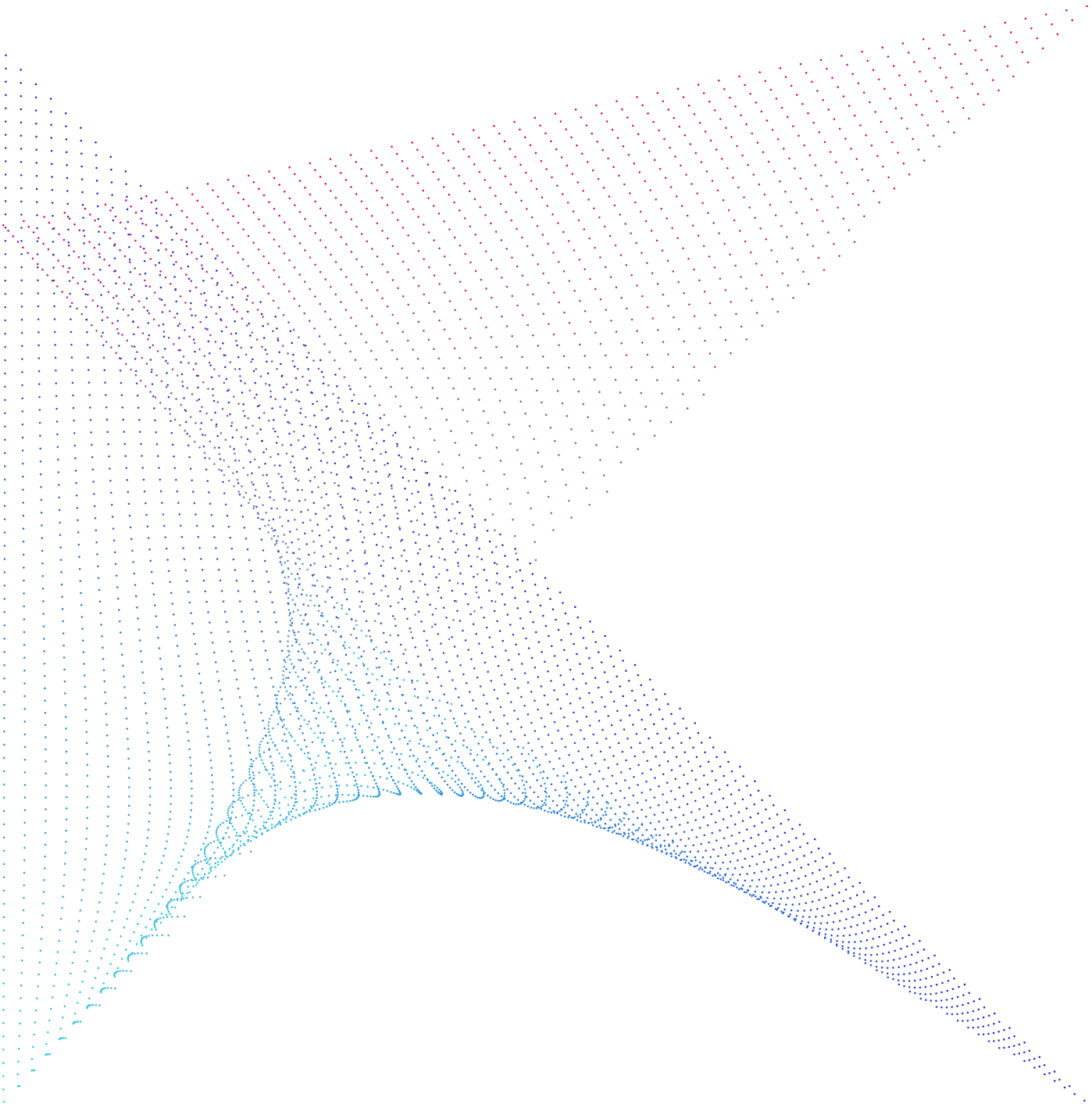

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Sommario

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

The synergy between vacuum and electromagnetic fields in the treatment of striae distensae: retrospective study on 917 patients with clinical and histological case records

A possible treatment for striae distensae

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Abstract

Striae distensae (SD) are dermal lesions that cause evident and unwanted imperfections. They may occur on arms, shoulders, breasts, abdomen, gluteus and legs, usually during puberty and pregnancy. At an early stage they feature a reddish-purple colour (striae rubrae) with an inflamed appearance; at the second stage, which is defined as the chronic stage, they are also marked by hypopigmentation and dermo-epidermal atrophy. During the past twenty years, various technologies have been put forth in the treatment of striae, which have shown encouraging outcomes in some cases. This retrospective study has been conducted on 917 patients that presented stretch marks on their body. Patients underwent a treatment based on the synergy between electromagnetic fields and vacuum; 6 to 9 sessions of treatment were performed for each patient once or twice a week. Clinical evaluation was carried out at the end of the treatment cycle; patients and doctors each rated their level of satisfaction on a scale from 0 to 100%. The outcome was documented through biopsies taken on 20 patients. All patients demonstrated an improvement of their stretch marks and 83% of the patients declared being very/extremely satisfied with the result. The results of the biopsies demonstrated a reorganization of the skin layers and a qualitative and quantitative increase of collagen and elastic fibres and all patients declared a total absence of side effects. The uniformity of the results, patient compliance and lack of adverse reactions proved that the synergy between electromagnetic fields and vacuum is an effective and safe treatment for stretch marks.

Introduction

During the first half of the XXI century stretch marks proved to be the most widespread aesthetic pathology in the world, affecting males and females indifferently from puberty. To date, according to the existing literature, there is no therapy that can be considered totally satisfactory and safe.

Dermabrasion provides a moderate improvement of red striae (1, 2). The percutaneous collagen induction therapy for treating red striae seems to be more effective (1, 3). Manuskiatti et al. (4) reported improvements on stretch marks treated with non-invasive resistive radiofrequency, whilst Dong-Hye Suh et al. (5) had minor results combining resistive radiofrequency with PDL (Pulsed Dye Laser). Shokeir et al. (6) compared IPL (Intense Pulsed Light) with PDL, which turned out to be more effective, obtaining good results only on red striae. Lee et al. (7) noted an improvement on each patient treated with 10,600-nm CO2 (carbon dioxide) fractional laser, while Khater et al. (8) claimed to not have observed any improvement in 50% of the cases. According to Yang et al. (9) 41.67% of the patients were unsatisfied with the results, while Tehranchinia et al. (10) achieved unsatisfying results on SD on high phototypes. In a preliminary study on 4 patients, Nouri et al. (11) had no improvement and nullified the research.

Wanitphakdeedecha et al. (12) had good results on almost all patients with Er:YAG fractional laser, on the other hand, Gungor et al. (13) claimed that "We observed no satisfactory clinical improvement in striae distensae alba

lesions although histopathological changes were seen". With 858 nm. Pulsed Dye Laser (PDL) Jiménez et al. (14) had modest results on 20 patients, while Nouri et al. (11) did not achieve any improvement.

Applying 1.064-nm Nd:YAG laser, Goldman et al. (15) reported positive results on early-stage red stretch marks. Elsaie et al. (16) documented a reduction from 5.73% to 13.47% in width of the stretch marks, although the biopsies demonstrated that "clinical improvement on striae are not relevant". Lastly, Gungor et al. (13) did not recommend it for striae alba.

Positive outcomes were consistently reported by De Angelis et al. (17) using a non-ablative fractional laser on 51 patients; Tretti Clementoni et al. (18) documented that the area of stretch marks showed filling in more than 50% of the cases. According to Guertler et al. (19), initially the reduction in depth of the furrow is equal to 32.07%, which lowers to 28.77% after six months. Contradictory outcomes were demonstrated by Yang et al. (9), a study conducted on 24 Asian patients. Stotland et al. (20) presented the blind evaluation of the results obtained on 8 patients, all of whom declared to have an improvement. Malekzad et al. (21) confirmed a lower performance of treatment on high phototypes.

Materials and methods

This retrospective study involved 917 healthy patients with intact skin burdened by stretch marks that were treated with a synergy between electromagnetic fields and vacuum in 2018-2019. The treatments were carried out in medical practices in Italy, Spain, United Kingdom and Turkey; each doctor documented the results observed on at least twenty patients.

For this study, patients between 15 and 60 years of age were selected, that presented stretch marks of any sort, location and cause, with no limitation of skin phototype.

Exclusion criteria were epilepsy, pacemakers, oncologic therapy undergone in the last 5 years, pregnancy and breast-feeding, open wounds, severe skin inflammation, varicose veins, phlebitis or thrombophlebitis in the area to be treated. All the patients signed the informed consent and agreed to share their personal data for this study. The total of 917 patients showed Fitzpatrick skin type between I and VI (Table I) with different dating of the striae (Table II), located in different body areas (Table III). Some of them underwent stretch mark treatments on multiple parts of the body, therefore on these 917 patients the results that were documented were obtained on 1.256 different body districts with on average 7.9 sessions per treated part for a total of 9.784 treatments delivered. The causes of the onset of the striae were detected (Table IV, V) and a total of 172 patients with striae rubrae and 745 patients with striae alba were treated. The patients declared to not have undergone other stretch mark treatments in the previous three months and that they would not wear any cosmetic products in the 24 hours preceding each treatment session. The treatments were performed by Bi-one® 2.0 MD and Bi-one® LifeTouchTherapy devices (Expo Italia Srl, Florence, Italy).

Table I. *Patients phototype*

Phototype	I	II	III	IV	V	VI
Patients	22	325	348	105	73	44

Table II. *The age of striae (of the 1.256 treated areas).*

Less than 2 years	2-5 years old	6-10 years old	11-20 years old	Over 20 years old
263	165	278	372	178

Table III. The body parts with stretch marks (of the 1*.256 treated areas).*

Arm	Breast	Abdomen	Kidney area	Gluteus	Thigh	Calf	Shoulder
90	146	322	63	346	215	42	32

Table IV. *Patient age and sex.*

	Women	Men
15-20 years old	92	18
21- 30 years old	309	34
31- 40 years old	291	11
41- 50 years old	99	4
41- 50 years old	65	0

Table V. *The suspected cause.*

Pregnancy	Puberty	Weightlifting	Hormone therapy	Other	No idea
407	221	9	85	64	131

These appliances function thanks to the synergy between electromagnetic fields and low-suction vacuum, usually between 10 and 15 hundredths of bar and with only 3-millimetre

skin dilatation, where the mechanotransduction activates (22). Mechanotransduction converts mechanical information into biochemical signs, increasing cellular conversation and activity; this determines a synergy with the electromagnetic fields also known as "shielded electrode" and affects epidermis and dermis, in fact, a relevant interaction between sodium (Na+) and potassium (K+) ions - noted for their cell membrane permeability - is appreciated (25). When the shielded electrode is positively charged, it pulls sodium and potassium ions, which are also positive, across the cell membranes though intrinsic proteins (26), consequently enhancing the supply of oxygen and nourishment. A negative phase follows the early positive one of the same duration and intensity. During this phase, sodium and potassium are attracted towards the outside of the cell membrane and become available for a new pumping action.

This technology uses a frequency ranging from 0.5 to 2 MHz and a 4-to-6 W mean power automatically set by the device's bio-feed-back system capable of reading the amount of the energy absorbed by the skin in real time, thus guaranteeing the maximum yield of the treatment and preventing overdose-related risks (27).

The synergy between the electromagnetic fields and the vacuum used is called Biodermogenesi®. A neutral non-alcoholic-based detergent was used to clean the skin before starting the treatment. On wide and sunken striae, a mechanical peeling was performed with a handpiece equipped with an interchangeable abrasive head, made of ISO 5832 standards-compliant non-cytotoxic steel, provided with the device. Afterwards, treatment was carried out by following the operating protocols to guarantee performance uniformity. The treatment lasted 25 minutes, during which a stimulation of the striae and of the surrounding tissue was provided by the movement of the handpiece along set paths, allowing to combine stretch marks regeneration and skin reshaping, and reduce the effects of gravity.

To corroborate Alberti and Laura's experience (28), who witnessed how stretch marks on 20 patients treated with the technologies that are subject of this study got tanned in total absence of side effects, the patients were invited to expose skin to the sun during the period of treatment.

During the first session, the patients with white stretch marks, excluding stretch marks on the inner thighs, were asked to expose to the sun and check whether the striae were able to positively react to ultraviolet rays and reactivate their tanning ability. Two-hundred-and-ninety-seven patients out of 312, exposed themselves to the sun regularly, encouraged by the fact that the treatment period coincided with Summer. The doctors compared the pictures taken of these patients before and after the treatment cycle and evaluated whether the pearly-white colour of the striae changed after exposure to sun and tanning. Seven days after the last session, the doctors who performed the treatments evaluated the outcome achieved, identifying 5 levels of result using an evaluation form based on the Likert Scale (I - none; II - mild improvement 1-25%; III - moderate improvement 26-50%; IV- good improvement 51-75%; V - excellent improvement 76-100%); in addition, the patient satisfaction score was rated using the following scale: 0 = not satisfied, 1 = slightly satisfied, 2 = satisfied, 3 = very satisfied, 4 = extremely satisfied.

Punch biopsy samples were taken from the most atrophic site of the stretch marks on 18 volunteers with over 20-year-old striae 3mm, before the first treatment and one week after the last one. On 2 volunteers, the second biopsy was taken after 2 sessions done 2 days apart. The sections of the excised skin were stained with haematoxylin and eosin and Masson trichrome stains; a dermatologist and an anatomopathologist evaluated the histological samples.

The doctor's evaluations and the patients' satisfaction were assessed using the Wilcoxon Signed Rank test to compare the final data and the starting point; P less than 0.05 was considered significant.

Results

The outcomes of the treatments were documented with VAS scale according to participants and doctors (Table VI). No patient declared to be unsatisfied, 2.47% of the patients declared slight satisfaction of the results (31 body areas), 14.57% declared to be satisfied (183 body areas), 41.64% declared to be very satisfied (523 body areas) and 41.32% extremely satisfied (519 body areas).

Table VI. *VAS scale according to the participating patients and doctors.*

	VAS doctor	VAS patient	
No improvement	0 (0%)	0 (0%)	Unsatisfied
1-25% of improvement	24 (1.91%)	31 (2.47%)	Slightly satisfied
26-50% of improvement	184 (14.65%)	183 (14.57%)	Satisfied
51-75% of improvement	485 (38.61%)	523 (41.64%)	Very satisfied
76-100% of improvement	563 (44.83%)	519 (41.32%)	Extremely satisfied

The evaluation of the doctors basically confirmed what had been declared by the patients: no improvement on 0 body areas (0%), mild improvement between 1-25% on 24 body areas (1.91%), moderate improvement between 26-50% on 184 body areas (14.65%), good between 51-75% on 485 body parts (38.61%) and excellent improvement between 76-100% on 563 body areas (44.83%). The renewed ability of stretch marks to gradually tan has been particularly

appreciated by the patients.

One week after the end of the treatment cycle, the doctors examined the 297 patients that exposed themselves to the sun; the pigmentation of the striae was evident in all of them. Stretch marks were darker in colour, more similar to the surrounding skin tissue and in some cases perfectly uniform and becoming invisible.

Upon first sun exposure which took place after 3/4 treatment sessions, the striae almost reached erythema and started to gain colour progressively, sometimes with less intensity than the surrounding tissue. In contrast to reports regarding other types of technologies, the vacuum stimulates skin remodelling, as documented by Moortgat et al. (23) while the electromagnetic field enables cellular and molecular multiplication (24) and skin reparative actions.

The electromagnetic field is generated through a high-frequency electrical signal directed to a specific handpiece with an electro-conductor inside. The external part is covered with a dielectric to prevent the signal from being discharged on the patient. The dielectric, relevant and uniform outcomes have been achieved on patients with phototypes V and VI as well as tanning of the striae.

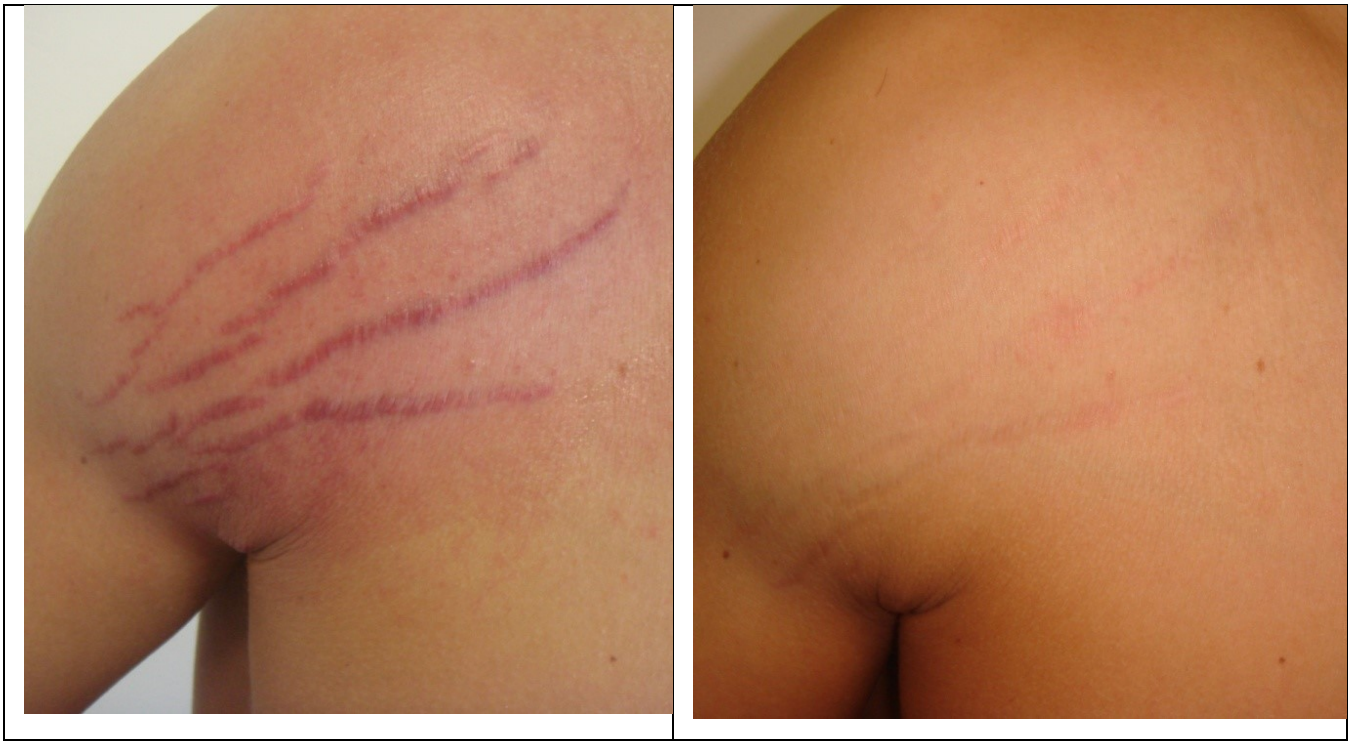

Fig. 1. *A young man with striae rubrae probably due to heavy weightlifting workout. After a treatment cycle the stretch marks are less evident and now tanned in a similar way to the surrounding skin tissue. Courtesy P.A. Bacci, Arezzo – Italy.*

The treatment was found to be safe, in fact only two patients out of 9.784 total sessions monitored by us had adverse reactions limited to mild skin erythema that dissipated on its

own within a week. A few minutes after the therapeutic treatment the patient felt a pleasant warmth, which lasted at least a few hours after the treatment terminated. Once the session was completed, the skin appeared blood-bedewed but not reddened. Since the treatment does not have any downtime, the patients can return to their normal daily routine without any limitation.

The biopsies taken on the 20-year-old white stretch marks confirmed the doctor's evaluation. Before starting the treatment session, all patients presented loss of volume of stretch mark epidermis and dermis, flattening of basement membrane, and collagen fibres destructured and parallel to the stratum corneum. In the bioptic analysis conducted at the end of the treatment cycle, an overall restructuring of the skin layers was noticeable: the epidermis was well-structured; the basement membrane has recovered its correct sinusoidal shape, a fundamental element to melanocytes, which, founding their correct position, enable stretch marks to tan when exposed to the sun; and the dermis has gained volume and new collagen fibres, being no longer parallel to the stratum corneum as in the case of the skin tissue featuring stretch marks.

The biopsies taken after two sessions confirm the presence of skin regeneration and show a mild but evident increase in collagen and elastic fibres.

