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Comparing the efficacy of Myjet-assisted tranexamic acid and vitamin C in treating melasma: A split-face controlled trial

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Abstract

Background: Melasma is a benign and chronic hypermelanosis characterized by irregular light brown to dark brown patches of hyperpigmentation on the skin. Oral tranexamic acid (TA) or vitamin C (VC) supplementation has been one treatment choice. TA interferes with keratinocyte-melanocyte interactions, and VC functions by reducing melanin production resulting in skin rejuvenation and whitening.

Aim: The aim of the present study was to compare the efficacy and safety of Myjet assisted transdermal injection of TA vs VC in the treatment of melasma.

Methods: In this split-face controlled trial, 17 patients were randomized to receive eight weekly transdermal injections of TA or VC via Myjet either on the right or the left side of their face. MASI was measured from each side of the face at the baseline, at the middle, and at the end of treatment.

Results: A reduction in MASI was observed for TA and VC separately (*P* value < 0.05). The difference in efficacy between TA and VC group was not statistically significant (P value 0.05). Both treatments were well tolerated, with no serious adverse events reported.

Conclusion: Weekly TA or VC transdermal injections can be an effective treatment for melasma. Further studies are required to validate these findings.

KEYWORDS
meliasma, tranexamic acid, transdermal injection, vitamin C

1 | INTRODUCTION

Melasma is an acquired, benign, and chronic hypermelanosis characterized by irregular light brown to dark brown patches of hyperpigmentation on the skin. Its prevalence varies according to ethnic background, skin phototype, and intensity of sun exposure.[1] The precise incidence of melasma remains unknown but both males and females can be affected in nearly every racial subgroup. Melasma is more common in darker skin types, particularly Fitzpatrick skin types III and IV, and often lasts for many years after pregnancy.[2] Melasma appears as light brown to dark, muddy brown macules and patches on the face, especially the forehead, malar areas, and chin, and it may last for decades, impacting on quality of life in those affected patients, such as emotional well-being and social life.[3] Interestingly, the negative effect on quality of life with melasma such as depression was not correlated with the severity of melasma, suggesting that even a small amount of pigmentation may have a significant emotional role.[2] The pathogenesis of melasma is complex, and its treatment remains challenging. While sun exposure, pregnancy and oral contraceptives are thought to be risk factors, much remains to be elucidated.[4] Therapeutic innovation for melasma remains a goal for dermatologists worldwide.

There are many treatment options for melasma, including topical drugs, oral drugs, chemical peels, and laser and light treatments.[5]

Topical hydroquinone has been the gold standard for the treatment of melasma for a long time, but in the recent years, due to its demonstrated efficacy and rarity of side effects, oral tranexamic acid (TA) has begun to emerge as the possible new standard therapy for melasma treatment.[6] In the past, TA, a synthetic derivative of the amino acid lysine, was a kind of hemostatic drug. The exact mechanism of action of TA in the treatment of melasma is not completely understood. TA displays both anti-plasmin and anti-inflammatory properties.[7] Clinical trials have proven that oral TA is an effective and safe therapy for the treatment of melasma.[8] Clinical response was usually observed after 1-2 months.[8-10]

Vitamin C inhibits melanin formation and reduces oxidized melanin, and systemic VC supplementation has been an effective alternative for treatment of melasma.[11] Chemical peeling is an adjunctive treatment modality for melasma due to its ability to increase keratinocyte turnover, increase epidermal remodeling, and increase pigment metabolism.[5] Moreover, many laser energy sources (such as Q-switched Nd: YAG, IPL) have been used and laser therapy has been investigated to treat melasma with varying clinical efficacy.[12-14]

Myjet (Myjet, TavTech) is a new device for facial rejuvenation and promoting transdermal absorption of topical drugs.[15] The Myjet can be described as using a mixture of water and oxygen forced into a channel, which accelerates the droplets through a specific nozzle at approximately 200 m/sec speed, delivering a powerful flux of microdroplets into the skin.[15,16] It is a safe and painless medical device which can be used for transdermal drugs absorption, skin cleaning, and dermoepidermal hydration. Moreover, it has been applied to treat androgenetic alopecia, hyperhidrosis, and fine wrinkles in clinical practice.[16,17]

The aim of this original research was to compare the efficacy and safety of Myjet-assisted transdermal injection of TA vs VC in the treatment of melasma.

2 | MATERIALS AND METHODS

2.1 | Participants

This was a single-center, prospective, split-face, randomized, double-blind study comparing the efficacy of Myjet-assisted TA and VC in the treatment of melasma. Altogether, 17 patients (1 male and 16 females) with bilateral symmetric facial melasma treated at the Plastic Surgery Hospital, CAMS&PUMC, Beijing, China between December 2017 and August 2018 were enrolled; including thirteen patients with Fitzpatrick skin type III and four patients with Fitzpatrick skin type IV, all had a clinical diagnosis of melasma. Each patient was randomized to receive TA and VC transdermal injection by Myjet either on the right or the left side of their face. Exclusion criteria included underlying chronic or inflammatory systemic disease, photosensitivity, pregnancy, breastfeeding, chemical peeling, and laser treatment history in latest six months. This study was approved by the Ethics Committee of Plastic Surgery Hospital, Chinese Academy of Medical. All the participants provided informed consent.

2.2 | Materials and procedures

At baseline, medical history was taken for each patient including demographic data, history of sun exposure and pregnancy, duration of melasma. Wood's light examination was used to categorize melasma according to the depth of melanin pigment into epidermal, dermal, and mixed. By performing simple randomization through random number generation, treatment decisions were made about split-face treatment side.

Localized Myjet-assisted injection of TA (0.5 g:5 mL; Salvage pharmaceutical co) and VC (1 g:2.5 mL; Huarun shuanghe pharmaceutical co) were applied on one side of the face by a trained dermatologist for eight sessions at one-week intervals.

After cleansing the face with water and facial cleanser, the doctor used normal saline, assisted by Myjet (Myjet, TavTech), to clean the entire face three times. The distance between the handpiece and skin was 5, 3, and 1 cm each time, and the angle between the handpiece and skin was 45 degrees. Distilled water was then used twice to clean the residual saline at a 45 degrees angle and 1 cm distance. TA and VC were transdermally injected by Myjet on either the right or the left side of the face, respectively. The Myjet handpiece was held vertical to the skin at a distance of 0.5 cm. The dosages of both TA and VC for each side did not exceed 2 mL per week. The duration of treatment was two months, and during that time, patients were instructed to apply an SPF 50 plus sunscreen before daily activities.

2.3 | Clinical assessment

Evaluation of treatment efficacy was based on clinical observations and photographic evaluations. The assessment of patient response was based on the hemi-MASI score of the right and left side independently by two experienced dermatologists. Evaluation was done at the beginning of treatment, at the end of fourth week, and one week after the last treatment session.

$$\text{hemi - MASH} = 0.15\,(D + H)\,A\,(\text{forehead}) + 0.3\,(D + H)\,A\,(\text{malar}) + 0.05\,(D + H)\,A\,(\text{chin}).$$

where D is darkness, H is homogeneity, and A is area.

The darkness of melasma (D) was compared to the normal skin and graded on a scale of 0-4 as follows:

- 0 = normal skin color without evidence of hyperpigmentation;
- 1 = barely visible hyperpigmentation;
- 2 = mild hyperpigmentation;
- 3 = moderate hyperpigmentation;
- 4 = severe hyperpigmentation.