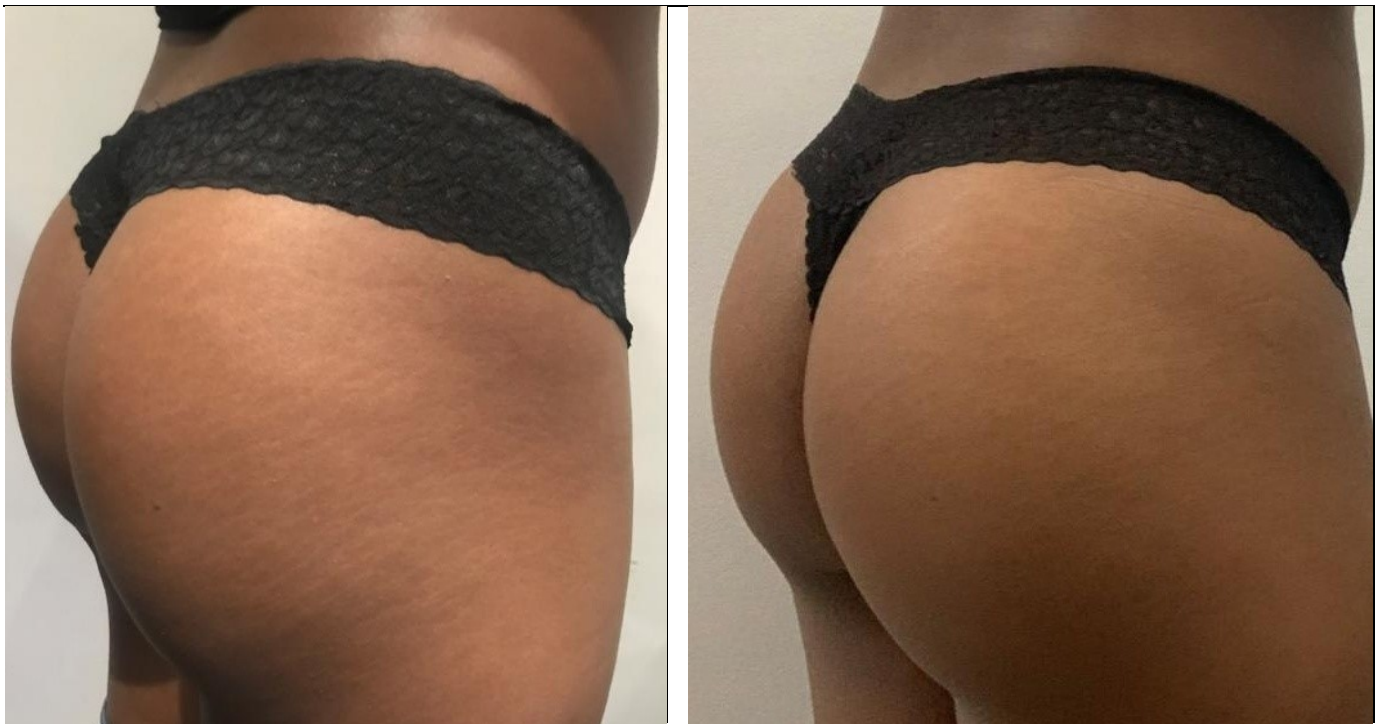

Fig. 2. *A patient with skin phototype V and 18-year-old stretch marks. After a 6-session Biodermogenesi® treatment cycle the stretch marks are filled and have the same colouring as the surrounding skin. Courtesy M. Wade – London, UK.*

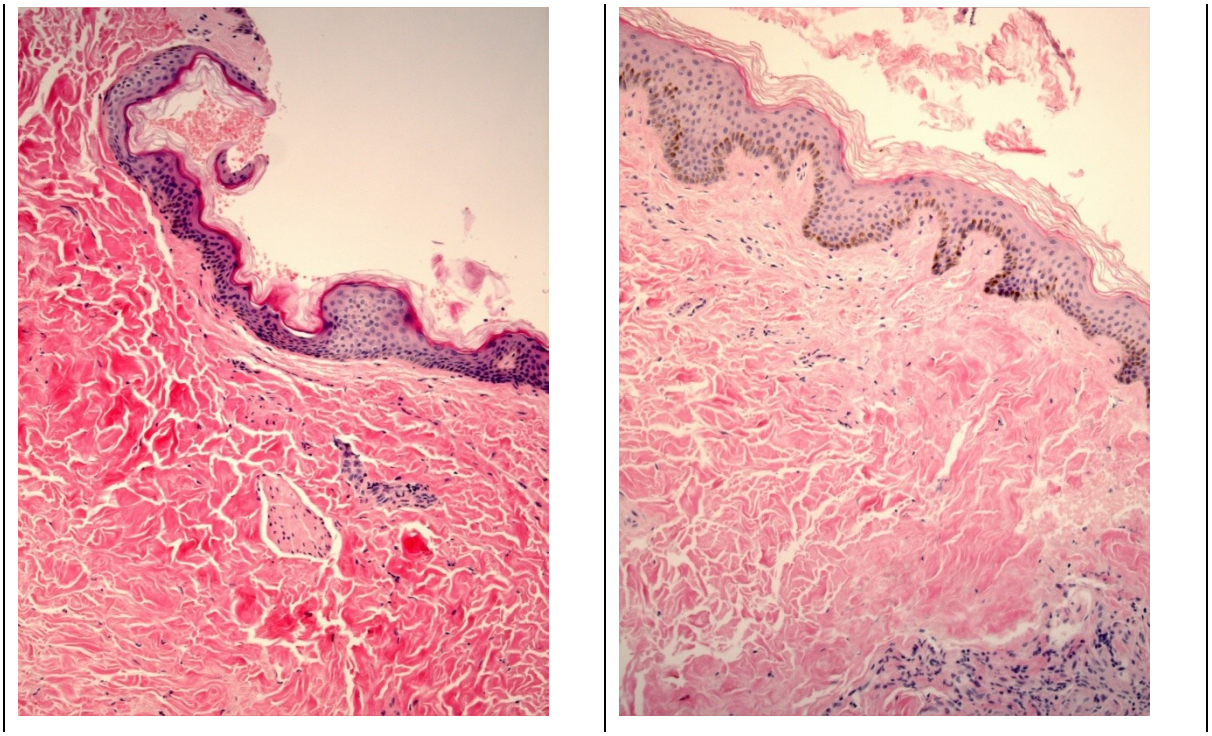

Fig. 3. *The biopsies before and after a 7-session Biodermogenesi® treatment cycle on a patient with skin phototype VI and 25-year-old striae are presented above. We witness the reorganization of epidermis, basement membrane and dermis, where a qualitative and quantitative increase in collagen fibers is noticeable. Courtesy A. Artigiani, Pisa, Italy.*

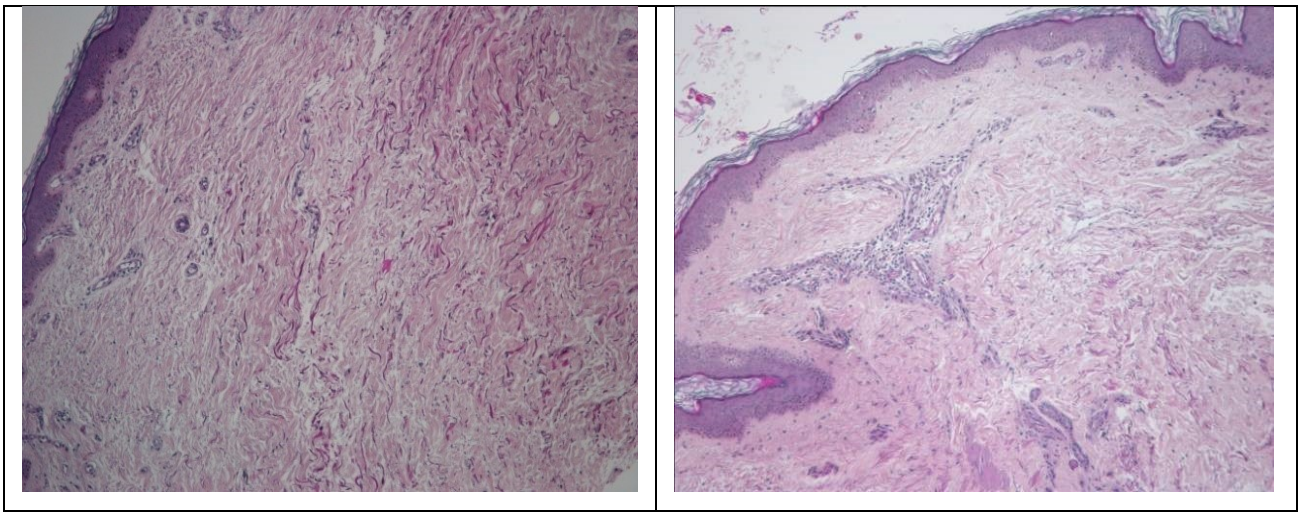

Fig. 4. *The biopsies before and after two Biodermogenesi® treatment sessions, two days apart on a patient with skin phototype II and 20-year-old striae. The microscopic analysis shows a mild but evident increase in collagen fibers. Courtesy P.A. Bacci, Arezzo, Italy.*

Discussion

We have to reflect on many limits of the previous studies executed on stretch marks treatments. The outcomes are generally documented on a low number of patients, sometimes 1 or 2, mostly between 10 and 40, with only one exception of a maximum of 51 patients (17) (non-ablative

fractional laser). Another limit is the lack of objective reports on the outcomes, like biopsies; moreover, when the biopsies are present, they are usually very few, from 1 to 4, and basic factors like the age of the patient, the dating and the severity of the striae are not provided. Through the comparison of those biopsies with Hague's (29) description of red and white striae's structural alterations, much more affinities with red stretch marks are found. A further limit is the often contradictory results mentioned in the pre-existing studies, where the researchers observed different outcomes although they used the same technologies.

Our perceptions are validated by other researchers (29) who claim that "No treatment has proved to be completely effective", Elsaie et al. (30) states that "None of the existing therapeutic options offer a complete treatment", Sardana (31) argues that in literature there are no high-quality studies involving a large number of patients and objective checks to guarantee a therapeutic prospect replicable on a high number of patients. First of all, the current study differs from the others for the significant number of patients with heterogeneous features and different skin phototypes coming from various Countries, which means for the first time there is a relevant sample for purpose of replication; having 20 biopsies taken on stretch marks of which dating and patient's phototype are known, together with the amount of information provided, makes this study more reliable than the others, with the awareness of the fact that such a wide pathology is worth a more detailed and specific comparative histological investigation.

The other difference is the patients' high level of satisfaction, with the 83% of patients rating the result as "good" or "excellent"; an additional confirmation is the assessment of the tanning, as a matter of fact stretch marks on all 297 patients who regularly exposed to the sun regained pigmentation.

All this data, together with the total absence of side effects, allows us to affirm that Biodermogenesi® is an effective and safe therapy that opens new and interesting perspectives in stretch mark treatment.

The comparison between the side effects arising from the synergy between vacuum and electromagnetic fields and other cutting-edge technologies is simple; comprehending that the contraindications of other treatment methods are mild, short-lived or statistically rare, the synergy matter of this study is preferred to the other methods for its lack of side effects, its safety and tolerability.

From 2008, P.A. Bacci conducted many studies on this technology (32), which have formed the basis for more recent developments. It is worth mentioning that, in the treatment of striae, Artigiani et al. (33) of the School of Dermatology at the University of Pisa achieved an actual regeneration of the skin tissue in total absence of side effects and histologically documented a qualitative and quantitative increase in the collagen and the elastic fibres. Alberti et al. (28) presented the restructuring of the skin featuring stretch marks by documenting its renewed ability to tan when exposed to sun and consequently the reorganization of the basement membrane and the reactivation of melanocytes.

Nicoletti et al. (34) documented the effectiveness of the treatment on post-surgical and burn scars

by underlining the reorganization of elastic fibers and collagen with no side effects. Considering the previous experiences, uniformity of the results obtained, patient compliance, the almost total absence of side effects, the downtime and the renewed ability of stretch marks to tan, it can be asserted that Biodermogenesi® is considered the most suitable treatment for its effectiveness, safety, tolerability, and replicability on stretch marks regardless of the age of the striae and the phototype of the patient.

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Letter to the Editor

Successful treatment of venous lake of the lip with a 577-nm pro-yellow laser: a novel approach

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key words: *Slip venous lake, laser 577-NM*

To the editor,

Venous lakes are benign vascular malformations caused by dilated venules in the upper dermis that typically occurs in sun-exposed areas of the body. Lips are the most common areas of venous lakes. Patients often request treatment to prevent recurrent bleeding and for cosmetic reasons (1). Successful results can be obtained with traditional treatments such as surgical excision, cryosurgery, sclerotherapy and electrocoagulation, but especially cosmetic results may not be satisfactory (2). Scar formation is an important cosmetic problem after these traditional treatments. Laser and light-based treatment modalities can offer a safe and effective alternative, successful results have been reported with intense pulsed light, argon lasers, pulsed dye lasers, Nd: YAG lasers, diode lasers, and carbon dioxide lasers systems in

the literature (2-6). To our best knowledge, venous lake treatment with pro-yellow laser has not been reported in the literature. Herein, we present a case of lip venous lake successfully treated with 577-nm pro-yellow laser.

A 45-years-old Fitzpatrick Skin Type III female case admitted to our cosmetology clinic with one-year history of previously untreated dark-blue stain on the lip. Venous lake lesion was seen on the left side of the lower lip (Fig. 1).

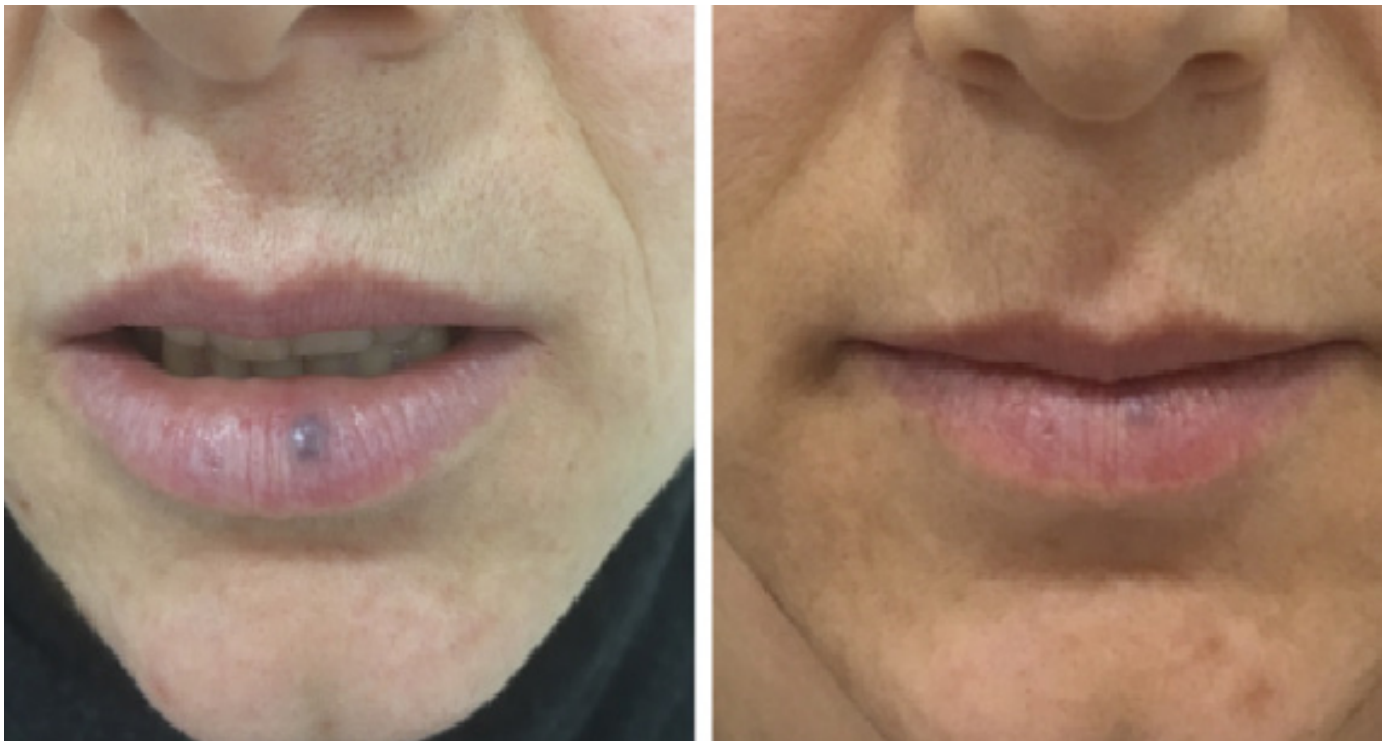

Fig. 1.*Venous lake on the lower lip and significant regression after 577-nm pro-yellow laser treatment.*

There were no additional features in the medical history of our case. The 577 nm pro-yellow laser treatment was chosen for the treatment of our case due to its effectiveness and safety in vascular lesions.

Pro-yellow laser treatment was applied two sessions with four-week intervals: 20 J / cm^2 (Basic mode 20 j / cm^2, 1 mm, 3 Hz) for the first session and 22 J / cm^2 (Basic mode 22 j / cm^2, 1 mm, 3 Hz) for the second session. After the laser treatments, the case experienced minimal edema and rash in the laser therapy area. The case was suggested to use sunscreen regularly. After the treatments, a significant regression was observed the lesion, no side effects developed (Fig. 1).

The main target chromophore in laser treatment of vascular lesions is hemoglobin, and also the main target chromophore in venous lake laser treatments is hemoglobin (2-6). The 577-nm pro-yellow laser is a safe and effective laser system

in the treatment of vascular lesions (7-9). In our case, 577 nm wavelength was used in venous lake treatment based on this vascular theory. In the literature, successful results with pro-yellow laser treatment have been reported in the treatments of facial erythema, rosacea, post-acne erythema, facial telangiectasis, hemangioma, poikiloderma of civatte, becker's nevus and port wine stain nevus (7-9). Our case is the first report in the literature that 577-nm pro-yellow laser treatment was used in venous lake treatment.

In conclusion, the 577-nm pro-yellow laser is a reliable and effective laser for the treatment of the venous lake of the lip. In the future, we think that pro-yellow laser can be advised in patients with venous lakes. Further clinical studies are required to improve our findings.

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A novel treatment of Striae distensae with pneumatic injection of hyaluronic acid

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key words: *striae distensae; stretch mark; hyaluronic acid; pneumatic injection; therapy*

Abstract

Treatment of striae distensae or stretch marks can present a therapeutic challenge as many modali-ties are partially effective. The present report indicates that pneumatic injection of hyaluronic acid with a jet volumetric remodeling (JVR) system is a well-tolerated and effective therapy for striae. In this series, three sites (left and right breasts, and abdomen) in two patients were treated – two sessions were performed 8 weeks apart. Improvement of striae was noted as early as 2 months af-ter the first session. Clinical assessment with a validated scar scale showed a 45.71% improvement at 6 months and 42.88% at 15 months post-procedure. Patients were satisfied with the results.

Introduction

Striae distensae (SD) or stretch marks are a common cosmetic problem that can present a therapeu-tic challenge. Common sites of involvement include the breasts, abdomen, thighs, buttocks, upper arms, and shoulders (1). Several therapies including topical tretinoin and silicone gel, chemical peels, radiofrequency, lasers and light sources have been tried with varying success (1). Here we describe substantial improvement of striae distensae with pneumatic injection of hyaluronic acid (HA) using a novel technology called jet volumetric remodeling (JVR) (2).. To our knowledge, there have been no similar reports.

Materials and Methods

Two patients were treated with JVR using an injection system (Enerjet 2.0; (PerfAction Ltd., Re-hovot, Israel). JVR technology involves targeted delivery of pneumatically accelerated jet of a solu-tion via a tiny entry point in the epidermis, allowing it to spread laterally in all directions in the dermis (2) (Table I).

Table I. *Clinical data and treatment specifics.*

Patient	Gender	Patient age (years)	Skin phototype	Stretch mark location	Treatment parameters	No of treatments	No of shots
1	Female	29	IV	Breasts	50% intensity 30% filling	2	200
2	Female	60	IV	Abdomen	50% intensity 30% filling	2	450

Patients had 2 treatment sessions 8 weeks apart. Lidocaine-based topical anesthesia was applied to the affected areas for 45 minutes prior to procedure. Treatment was performed with a mixed solu-tion of saline and non-cross-linked HA (H-100, World Dermic) at a 9:1 ratio (treatment parameters in Table I). The solution was pneumatically injected through an entry point and then dispersed across a 1 cm2 area in the dermis. During treatment, transient bumps and pinpoint bleeding at the entry points were observed. Mupirocin ointment was applied after treatment (Fig. 1).

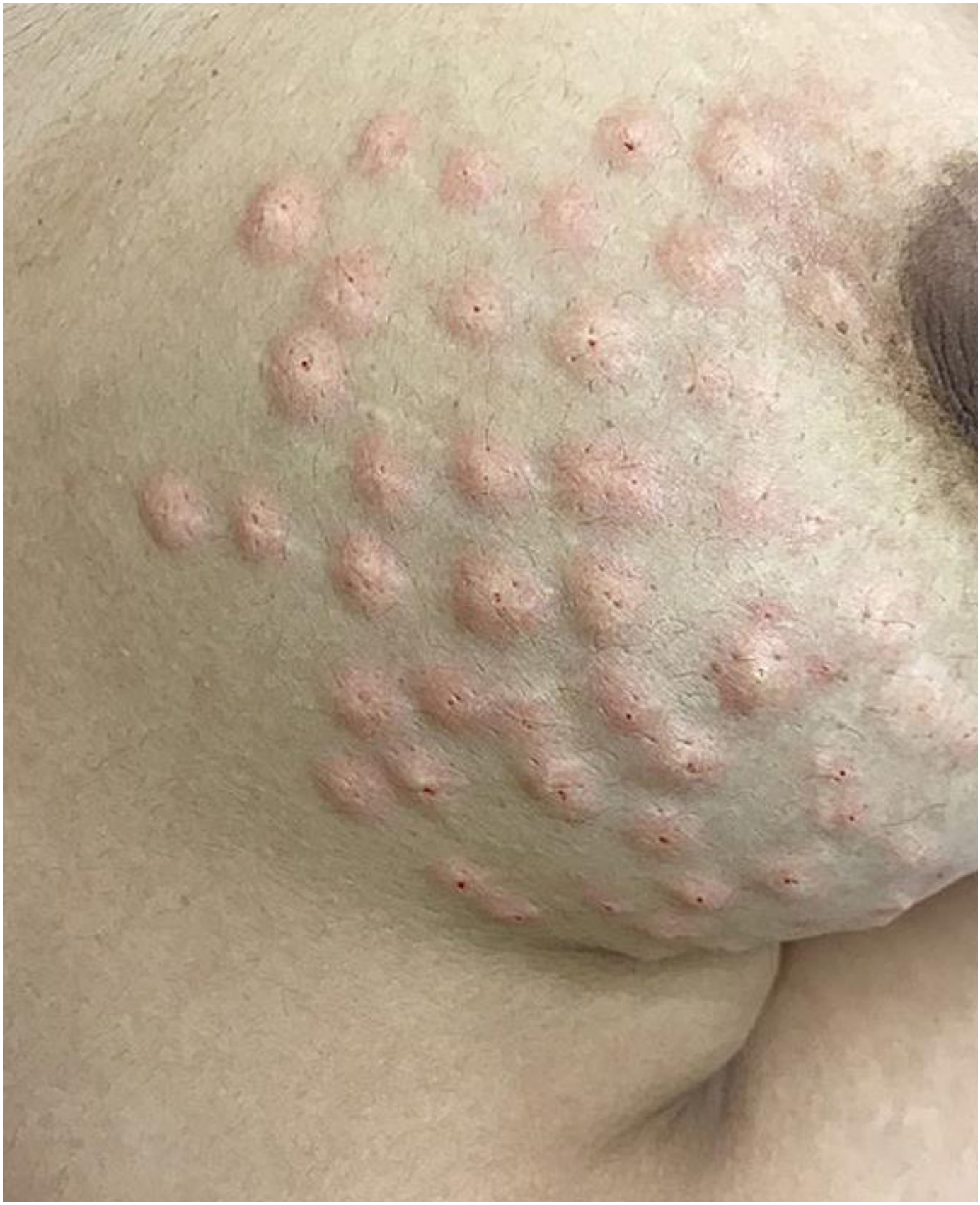

Fig. 1. *Patient 1: during treatment, transient bumps and pinpoint bleeding at the entry points were observed.*

Clinical Assesment

Preoperatively, striae were clinically assessed by the same investigator. The assessment was carried out with the Manchester scale, a validated scale that includes scar color, contour, texture, and dis-tortion domains (3) (Table II). Assessment was repeated at 6 and 15 months after the second session.

Table II. *Manchester scar scale. The original scale also includes a visual analogue scale of 1-10 that describes the cosmetic appearance of the scar.*

Parameter		Score
Color	Perfect	1
	Slight mismatch	2
	Obvious mismatch	3
	Gross mismatch	4
Finish	Matte	1
	Shiny	2
Contour	Flush with surrounding skin	1
	Slightly raised or indented	2
	Hypertophic	3
	Keloid	4
Distortion	None	1
	Mild	2
	Moderate	3
	Severe	4
Texture	Normal	1
	Just palpable	2
	Firm	3
	Hard	4

Photographic Assessment

All patients had images of their striae captured before treatment as well as at 6- and 15-months post-procedure. Photos were always taken at the same location, with one camera and same lighting. A Nikon D90 DSLR camera (12.3 megapixels, no flash) was used.

Result

Treatment was tolerated well, and patients experienced only mild discomfort during procedure. Slight edema at the treatment sites was noted up to 72 hours post-treatment. No adverse effects were noted at the follow up visits. Substantial improvement in color and texture as well as thinning and fading of the stretch marks were noted as early as 2 months after the first session (time of sec-ond session). Improvement was also noted at 6 months and 15 months after final session (Fig. 2, 3).

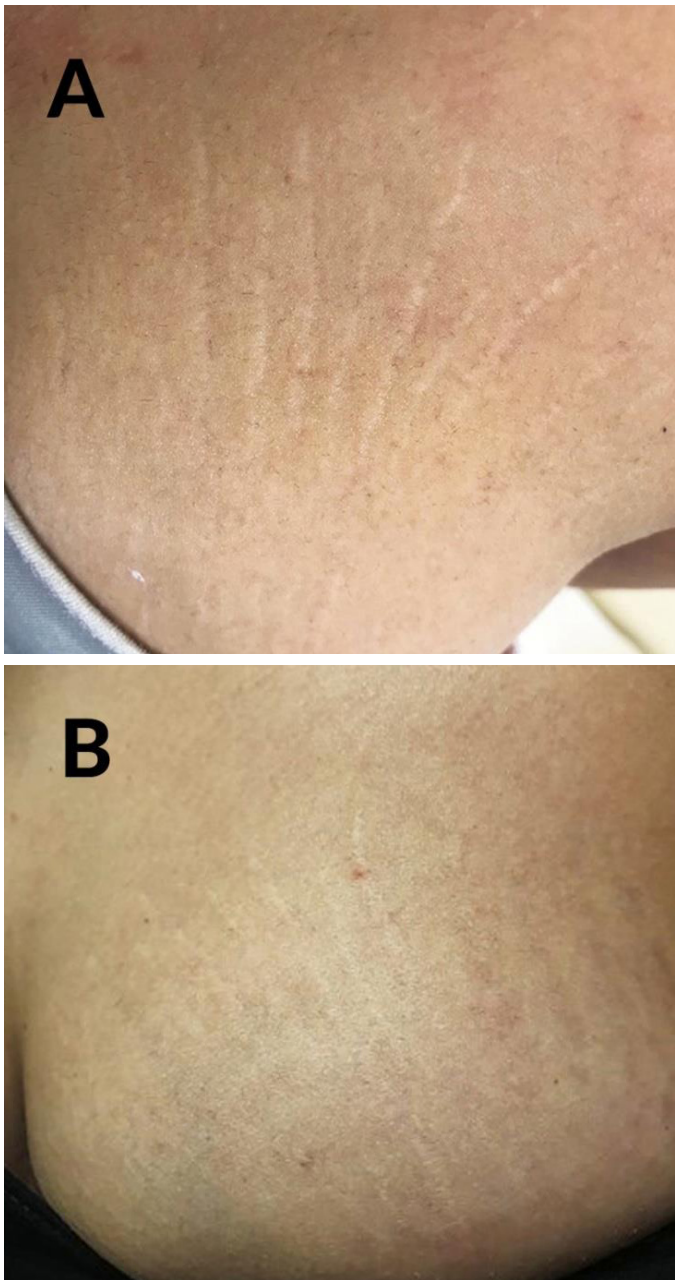

Fig. 2. *Patient 1: stretch marks on the left breast are shown before (A) and 15 months post 2 sessions (B).*

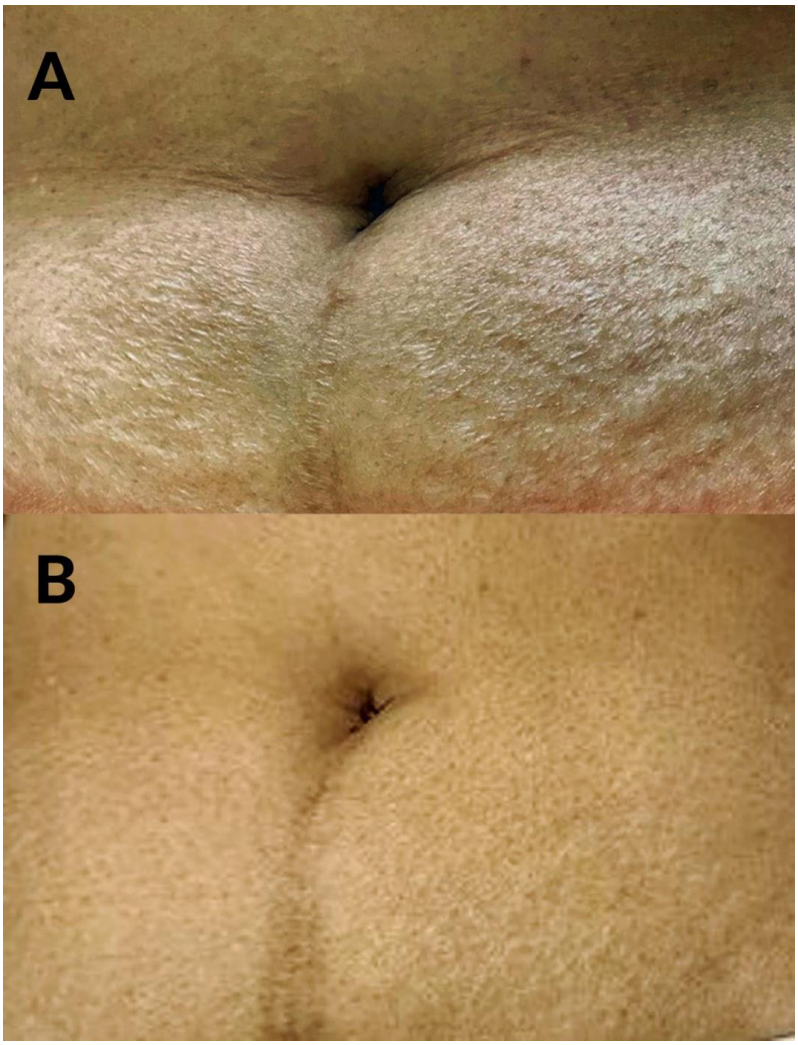

Fig. 3. *Patient 2: a vertical caesarean section scar and stretch marks on the abdomen are shown before (A) and 15 months post 2 sessions (B).*

The pre-procedure average Manchester scar scale score for the 3 sites (left breast, right breast and abdomen) was 11.66. The respective post-procedure scores were 6.33 at 6 months (-5.33 from baseline; 45.71% improvement) and 6.66 at 15 months (-5 from baseline; 42.88% improvement). Patients were satisfied with results and did not request additional treatments.

Discussion

EnerJet is a skin remodeling system that utilizes a needle-free, liquid jet technology for delivery of therapeutic agents into the skin. It enables a high velocity pneumatic introduction of agents like HA, corticosteroids, botulinum toxin, and 5-fluorouracil into the dermis. This creates a microtrau-ma which stimulates a wound healing response and neocollagenesis (4-6). The

procedure is associ-ated with a short downtime and has yielded good results in scars (6, 7), upper lip rhytids (8,9), fa-cial rejuvenation (5), and skin remodeling (10) (Table III). A histologic study demonstrated the stimulation of collagen synthesis 4 months after JVR treatment (10).

Table III. *Studies of pneumatically injected hyaluronic acid.*

Study	Indication	No of patients	No of sessions	Outcome
Lee et al (6)	Acne scars	10	3 Rxs at 4-wk intervals	3 months post last Rx , 2 patients had improvement of greater than 75%, 6 had 50% to 75% and2had25%to50% improvement in acne scars
Kim et al (7)	Keloids on upper arm	10	3 Rxs at 3-wk intervals	Vancouver scar Scale decreased from 8.8 before Rx to 5.6 three months post last Rx
Naranjo Garcia et al (8)	Upper lip rhytids	3	Once a month for 3 months	3-D imaging and skin sonography showed a decrease in the wrinkle severity score from 3.7 to 2.3; average reduction in skin roughness index by 13.4 %; increase in dermal height by 0.4 mm
Kobus et al (9)	Upper lip rhytids	20	3 Rxs at 3-4-wk intervals	Sonography showed increase in skin thickness by an average of 1.3 mm
Mashiko et al (5)	Facial rejuvenation	30	3 Rxs at 4-wk intervals	More than half of patients showed mild to moderate improvement; patients satisfied
Levenberg et al (10)	Wrinkles (face, neck, décolleté, dorsal hands)	34	3 Rxs at 3–4-wk intervals	The mean Fitzpatrick-Goldman wrinkle score for face and neck was reduced by 39.4% and 30.4%, respectively

Abbreviations: No: number; Rx: treatment; wk: week.

To our knowledge, the present series is the first report of Enerjet treatment of striae. A 45.71% im-provement at 6 months and 42.88% at 15 months post-treatment was documented with a validated scar scale. It is noteworthy that the improvement was maintained between the 6 and 15 months post-treatment time points. These are promising results, especially if one takes into account that treatment of striae with energy-based devices such as lasers and radiofrequency typically requires more than two sessions. The procedure was tolerated well, and our patients were satisfied with the outcome.

An advantage of Enerjet, when compared to modalities such as fractional lasers and microneedling radiofrequency, is that it does not cause any thermal damage to the epidermis and der-mis which is important when treating the atrophic skin of striae. Another benefit is that Enerjet tar-gets the affected areas while sparing the surrounding normal skin. Additionally, HA molecules have a temporary filling effect that is beneficial for stretch marks. Finally, HA attracts water mole-cules in the dermis which results in increased hydration and dermal thickening with subsequent re-duction of skin roughness and wrinkling (9). These effects can contribute to texture improvement over the striae (Fig. 2).

In conclusion, our report indicates that JVR technology can improve striae distensae. The procedure is safe in skin of color because, unlike radiofrequency and laser/light treatments, it does not involve thermal damage. It is well tolerated, has very short downtime and no long-term adverse effects. The improvement was maintained up to 15 months post-treatment. Still, larger studies with patients of different age groups and skin types, and longer follow up periods are required to evalu-ate treatment outcomes with this promising technology.

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Clinical monitoring of safety and efficacy of organic cotton medical device for light incontinence to prevent skin irritation

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key words: *urinary incontinence, cotton fibre, organic cotton, erythema, feminine hygiene products, clinical trial*

Abstract

The prolonged use of absorbent products for light incontinence treatment can lead to the onset of skin irritation side effects. The introduction of "breathable" materials into incontinence devices, such as cotton, represents an essential step for improving skin health. Clinical and in-vitro studies were performed on "Organyc Light Incontinence (bladder leakage control pads)" in order to assess their safety and efficacy, moreover, it was evaluated if their use can prevent the onset of irritant conditions. In-vitro tests were performed to understand if the bladder leakage control pads are able to prevent the onset of irritating phenomena that usually occur during and after the use of non-cotton pads. Regarding the self-evaluation parameters reported, it was noticed that "Organyc Light Incontinence (bladder leakage control pads)" was significantly better than competitor in softness, absorbency and leak protection, protection for sensitive skin, prevention of irritation and redness, breathability, in keeping the person dry, comfort, and the

importance of being made by natural ingredients was greatly appreciated. “Organyc Light Incontinence (bladder leakage control pads)” has proven to significantly reduce erythema and oedema of the skin and the vaginal mucous caused by the prolonged use of non-cotton medical device. Results also demonstrated good compliance with use.

Introduction

Introduction and prevalence

Urinary incontinence (UI) is defined by the International Continence Society as “the complaint of any involuntary loss of urine” (1, 2), which occurs in both sexes and affecting more than 200 million people worldwide (3).

The prevalence of stress incontinence peaks in the fifth decade of life, and thereafter the prevalence of mixed and urgency incontinence continues to increase (Fig. 1). The prevalence of this condition is higher in women than men, with approximately 10% of adult women suffering from UI (4, 5). The prevalence rate increases with age, reporting more than 40% in over-70 female populations (6). Studies project that the prevalence of urinary incontinence and other pelvic floor disorders, such as pelvic organ prolapse and faecal incontinence, will increase as the global population ages (7).

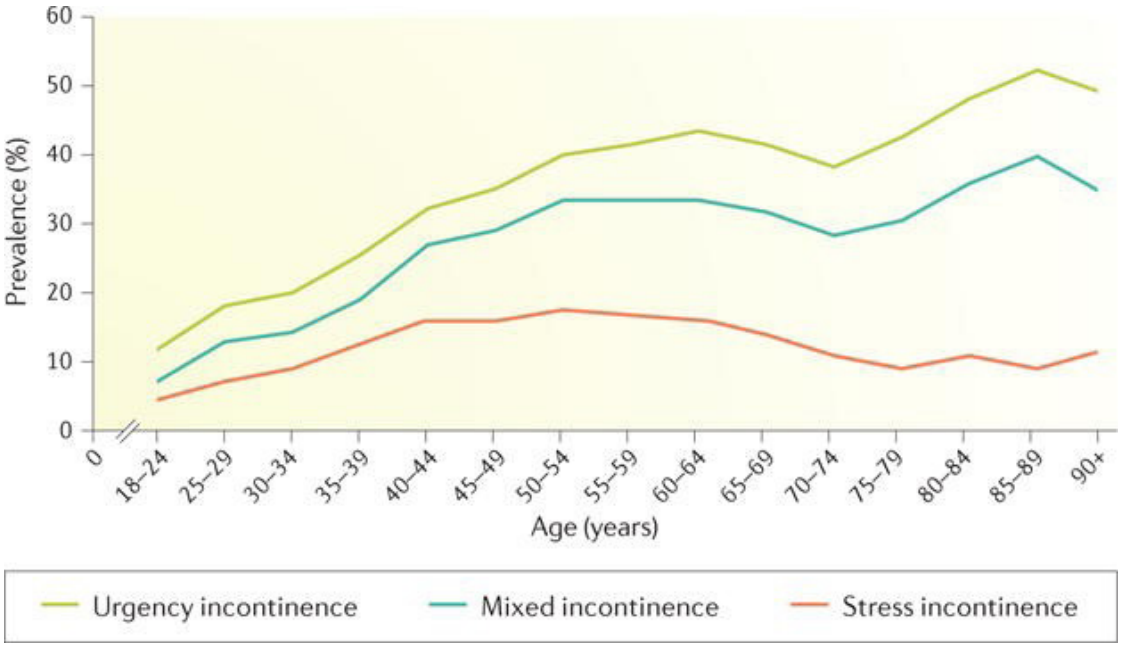


Fig. 1. *Prevalence of stress incontinence peaks in the fifth decade and then declines, whereas the prevalence of both mixed and urgency incontinence continues to increase with age (8).*

This condition is considered to have a relevant impact on a woman's quality of life regarding physical, social, economic, and psychological well-being. Despite the relevance of this condition, many women do not seek supporting solutions due to the sensitive nature of the topic, the reluctance to discuss symptoms or a lack of knowledge of existing treatments.

Urinary Incontinence subtypes

Incontinence is categorized by the type of problem; three major distinct subtypes can be recognised:

- Stress urinary incontinence represents a widespread condition affecting one-half of incontinent women aged between 18 and 90. Stress UI is the involuntary loss of urine during an increase of intra-abdominal pressure produced from activities such as coughing, laughing or exercising. The involuntary loss of urine is caused by a weakening of the muscular support at the uretrovescical junction.
- Urge urinary incontinence, defined as a sudden urgency to void associated with a difficulty to defer. In combination with other symptoms such as increasing voiding frequency and nocturia, this condition is part of the overactive bladder (OAB) syndrome, which has a prevalence rate of 16.9% in women (9).
- Mixed urinary incontinence (MUI) is the involuntary leakage associated with a strong, uncontrollable urge to void accompanied by loss of urine during physical activity.

Risk factors

Different risk factors can be observed according to the UI subtype. Pregnancy and childbirth are recognised as established risk factors in the context of stress urinary incontinence, showing a prevalence rate of 21% in women who have delivered vaginally out of a total of 15.000 women (10). It can be explained by the impairment of the pelvic floor musculature and the connective tissue and nerve damage resulting from pregnancy and labour. Hysterectomy may cause damages to the pelvic floor musculature and, therefore, represents another condition associated with the outbreak of stress UI (11, 12), which has also been associated with vaginal prolapse, including cystocele (prolapse of the bladder), rectocele (prolapse of the rectum) (13), uterine prolapse (14), and vaginal vault prolapse. Frequent urinary tract infection is considered independently associated with urge UI, representing an easily treatable cause of this condition (15). Other risk factors or conditions that can exacerbate stress and urge urinary incontinence are higher body mass index (11, 14) and elderly (16). In addiction smoking (17) can also contribute to stress UI due to its association with chronic cough.

Treatment for urinary incontinence

According to the severity of symptoms and the type of incontinence, different treatments are available to manage this condition, from simple lifestyle interventions, such as the reduction of critical behaviours associated with the onset of UI and pelvic floor muscular training, to pharmacological treatment (anticholinergic, beta-agonists, onabotulinum Toxin A, and oestrogen) and different surgical procedures (injectable bulking agents, fascial slings). Pharmacological treatment, especially with anticholinergic agents, rarely resolve incontinence symptoms, and medication side effects result in a reduced patient's adherence to therapy. Therefore, pharmacological options should be given when conservative treatments fail. Surgical treatments are only recommended for highly severe incontinence conditions after the failure of both conservative and medical therapies since they may be associated with postoperative complications (18).