Homogeneity of hyperpigmentation (H) was also graded on a scale of 0-4:

- 0 = normal skin color without evidence of hyperpigmentation;
- 1 = specks of involvement;

TABLE 1 Patient demographic and baseline clinical information

Item	Number
Age (y) mean ± SD	39.47 ± 6.05
Gender	
Female	16
Male	1
Fitzpatrick skin type	
III	13
IV	4
Duration of melasma (y) mean ± SD	6.24 ± 3.97
Melasma type, number	
Epidermal	5
Dermal	6
Mixed	6
Trigger factors, number	
Pregnancy	3
Sun exposure	5
Others	6

- 2 = small patchy areas of involvement with a diameter of 1.5 cm and below;
- 3 = patches of involvement with a diameter of 2 cm and above;
- 4 = uniform skin involvement without any clear areas.

Area (A) was assigned for the percentage of involvement as follows:

- 0 = no involvement;
- 1 ≤ 10% involvement;
- 2 = 10%-29% involvement;
- 3 = 30%-49% involvement;
- 4 = 50%-69% involvement;
- 5 = 70%-89% involvement;
- 6 = 90%-100% involvement.

Standardized digital images taken with a digital camera (Cannon EOS 750D) and VISA pictures by Visa System (Canfield Scientific Inc) were taken at baseline, at the end of fourth week, and one week after the last session. Patients were also asked to report their degree of pain, discomfort, postinflammatory hyperpigmentation (PIH), and erythema on each side of their face throughout the study period.

Improvement in melasma was evaluated as follows: (a) Excellent: melasma area decreased by 90% or hyperpigmentation almost vanished; (b) Good: melasma area decreased by 60% or significant reduction of hyperpigmentation; (c) Fair: melasma area decreased by 30% or visible reduction of hyperpigmentation; and (d) Poor: melasma area decreased less than 30% or no visible reduction of hyperpigmentation.

After eight treatment sessions, patients were asked about their degree of satisfaction: highly satisfied, moderately satisfied, fairly satisfied or not satisfied.

TABLE 2 Changes in hemi-MASI after topical TA and VC application

	Hemi-MASI					
	Baseline		1st follow-up[a]		2nd follow-up[b]	
Patient	TA	VC	TA	VC	TA	VC
1	2.7	2.7	2.7	2.7	0.6	0.6
2	1.2	0.6	1.2	0.6	1.2	0.6
3	6.0	6.0	2.4	2.4	1.2	1.2
4	3.0	3.0	1.5	1.5	1.2	0.6
5	12.3	10.8	9.0	7.8	4.8	6.0
6	7.2	3.6	2.4	2.4	0.6	0.6
7	10.2	14.4	10.2	13.2	3.9	5.4
8	2.5	2.5	2.5	2.5	2.5	2.5
9	8.4	9.0	5.6	6.0	2.4	3.9
10	2.4	1.8	1.8	0.9	0.6	0.6
11	4.2	3.6	3.9	3.6	1.2	0.6
12	7.2	9.6	7.2	9.4	3.6	1.8
13	9.9	7.5	4.8	4.8	1.2	1.2
14	12.3	12.3	9.3	9.3	5.1	5.1
15	10.5	10.5	10.2	7.8	7.8	7.8
16	12.3	12.0	12.0	12.0	9.0	12.0
17	7.2	8.1	5.4	6.3	3.6	6.0

Abbreviations: TA, tranexamic acid, VC, vitamin C.
[a]1st follow-up: at the end of fourth week.
[b]2nd follow-up: 1 wk after the last session.

Adverse events, including erythema, scaling, erosion, itching, and burning, were recorded at each visit. Two months after the last session, the recurrence was also noted based on an increase of 20% or more in MASI scores.

2.4 | Statistical analysis

The SPSS17.0 software (SPSS) was used to analyze all data. An independent *t* test was used to compare baseline MASI scores. A paired-sample *t* test was used to compare MASI reductions from baseline at each treatment timepoint separately. Data were evaluated using statistical methods (mean, standard deviation, frequency, ratio, minimum and maximum). *P* value < .05 was considered statistically significant for analyses.

3 | RESULTS

Nineteen patients were initially enrolled, and seventeen patients completed the study after two had dropped out. The mean age of the study population was 39.47 ± 6.05 (ranged between 30 and 48 years of age). The demographic and baseline characteristics are shown in Table 1. Table 2 shows the changes in hemi-MASI after

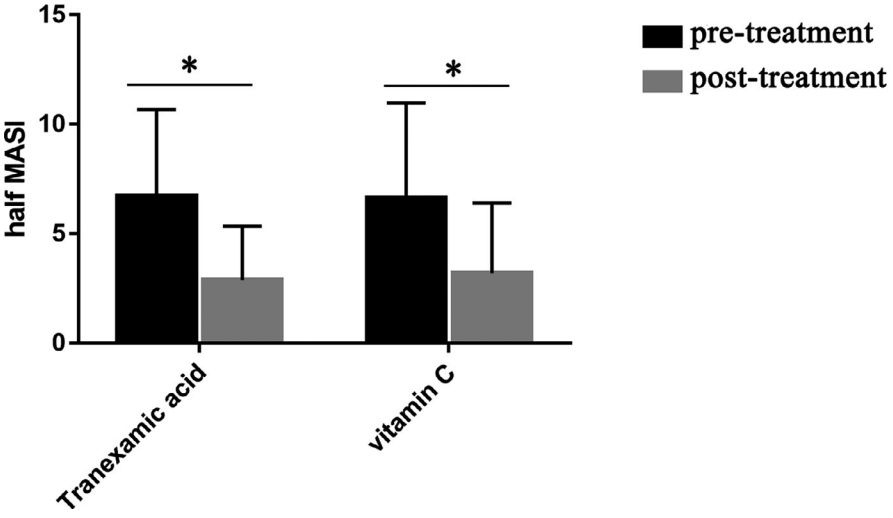

FIGURE 1 Change in hemi-MASI for tranexamic acid (TA) and vitamin C (VC) sides after treatment. *P < .05

topical TA and VC application. At baseline, there was no difference between the hemi-MASI on both sides (7.03 ± 3.84 vs 6.94 ± 4.28; P value = .950). The hemi-MASI mean value ± SD at baseline, end of 4th week, and one week after the last session were 7.03 ± 3.84, 5.42 ± 3.56, and 2.97 ± 2.53 for the TA side and 6.94 ± 4.28, 5.48 ± 3.91 and 3.32 ± 3.30 for the VC side, respectively. By considering the interventions separately, a significant reduction was observed for both sides (TA: 7.03 ± 3.84 vs 2.97 ± 2.53, P value = .001; VC: 6.94 ± 4.28 vs 3.32 ± 3.30, P value = .01; Figure 1, Table 3). Figure 2 illustrates the variation tendency of hemi-MASI during the treatment period. There was no significant difference between TA and VC treated sides regarding reduction in hemi-MASI (4.06 ± 2.62 vs 3.62 ± 2.79, P value = .638).

After two months of treatment, the results were as follows: excellent (0%, 0/17), good (70.6%, 12/17), fair (17.6%, 3/17), and poor (11.8%, 2/17). Thus, the total improvement rate for melasma was 70.6% among all subjects.

At the end of the treatment, 11 patients (64.7%) in the TA group and 10 patients (58.8%) in the VC group were at least satisfied with the final results. On the other hand, six patients (35.3%) in TA group and seven patients (41.2%) in VC group showed fair satisfaction or no satisfaction with the final results (Figure 3).

TABLE 3 Evaluation of treatment efficacy by hemi-MASI in TA and VC groups

	TA	VC	*P* value
Baseline (mean ± SD)	7.03 ± 3.84	6.94 ± 4.28	.950
1st follow-up (mean ± SD)	5.42 ± 3.56	5.48 ± 3.91	.960
2nd follow-up (mean ± SD)	2.97 ± 2.53	3.32 ± 3.30	.728
Baseline-2nd follow-up (mean ± SD)	4.06 ± 2.62	3.62 ± 2.79	.638

Abbreviations: TA, tranexamic acid, VC, vitamin C.
[a]1st follow-up: at the end of fourth week.
[b]2nd follow-up: 1 wk after the last treatment session.