Conversely, women who suffer from light incontinence manage this uncomfortable condition with the help of absorbent products, existing in a wide range according to the degree of absorbency (20-300 mL). They are specifically designed to absorb urine, minimise odour, and keep the patient dry. Absorbent products used include underpads, panty shields, pant guards, adult diapers, various washable pants and disposable pad systems, or combinations of these products. Research has shown that small disposable pads provide good absorbency and protection for women with light bladder leakage (19).

Absorbent products, whether disposable or reusable, show relevant differences in the design details; however, they always rely on the presence of an absorbent core interposed between a waterproof back sheet below and a water-permeable top sheet in contact with skin. Absorbent cores can be composed of fluffed wood pulp fibres and contain superabsorbent polymers (SAP), designed for holding a major urine volume. Thermoplastic fibres are sometimes included in absorbent cores to reduce structure damages when wet (20). Top-sheets are usually composed of nonwoven fabrics, defined as open-structured, fibrous materials that support the absorbent core's stabilisation, allowing urine to be absorbed from the absorbent layer. Top-sheets are usually made with either cotton – which is hydrophilic and offer a good dry comfort – or with a polyester web treated with a hydrophilic finish or a spun-laid polypropylene nonwoven (21).

The use of absorbent products to treat incontinence could influence skin health, contributing to microclimate changing and resulting in irritant contact dermatitis, such as diaper dermatitis (DD) or incontinence-associated dermatitis (IAD) (22). These pathologies are common inflammatory skin conditions characterised by erythematous and pruritic skin lesions, causing pain, redness, swelling and excoriation, which may evolve in complications such as skin infections (23). Prolonged contact with urine causes ammonium exposure, a chemical irritant in the urine responsible for a pH shift to alkaline levels, thus disrupting the skin and altering its flora. Moreover, skin wetness and over-hydration, caused by long-lasting exposure to moisture, increase skin disruption and, thus,

shear stresses and mechanical factors such as friction with incontinence devices are more likely to aggravate skin damage (24). Furthermore, as reported in the literature, the use of tampons or pads can interfere with local vaginal homeostasis mechanisms, increasing the onset of infection and skin irritation (25-27).

A different design of the incontinence products can support the epidermal barrier function, reducing skin irritation onset in incontinence patients. Highly breathable materials reduce the occlusive effect of diapers, minimising over-hydration and thus the onset of skin erythema or oedemas (28). Moreover, replacing an impermeable plastic barrier with a breathable material could maintain local temperature, enabling air circulation in the genital region (29-31). Among breathable nonwoven fabrics, cotton shows excellent properties, like breathability, hypoallergenic, comfort, and good wet strength. The softness of this material also lowers friction between the device and the skin, further contributing to the reduction of skin irritation associated with the prolonged use of incontinence devices. Besides, cotton can be recycled and disposed of by the biodegradation process, answering an increasing demand for more sustainable products (32). These features make cotton an excellent alternative material – compared to plastics and superabsorbent polymer (SAP) – for the industrial production of absorbent products for managing incontinence, decreasing the chances of skin irritation, thus contributing to a significant improvement of female quality of life.

Previous studies have demonstrated the high skin tolerability of cotton-organic cotton and other organic fabrics in pads and adsorbent products compared to plastic and superabsorbent polymer (SAP) (28, 33, 34). However, it is important to evaluate the characteristics of each new product since the efficacy and the safety of use, and the overall customer satisfaction with the product could be affected by the whole pad composition.

Aim of the work

Considering the findings mentioned above reported in the literature, CORMAN S.P.A. has developed a new cotton-based medical device, the "Organyc Light Incontinence (bladder leakage control pads)", to improve the quality of life of female patients by reducing erythema and oedema of the skin and mucous membranes caused by the prolonged use of non-cotton incontinence devices. The safety and efficacy of using the medical device was investigated during clinical monitoring to verify its preventive and soothing action in the onset of skin irritation and slight side effects compared with a competitor medical device as the primary objective. The degree of acceptability and compliance of patients using the device was also evaluated as an additional objective.

In-vitro tests were performed to understand if the bladder leakage control pads can prevent the onset of irritating phenomena that usually occur during and after the use of non-cotton pads. A pro-sensitizing test was carried out on human monocyte cell line, since skin sensitization is defined as the toxicological endpoint associated with chemicals that have the intrinsic ability to cause skin allergy in humans. This process, also

called allergic contact dermatitis (ACD), is a cell mediated hypersensitivity immune response. In-vitro models studying human skin are important tools in the field of research and development of pharmaceutical and cosmetic industries (35-38).

Materials and Methods

In vitro test - Pro-sensitizing test (OECD 442E)

The test was carried out on human monocytes THP-1, used as surrogates for dendritic cells. It is known that THP-1 cells show enhanced CD86 (Sysmex Partec) and/or CD54 (Sysmex Partec) expression when rated with sensitizers. THP-1 cells were cultured in RPMI-1640 (Euroclone) medium supplemented with fetal bovine serum (10%) (Euroclone), 2-mercaptoethanol (0.05 mM)/2,4-dinitrochlorobenzene (DNCB) (Merck life Science) and antibiotics (1%) (Euroclone). Cells were incubated at standard culture conditions (37°C, 5% CO2).

The tested product was incubated overnight in complete culture; the cells were treated with the liquid of maceration (filtered through a 0.22 µM) and subsequent dilutions 1:2. As positive control we used 2.4-dinitrochlorobenzene (DNCB) at the concentration of 4 µg/ml. The product underwent a preliminary cytotoxicity screening on the THP-1 cells to choose a non-cytotoxic concentration to use in the pro-sensitising assay. The cell viability was evaluated through MTS test (Promega). The assay was performed after a 24 hours-treatment period by adding a small amount of the MTS solution directly to culture wells, incubating for 1–4 h and then recording the absorbance (optical density,OD) at 450 nm with a 96-well plate reader. The quantity of formazan product as measured by absorbance at 450 nm is directly proportional to the number of living cells in culture.

A suitable number of THP-1 cells was pre-cultured for 48 hours, seeded into a 24 well flat-bottom plate and treated for 24 hours with test sample and with the positive control. Untreated cells in culture medium were used as negative control. The expression levels of CD86 and CD54 were analysed through flow cytometry. Based on the geometric mean fluorescence intensity (MFI), the relative fluorescence intensity (RFI) of CD86 and CD54 for positive control (CTRL) cells and chemical-treated cells are calculated according to the following equation:

$$RFI = \frac{MFI\ (chemical\ treated\ cells) - MFI\ (IgG1\ treated\ cells)}{MFI\ (CTRL\ cells) - MFI\ (IgG1\ CTRL\ cells)} * 100$$

For CD86/CD54 expression measurement, each test chemical is tested in at least two independent runs to derive a single prediction (positive or negative).

In vitro evaluation of soothing activity of a medical device

This test was conducted to verify whether the tested product, at different concentrations, can reduce the production of cytokines in vitro: interleukin-6 (IL-6) and interleukin-8 (IL-8). It is believed that this ability makes the product a potential soothing candidate in vivo, able to counteract the process of skin irritation and redness.

Keratinocytes cells monolayers are highly representative of the target tissue in vivo. Huker cells were cultured in DMEM (Dulbecco's Modified Eagle's Medium) (Euroclone) supplemented with fetal bovine serum (10%) (Euroclone) and glucose (4.5 g/l) and incubated at standard culture conditions (37°C, 5% CO2). Good cell culture practices were used.

The tested product was incubated overnight in complete culture; the cells were treated with the liquid of maceration and subsequent dilutions.

A cell viability assay was performed prior the cytokines dosage to choose the concentrations to use for the analysis of cytokines. The viability assay was repeated to assess the potential negative effect of the treatments performed on the cells. The cell viability was evaluated through a MTT test (Euroclone). Based on obtained results the concentrations of 50%, 25% and 10% were selected to perform the interleukins assay.

The test was performed in parallel on two sets of cells: one untreated and the other treated with lipopolysaccharide (LPS) (Merck Life Science) to stimulate the production of interleukins. The cells were treated with the chosen concentrations of the tested product and the positive control (CQ) was a substance with well-known anti-inflammatory activity (PC). Cells not treated with the sample were the negative controls. The content of interleukins in the culture medium was determined by ELISA (enzyme-linked immunosorbent assay) (Peprotech). The results were read with a spectrophotometer at 450 nm. The values obtained were then interpolated in a standard curve of interleukin.

Clinical trial - study design

The medical device "Organyc Light Incontinence (bladder leakage control pads)" was investigated during a monocentric randomised clinical monitoring of acceptability, safety, and efficacy of use compared to a benchmark medical device ("Competitor"). The study was performed following the current legislation (Italian Legislative Decree n.46 of 24 February 1997 amended by Italian Legislative Decree n.37 of 25 January 2010 – Acknowledgment of Directive 93/42/EEC and 2007/47/EC) and the declaration of Helsinki. The clinical protocol was assessed and approved by the Technical Scientific Committee (TSC) of Bio Basic Europe S.r.l. and was validated by Bio Basic Europe Technical Scientific Director and the investigator/CDC Dermo-Clinical Research Institute Health Director. Report no. 2013E26F-1 issued on 4 December 2020 is the reference report for this clinical monitoring study.

Written informed consent to participate in the study was obtained from all participants and was managed and archived according to internal procedures of Bio Basic S.r.l. Quality Management System. Before signing the consent form, all

volunteers were adequately informed of the aims, methods, clinical trial details, anticipated benefits and potential undesirable effects of the study.

Participants selection

The study involved 182 eligible female subjects aged between 35 and 70 and with light incontinence. Inclusion criteria were the following listed below:

- sensitive skin;
- slight incontinence due to postpartum/post-surgery/obesity/other problems related to bladder leaks among which, menopause;
- non-cotton light incontinence device users with slight irritations due to their use;
- good state of health and absence of psychological and/or cognitive disorders;
- signature of the informed consent.

Exclusion criteria were the following:

- dermatopathies and allergic pathologies (to cosmetics or other specific excipients) or other pathologies (as of unknown irritant responses);
- ongoing pharmacological treatments that could affect the results of the test;
- participation in other clinical trials during the previous 30 days.

Simple randomisation was performed, derived from tables of random numbers, for the assignment of the product under study ("Organyc Light Incontinence") and the non-cotton benchmark product ("Competitor"). The "Organyc Light Incontinence" and "Competitor" devices were tested by 91 subjects each. The randomisation data were kept strictly confidential to limit potential biases that arise from the influence that knowledge of the treatment could have on the recruitment and assignment of products to subjects. None of the subjects nor the people involved in conducting the trials had access to this information.

The device

The medical device "Organyc Light Incontinence" is a bladder leakage pad composed of topsheet (100% Organic Cotton), core (100% Cotton), storage layer (Airlaid cellulose, SAP Superabsorbent Polymer), backsheet (Mater-Bi® film), certified odor control.

A commercial non-cotton pad represents the "Competitor" for incontinence.

Samples of the products [both "Organyc Light Incontinence (bladder leakage pads)" and "Competitor"] were applied following their usual use for 35 consecutive days.

Execution of the test

The study's primary endpoint (35 days) was clinically evaluated through a clinical examination of the vaginal skin to evaluate the presence or absence of mucosae alterations, primary erythema and oedema. The evaluations of the clinical parameters were performed in the

study by the same examinator:

- at the beginning of the study (T0), before the use of the medical device
- after 35 days of use of the medical device (T35).

To evaluate the variations of the target clinical parameters, a 0-4 Erythema and Oedema Severity Score scale was employed, as reported in Table I.

Table I. *Erythema and Oedema Severity Score Scale to assess vaginal skin and mucosae alterations.*

Vaginal skin and mucosae alterations (erythema and oedema)			
Erythema	**Score Scale**	**Oedema**	**Score Scale**
No Erythema	0	No Oedema	0
Slight Erythema (hardly visible)	1	Very slight Oedema	1
Clearly visible Erythema	2	Slight Oedema	2
Moderate Erythema	3	Moderate Oedema (about 1mm raised skin)	3
Serious Erythema (dark red with possible formation of light eschars)	4	Strong Oedema (extended swelling even beyond the application area)	4

The secondary endpoint was to assess the degree of acceptability (consumer satisfaction) of the medical device by the subjects through a short questionnaire collected at the end of the test (T35).

The following product characteristics have been evaluated using a numerical 11-point assessment scale (0-10 VNS) with 0 corresponding to not at all and 10 corresponding to extremely satisfied/important: 1) Softness; 2) Absorbency and leak protection; 3) Sensitive skin protection; 4) Preventing of irritation and redness; 5) Breathability; 6) Keeping the subject dry; 7) Composition with natural ingredients; 8) Comfort; 9) Ability to stay in place; 10) Rating on an overall basis; 11) Level of irritation compared to the usual product.

The questionnaire also included 4 self-evaluation questions assessed by means of a numerical 5-point scale (with 1 corresponding to not at all and 5 corresponding to definitively yes), 2 yes/no questions and 1 multi-choice question to assess overall consumers' satisfaction with the tested product over their usual bladder leakage product and their intention to use and/or buy the tested product in the future.

Statistical analysis

Statistical analysis was performed using RStudio Version 1.3.959 © 2009-2020 RStudio, PBC. The sample size was statistically calculated assuming: 1) a difference in erythema (primary endpoint) of at least 0.4 with a standard deviation of 0.7 as clinically relevant; 2) first type error equal to 0.01; 3) 90% power.

The data of the qualitative endpoint were described using position, and dispersion measurements (median and interquartile range) and their variable symmetry of the distribution of the differences between the paired evaluations was verified. The most appropriate non-parametric test for paired data was applied (Wilcoxon signed rank test / Sign test) to compare the data obtained at the two observation times.

For discrete quantitative variables (questionnaire of acceptability) the Mann-Whitney U test was applied to compare the data of the two groups. A significance level of <0.05 for the p-value was considered.

Results

Pro-sensitizing test (OECD 442E)

The test was conducted on bladder leakage control organic cotton pads. The product underwent a preliminary cytotoxicity screening on THP-1 cells where non-cytotoxic concentrations to be used were chosen through an MTT Test.

The expression of CD86 and CD54 was evaluated at least twice in independent runs. The prediction is to be considered positive if at least one of the following conditions is met in 2 of 2 or in at least 2 of 3 independent runs, otherwise the prediction is considered negative: a) The RFI of CD86 is equal to or greater than 150% at any tested concentration (with cell viability ≥ 50%); b) The RFI of CD54 is equal to or greater than 200% at any tested concentration (with cell viability ≥ 50%). The calculated of RFI values calculated for CD86 and CD54 are reported in Table II.

Table II. *The table shows the values for positive control (DNCB) and the 8 concentrations of the tested product..*

	DNCB	Sample concentration (%)							
		50	25	12,5	6,25	3,125	1,5625	0,7813	0,3906
CD86	159,05	110,48	110,95	110,95	106,19	109,52	118,10	112,38	107,62
CD54	213,53	109,02	117,29	115,04	107,52	112,03	112,03	115,79	108,27

The calculated RFI values do not exceed the limits of the prediction model. Co-expression of CD86/CD54 has not been observed. These results have proved that bladder leakage control organic cotton pads do not have pro-sensitising potential.

In vitro evaluation of soothing activity of a medical device

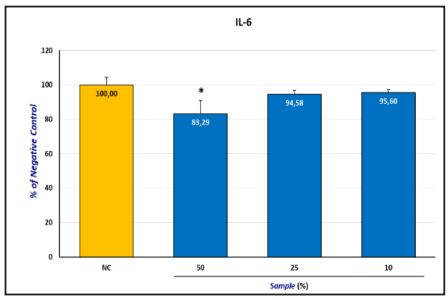
The soothing activity of the tested product has been assessed by measuring its ability to prevent the formation of cytokines (interleukin: IL-6 and IL-8) in cell cultures of human keratinocytes. Before studying interleukins production, the viability cell test is carried out to understand which range of concentrations is safe for cell cultures. Viability of cells in contact with liquids of maceration obtained from different components of the tested sample has been calculated.
Table III shows cell viability related to the different concentration.

Table III. *The optical density (OD) measured at 540 nm is proportional to cell viability. Percentages were calculated based on the absorbance values at 540 nm and taking as 100% the absorbance of the negative control (untreated cells).*

	SAMPLE (%)							
	0,7813	**1,5625**	**3,1250**	**6,2500**	**12,500**	**25,00**	**50,0**	**100,0**
Cell viability (%)	98,22	99,47	103,29	105,30	101,22	97,19	96,27	86,76

ELISA Assay was used to evaluate the concentration of cytokines. The tested product demonstrates to have non cytotoxic effects on keratinocyte cell culture and absorbance values measured at 450 nm are directly proportional to the quantity of IL-7 and IL-8 produced by cells.
Figure 2 shows the graphical evaluation of soothing activity of the tested product (Organyc Light Incontinence: bladder leakage control pads) in terms of IL-6 and IL-8 production. The tested product has proved to significantly reduce IL-6 and IL-8 at tested concentration of 50% (respectively reduction of 16.7% and 15.8%).

	Control	SAMPLE %			PC
		50	25	10	
IL-6 mean value (g/ml)	1137,00	947,00	1075,33	1087,00	837,00
IL-6 (% of NC)	100,00	83,29	94,58	95,60	73,61
IL-6 reduction (%)	0,0	16,7	5,4	4,4	26,4



	Control	SAMPLE			PC
		50	25	10	
IL-8 mean value (pg/ml)	232,67	196,00	217,67	214,33	176,00
IL-8 (% of NC)	100,00	84,24	93,55	92,12	75,64
IL-8 reduction (%)	0,0	15,8	6,4	7,9	24,4

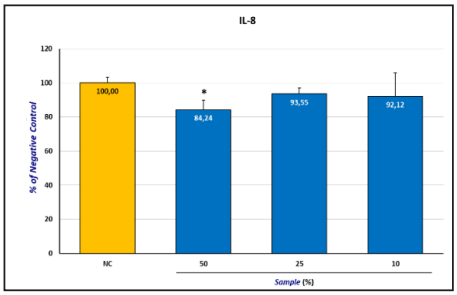


Fig. 2. *The absorbance measured at 450 nm is directly proportional to the quantity of interleukin produced by the cells. The values are expressed as means ± standard deviation. Statistical data processing was performed by Student's t-test. We considered significative values of p <0.05. NC = untreated control cells; PC = positive control (cells treated with a well-known anti- inflammatory drug). *p<0.05 vs NC; **p<0.01 vs NC.*

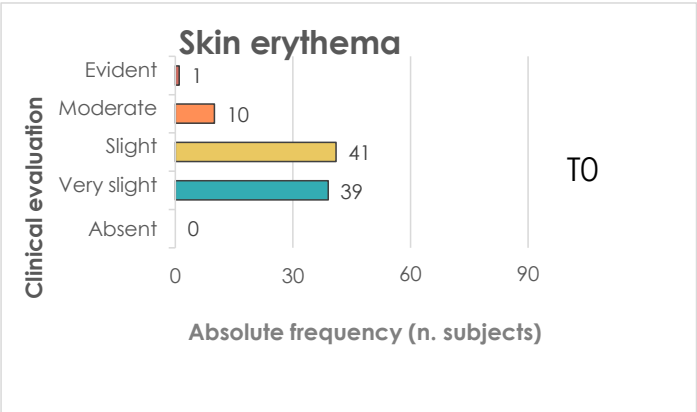
So, it is possible to conclude that the product tested (organic cotton pad light incontinence) is able to reduce the synthesis of interleukins production IL-6 and IL-8 in cell cultures of human keratinocytes in vitro.

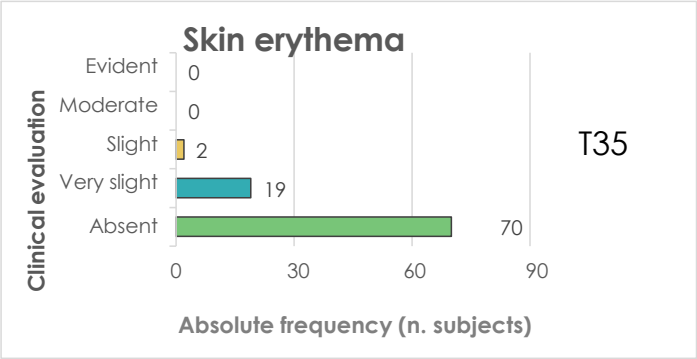
Evaluation of skin erythema using "Organyc Light Incontinence"

The results regard the description of the variable skin erythema and table of the absolute frequencies of the judgments regarding skin erythema at the two observation times (T0 and T35) are reported in Table IV.

Looking at the frequencies of judgments regarding skin erythema, it is noted that they have a distribution that shifts towards more positive categories after 35 days of Med.Dev use. Skin erythema reduces in 89% of the volunteers after 35 days of Med-Dev use. A statistically significant difference between the two observation times was demonstrated. Application of the medical device "Organyc Light Incontinence" had a significant effect on skin erythema.