Most patients showed clinical improvement with treatment (Figure 4 and Figure 5). Two patients reported mild erythema, and one patient felt stuffy during the injection process. These symptoms generally disappeared after approximately ten minutes. No other side effects were reported. At the two-month follow-up point, one case of recurrent melasma was observed; a 48-year-old housewife with Fitzpatrick skin type IV and no history of excessive sun exposure.

4 | DISCUSSION

Melasma is a chronic and common pigmentary disorder among Asian women, usually appearing as a symmetric facial condition characterized by irregular light brown to dark brown hyperpigmented patches. This condition is often psychologically distressing in affected patients. The predisposing factors for this disease are intricate, and its multifactorial pathogenesis remains to be elucidated.

Treatments for melasma include topical and oral drugs, chemical peels, as well as laser and light treatments. Treatment strategies are broken down into three levels: the first line is topical skin-depigmenting agents, or broad-spectrum sunscreens and camouflage, the second line is chemical peels, and the third line is the laser or light treatment.[18-20]

Tranexamic acid is a kind of hemostatic drug which can bind to lysine residues of plasminogen and prevents its conversion to plasmin. Furthermore, it can decrease the generation of arachidonic acid and α-melanocyte-stimulating hormone (α-MSH), resulting in reduction of pigment production in melanocyte.[21,22] A study by Kim et al[23] indicated that suppression of endothelin (ET)-1 could be one of the mechanisms of action of TA in melasma. Since, TA has been used more in recent years, there are many clinical trials to verify its effectiveness and safety. Lee et al[24] performed the first preliminary clinical trial on the efficacy of localized intradermal microinjection of TA in 2006, where they reported a significant decrease in the MASI at weeks 8 and 12 from the baseline. In 2012, Wu[8] and colleagues conducted a study which indicated that oral administration of TA was an effective

treatment for melasma and the initial reduction of pigmentation was usually observed after 1-2 months. Additionally, Najmolsadat et al[25] performed a randomized comparative study of topical tranexamic acid and hydroquinone in treatment of women with melasma; both groups showed improvement in the MASI score but there was no significant difference between the two groups. Nasrin et al[26] showed that monthly intradermal TA microinjection was an effective treatment for melasma. These studies show that oral administration, topical application, and microinjection of TA are effective. Notable adverse effects of oral TA include abdominal bloating, headache, tinnitus, menstrual irregularities, and, rarely, deep venous thrombosis (DVT).[21] DVT is a relatively serious adverse effect, and patients with risk of blood clots should not receive systemic TA.

Application of topical VC is very common in the daily care of melasma, other pigment disorders and skin whitening. VC is effective in reducing melanin formation by interacting with copper ions at the tyrosinase-active site that leads to inhibition of tyrosinase enzyme.[27] Several trials on the effect of VC on treating melasma have been reported. Lee et al[28] demonstrated significant improvement with ultrasonic application of VC compared to laser monotherapy. In 2017, Pelin et al[14] compared the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C and Q-switched- Nd:YAG laser alone, including sixteen patients with recalcitrant melasma, suggested that VC application with microneedling immediately after treatment with Q-switched Nd:YAG laser for four sessions at four-week intervals is a promising adjunctive method for the treatment of recalcitrant melasma. In another study, Ismail et al[29] reported thirty female patients with melasma received six sessions of microneedling with addition of topical VC every two weeks, all patients showed improvement at the end of the sessions.

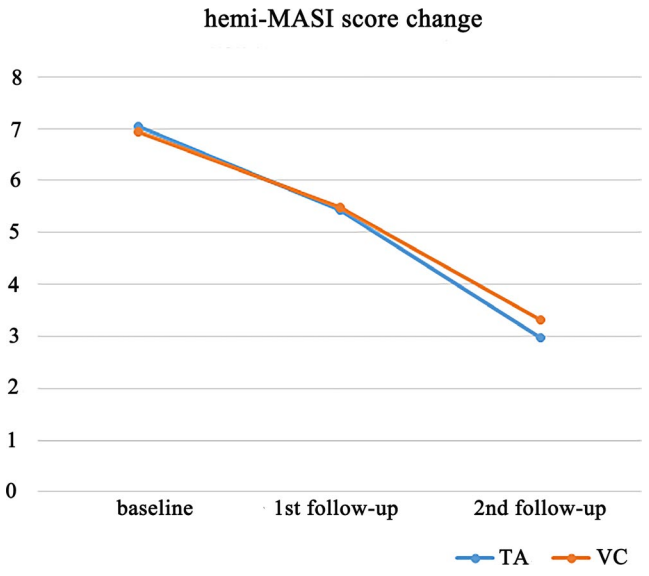

FIGURE 2 Variations in hemi-MASI during the treatment period

Myjet (Myjet, TavTech, Israel) is a device developed for facial rejuvenation and promoting transdermal absorption of topical drugs.[15] It consists of three parts: a handpiece, a control unit (on device body), and a footswitch. The basic principle of Myjet can be described as a mixture of water and oxygen forced into a channel, which accelerates the liquid through a nozzle at approximately 200 m/sec speed, delivering microdroplets of drug (diameter <3000 dalton) into the skin surface.[15,16]

Hemi-MASI was significantly decreased by transdermal injection of TA and VC after eight weeks, with no significant difference between the two drugs regarding the total reduction. Apparently, hemi-MASI in both sides decreased along with time, and the therapeutic effect of TA and VC occured after four weeks. Generally, the initial reduction of pigmentation in previous studies was usually observed after 1-2 months, but varied in different trials depending on the delivery method.[8,24,30] Our results are consistent with previous findings, and we concluded that Myjet-assisted TA or VC transdermal injection can assist pigment elimination. In this

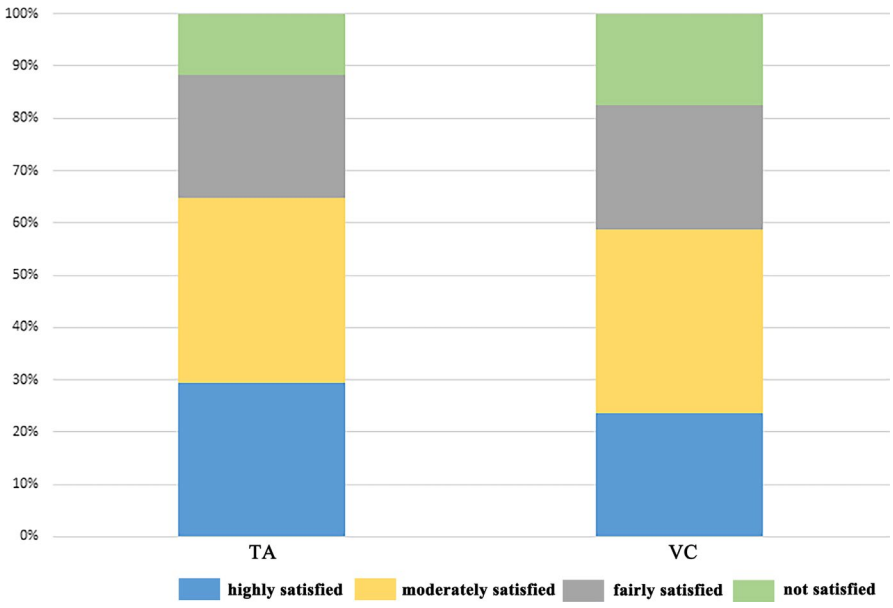

FIGURE 3 Patient satisfaction with tranexamic acid (TA) and vitamin C (VC) treatment