Table IV. *Organyc Light Incontinence. Graphs of the absolute frequencies of the judgments regarding skin erythema at the two observation times.*

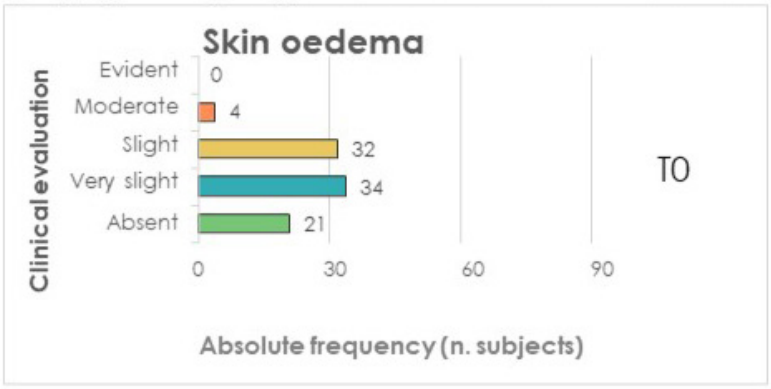


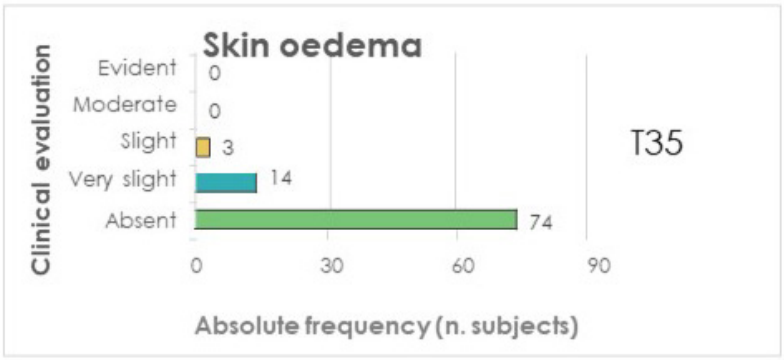


Evaluation of skin oedema using "Organyc Light Incontinence"

Description of the variable skin oedema and table of the absolute frequencies of the judgments regarding skin oedema at the two observation times (T0 and T35) are reported in Table V. Looking at the frequencies of judgments regarding skin oedema, it is noted that they have a distribution that shifts towards more positive categories after 35 days of Med.Dev use. Skin oedema reduces in 70% of the volunteers after 35 days of Med.Dev use. A statistically significant difference between the two observation times was demonstrated. Application of the medical device "Organyc Light Incontinence" had a significant effect on skin oedema.

Table V. *Organyc Light Incontinence: graphs of the absolute frequencies of the judgments regarding skin oedema at the two observation times.*

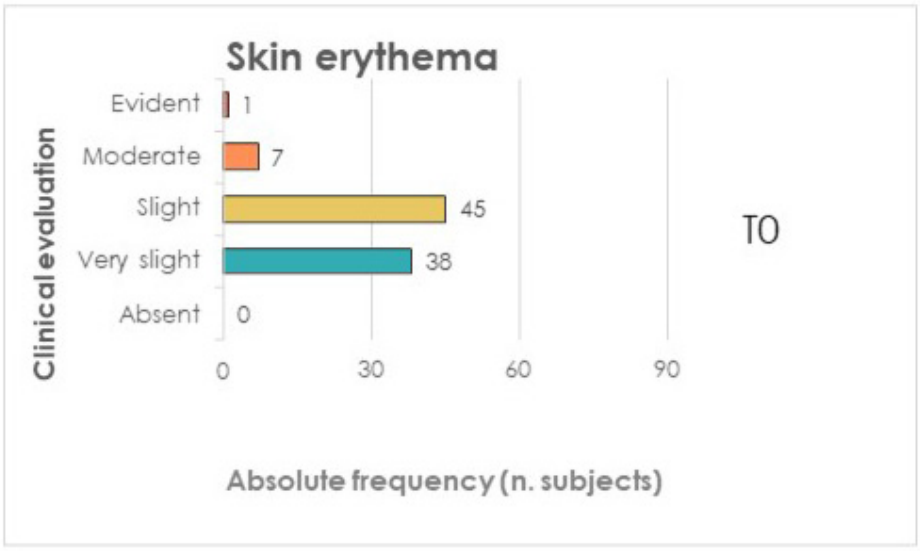


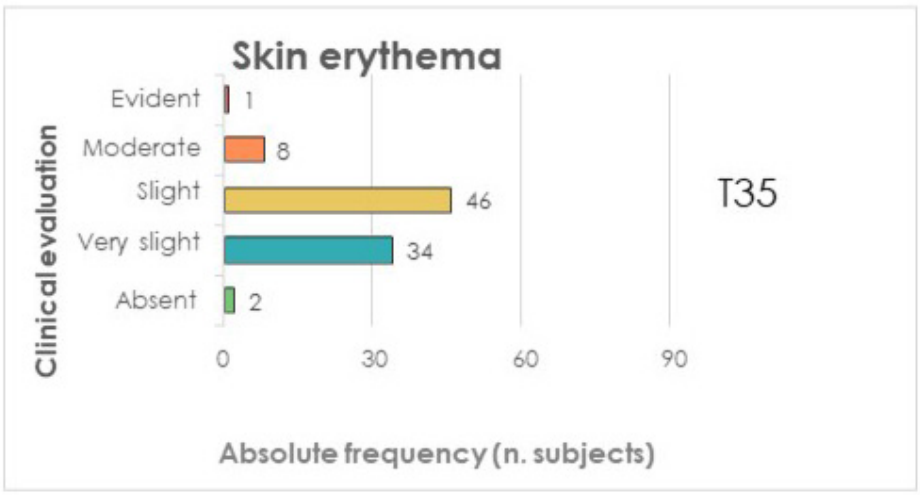


Evaluation of skin erythema using "Competitor"

Description of the variable skin erythema and table of the absolute frequencies of the judgments regarding skin erythema at the two observation times (T0 and T35) are reported in Table VI. Looking at the frequencies of judgments regarding skin erythema at basal time and 35 days of Med.Dev. use, it is noted that they have approximately the same distribution. There was no statistically significant difference between the two observation times. Application of the medical device "Competitor" had not a significant effect on skin erythema.

Table VI. *Competitor: graphs of the absolute frequencies of the judgments regarding skin erythema at the two observation times.*

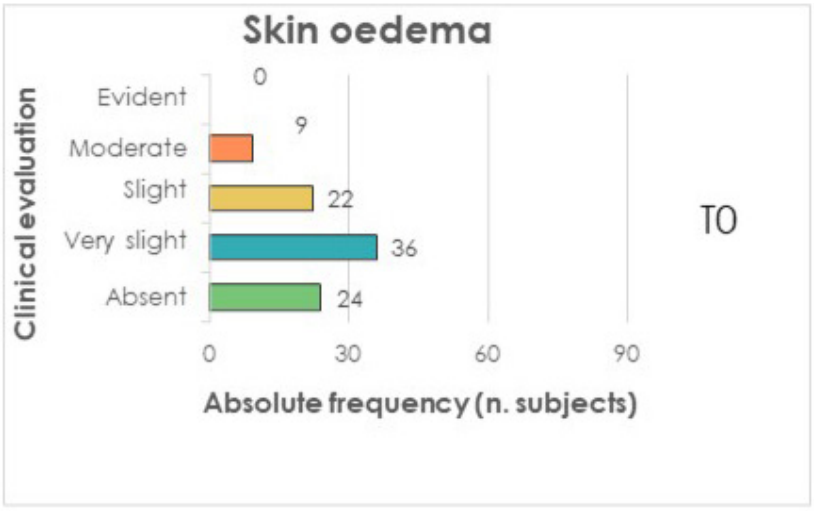


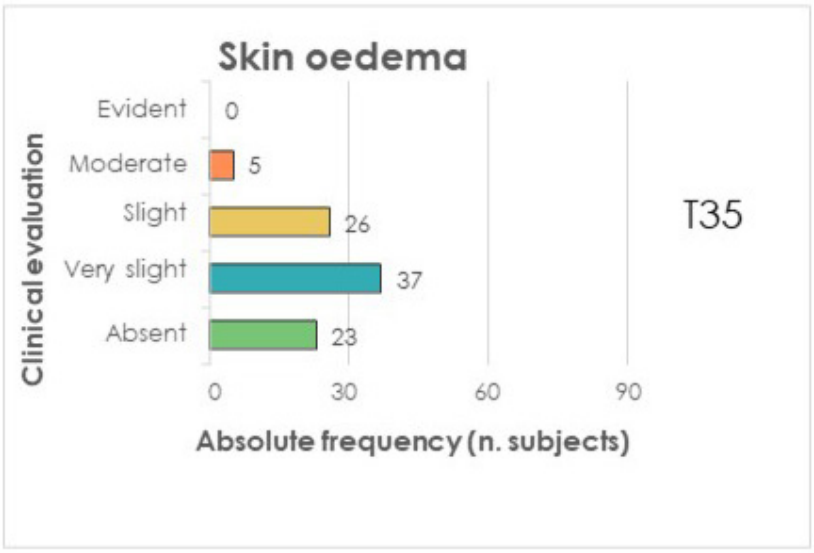


Evaluation of skin oedema using "Competitor"

Description of the variable skin oedema and table of the absolute frequencies of the judgments regarding skin oedema at the two observation times (T0 and T35) are reported in Table VII. Looking at the frequencies of judgments regarding skin oedema at basal time and 35 days of Med.Dev. use, it is noted that they have approximately the same distribution. There was no statistically significant difference between the two observation times. Application of the medical device "Competitor" had not a significant effect on skin oedema.

Table VII. *Competitor: Graphs of the absolute frequencies of the judgments regarding skin oedema at the two observation times.*





Self-evaluations

Regarding self-evaluations, the following parameters have been investigated:

a. SOFTNESS in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

b. ABSORBENCY AND LEAK PROTECTION in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been

compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

c. PROTECTION AND SENSITIVE SKIN in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

d. PREVENTING IRRITATION AND REDNESS in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

e. BREATHABILITY in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p value < 0.01).

f. DRYNESS compared to competitor.

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups.

g. IMPORTANCE of manufacturing with natural ingredients.

The patients have been asked to express their opinion from not at all important (0) to extremely important (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

h. COMFORT in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test, and show a statistically significant difference between the two comparison groups (p-value < 0.001).

i. ABILITY TO STAY IN PLACE in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.03689).

j. RATE THE PRODUCT ON AN OVERALL BASIS in comparison to competitor

The patients have been asked to express their opinion from not at all satisfied (0) to extremely satisfied (10). The results have been compared with Mann Whitney U test and show a statistically significant difference between the two comparison groups (p-value <0.001).

Fig. 3 reports the medians of the main points of the questionnaire for both the Organyc Light Incontinence (bladder leakage control pads) and the competitor. The results of the medians confirm the differences between the two products for all points. The parameter "Ability to stay in place" has for the two products the same medians but the statistically significant difference is present as confirmed by the Mann Whitney U test (p-value < 0.003689).

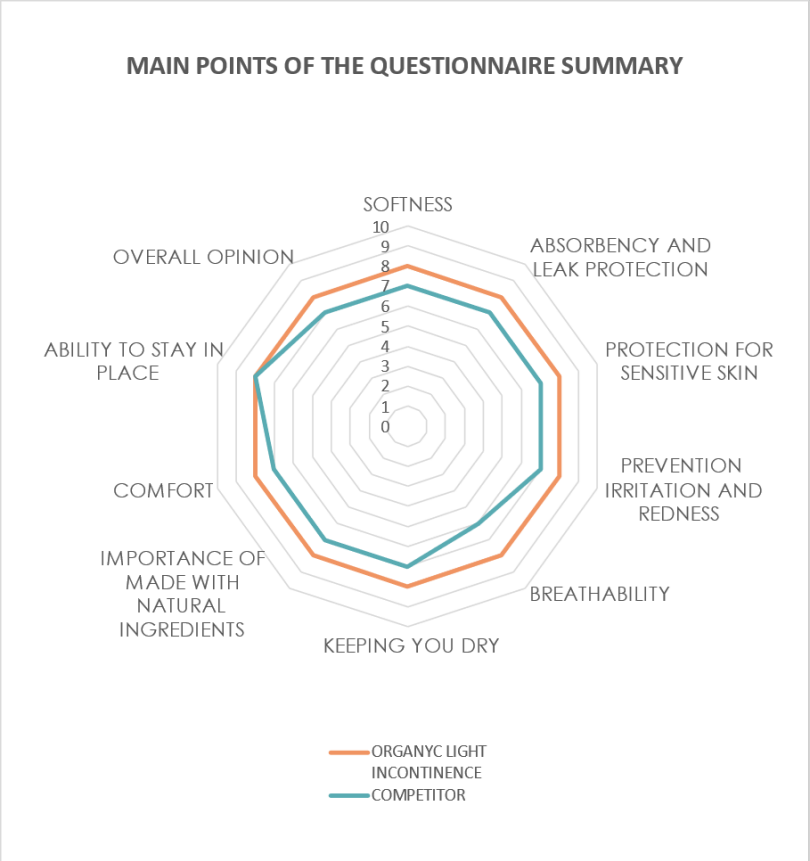


Fig. 3. *Graphs of median of evaluation of the judgments regarding self-evaluations.*

Discussion

Application of the medical device "Organyc Light Incontinence" had a significant effect on skin erythema and on skin oedema, otherwise differently from the competitor considered that did not show any of the two effects. Regarding the skin erythema, at T35 it is noted that 70 patients reported absence of the symptoms, in comparison to T0 when almost all the patients reported from moderate to light/very light symptomatology. Regarding the skin erythema, the same improvement of symptomatology is reported.

Regarding the self-evaluation parameters reported, it was noticed than "Organyc Light Incontinence" was significantly better than competitor in softness, absorbency and leak protection, protection for sensitive skin, prevention of irritation and redness, breathability, in keeping the person dry, and comfort. In addition, the importance of being made by natural ingredients

like organic cotton was appreciated. The ability to stay in place was rated as the competitor. Giving these points, the overall opinion of the patients regarding the product was significantly better than the competitor.

Conclusions

The results of the monocentric clinical trial reported in this article showed that "Organyc Light Incontinence (bladder leakage control pads)" medical device was safe to use and significantly reduced erythema and oedema of the skin and the vaginal mucous in female patients with light incontinence in comparison with another non-cotton medical device ("Competitor"), also after prolonged use (every day for 35 consecutive days). A customer satisfaction analysis also demonstrated wide acceptability and good compliance of the new product and female patients' interest in buying the tested product in the future.

Therefore, this article's findings suggest that the "Organyc Light Incontinence (bladder leakage control pads)" medical device could help to improve patients' quality of life affected with light incontinence by reducing skin irritation side effects caused by the prolonged use of non-cotton medical devices.

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Low-Level Laser Therapy in fat reduction: what evidence do we have?

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key words: *Low level laser therapy, LLLT, fat reduction, body shaping, body contouring*

Abstract

Low level laser therapy (LLLT) dates to early '70 to induce hair and wound regeneration then to reduce inflammation, edema and chronic pain and in present times is widely used for cosmetic fat reduction but despite the presence of many LLLT devices on the market the exact biochemical mechanism to explain its therapeutic effects is yet to be fully understood. Published data from treatments used to achieve fat layer reduction were pooled and reviewed to assess efficacy, safety and patient satisfaction and proposed models of LLLT biological action are discussed.

Introduction

Low level laser therapy was first attempted in early '70 when Mester and other Authors found that applying a laser light on shaved mice induced a quicker hair regrowth and regeneration than in

unexposed mice (1-2). Later the same Authors reported that HeNe laser could stimulate wound healing also in humans and has a beneficial effect in inflammation, edema, and chronic pain (3).

The main mechanism of this therapy is to expose tissues to low energy levels (if compared to those used for ablation) of near infrared (NIR) light, levels of energy low enough to not produce an important heating of the tissues.

The exact biochemical mechanism to explain LLLT's therapeutic effects is yet to be fully understood. Under LLLT stimulation a cascade of events at molecular level are reported, probably due to absorption of NIR light by mitochondrial chromophores, in particular cytochrome C oxidase (CCO): an increase of enzyme function with adenosine triphosphate (ATP), a reduction of reactive oxygen species (ROS) and increase of transcription factors like cAMP-response element–binding protein (ATF/CREB), redox factor-1 dependent activator protein-1 (AP-1), hypoxia-inducible factor (HIF)-1with HIF-like factor and p53 (4-6).Those molecular effects also have strong consequences at cellular level with degranulation of some immune cells like mast cells with release of chemotactic, growth and inflammatory factors (7-9).

LLLT in Fat Reduction

LLLT was proposed to assist surgical lipectomy first by Niera et al. (10) because caused a certain amount of fat liquefaction that helped surgical aspiration; further evidence showed that wavelengths between 630 and 640 nm were the best to assist lipoplasty (11-12). Jackson et Al. in a controlled, randomized, multicentered clinical study confirmed that laser assisted liposuction decreased operating room times, increased fat extraction volume and improved overall patient recovery (13).

Most studies use in vitro models of human adipose tissue like the work by Niera et Al. that after an external irradiation with a 635-nm laser with total energy values between 1.2 and 3.6 J/cm2 for up to 6 minutes showed that the amount of fat liquefaction was time dependent: after 4 minutes of laser exposure 80% of the fat was released from the adipose cells and after 6 minutes all the fat was released from the adipocyte. The lipolythic effect was attributed to the creation of micropores that allowed intracellular lipids to come out of the cell without destroying it and those micropores were reported to be present at electron scan microscopy (11). Caruso-Davis et Al. in a randomized study demonstrated that laser don't activate the complement cascade, do not kill adipocyte and increase triglyceride release but not lipolysis. After irradiating human subcutaneous fatty tissue with 635–680 nm for 10 min, there was no increase of glycerol and fatty acids in cell culture medium, suggesting that fat loss in laser treatment was not due to a stimulation of lipolysis, but could be caused by pores in adipocytes as Niera suggested (14). The phenomenon was explained with the increase of ROS levels that caused a peroxidation of lipids in cellular membranes thus damaging only

temporarily them (15-16). Also, it is possible that LLLT stimulation with a subsequent ATP synthesis increase leads to an cAMP upregulation that could activate a cytoplasmic lipase causing pores in cellular membrane and loss of fatty acids (17). Unfortunately, other attempts to replicate Niera's experiment by other Authors failed to spot micropores with electron scan microscopy (18-19) also another work, questioning the ability of red light (635 nm) to penetrate effectively under the skin to ipodermic level where the fat is located, added more uncertainty to any possible explanation of LLLT effect in fat reduction (20).

Materials and methods

A search on PUBMED online library with the query "LLLT fat reduction" and "LLLT body conturing/ shaping" found 72 works but only 16 contained original, prospective clinical trials. Data from LLLT clinical and pre-clinical treatments used to achieve fat layer reduction were pooled and reviewed to assess efficacy, safety and when feasible patient satisfaction.

Results

We identified 16 prospective clinical trials based on in vivo evaluation, only one based on bioptic samples and two based both on in vivo measurements compared with bioptic samples with a total of 1211 patients involved. All studies are summarized in table I (11, 14, 21-34). As expected, the laser equipment used is never the same and there are some differences in treatment methods used between studies as reported in Table I, mostly regarding number of applications and timing of applications. Nearly all studies were performed on people with a body mass index lower than 30 and without age, sex, or ethnicity exceptions.

Table I. *Summary of LLLT clinical works.*

Author	Journal	Patient N.	BMI Eval.	Circumf. Eval.	Other Eval.	Result	Patient Satisf.
Elm CM 2011	Las. Surg. Med.	5	yes	yes	US	NO difference	no
Neira R 2002	Plast. Rec. Surg.	12	no	no	US/ Biopsy	80% reduction	
Carniol PJ 2008	J. Cosmet. Las. Ther.	10	no	yes		NO diff	yes
Jackson RF 2009	Las. Surg. Med.	67	no	yes		Significant reduction	
Mostafa MS 2016	Las. Surg. Med.	15	yes	yes	MRI	NO difference	no
McRae E 2013	Las. Surg. Med.	86	no	yes		Significant reduction	
Vas K 2019	J. Biophotonics	10	yes	yes	US	Significant reduction	
Caruso-Davis MK 2011	Obes surg.	40	yes	yes	Biopsy	Significant reduction	yes
Wallander ID 2011	Las. Surg. Med.	5	yes	yes	US	NO difference	no
Jankowski M 2017	Las. Med. Sci.	24	yes	yes	US	NO difference	
Jackson RF 2012	Las. Surg. Med.	689	no	yes		Significant reduction	
Lach E 2008	J. Cosmet. Las. Ther.	74	no	yes	MRI	NO difference	32% satisfied
Gold MH 2011	J. Cosmet. Las. Ther.	83	no	yes		Significant reduction	

Nearly all studies (except the bioptic one) used body circumference as the main outcome indicator and there was no significant weight change in subjects enrolled over the study period, thus allowing any circumference change to be attributed to the treatment itself.