FIGURE 4 VISA image of a representative case showing clinical improvement by tranexamic acid (TA). A 47-year-old female (patient number 13 in Table 2) was treated with Myjet-assistant TA transdermal injection on the right side. The melasma on the right malar area showed gradual improvement (black arrows), and the brown spots in the lower panel showed a fading trend

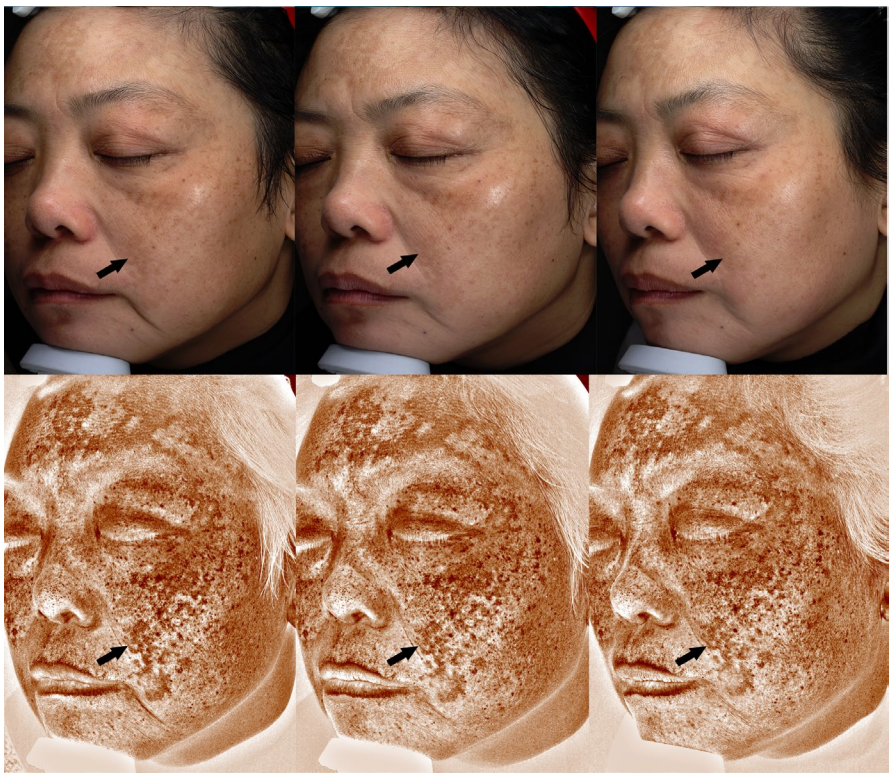

FIGURE 5 VISA image of a representative case showing clinical improvement by VC. A 47-year-old female (patient number 13 in Table 2) was treated with Myjet-assisted vitamin C transdermal injection on the left side. The melasma on the left malar area showed gradual improvement (black arrows)

split-face study, a statistically significant decrease in hemi-MASI was observed in the two study groups, indicating that weekly TA or VC transdermal injections may be a promising adjunctive treatment for melasma.

The total improvement rate in TA and VC groups was 76.4% and 64.7%, respectively. Two participants dropped out of this clinical trial, due to melasma aggravation after four weeks. We suspect that this may have been due to the powerful flux of microdroplet, which

stimulated the facial blood vessels. Three participants who received IPL treatments and one participant received picosecond laser in our study did not show clinical response, we doubt that the previous unsuitable laser/light parameters treatment stimulated melanocyte, and further study needs to be conducted. The adverse effects mainly included mild erythema and a stuffy feeling during the injection process, and they generally disappeared after treatment.

The advantages of our study include the split-face design, and the use of digital and VISA images for evaluation, since VISA has a higher light stability. Another advantage was the use of Myjet-assisted TA or VC in treating melasma, which may be a effective way for drug delivery.

There are several limitations in our study that should be noted. As observed in our study, the overall reduction in hemi-MASI was not different according to different drug. Due to the small sample size of the study group, there is a possibility of bias. Future studies with larger sample sizes may confirm our findings. Another limitation was the lack of blank control. Seasonal change is also a trigger factor when treating melasma, since sunlight increases during summer and might interfere with the treatment. Though participants in our study were instructed to apply an SPF 50 plus sunscreen during the treatment period, the other drawback of the study was the extended treatment period from winter to summer. The cure rate in the two groups was still limited, but may be a longer treatment duration is required to achieve greater improvement. Multiple factors may contribute to these differences including drug concentration, dosing and injection technique, severity, duration and type of melasma and so forth. Future studies are needed to resolve these issues.

5 | CONCLUSION

Our study revealed that Myjet-assisted TA or VC can be effective in treating melasma and may be more beneficial than systemic application in some patients with risk factors. However, further studies are required to address such point.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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A Novel Needleless Delivery System for Scalp Platelet-Rich Plasma: Pilot Study

The current delivery methods for scalp platelet-rich plasma (PRP) involve the use of needles to administer local anesthesia and/or PRP. Platelet-rich plasma delivered to the scalp without needles, using jet propulsion transdermal technology called JetPeel, would expand the noninvasive treatment options for patients with androgenic alopecia. We sought to prospectively evaluate the efficacy and usability of a needleless delivery mechanism for scalp PRP in patients with androgenic alopecia.

Methods

Men and women with androgenic alopecia underwent 3 sessions of needleless PRP, each 1 month apart for a total of 3 treatments. Platelet-rich plasma was collected and processed using the Emcyte 60 mL PurePRP II Kit and centrifuge. Briefly, 60 mL of venous blood were collected and underwent 2 spin cycles to first separate the red blood cells and then the platelets. The platelets were resuspended in 5 mL of plasma in preparation for delivery. Each patient received 5 mL of PRP using the needleless system.

The needleless system, manufactured by TavTech, is an Food and Drug Administration-approved technology that resurfaces the skin via a 2-phase stream that combines oxygen and any liquid into a jet that incorporates the liquids into the skin at subsonic speeds. Travelling at 600 ft/s, the jet of air exfoliates dead skin cells and can provide penetration of up to 1.4 mm, allowing for transdermal transfer. It has been used in aesthetic medicine for noninvasive skin treatments and in wound cleaning and debridement.[1]

Independent-samples *t*-tests were used to compare the photography results, calculated using a validated 15-point Jaeschke scale,[2] at the start of the study (T0) and at 6 months (T1). The lead author (G.L.) evaluated the patient in-person before and after treatments. The before and after photographs were then evaluated by G.L. and by 2 independent observers, and the Jaeschke scale was used by each observer to rate the change from before to after.

TABLE 1. Demographics and Analysis

	Frequency (*n*)	Percentage (%)	Average	Range	SD
Gender					
Female	5	36			
Male	9	64			
Age, yr			37	26–70	12
Photo scores (scale −7 to −7)			2.2	−0.7 to 5.3	1.8
Improved	12	86			
Interobserver reliability	0.85 (Kappa)				
Precondition severity					
Post photograph location					
Survey (scale 0–10)					
Comfortable during			10	10–10	0
Comfortable after			9.9	9–10	0.3
Pain during			0		
Pain after			0		
Satisfied			8.1	4–10	2.1
Recommended	13	93			

Intraclass correlation, 2-way mixed model (consistency, average measures), was used to calculate interrater reliability for all photograph raters (>0.6 = substantial

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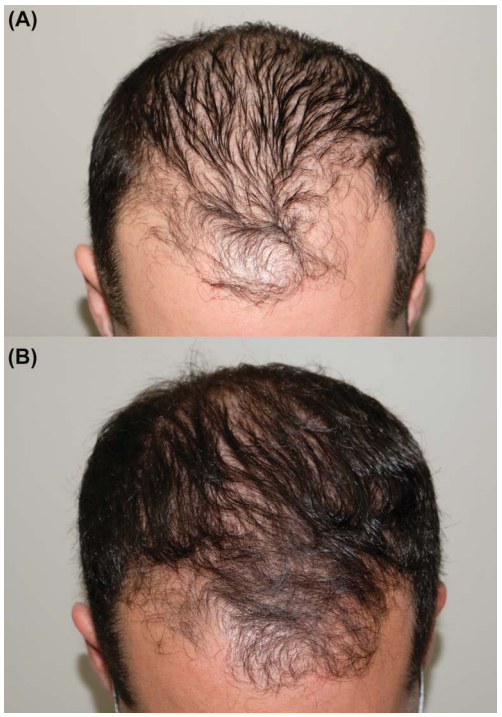

Figure 1. A 31-year-old man 6 months after 3 consecutive sessions of needleless scalp PRP. The top image (A) represents the pretreatment photographs and the bottom photograph (B) captures the final results after 6 months. Jaeschke scale average score 4.3. PRP, platelet-rich plasma.

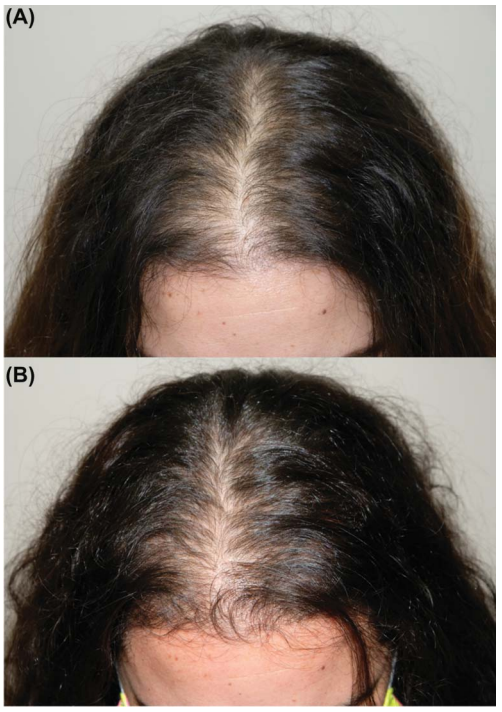

Figure 2. A 33-year-old woman 6 months after 3 consecutive sessions of needleless scalp PRP. The top image (A) represents the pretreatment photograph and the bottom photograph (B) captures the final results after 6 months. Jaeschke scale average score 3.0. PRP, platelet-rich plasma.

agreement). Statistical analysis was performed using SPSS Version 22.0 (SPSS, Chicago, IL).

Results

Fourteen patients with androgenic alopecia were enrolled and received the needleless scalp PRP treatment. The mean age was 37 years (range, 26–70 years). Sixty-four percent of patients were men. Eighty-six percent of patients showed improvement in overall hair restoration based on the Jaeschke scale (average score 2.2). There was an almost perfect interobserver agreement at 0.85 Kappa. On the questionnaire, 93% of patients stated that they would recommend this treatment to others, and the overall satisfaction score was 81%. Pain was reported as 0% during and after the treatments. Patients reported that their comfortability was 100% during the procedure and 99% in the 24 hours after treatment. There were no adverse events throughout the study. The whole-blood platelet count for the 6 randomly sampled patients was 259,000 μL (range, 197,000–340,000 μL).

Given that the T1 time point occurred during the time of the COVID-19 pandemic, several patients did not return to clinic for final photographs but instead chose to electronically send in their surveys and photographs. An analysis was done to see if ratings for pre/post photographs taken in the office versus those sent in by patients from home were different. In fact, the scores were higher when the after photographs were captured in the office (2.9 vs 0.78).

Gender and pretreatment severity of male pattern hair loss or Female pattern hair loss did not appear to impact photograph ratings. However, the more advanced the hair loss before treatment, the more the trend toward potential gain with PRP seemed to be. Additionally, the age of the patient appeared to impact photograph ratings, in that the scores were higher in the older group (>40 years old; 3.4 versus 1.5). Patient demographics and analysis results are summarized in Table 1. Representative male and female patients at 6 months after 3 consecutive sessions of needleless scalp PRP are shown in Figures 1 and 2.

Discussion

Our study found that needleless PRP was very well tolerated, with patients reporting no pain and excellent comfortability during and in the 24 hours after treatment. This in turn can improve patient compliance and adherence to PRP therapy. Based on our data for needleless PRP, 86% of patients improved according to expert review of photographs, the satisfaction rate was 81% and 93% of patients indicated that they would recommend the treatment series to others. For comparison, Schiavone and colleagues[2] reported a clinically important improvement of needled PRP for androgenic alopecia of 40% to 55%. Tawfik and colleagues[3] reported a satisfaction rate of 71%,

and Gkini and colleagues[4] incidentally also reported a satisfaction rate of 71%. Other studies have reported satisfaction rates ranging from 48% to 100%. For studies evaluating hair density and diameter, the average increase in those parameters across the literature ranges from 15% to 50%.

One limitation of our study is the relatively small number of patients. Another limitation is the lack of a control arm. Future research might compare needled with needleless PRP in a split head study to test the 2 delivery methods directly, as well as a saline placebo treatment arm to assess the baseline effect of the needleless jet mechanical stimulation of the scalp.

We have shown that needleless PRP for treating androgenic alopecia in men and women is a viable hair restoration option. Patients who fear needles and want a painless experience, but still yearn for the benefits of PRP, may improve with needleless PRP therapy.

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Transdermal delivery of a new hair growth promoting solution in patients with hair loss

Dong Hyun Ahn, Insoo Kang

ABSTRACT

Introduction: Male pattern alopecia or hair loss has been treated using various treatment approaches including hair transplantation, oral medications, sprays, mesotherapy and stem cell therapy. However, response rates to such treatments are variable. Case Series: In this case series, 6 Korean patients (5 males and 1 female) with hair loss were treated for three months with hair growth promoting Mr. Care Hair Vital Ampoule® or Mr. Care Hair Vital Ampoule plus® (Mr. Care Co., Seoul, South Korea) using the high-pressure transdermal delivery system JetPeel™ (TavTech Ltd., Yehud, Israel). Either Mr. Care Hair Vital Ampoule or Mr. Care Hair Vital Ampoule plus was sprayed on the affected area(s) of the scalp once a week for three months via the Jet Peel™ system. Conclusion: We found that all the patients had less hair loss and thicker hair after this treatment. Based on our findings, we believe that additional placebo-controlled studies are needed to evaluate the efficacy of our combination treatment.

Keywords: Hair loss, Hair growth promoting solution, Hair growth, Transdermal delivery

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INTRODUCTION

Hair loss is common in the general population [1–3]. Although it can occur due to various medical conditions and medications, the most common type of hair loss is male pattern hair loss. The number of scalp hairs that undergoes a cycle of falling out and growing in a lifetime is approximately 100,000–150,000 [1]. Typically, 50–60 hairs fall out of the scalp a day. Alopecia or hair loss is clinically suspected if >100 hairs fall out in a day [1, 3]. The most common form of androgenic alopecia in men is retraction of both sides of the frontal hairline showing M-shaped or vertex hair loss [3]. In most women, hair loss spreads throughout the scalp from the vertex area [3]. Possible causes of hair loss include functional deterioration of hair follicles and impaired local blood flow in the scalp secondary to scalp tension, malnutrition, stress, medications, genetic factors, chemicals and diseases [3].