All in vivo studies performed abdomen treatment and most report a circumference reduction: overall reduction is reported in 1011 (83.5%) of the total 1211 patients pooled in this review, with 10 works showing a significant reduction (11, 14, 22-24, 26, 28, 30, 31, 34) and 6 works showing no reduction or a not significant one (21, 25, 27, 29, 32, 33). We decided to not compare reduction measurements because of the different treatment protocols applied, mostly by the number of applications and the total time of treatment, that made such comparison obviously meaningless but reduction as much as 6,86 cm of abdomen circumference were recorded (28), however, most works reported a reduction between 2 and 3 cm (14, 21, 24, 34). In different body areas, the same results were studied and shown a common circumference reduction of 1.9-2.5 cm for hips and 2.9-3.9 for thighs. One study (22) reported a mean combined reduction of 3.7 cm of circumference in both arms.

Because the technique used is described as noninvasive most works did not record adverse effects and the few that did, recorded only mild and transient effect that resolved spontaneously. One work reported serious adverse effects on 2 patients that developed skin ulcerations upon area of laser application (29). Common side effects recorded are mild discomfort during the application, erythema lasting few hours and swelling or tingling sensation always of short duration.

Only 8 out 16 of our chosen studies reported patient satisfaction and only 3 reported a certain percentage of unhappy patients; of the 286 patients pooled from studies that recorded patient satisfaction 195 (68.2%) expressed satisfaction after completion of treatment and 91 (31.8%) expressed no positive or an utterly negative evaluation.

Discussion

All studies made to investigate such devices have different treatment protocols, so it is very difficult to directly and accurately compare their results and it is impossible to compare effectiveness of different devices. In our work we excluded all papers that used simultaneously laser treatment and diet to reduce fat to remove another possible confounding factor.

The most important evidence is that all trials, with the exclusion of the one performed on bioptic specimens, required many applications (mean 7 applications, SD 2, 9) to indicate that LLLT needs weeks of time to exert and develop its biological effects and this is consistent with all the proposed models of action: in Neira's model of adipocite's cell membrane disruption by LLLT and lipids spillage (11) even if the effect is almost immediate it requires time to deplete adipocyte and thus be noticed. In the alternative hypothesis of triglyceride mobilization proposed by Caruso-Davis, (14) with unharmed or only temporarily damaged cells, the time lapse is even

more self-evident since it might require days to activate all the metabolic pathways necessary for the fat reduction effect to be evident. The model of metabolic activation is supported also by the study of Jackson et al. (24) that suggest an autocrine/paracrine activation and corroborated by animal studies made by Aquino et al. (35) where in sedentary animals LLLT increased fat volume while decreasing it in active and trained animals. This effect could explain the failure of LLLT treatment in some patients and the reported paradoxical "fat increase" effect reported in few patients by some authors (29, 34).

Despite the mechanism involved lipid in excess are expected to be cleared through lymphatic system but there has been recorded no increase in serum lipid levels but rather cholesterol and leptin levels have been observed to decrease after the treatment (36-38) and this can also be considered supportive to the metabolic activation model. There's a large body of evidence to suggest that vascular oxidative stress induces obesity and metabolic syndrome (39) and oxidative stress in adipose tissue decreases adiponectin secretion with a reduction of adiponectin-induced energy expenditure associated with protein uncoupling (40, 41). Since it is demonstrated that LLLT reduce oxidative stress in other tissues like neural and muscular, another model has been proposed: LLLT-induced reduction of adipose tissue thickness as result from decreased oxidative stress and consequently an increased adiponectin secretion and decreased insulin resistance (29).

Conclusions

Overall evidence shows that LLLT used to for reduce subcutaneous fat tissue is safe and, in most cases, effective but lack of standardized protocols and, most importantly, the exact knowledge of its biological mechanism made it difficult to assess its exact clinical indications and for what kind of patients is best suited for. Further standardized studies are required to make LLLT a powerful tool in aesthetic fat reduction.

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Mucoid pseudocysts – clinical presentations, classification, and treatment

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key words: *Mucoid pseudocyst, myxoid cysts, classification, surgery, laser, treatment*

Retrospective Study

Abstract

Mucoid pseudocysts (syn. myxoid pseudocysts) are benign lesions of the distal parts of fingers and toes. Traumata and osteoarthritis seem to be involved in pathogenesis. Based upon their localization, three subtypes can be differentiated. We report a retrospective investigation over 20 years on MP's, demographics, classification and treatment. We identified 22 patients with 23 lesions. The male to female ratio was 2.3. The mean age was 55.1 years with a range of 26 to 77 years. The majority of lesions belonged to type A, while type C was the least common. Surgery with Oberst block anesthesia was performed for 15 lesions with a cure rate of 100%. The cure rate with laser therapy was 86%. Laser therapy is an alternative for type A lesions only.

Introduction

Mucoid pseudocysts (MP) also known as myxoid cysts are benign ganglioma-like lesions of fingers and toes. Based on clinical findings, three major subtypes can be differentiated. The most common type A is located dorsally or laterally to the distal interphalangeal joint. Type B is

located subcutaneously on the proximal nail fold. When it grows it can cause nail dystrophy. Type C, the less common type, occurs subungual. Nail dystrophy is a possible consequence. Most of MP's are asymptomatic, but type C MP's may become painful (1).

Histologically, MP has no epithelial lining. The center consists of viscous, gelatinous fluid that compresses neighboring tissue. The connection to the interphalangeal joint can get lost (1). There are several pathogenetic factors discussed, which may be responsible for the developments of MP. Exit of gelatinous synovial fluid from the capsule of the distal interphalangeal joint after repetitive trauma is the most favored. Other possibly contributing factors are herniation of tendon sheaths or synovial linings and degenerative joint diseases (osteoarthritis) in elderly patients. Histologically ganglion-like and myxoid degenerative cases have been described (2). Dermoscopy of MP reveals arboriform telangiectasias over white, bluish, and reddish-orange diffuse areas (3). Another dermoscopy study described vascular patterns with arborizing vascular patterns with dotted vessels, linear vessels or polymorphous vessels, red-purple lacunas and white shiny structures (4). Magnetic resonance imaging (MRI) demonstrates a high signal intensity and sharp borders on T2-weighted images. Intracystic septa and satellite cysts may be present in some patients (5).

Patients and methods

This is a retrospective study. We investigated the files of the Department of Dermatology and Allergology from February 2001 to February 2021 for patients with MP who underwent either surgery or laser treatment. We report demographic data, clearance rate, recurrence rate and adverse events. The operation field was disinfected carefully using 72% propan-2-ol (Cutasept F®; Bode, Hamburg, Germany) or 45% 2-propanol, 10% 1-propanol, 30% hydrogen peroxide with biphenyl-2-ol (Kodan®, Schülke & Mayr, Norderstedt, Germany) before and after the procedure.

We employed the following lasers: Erbium-YAG-laser MCL 29 Dermablate (Asclepion Laser Technologies, Jena, Germany). The wavelength of this laser is 2,940 nm. The focus diameter varied between 1.6 mm and 3 mm. We used a frequency of 8 Hz. The pulse energy was between 800 to 1,000 mJ. The ultrapulsed 980 nm diode laser Ceralas HPD (Biolitec, Jena, Germany) was used with a focus diameter between 0.6 and 1.0 mm. The maximum power of this laser is 120 W. Laser treatment was individually tailored by power, pulse duration, and pulse pause. On average 80 W, 0,1 sec pulse duration and 0,02 to 0,05 sec pulse pause were used. The dual diode laser Leonardo Dual 45/100 (Biolitec Biomedical Technology GmbH, Jena, Germany) combines 980 nm and 1470 nm. Each wavelength can be individually selected or blended together to obtain the perfect effect. Hand pieces with spot sizes of 1 mm and 1.5 mm were used, depending on the size of the lesion. The maximum power for dual mode is 45 W with up to 30 W (range 0-30 W) for the 980-nm diode laser and up to 15 W (0-15 W) for the 1470-nm diode. The laser offers continuous wave (CW) or pulse mode, but

we preferred CW mode. Patients and staff carried protective goggles during any laser treatment. All treatments were performed with Oberst block anesthesia: A subcutaneous deposit of prilocaine 1% local anesthetic is administered dorso-radially and dorso-ulnarly at the metacarpophalangeal or metatarsophalangeal joint (6). In case of surgery the method dependent on the location. In Type A and B MP's, the MP was completly removed after careful preparation of the lesion with suturing. In type C MP´S partial or complete nail plate removal using a nail plate elevator was followed by complete excision.

In laser treatment, the lesion was perforated, the fluid was expressed, and a second laser application followed to obtain thermal injury to collapse the tissue space. The healing was faster and necrosis more limited with dual diode laser than with ultrapulsed 980 nm diode laser (7).

Results

A total of 22 patients with 23 MP's could be identified. There were 14 men and 6 women (ratio 2.3). The median age was (55.1 ± 18.3) years with a range of 26 to 77 years. MP were located on fingers in 17 cases and on toes in 6 cases. One patient developed two consecutive MP's on the thumb. Two lesions were ulcerated. MP's could be classified into type A (n=12), type B (n=7), and type C (n=4) (Fig. 1).

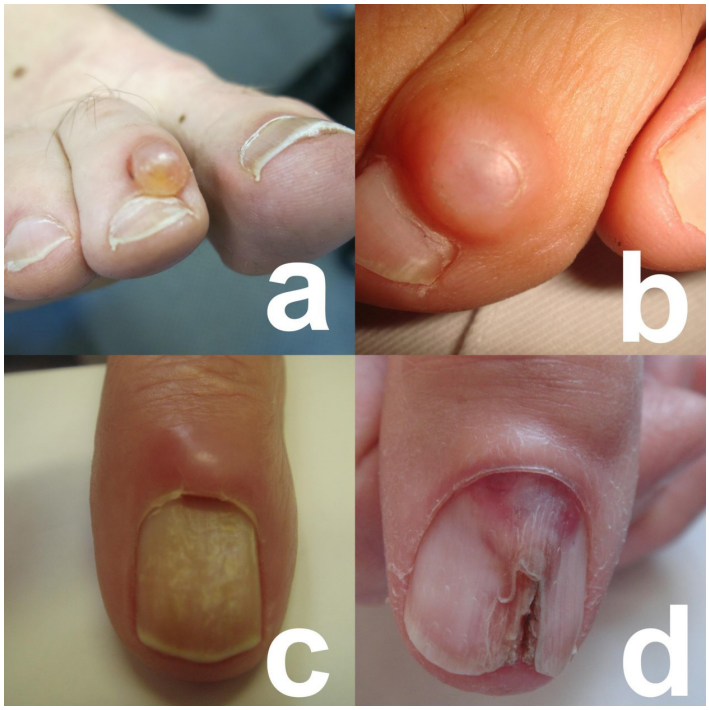

Fig. 1.*Various presentations of MP's. (a): Type A; (b) and (c): Type B; (c): Type C with destruction of the nail plate.*

Mean follow-up was (27 ± 16) months. The lesions were treated by surgery in 15 patients (Fig. 2). Surgical defects could be closed by skin advancement flaps or, in case of larger lesions, with bilobed or bipedicled flap from the lateral aspect of the distal phalanx (8).

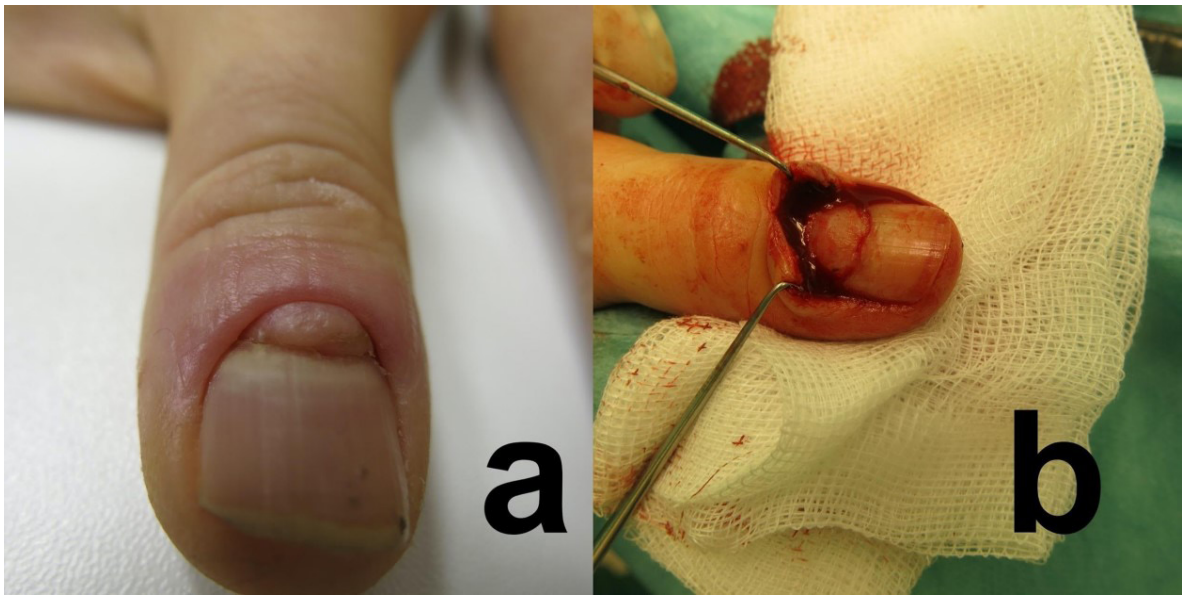

Fig. 2. *MP-surgery. (a): Clinical presentation of a type A MP; (b): After surgical removal.*

No relapses were observed. Seven patients underwent a laser therapy (Fig. 3). Two patients were treated by erbium-YAG, 3 by 980 nm diode laser and two MP's of on patient was treated by 980nm/ 1470 nm dual diode laser. Treatment was well tolerated. We observed no infection or joint affections, no hypertrophic scars. One patient with a type B lesion experienced a relapse after erbium-YAG laser treatment. She was cured by surgery. No relapses were observed after diode laser therapy.

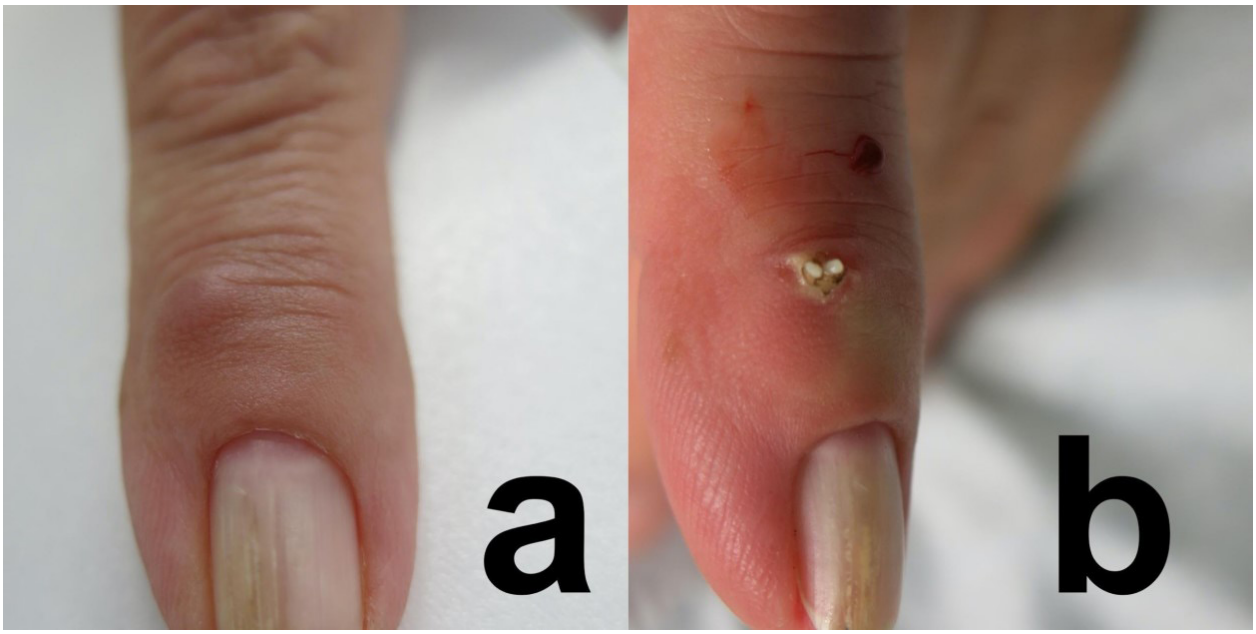

Fig. 3. *Laser therapy of a type A MP. (a): Clinical presentation; (b): After laser perforation. Viscous fluid can be expressed.*

Discussion

There is no standardized treatment algorithm available for MP's. Aspiration and injection of a sclerosant such as sodium tetradecyl sulfate into MP's seems convenient (9, 10), but recurrence rates of 22% to 40% within 2 years of follow-up have been described, which seems too high (11, 12). Intralesional steroid injections have relapse rate of 40% (12).

Cryosurgery with intermittent spray technique is compromised by a high relapse rate (13). The effect is insufficient for type B and C MP's anyhow. Surgery with complete excision with careful tying off of the channel to the joint has been shown a high remission rate. Among 100 MP's the recurrence rate was only 2% (14). These results were confirmed by others (15).

An Italian study analyzed 53 MP´s in 51 patients. They were treated by surgical excision with a cure rate of 72.6% at a mean recurrence time of 160 days with a mean follow-up of 3.6 years (16). Dockery (1994) reported retrospective results of 25 consecutive complete excisions with Schrudde rotation flap defect closure for MP's type A (17, 18). The long-term results after at least 12 months demonstrated a relapse rate of 6% (17). Blume et al. (2005) used a bilobed flap for defect closure. During a follow-up for 4.6 years on average no recurrence was noted (18). In a meta-analysis of more than 1,000 published cases surgery achieved a cure rate of 95%. In contrast, sclerotherapy had a cure rate of only 77%, cryotherapy of 72%, intralesional corticosteroid injection of 61%, and expression of cyst content achieved less than 40% (19).

Among those with nail involvement, 78% achieved a marked improvement or complete resolution. However, recurrence of the digital mucoid cysts was observed in 22.5% (20). In our smaller single center study, the cure rate after surgery was 100%. Laser therapy is an alternative to surgery. Different laser types have been employed such as 10,600 nm CO2-laser (21, 22), 1,444-nm neodymium-doped yttrium aluminum garnet (YAG) laser (23), 2,940 nm erbium-YAG-laser (24), or 980 nm diode laser (25).

Unfortunately, there are no comparative studies for laser and surgery. CO2-laser therapy achieved cure rates of up to 80% in particular in type A MP's (26, 27). We have used both erbium-YAG and diode lasers. Laser therapy is appropriate for type A MP's. For types B and C, we would prefer surgery since we experienced a relapse after two sessions with diode laser. In conclusion, MP's are benign pseudocysts of fingers and toes. Traumata and osteoarthritis are involved in pathogenesis. Type B and C MP`s can lead to secondary nail involvement. Complete excision is the treatment of choice. Laser therapy may be an alternative.

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Various skin reactions to tattoos – review literature

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REVIEW

Abstract

The tattooing process relates to the introduction of exogenous pigments that color the dermis in order to obtain a permanent, desired pattern. The complications associated with the tattooing process have been reported since the end of the 19th Century. Despite the prevalence of tattoos, public awareness of possible related complications and health risks is low. The exact pathogenesis of adverse tattoo reactions on functioning and microstructure of skin, still remains unknown. Potential local and systemic adverse reactions of the tattoos, as well as the reactions to the tattoo pigments used during this process, are inaccurately understood and poorly described. The aim of this study was to review the literature regarding skin complications after having a tattoo. This review of literature will allow the authors of this publication, to specify the aim of future studies, which will allow to precisely determine occurance of potential complications after having a tattoo.

Introduction

The history of tattooing is as old as humanity. The roots of the word "tattoo" can be seen in the Tahitian term "tattoo", which literally means "the results of tapping". The practice of ornate tattooing, however, was popular even before the rise of the first Polynesian tribes, back in ancient Egypt (1).

It is difficult to determine exactly when the tattoo art was created. Evidence of non-removable skin marks have been found in work of art and ancient texts from whole world. The history of tattoos shows that they were used by different cultures for various purposes: religious expression, group hierarchy, identity, punishment or sign of social status ending with body decoration. Probably the origins of the tattoo date back to ancient Egypt around the second millennium BC, where Egyptian mummies with tattoos were discovered. Tattoos were to protect against evil spirits and were attributed to various social groups. In ancient Greece, the tattoo had a solely decorative role.

The Romans tattooed escaped slaves and the Japanese tattooed criminals and others unsavory inhabitants of society. The first Christians tattooed symbols of faith on their bodies. Inglorious World War II went down in tattoo history. The Nazis marked concentration camp prisoners by tattooing registration numbers on their forearms. In the 17th-18th Centuries, the tattoo began to be equated with sailors, criminals and prisoners. In the late sixties, tattoo began to be more accepted as part of the culture when the stars, especially the music, started making them (2).

Nowadays, in contrast to the recent past, tattooing is rarely associated with mysticism, rather it is a popular trend in the world. Tattoos are often the result of fashion adopted in the western world to stand out, be original, individual and associated with belonging to a group (3). Currently, the beautifying nature of the tattoo outweighs other cultural functions. Therefore, we can distinguish several types of tattoo: permanent decorative tattoos: the most popular, colorful or one-colored (usually black), involving the introduction of pigment inside the dermis (about 1-2 mm depth) using a tattoo machine to achieve a lasting pattern; temporary tattoos: tattoo made with removal natural henna (extract from the leaves of the shrub Lawsonia inermis); medical tattoos: used to camouflage skin lesions, improve the esthetic appearance in vitiligo, scars, partial alopecia or use in final stages in reconstructive surgeries; cosmetic tattoos (permanent makeup): also called micropigmentation, involves the introduction under the skin of dyes, which are implemented into the second or third layer of the epidermis (about 0.3-0.5 mm), shallower than that of traditional tattoo, used to improve the appearance of eyebrows, eyelids and lip contour (4).

In the process of tattooing, colorant suspension is deposited in the dermis by puncture the skin with tiny needles that are immersed with tatoo dye. The colour of the tattoo is the result of injecting pigments into dermis where the fractions of colorant stays (5). As Shinohara et al. shows, the histopathology of a tattoo typically shows clumps of free pigment in the dermis and within dermal macrophages. Older tattoos show a decline in general pigment, with

less free pigment, and the remaining pigment spreaded in perivascular macrophages (6). About a dozen percent of the world's population have a tattoo. This is accompanied by an increase in the incidence of acute and chronic complications of having a tattoo. Tattoo complication is a very complex issue and has already been introduced as subspecialty in dermatology.

Results

So far a clear clinical classification for the diagnosis of tattoo complications has not been established. It is also due to the lack of knowledge about the dosage and precise composition of tattoo inks, their impurities and toxicity. The uncertainty also includes the microbial contamination that have been found in many tattoo products labeled "sterile." The classification of complications is made difficult by lack of detail or uncertainty as to final diagnoses as well as no reference to some established nosological unit. Additionally, tattooed people are always at risk of bacterial and viral infections as well as allergies.

According to a study of Serup et al. the classification includes infectious, non-infectious, acute and chronic complications (which are most often associated with significant itching and discomfort comparable to other pruritic dermatosis) (7). Following Körner et. al., an increasing number of complications have been observed after tattooing: infections, allergic reactions, pseudolymphoma and malignant tumors (squamous cell carcinoma or malignant melanoma). Skin reactions can also be sarcoidal or granulomatous type (caused by mercury, chrome, cobalt). This is probably due to the increase in the popularity of tattoo in the world in recent decades.

Complications in the form of skin reactions may occur immediately after the application of pigments into the skin or may appear after months or years. According to this study, mostly allergic skin reactions are caused by the red pigment or can also be due to common triggers of contact dermatitis – nickel. Pigments in permanent tattoo can only be eliminated by surgical removal or a laser treatment. Additionally, foreign body reactions may occur while removing the tattoo by IPL (intense pulse light) by trigerring a brisk immune reaction: destructing of pigment, inducing a physical or chemical modification of the previously inoculated pigment or reaction to a previously confined tattoo antygen (8).

Tattoo ink consists of pigment and the carrier, which works like a solvent for the pigment. Organic dyes and metallic salts are currently used as pigments. Dyes have a variety of colors but general and widely used one is black (which is composed mostly of iron oxides and diverse carbons). Blue inks contain chromium, cobalt and copper salts; red include high levels of mercury; green inks primarily chromium and copper, and yellow cadmium salts.

The composition of tatto inks is highly changeable, they can include abundant potentially allergenic or carcinogenic compounds. Adverse inflammatory reactions (infections, allergic reactions, malignancies, inflammation of existing dermatosis) to tattoo pigments have been reported and described (2). The latest research reports that black, dark blue and red inks have carcinogenic potential. Although tattoo

pigments are believed to be carcinogenic, there are no regulations regarding their safe use.

The exact composition of the tattoo ink is not required, nor is it internationally standardized. Black inks contain carcinogenic substances such as soot, iron and phenols. The red ones contain potentially carcinogenic substances including mercury, monoazo pigments, dioxazine, copper phthalocyanine, cadmium, cobalt and chromium. Some studies have also suggested skin carcinogenic effects of chemicals used to lighten tattoo inks (such as titanium dioxide and aluminium). The tattoo dye injected into the skin is detected by immune system. It is identified as a foreign substance and consequently absorbed by phagocytes. The dye is finally enclosed in fibroblasts in the dermis, where granulation occurs and connective tissue is formed.

The highest concentration of the exogenous pigment inside the proper layer is observed below the epidermal-cutaneous junction. While it is usually stable in this area, it occasionally slides deeper into the dermis. Therefore, the delay between the tattoo application and the first skin problems or symptoms appearance can range from hours to several years (9).

Accurate pathogenesis of adverse tattoo inflammatory reactions (except for infection) remains elusive. Tattooing complications have been reported since the end of the 19th century. The frequency of skin complications after tattooing is unknown. Cutaneous complications can be classifed in different ways: in accordance with the length of their evolution (acute and chronic reactions); the delay of onset after tattooing (early, during the healing phase or delayed, after tattoo healing) or the type reaction: infection, hypersensivity reaction, etc.

Clinical and pathological classification seems to be the easiest and most convenient for us (10). Wenzel et al. analyzed the results of studies and medical records from 1991–2011 on adverse reactions related to tattooing. They assigned the following categories to the published cases: granulomatous, lichenoid or allergic reactions, infections and tumors. The results show that adverse skin reactions are more often associated with a colored tattoo (83.3%) than a black tattoo (12.5%). High incidence of side effects of a color tattoo may be due to the complex chemicals contained in the colored pigments. Research shows that coloured tattoos presented more complications than black tattoos and are more likely to cause skin problems related to lichenoid, granulomatous, or hypersensitivity alergic reactions.

It also indicates that adverse reactions to tattoo occurred more often on the limbs than on the trunk, probably due to the photosensitizing reaction of pigment components, present in the tattoo ink, with the sunrays (which occurs when exposed to them). The interpretation of the results was limited by the difficulties in the diagnosis of allergies and in the interpretation of the granulomatous reaction (11). Between 2007 and 2007, Klügl et al. assessed 3.411 reports of complications after tattooing in German-speaking countries.

A wide range of skin problems (67.5%) and systemic reactions (6.6%) were recorded. There was a significant correlation between skin reactions to black and color tattoo pigment. Skin problems associated with color tattoos were

more frequent and included granules, swelling, lumps and itching (during exposure to solar radition). Some azo pigments in tattoo dyes may be responsible for these adverse skin reactions, as they may strongly absorb some radiation and thus photosensitize (12). A prospective observational study conducted in India 2012–2013 (Indira Gandhi Medical College, Shimla, Himachal Pradesh) recorded a total of 33 cases (19 men and 14 women) with complications after having tattoos. Twenty-one (63.6%) had acute complications, and twelve (36.3%) had chronic complications.

Histological examinations were performed on the basis of which, there were found lupus vulgaris, foreign body granuloma, chronic granulomatous changes, spongiotic dermatitis and lichen planus hypertrophicus (13). Serup et al. conducted a review of 493 tattoo complications in 405 patients of the Bispebjerg University Hospital in Copenhagen, Denmark, between 2008 and 2015.

Patients with complications of tattooing were diagnosed on the basis of the patient's history and systematic clinical examination supplemented with histology. The study reflects complications originating from presently used tattoo inks. Apart from specific diagnostic units, skin complications were observed: allergic reactions mainly seen in red tattoos, papulo-nodular reactions in black tattoos, bacterial infections and solar invulnerability. No cases of skin tumors or other malignancies have been reported. Sarcoidosis was common (7).

The latest review deals with the collection and initial classification of clinical complications after tattooing. Infectious complications can be acute, delayed or systemic and include bacterial infections mainly caused by Staphylococcus, Streptococcus, Pseudomonas, Clostridium, but also Mycobacteria. Among non-infectious complications, we can mainly talk about hypersensitivity reactions often related to problems with exposure to the sun.

The dominant symptoms are itching or stinging feeling swelling and burns. Histological reactions they can be egzema, psoriasis-like, interfacial reactions lichenoid or vacuolar. Nodular changes may correspond to granuloma, reactions sarcoidosis, purulent granuloma or necrobiotic granuloma. Research has shown that laser irradiation of some organic pigments (during tattoo removal) releases products decomposition and is responsible for it carcinogenic properties (14). It is thus far completely unclear, as to how often health problems occur in association with tattoos.

Most tattoos are made in tattoo studios, however, we can expect complications, often infections, allergies and systemic reactions. So far, infectious reactions with Staphylococci, Streptococci and Pseudomonas spp. bacteria from contaminated tattoo inks have been described. Unsanitary procedures, bad disinfected skin or unsanitary treatment of skin immediately after tattooing, are also the cause of complications (15). According to Laux et al. about 1–5% of tattooed people have tattoo-related bacterial infections after receiving a tattoo. Fungal infections and blood – borne viruses (such as hepatitis C or B or HIV) are rare. As a causative factor many infections related to tattoo environmental pathogen Mycobacterium chelonae has been identified. Adverse reactions can appear months

or years after the tattoo was made. Intradermal deposition of tattoo pigments causes exposure to delayed complications which last throughout life (16).

Discussion

Recently, scientists have identified toxicological evidence of the health risks posed by tattoo inks, but the first epidemiological works on safety of tattoo inks and systemic diseases, including cancer, are only beginning now. Tattoo inks are widely perceived as being safe by tattoo artists, ink manufacturers and consumers. In addition to being proven to potentially cause skin irritation in response to exposure to various factors, their subcutaneous application is not tested on humans or animals.

International Agency for Research on Cancer (IARC) reveals the presence of high levels of substances classified as carcinogenic or possibly carcinogenic to humans in tattoo dyes, in which we can find polycyclic aromatic hydrocarbons (PAHs), primary aromatic amines (PAA) and metals. The exposure way, where ink is injected directly into the dermis, varies greatly the absorption routes used to assess the hazards of these substances. There are only a few studies with comparable intradermal routes of administration (17). In case of a tattoo, highly concentrated pigments are injected into the skin. Consequently, through direct contact with dermal tissue and lymphatic system, pigments can stay in the lymph nodes, or in other organs, for a long time because of their insolubility.

The chemical complexity of pigment, their insolubility and the difficulty in quantitative extraction from the tissue, are the reasons why there is little information published about the fate of pigment after making a tattoo. Ostensibly, the amount of pigment placed in the body should be equal to the amount directly implanted after tattooing. However, an unknown fraction of pigment is transported away from the skin. Engel et al. have documented the existence of coloured lymph nodes in tattooed skin areas as evidence of transport to the lymph nodes and the rest of the pigment remains at the site of injection.

Using a mouse model, noted that pigment concentration of PR 22 that was intradermally injected in mouse skin decreased by 30% within 6 weeks after tattooing. Given these results, further tests should be conducted to evaluate health risk of tattooing humans. This and hopefully further research will shed light on the harmfulness of pigments as potential carcinogens (18).

Tattoo inks are a mix of several chemicals and may contain over 100 different chemical compounds including organic and inorganic dyes, metals and solvents. They might have a hazardous effect on the human body such as skin allergies or other serious impact on skin including cancer or genetic mutations (19). Tattoo artists and people who perform permanent makeup (PMU) use various companies which produce tattoo dyes and suspensions.

The inks differ from each other not only in their chemical composition, but also in consistency, colors and prices depending on the brand. The chemicals used in the inks are not always approved by the European

Chemicals Agency (ECHA) or the Food and Drug Administration (FDA) (20). Although tattoo dyes and PMUs are injected subcutaneously, their suspensions are neither cosmetic, medical or pharmaceutical substances, and do not have to meet injection certification standards. The quality of the ink depends on the standards adopted by a specific manufacturer (21).

The majority PMU and tattoo dyes consist of both organic and inorganic pigments and complex suspensions of many different chemicals. Inorganic pigments are a widely used group of pigments in permanent makeup, likely due to a lower risk of allergic reactions and giving a more stable result when used for shading techniques due to the fine distribution of pigment particles. The chemical synthesis of pigments has many tiny insoluble particles, which have diameters from a few tenths of nanometers up to a few micrometers. PMU pigments stay in the skin for a period of time because of the particle size (bigger than that used in tattoo ink), which the body eventually breaks down and absorbs. The difference between a tattoo dye and a permanent make-up dye is basically the size of the pigment particles. In addition, permanent makeup is made shallow, with special machines, and the smaller particles of the tattoo ink are deposited much deeper (22, 23).

Tattoo and PMU ink markets are spread all over the world. Most of the inks used for tattoos are manufactured outside of Europe (especially in the USA), while permanent makeup inks are mainly produced in Europe (estimated at 70-80%, predominantly in Germany, England, France, Spain, Italy). The Asian market for both types of pigments is also widely developed, nevertheless, Asian inks are mainly distributed to non-professionals. The pricing policy of these products vary in every country, with the Asian market being the most competitive.

Individual European countries are gradually taking steps to improve the safety of tattoos and permanent make-up. Many of the hazardous chemicals in tattoo inks and PMUs are restricted in the EU under the regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (24). Until now, the basis for the safety requirements and criteria for tattoo inks and PMUs were the limits contained in two resolutions published by the Council of Europe (RE), ResAP (2003) 2 and ResAP (2008) 1. Resolutions published by the Council of Europe include pollution limits, bans for several chemicals and product labeling instructions. The most important requirement is that the inks cannot endanger health or safety. In addition, the inks must not contain substances that are carcinogenic, mutagenic or harmful to reproduction, categories 1, 2 and 3, classified in EU Directive 67/548/EEC. The limits also stayed set for polycyclic aromatic hydrocarbons (PAHs) and metals. So far, the ResAp was the only instrument attempting to regulate the safety requirements and criteria for products intended for tattooing and permanent make-up (PMU). Poland has not signed the resolution (25).

More and more tattoo ink manufacturers are following to the guidelines listed in ResAP as the minimum standard for their products. Some of them choose manufacturers who additionally analyze and certify their components in external companies that test them rigorously. In Germany, CTL® GmbH Bielefeld has been researching PMU

and tattoo dyes since the last decade, and the certificates issued by them are recognized all over the world. Irrespective of which is the correct method for detecting metals in tattoo inks, the focus should be on the actual amounts of ink in the skin. CTL® has conducted experiments to determine these amounts and these experiments are crucial for toxicological evaluations and for setting legal limits.

It must be accepted that there are still scientific gaps with regard to tattooing that need to be researched in the future. For safety, each country should be responsible for providing lists of prohibited substances in tattoo and PMU dyes, and perform random ink import checks. In addition, all tattoo artists should be properly trained in identifying harmful components written on the product packaging (26).

To standardize and harmonize regulations, the European Union is working on a new regulation REACH (Regulation, Authorization and Restriction of Chemicals), which sets the strictest and most stringent requirements for tattoo inks and PMUs in the world to keep people safe. REACH will completely replace Resolution ResAP (2008) 1. Under REACH, the main aspects of consumer safety will be discussed: regulation, evaluation, authorization and restriction of chemicals. In this way, the harmonized classification of the specific substances of the tattoo ink components and their prohibition guarantee the absence of chemical hazards in the ink. However, whether the safety of the end product can be guaranteed under such guidelines remains unclear (27, 28).

This review shows that there are many and varied complications of tattoos. Perspective research is necessary to understand better the complications of getting a tattoo. Public information about complications should be crucial. It is currently unclear when and to what extent the complications with tattoos will be resolved through appropriate legal regulations (this especially applies to the presence of allergenic substances, following the rules of hygiene, but also avoiding toxic and carcinogenic substances in tattoo pigments).

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Patient satisfaction in the use of a topic system based on mix acids (peeling) and moisturizing and anti-ageing substances in combination with drink supplement intake.

Running head: Customer satisfaction: topic system and drink supplements.

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Abstract

The field of aesthetic medicine is always eager to new mini-invasive treatments. In this paper we present a customer satisfaction report of a topic treatment (peeling and other anti-aging substances) combined with supplement drinks. We used a mixture of acids (chemical peels) altogether with moisturizing and anti-ageing substances and supplement drink. Chemical peels are some of the most used tools in this aesthetic medicine. We used one peel based on trichloroacetic acid

(TCA) and alpha-hydroxy acids (AHAs), mandelic, lactic and malic acids. To enhance its effect and to achieve additional treatment, we included specific oral supplements to improve and balance the skin from the inside. There is little literature on the effects of supplements to treat skin, and even less in combination with other treatments. In addition, we reported the combined action between a chemical peel and the boosting effect of supplements to enhance the revitalizing effects from the inside out. We divided our female patients in two groups. The first group had the procedure of peeling performed. The second group was given the supplement intake, in addition to peeling. After that a satisfaction questionnaire was carried out.

Although both groups were happy with their results, a difference in satisfaction was seen in the group which combined both treatments. They stated that the positive effects on the skin were maintained for a longer period. This could give an indication that taking specific food supplements can be beneficial on improvement to overall skin care and perceived well-being.

Introduction

The skin is a crucial organ in regulating homeostasis. The skin acts as a barrier between external and internal environment, it has also a crucial role in the feeling of well-being and physical attractiveness. There are many components that determinate the appearance of the skin: the color, texture, elasticity, sebum production, scent, sweat (1).

During its lifespan, skin is exposed to factors that modify its characteristics. These factors can come from external environment, such as ultraviolet (UV) light irradiation, allergic or toxic substances, free radicals, mechanical damage; and internal factors such as ageing, changes in the activity of the immune system, inflammation, homeostatic disorders, genetic skin diseases (2, 3).

The functionality and beauty of the skin are conditioned by nutrition. This effect can be evidenced by the appearance of skin lesions in response to nutritional deficiencies. The intake of food supplements with vitamins, fatty acids and minerals improves the quality and appearance of the skin (4).

Drink supplements

The integrity of the skin deteriorates with the effects of chronological-ageing and photo-ageing, hormonal deficiencies, and environmental influences (5). Histologically, it is perceived as a decrease in the thickness of the dermal matrix. This also contributes to the formation of wrinkles (6) which is the most prominent recognized sign of skin aging (7, 8).

In recent years, the relationship between nutrition and skin health has been studied. The functionality of the skin and its relationship to a healthy skin appearance depends, to a large extent, on the incorporation of essential nutrients. Some clinical studies shown that it is possible to modulate or delay skin aging through the use of supplements. For example, vitamins C and E have been shown to be effective against UV rays in the prevention of sunburn (9).

It is a well-known practice to use hydrolyzed collagen as a dietary supplement to improve the synthesis of the extracellular matrix to improve joints, nails and hair (10). Oral administration of collagen peptides is especially effective against skin-aging and is proven in several research (11-14).

Chemical peeling and anti-aging complex

A chemical peel consists of the application of a substance on the skin in order to produce a desquamation of the stratum corneum, the normalization of the epidermis and induce a remodeling of the skin with which a wide variety of skin alterations are improved. It is widely used in the field of aesthetics (15). Depending on the active ingredients present in the peel, the mechanisms of action will be different.

Superficial peels act at the epidermal level without going beyond the basement membrane. They stimulate keratinocyte renewal starting from the basal layers of the epidermis and produce reactive inflammation in the upper dermis which stimulates collagenogenesis by activating fibroblasts that synthesize new collagen (types I and IV) and elastic fibers. They can act at the level of the dermis by directly inducing the synthesis of collagen of type I, collagen synthesis by fibroblasts or by indirect mechanisms, through the indirect mechanisms, through the action of keratinocyte-derived factors that secondary keratinocyte-derived factors which secondarily stimulate collagen production by dermal fibroblasts. (15-17).

The main indications for peel treatments are: melasma, ephelides, post-inflammatory hyperpigmentation, photo-aging, dark circles under the eyes, acne vulgaris, rosacea and scars, among others (16).

The type of acid used, the vehicle, the concentration, the number of layers and the contact time, among others, are factors that will determine the depth of action of the peel and its possible complications. In the case of glycolic acid, the pH and degree of neutralization will also be determining factors (18, 19). Some of the most used peels in the medical aesthetic sector are listed below.

Alpha-hydroxy acids (AHAs) are week organic acids which can be found naturally in many foods and milk sugars (20). The acids included in this category that are most widely used in the cosmetics sector are lactic acid, mandelic acid and malic acids, among others. These organic acids are commonly used in dermal practice for many years as superficial and medium depth peels to treat acne, scars, melasma, hyperpigmentation, roughness, age spots, and seborrhea (21). These can be used in all types of skins with minimal risk. Several studies with AHAs, demonstrated that can improve wrinkled skin by increasing the synthesis of glycosaminoglycans and thickening skin (22, 23).

Lactic acid is well known for lighting up the skin and its moisturizing effect (24). The mechanism of action is to decrease corneocyte cohesion by reducing the thickness of the stratum corneum (25). It has been reported a pilot study in which a 92% LA peeling improved superficial acne scarring, improved texture, pigmentation and improved the overall appearance of the treated

area (26).