In addition to cosmetic concerns, hair loss can affect mood and quality of life [3]. In fact, different approaches have been used to treat male pattern alopecia or hair loss [3], including hair transplantation [3], sprays [3, 4], oral medications [3, 5–7], mesotherapy [1, 8, 9] and stem cell therapy [2]. However, these treatments frequently involve injections [10], surgeries [11] and/or oral medications with variable response rates. Here, we report in 6 Korean patients (5 males and 1 female) with hair loss who were treated for 3 months with a combination of hair growth promoting Mr. Care Hair Vital Ampoule® or Mr. Care Hair Vital Ampoule plus® (Mr. Care Co., Seoul, South Korea) using the JetPeel™ [12] high-pressure transdermal delivery system (TavTech Ltd., Yehud, Israel). Our primary objective was to report the effect of a new hair growth promoting solution for hair loss.

CASE SERIES

The present study is a retrospective case series including six patients. All the participants provided written informed consent to participate in the study. Patient consent was obtained for treatment with the new hair growth promoting solution as well as the use of their clinical data. This method is repeatable and reproducible. The diagnosis of hair loss was made on physical examination. The SM-Q925S camera (Samsung Electronics Co. Ltd., Gyeonggi-do, Korea) and APM-AH-300 diagnostic system (phototrichogram) (Aram Huvis Co. Ltd., Gyeonggi-do, Korea) were used to evaluate the clinical features of hair loss type, scalp condition, hair density, scalp keratin, scalp blood vessel exposure, pore condition, hair thickness and hair shaft cuticle. We excluded patients if they had been treated for hair loss with topical and/or oral medications, including minoxidil, prostaglandin analogs, finasteride, dutasteride and anti-androgens; mesotherapy (including microneedle treatment) and intra-perifollicular injection therapy; laser/light-based therapy, including fractionated laser treatment and low-level light therapy; intra-perifollicular platelet-rich plasma preparation injection and hair transplantation in the previous six months. After obtaining written informed consent, we applied either Mr. Care Hair Vital Ampoule, (6 ml mixture of human stem cell culture media (2 ml), panthenol, niacinamide, biotin and zinc sulfate) or Mr. Care Hair Vital Ampoule plus (6 ml mixture of human stem cell culture media (3 ml), panthenol, niacinamide, biotin and zinc sulfate) to the frontal, mid and vertex areas of the scalps of three patients in group 1 (Mr. Care Hair Vital Ampoule, mean patient age, 52 years, range, 51–54 years) and 3 patients in group 2 (Mr. Care Hair Vital Ampoule plus, mean patient age, 40 years; range, 33–49 years) using the JetPeel system (microdroplet: 5~20 micron, pressure: 90 PSI, velocity: 200 m/s).

Both hair growth promoting agents were registered previously as hair care products (cosmetics) in Korea, and Mr. Care Hair Vital Ampoule plus was also FDA (Voluntary Cosmetic Registration Program [VCRP]) registered in the U.S. The transdermal delivery system JetPeel was already attempted transdelivery of other solutions; JetPeel-assisted topical minoxidil is effective during the treatment of androgenetic alopecia. Either Mr. Care Hair Vital Ampoule or Mr. Care Hair Vital Ampoule plus was sprayed on the affected area(s) of the scalp once a week for three months via the JetPeel system. Before each treatment, we cleaned the scalp with normal saline. Local anesthesia was not used in the procedures. The patients were advised to refrain from using other hair loss products during the treatment and follow-up periods. Digital images of the scalp and hair were captured at x1 and x60–x200 magnification using a computerized microscope to objectively evaluate the images at baseline and at one week after the final treatment. The Aram Viewer (Aram Huvis) computerized software was used to capture the digital images. The camera was positioned at the baldest area (usually the vertex area) of the scalp. Next, relative values for hair counts and thickness were measured. The patients were asked about any side effects associated with treatment, including scalp redness, edema, crusting, hair loss, allergic reaction, etc. The patients in both groups demonstrated considerable improvement in both hair counts and hair thickness compared to baseline values at one week after the final treatment session. The treatment session took ≤20 min. No patient in either group reported pain during the treatment. No other possible side effects, including infection, itching, allergic reaction and progression of hair loss, were reported by the six patients.

Representative cases of treatment groups 1 and 2 are shown below. Figure 1 presents changes in hair growth as measured by gross and microscopic hair examinations in a 54-year-old male patient who received 6 cc (1 ampule) of Mr. Care Hair Vital Ampoule weekly for three months using the JetPeel transdermal delivery system (group 1). Another case with vertex alopecia responded to the same treatment, resulting in hair growth (Figure 2). Interestingly, the treatment also promoted hair growth in a male patient with alopecia areata (Figure 3). We noticed similar improvements in patients in group 2, including a patient with failed hair transplantation, who received 6 cc (1 ampule) of Mr. Care Hair Vital Ampoule plus weekly for three months using the same transdermal delivery system. For example, a 33-year-old female patient with vertex alopecia was treated using the protocol for group 2. The treatment resulted in substantial hair growth (Figure 4). In addition, a 49-year-old male patient who previously received two sessions of hair transplantation underwent our weekly treatment for three months with Mr. Care Hair Vital Ampoule plus. He exhibited hair growth in the vertex as shown by gross and microscopic hair exams (Figure 5), suggesting that our treatment might have benefit to patients who have previously failed hair transplantation. Overall, the responses we noted in our cases support the role of Mr. Care Hair Vital Ampoule and Mr. Care Hair Vital Ampoule plus in improving different types of alopecia including male pattern, female pattern, alopecia areata, and hair that has failed hair transplantation.

DISCUSSION

Currently, the most commonly utilized method for treating alopecia is hair transplantation surgery where the patient's own hair is transplanted on to the scalp. In addition, drug treatment with minoxidil and propecia is prescribed regularly. Minoxidil dilates the blood vessels to increase the nutrient supply to hair follicles and has a potassium channel opening effect to induce hair growth [4], and propecia has a dihydrotestosterone (DHT) formation inhibitor effect to induce hair growth [6, 7]. Recently, gene therapy performed by a method of delivering alopecia-associated genes to the follicles

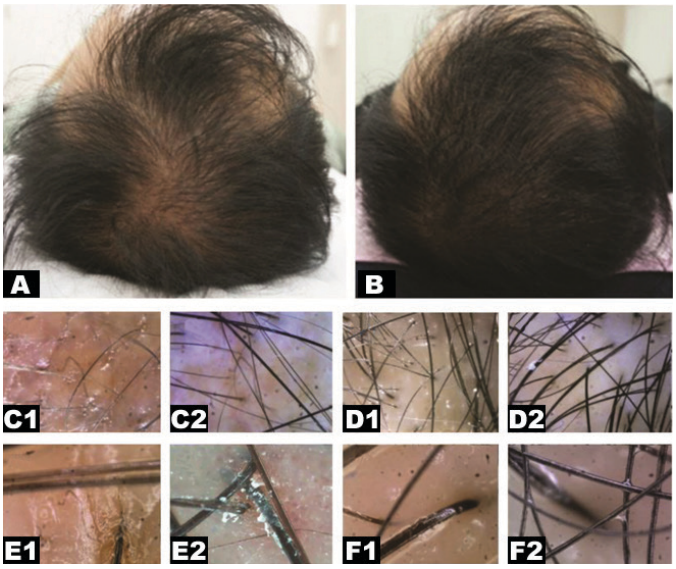

Figure 1: Picture A was taken before treatment and B was taken after 3 months of treatment (original magnification x1 [above]). Pictures C1, C2, D1, D2, E1, E2, F1, and F2 were taken with a hair analyzer, APM-AH-300 diagnostic system (phototrichogram) at the vertex. Pictures C1 and C2 and E1 and E2 were taken before treatment and D1 and D2 and F1 and F2 were taken 1 week after the last treatment (original magnification x60 [C1, C2, D1, D2], x200 [E1, E2, F1, F2].

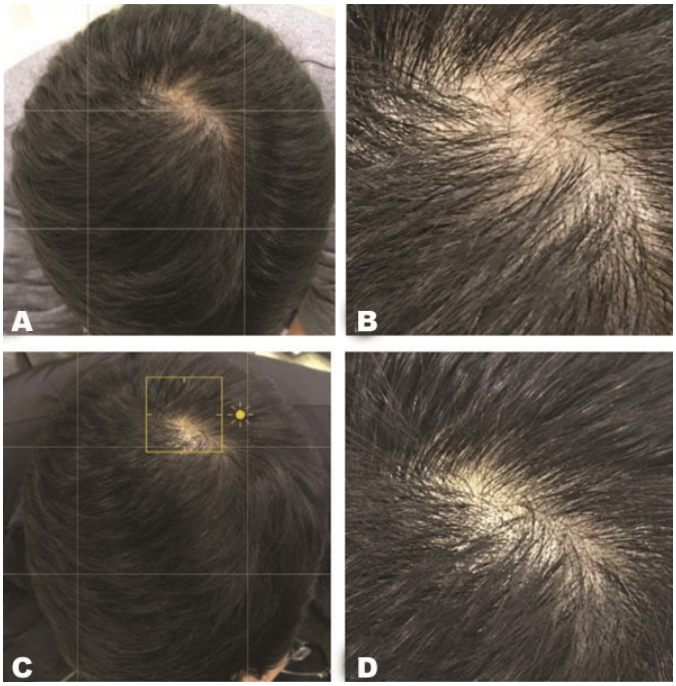

Figure 2: Pictures A and B were taken before treatment and C and D were taken 1 week after the last treatment of 51-year-old man who was treated once a week for three months by spraying his scalp with 6 cc of Mr. Care Hair Vital Ampoule via the JetPeel system (group 1).

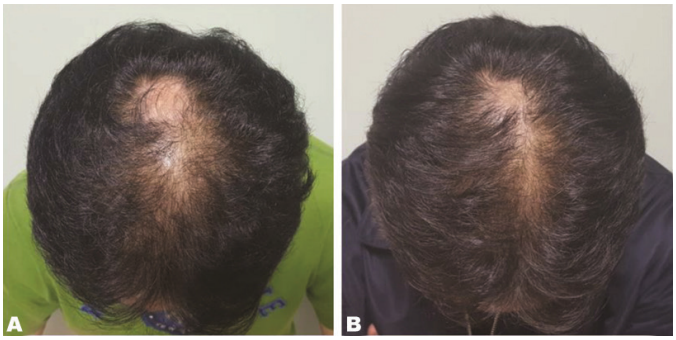

Figure 3: Picture A was taken before treatment and B was taken three months after the last treatment (original magnification x1) of 51-year-old man who had hair loss including alopecia areata and was treated once a week for three months by spraying his scalp with 6 cc of Mr. Care Hair Vital Ampoule using the JetPeel system (group 1).

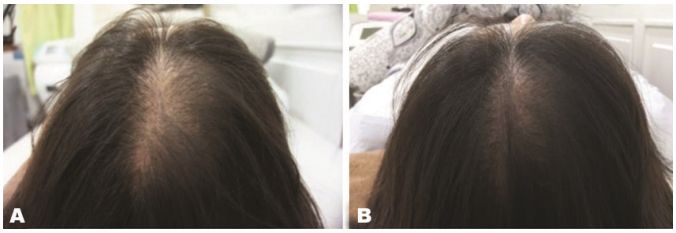

Figure 4: Picture A was taken before treatment and B was taken one week after the last treatment (original magnification x1) of 33-year-old woman who had hair loss around the vertex and was treated once a week for three months by spraying her scalp with 6 cc of Mr. Care Hair Vital Ampoule plus using the JetPeel system (group 2).

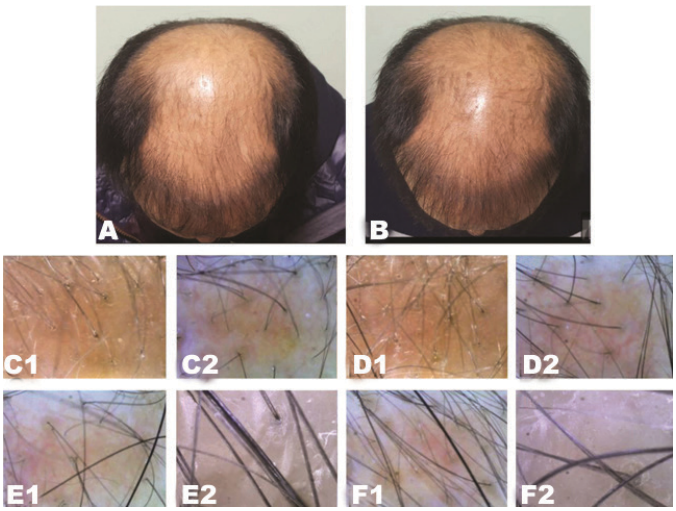

Figure 5: Picture A was taken before treatment and B was taken one week after the last treatment (original magnification x1) (above) of 49-year-old man who had two previous hair transplants and progressive hair loss. He was treated once a week for three months by spraying his scalp with 6cc of Mr. Care Hair Vital Ampoule plus using the JetPeel system (group 2). Pictures C1, C2, D1, D2, E1, E2, F1, and F2 were taken with a hair analyzer, APM-AH-300 diagnostic system (phototrichogram) at the top of the vertex. Pictures C1 and C2 and E1 and E2 were taken before treatment and D1 and D2 and F1 and F2 were taken one week after the last treatment (original magnification x60 (C1, C2, D1, D2), x200 (E1, E2, F1, F2).

or inhibiting gene expression has been developed, but therapeutic efficacy and safety are uncertain, and the cost of treatment is high, as it is extremely complicated clinically to apply gene therapy [13]. Moreover, a method using stem cells has recently been introduced [14]. Currently, in most cases the stem cell method of treating alopecia is performed by directly injecting the stem cells into an alopecia or hair less site to induce differentiation of follicular cells. However, this method has disadvantages in that treatment is impossible without the use of autologous stem cells, a therapeutic effect is not continuously maintained and it is not time or cost effective [14]. To solve these problems, a method using a culture solution (instead of the stem cells) [15–18], which is produced at the time of stem cell culturing has been performed; however, the efficiency of this method for commercial production is not known yet. Fukuoka et al. [18] demonstrated that treatment with adipose-derived stromal vascular cell-conditioned media effectively activated hair regeneration; this media is rich in growth factors such as vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor and insulin-like growth factor 1. The injected cells might release growth factors, thus, promoting vascularization, encouraging the formation of new capillaries, increasing hair production and improving the blood supply to the scalp [19].

This provides an ideal environment for hair follicles to grow new, denser and healthy hairs [19]. Moreover, a study on female pattern hair loss treated with adipose-derived stromal vascular cell-conditioned media exhibited increased hair density and thickness [20]. Based on these articles, we aimed to contribute to hairloss management by utilizing a new hair growth promoting solution synthesized with various growth factors from human stem cell-conditioned media and biotin [21], zinc [21], niacinamide [22, 23] and panthenol [23]. Biotin is a coenzyme for carboxylase enzymes that assist various metabolic reactions involved in fatty acid synthesis, branched-chain amino acid catabolism, and gluconeogenesis, which is important for maintenance of healthy skin and hair [24]. Panthenol has hygroscopic properties and a moisture-retaining capability [25]. Hyperthyroidism is a common and well recognized cause of diffuse hair loss. Zinc and other trace elements including copper and selenium are required for the synthesis of thyroid hormones [26].