Mandelic acid is a large alpha-hydroxy acid molecule, therefore a low penetrating acid, which makes it a safe peeling agent (24). Much of the literature highlights its capacity for improvement of acne scars, hyperpigmentation (27-29) and skin rejuvenation and lightening (27-30).

Malic acid is an organic acid derived from apples. As a member of the AHAs, helps to diminish hyperpigmentation derived from UV-B light, increases epidermal thickness and dermal glycosaminoglycan without inflammation (31) In vitro studies reveal cell and fibroblast proliferation in dose-dependent way (32).

Trichloroacetic acid (TCA), also known as trichloroethanoic acid, is an acetic acid composed by the chlorination of 3 hydrogenated ions. Induces a coagulative necrosis of proteins and cells. The main indications for TCA peeling are hyperpigmentation (specially melasma), photo-ageing, scars, dark circles under the eyes, among others (15). The depth of action depends on various factors, especially the number of layers applied or whether it is combined with substances that enhance or regulate skin penetration. The concentration also represents a key factor on the rate of skin penetration (33).

In this study, was used a chemical peeling that is combined with an anti-aging complex. This complex is composed of a mix of peptides and other revitalizing substances. The addition of these peptides includes tripeptides (Arg-Gly-Ser) and hexapeptides [(Gly-Pro-Glc2)], which are reported to be efficient in improving skin wrinkles (34). These, mixed with HA and panthenol sorbitol, gives to this type of substances the capacity to help to stimulate bioredensification, lifting action, hidratation and soothing, anti-wrinkle, among other actions (35).

While there are a wide variety of clinical studies on the use of peeling to improve skin condition, there are no reports that show the combined effect of drinks and peeling. The aim of this project is to evaluate the supplemental effect of drinks when added to peeling treatment.

Materials and methods

Patients

The study was performed on 20 healthy women, aged between 30 and 60 with a Fitzpatrick's phototypes from II to V. Throughout the entire protocol, patients were asked to continue they alimentary habits.

All volunteers presented benign skin lesion, dryness, wrinkling, mild acne, or mild hyperpigmentation. Prior entering the study, an informative lecture was provided to all participants and signed an informed consent. None of the patients presented acute skin diseases or other dermatological disorders or food allergies to the products. Another exclusion criterion was systemic medication with anti-inflammatory medicines or antibiotics and severe disorders like cancer or post-cancer. Between peels, the volunteers were asked to take care of their skin only with a hydrating cream and a 30 SPF sunscreen. Free samples were given to them during the procedure.

Protocol

The subjects were divided in two groups of ten women: Group DRINK- (PEELING) and Group DRINK+ (PEELING + DRINK). The patients underwent the peeling treatment one time and took a customer satisfaction survey 14 days after treatment. During this questionnaire, they subjectively evaluated in a scale from 1 to 5: general discomfort (itchiness, burning etc.), appreciation about the procedure, general facial sensation etc. (table I). For each volunteer before and after treatment photos have been taken.

PER PIETRO: INSERIRE TABLE I

Group B also had an intake of two diverse alimentary supplements collagen-based: SkinBOOSTER and SkinREPAIR. The choice of the two supplements was made based on skin status of each patient. We used FACE3 skinBOOSTER (CAROMED Italia), which is a drink containing substances to stimulate skin immune system and protect the skin, encourage the production of collagen, and regulate sebum and hydration levels. Other than being collagen based, it contains antioxidants such as vitamin A, C and E and sea buckthorn extract, known for being a strong antioxidant, for delaying cell ageing and stimulating regeneration (36). We used FACE3 skinREPAIR (CAROMED Italia) which is also collagen-based, helps to restore the skin and has calming and anti-inflammatory effect. One of its main active ingredients is aloe vera, which is well-known for its anti-inflammatory effects, antiviral and antitumor activity, wound healing, and antioxidant (37). The consumption of the beverage was daily basis and was arranged as follows: SkinBOOSTER for fourteen days before the peeling and SkinREPAIR for fourteen days after the peeling.

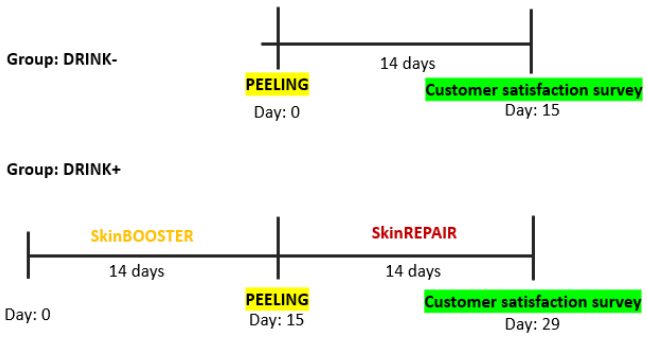

Fig. 1.*Outline of the treatment for both groups. Pictures were taken before and after the peeling.*

Peeling application

The peeling used in this protocol is composed by four types of acids: trichloroacetic acid, malic acid, lactic acid and mandelic acid, and a mix of anti-aging peptides.

A map was designed to follow for the application of the acids (Fig. 2). The face was divided into

sections. The operator was standing behind the patient's head and with the left hand treat the left part of the face. Instead for the right part of the face, used the right hand. The number of passes through the zones was identical (38). In this way, the procedure is standardized and all patients receive the same number of acid passes per zone.

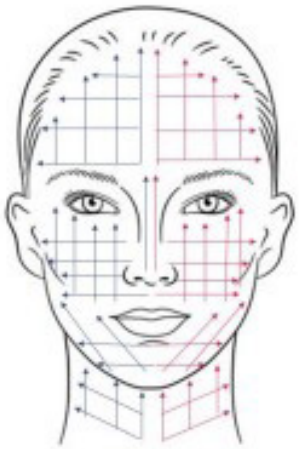

Fig. 2. *Peeling application scheme. The arrows represent the direction of the movement of the dermatologist when applying the peel. Blue arrows indicate right side of the face and red arrows left side.*

The product was applied to the face with an electric device (VIBE) which exerts a vibration of 50 Hz. This device increases the degree of penetration of the product into the skin as well as providing a certain degree of comfort to the patient. The application of peeling was carried out by the same professional, in all patients.

The protocol of application was performed as follows:
1. Clean of the face with facial disinfectant solution.
2. With the dropper, aspire the amount needed of product (2 ml for face, 1 ml for neck). 3. Application of the peel and spread out on the face using the vibrator device.
4. Leave the product for 2 to 5 minutes. The exposure time of the peel will depend on the Fitzpatrick phototype of each patient.
5. Rinse off the peel.
6. Application of hydrating cream and sunblock (30 SPF). (Fig. 3).

Fig. 3. *Peel application sequence: 1): After cleaning the face, aspire peeling and place drops; 2): spread the product homogeneously with the vibrator device, following the guidelines in figure 2; 3): Allow the compound to perform; 4): Rinse off.*

Results

The protocol was performed on 20 women of different ages divided into 2 groups. After the application of the peeling (Fig. 4), both groups perceived a range of effects. The main results subjectively stated by patients were: increased brightness, lifting effect, hydration feeling and a deep cleansing sensation. Some added the reduction of pore size and fine wrinkles. Between the groups, similar trends are seen, although group B shows a slight increase in the appreciation of effects achieved.

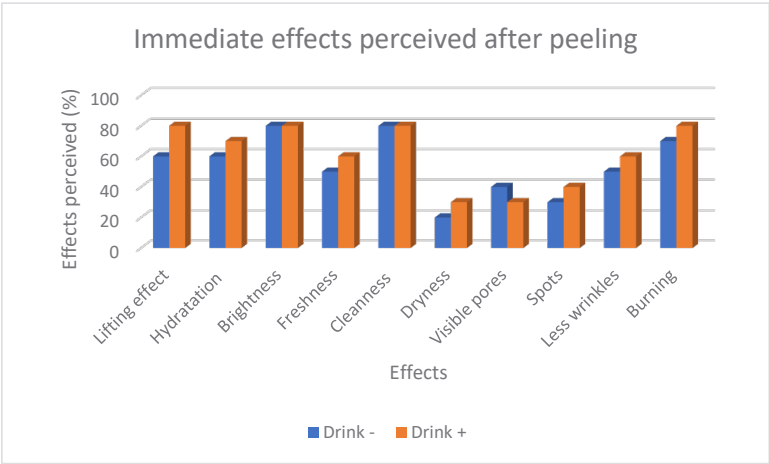

Fig. 4. *The graph represents the effects that were perceived by both groups (expressed in %) after the end of treatment with the topic system.*

Regarding the sensation of heat or burning (fig. 5), 70% of the whole sample reported that the sensation of discomfort was slight and moderate, no cases of intense discomfort were determined for this specific sample. Is important to mention, that the burning was felt only during the application of the topic system, once it was rinsed out, the feeling stopped. Many identified the forehead and around the nostrils as the most sensitive areas.

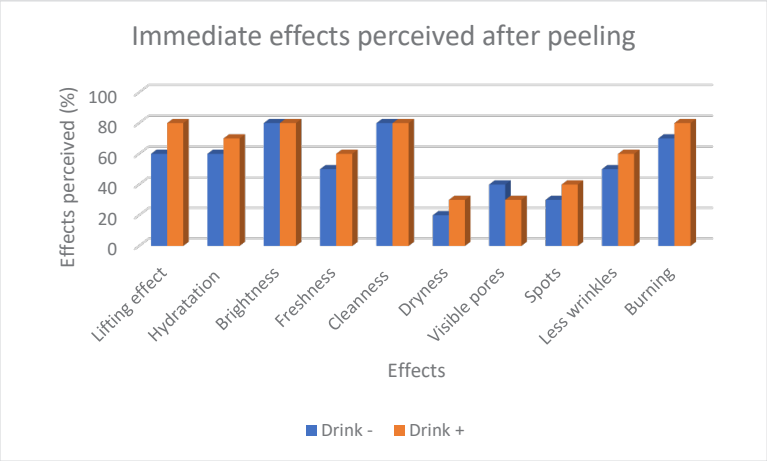

Fig. 5. *The graph represents the effects that were perceived by both groups (expressed in %) after the end of treatment with the topic system.*

Two weeks after the application of the topical system, the survey was carried out again (Fig. 6). As expected, both groups underwent exfoliation of the treated areas. Although the two groups still report different results, two weeks later, group B, had a clear higher tendency than group A to maintain the results over time. In both cases, a decrease in sebum levels was reported. Patients with more pronounced wrinkles noticed a decrease in fine wrinkles during this period.

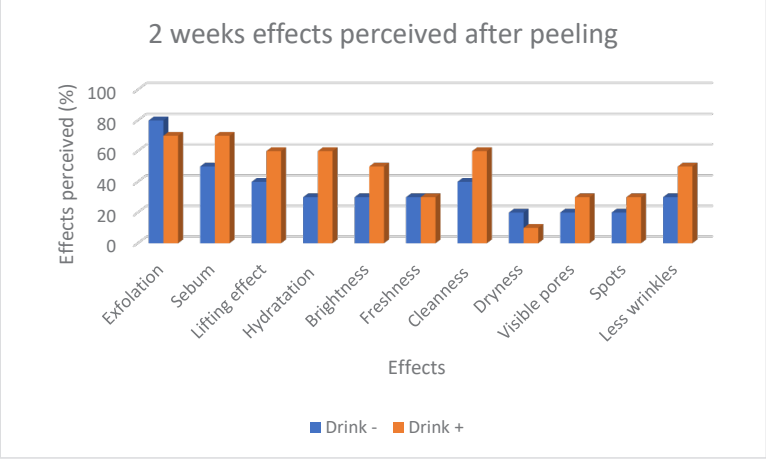

Fig. 6. *Representation of the effects perceived by the whole sample (in %) two weeks after the application of the peel.*

The subjects completed the satisfaction questionnaire and of the total sample 75% responded positively (Fig. 7). Looking in detail, almost the totality of group B was very satisfied with the results, while in group A, there were only more than 50% of positive votes.

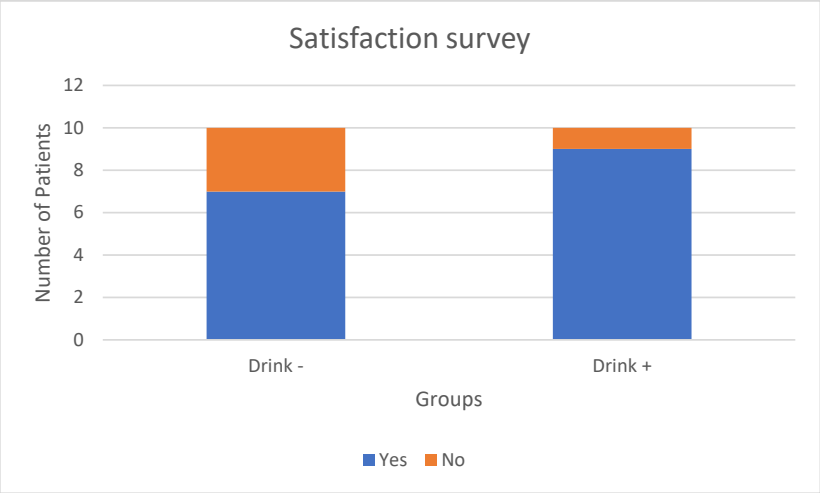

Fig. 7. *TThe graphic represents the subjective evaluation of degree of satisfaction in both groups.*

The entire sample appreciated the use of the vibe as an instrument to increase comfort and decrease the burning sensation. It should be noted that 11 of the 20 patients already had experienced this type of treatment before but found this application instrument innovative and practical.

Discussion

The study aimed to report the patient's satisfaction obtained from a new topic alternative (peeling and anti-aging complex). The main immediate results after topic system application were: increased radiance, lifting effect, feeling of deep cleansing among others. The resolution between the two groups was similar. However, there were differences after two weeks, group B sustained the results over time while for group A decreased considerably. This might be due to the positive effect of supplements. It is important to highlight that group B used 2 types of beverages, one pre- and one post-treatment. Although they are both collagen-based, they contain many substances that could continuously stimulate the quality of the skin from the inside out. This effect may be seen especially in patients with more pronounced chrono-aging who showed a decrease in fine wrinkles.

The positive effects of supplements (aloe vera, vitamin C, seabuckthorn) on the skin are widely reported (11-14), an improvement in Group B was expected. With the results obtained from this trial, it could be inferred that the effect of the supplements contributes to the improvement in skin quality. It would be interesting for further studies to evaluate if there is, and to what extent, there is a synergistic action between the use of a

chemical peel and the use of supplements rich in active ingredients.

The reported sensation of pain or burning is a subjective characteristic. However, during the application of the peel, it was attenuated by the vibrating device. Although 70% of the subjects stipulated that it generated a burning sensation, no case reported that the pain was intense or non-tolerable.

The article also reinforces the current literature that the application of the peeling technique that is simple, safe, and reproducible (15). Our results show that application of a peeling with TCA and AHA's acids have homogeneous results on the face and neck. It is a sophisticated, minimally invasive method of skin improvement that requires little equipment.

Skin appearance and physical attractiveness are highly interrelated components. It is not surprising that a major dermal improvement leads to an increase in the well-being. Patient satisfaction was high in the total sample, but higher in the group that took supplements. It is imperative to mention that this is the group that noticed that the results were maintained after 14 days. The high degree of satisfaction of the subjects, together with the results obtained and the effectiveness of the treatment, make the chemical peeling an excellent tool in the field of aesthetics. This type of peeling has the advantage that it can act on different ways and may obtain additional results when combined with other types of treatments such as the intake of supplement drinks.

This study has some limits. We would have had a better understanding of this treatment modality if we had enrolled a third group of patients, the drink-alone group. Another limit of this study is the fact that the choice of the two supplements was subjectively made based on skin status of each patient. Randomization of patients in each group would have been more helpful on understanding patient's satisfaction. In this study, randomization was not feasible due to the small number of patients. Short follow-up is another limit of our study. With the results obtained, we cannot anticipate whether the results of both groups would be comparable after a longer period, or not. Further studies with larger participants and longer follow-up are needed to better evaluate our treatment of choice.

Conclusion

This article shows that, when following a proper guideline, the mix of TCA and AHA's acids peeling, anti-aging complex and/or supplements intake, improves skin condition and quality in diverse skin types and, as patients described, enhances well-being. It is an effective procedure that can be easily combined with other cosmetic practices. It is important to offer patients less invasive treatment options with long-lasting results that might be achieved through a combination of procedures. Chemical peeling continues to be a safe and effective tool to improve various aesthetic conditions of the skin and with moderate financial investment. To increase the aesthetic result and avoid possible complications associated with peeling, it is essential to know the appropriate

indications, convey realistic expectations to the patient and master the application technique.

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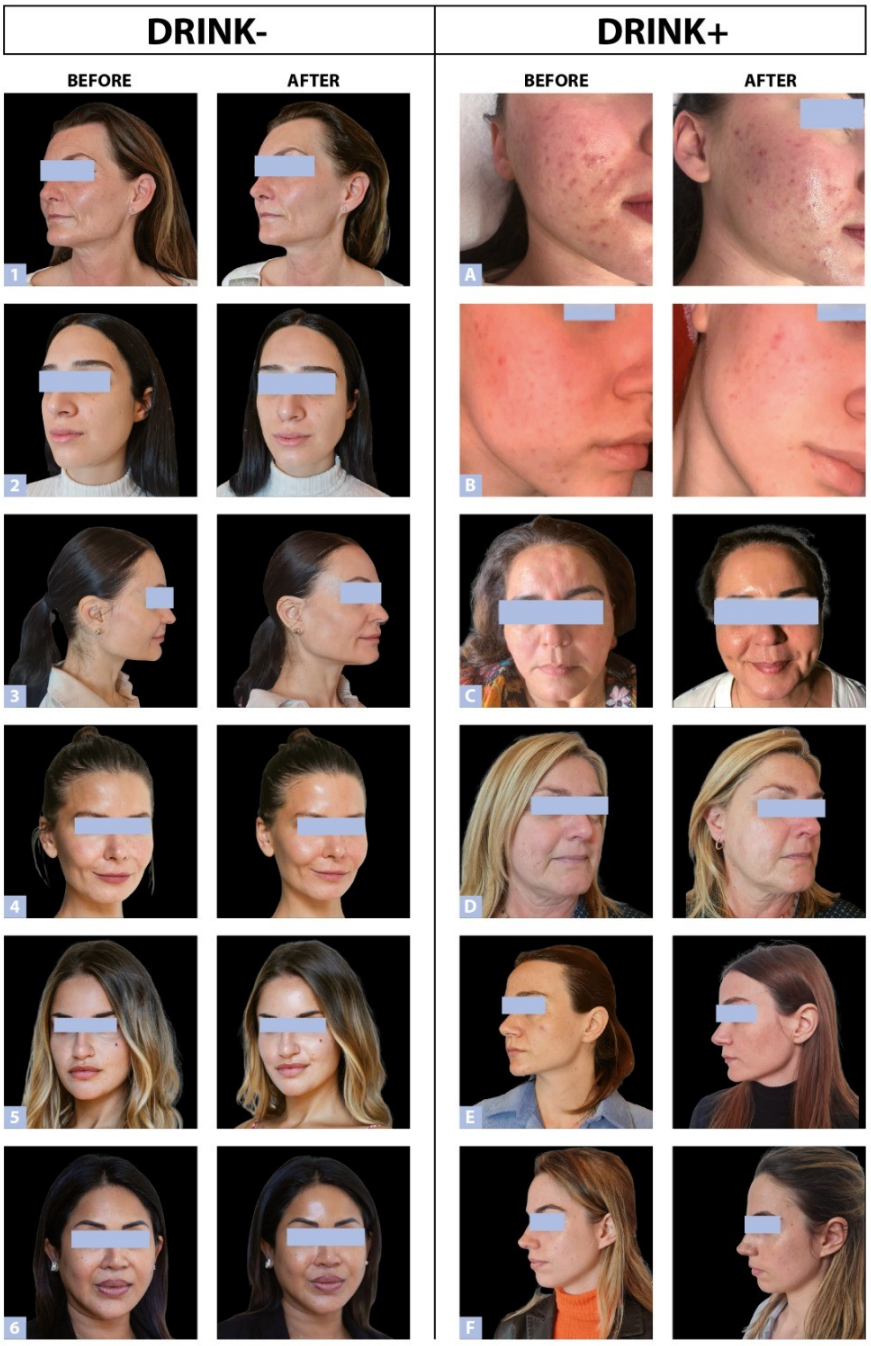

Annex Fig. 1. *Before and after photos from some of the patients from both groups. Patients signed a personal data sharing agreement and consented to the publication of their photos. The ages of the participants are detailed as follow:*

Group DRINK- (peeling and anti-age complex):
1) 55 years old
2) 30 years old
3) 33 years old
4) 34 years old
5) 31 years old
6) 37 years old

Group DRINK + (peeling and anti-age complex, and drink treatment)
A) 32 years old
B) 32 years old
C) 57 years old
D) 53 years old
E) 31 years old
F) 30 years old