The objective of our study is to present a new hair growth promoting solution, which is composed of proper formation of multiple ingredients helpful for hair growth promotion, can be delivered to hair follicles and be useful for hair loss patients. Even if new hair growth promoting solution is applied to the scalp, it may slow down and manage the progression of hair loss. As hair loss varies depending on the patient's sex, age, cause, and degree of progression, it is considered to serve as a complementary treatment even if this treatment cannot have an absolute effect on all hair loss patients. However, it might serve as an assistive treatment for alopecia. Our study has limitations such as small sample size and no control cases. Additional studies addressing these points are warranted.

CONCLUSION

Further investigation is required to evaluate the effects of this new hair growth promoting solution for hair loss, and placebo-controlled studies are needed to evaluate the efficacy of a new hair growth promoting solution.

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Dong Hyun Ahn – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Insoo Kang – Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest
DH Ahn has a pending patent application for solution "Hair Growth promoting Composition" in USA. I. Kang is an advisor of Mr. Care Co. and DH Ahn is the director of Mr. Care Co.

Data Availability
All relevant data are within the paper and its Supporting Information files.

125047, Moscow

The Cosmetology Research and Science Center

independent non-profit organization

08-44-47

Т.В.Маяцкая

21.11.05

PROTOCOL No. 2-05

Of

Clinical trials of the JET PEEL medical system for Dermatology and Cosmetology manufactured by Tav Tech ltd. Israel

Moscow
2005

1. The clinical trials of the JET PEEL medical system manufactured by TavTech Ltd. (Israel) for application in Dermatology and Beauty Therapy were undertaken by the independent non-profit organization The Cosmetology Research and Science Center in the period of September 14, 2995 through November 21, 2005. The trial and study were performed using the demonstration prototype referred to as DEMO.

2.The objective of the study was to evaluate possibilities of use of the said system in the medical dermatological and beauty practice in the Russian Federation.

3. To complete the study the following was provided:
a. the completely furnished working prototype of the JET PEEL system model JTP-222 (DEMO), manufactured by TavTech, one unit;
b. a set of sterile attachments;
c. saline solution for infusions supplied in sterile plastic bags;
d. operation manual.

4.Technical properties and general description of the principles of the system's operation:

Gas source:	compressed oxygen tank
Gas pressure:	100 PSI (6.8 atmospheres).

The device's operation is based on the use of the energy of the jet bi-phase flow (mixture of saline solution and oxygen) with the purpose of desquamation of epidermal and dermal skin layers.

The action mechanism is based on the exfoliating effect resulting from the treatment of skin with the jet of high energy spay that is formed by mixing sterile saline solution and gas (oxygen) in the special container (sterile attachment). The source for the compressed oxygen connected to the main control unit, supplies gas with the pressure of 6.8 atmospheres, which pulls out the saline solution out of its container. The liquid portion of the spray exits the nozzle attachment in the form of the 5-200 nm diameter drops, going at the speed of 200 m/sec, which is ensured by the 3-spray nozzle attachment system.

Report

Objectives of the study:
1. To study the safety of using the said system in the field of clinical beauty therapy – evaluation of the irritation and allergy-inducing effect from physical and chemical properties of the system during peeling procedures.
2. To evaluate a degree of efficiency in using the device on physical defects: hyperkeratosis, hyperpigmentation, wrinkles as indicated:
   2.1. skin profile (depth and width of wrinkles);
   2.2. degree of hyperkeratosis;

2.3. Degree of hyperpigmentation of skin before and after the series of treatment using the studied device.

The study also used the Skin Sys skin diagnostics system (USA).

Description of the group of volunteers

The study was performed on 25 (female) patients aged 29 through 60 who demonstrated signs of aging skin – hyperkeratosis, hyperpigmentation, mimic and age-related face and neck wrinkles with various degree of prominence. All volunteers were familiarized with the objective of the performed study and they all provided voluntary consent to receive the series of peeling treatment using the JET PEEL system. The basic profiling survey of the patients with the study of their medical history, corresponding diseases, and allergy status didn't establish any contra-indications with regard to the performed peeling and physical therapy procedures.

Method of application

The peeling session was performed on a weekly basis. The average duration of the session lasted from 15 to 20 minutes depending on individual properties of the patient's skin and its sensitivity. Following the makeup removal and treatment with the antiseptic solution (without preliminary local anesthesia), the skin of the patient's face and neck was subjected to the effect of the jet stream of the gas and liquid mix supplied through the sterile one-time use nozzle attachment under the 50-70C towards the skin surface. The distance between the area of treatment and the attachment varied from 0.5 to 1.5 cm. The treatment of the skin of face and neck was performed following traditional massage lines, in smooth slow movements with a longer and more forced action on the problem area (wrinkles, hyperpigmentation spots) resulting in punctate hemorrhage (so called "blood dew"). The skin in the periorbital area wasn't treated. Pantenol-spray was applied to the skin of face and neck after the treatment on the skin was completed.

Results of the study

1. The following parameters were considered as parameters of safety: absence of allergy-inducing effect and presence of a slight irritation effect from physical and chemical factors of the system (in accordance with the stated objectives of the system's action).

1.1. The clinical evaluation of the irritation effect based on degree of inflammatory erythema and its prominence following the procedure session.

Table 1

Degree of the erythema prominence in grades*, average meaning in the group of volunteers			
After the procedure	30 minutes later	1 hour later	3 hours later
1.8	1.2	0.6	0.26

- Grade evaluation of the erythema degree

Very prominent	4
Prominent	3
Moderate	2
Slight	1
None present	0

Conclusion: After the peeling session, an irritation effect was confirmed, which was demonstrated through a severely or a moderately expressed erythema that was maintained for no longer than three hours.

1.2. No patient demonstrated any allergy-induced response.

2. The following parameters were considered as parameters of the treatment effectiveness:

2.1. a. Clinical:

In the course of the treatment session – change of the skin color of the treated read towards a paler shade as a result of the reflector spasm of smaller capillaries, the focal areas of punctate hemorrhage ("blood dew") after the treatment – moderate degree hyperemia as well as slight swelling of skin;

b. Subjective: In the course of the treatment session – the sensation of "cold and skin being prickly", after the treatment – the sensation of "burning" that lasts no more than one or two hours.

2.2. The evaluation of the beauty correction with the help of the Skin Sys unit based on the following parameters:

a. Degree of exfoliation (hyperkeratosis)

Table 2

Degree of skin exfoliation, in grades		Average data on the degree of hyperkeratosis in the group of volunteers	
		Source level	After the series of treatment sessions (2 months later)
Very high High Average Low Very low	4 3 2 1 0	1.4	0.26
Assessment of the keratolytic (exfoliating) effect in %		**100**	**-81**

Conclusion: The course treatment with the use of the JET PEEL system in order to specify the keratolytic (exfoliating) effect demonstrated expressed exfoliation of the horny layer cells which was confirmed by the significant average decrease in the skin hyperkeratosis by 81% which proved positively high effectiveness of treatment sessions on the keratinization process as a whole.

b. Degree of hyperpigmentation.

In order to evaluate the de-pigmentation effect of the treatment with the use of the JET PEEL system, the areas of study included the parts of face with diffuse (generalized) hyperpigmentation as well as hyperpigmentation focal points with localized dyschromia (the current study didn't take into account causes of pigmentation).

Table 3

Degree of the pigmentation prominence, average statistical indicators in the group of volunteers	Source level	After the series of treatment sessions (2 months later)
Standard conv. units	3.93	1.26
%	100	**-67.9**

Conclusion: The application of the JET PEEL system (multiple – as a course or one or two episodes with the engagement of the skin's papillary level) demonstrated expressed effect of the de-pigmentation action which resulted in the average 68% decrease of the hyperpigmentation of the skin of face.

c. Skin profile (depth and width of wrinkles).

Table 4.

Dynamics of depth and width of wrinkles, average statistical indicators in the group of volunteers	Source level	After the series of treatment sessions (2 months later)
Standard conv. units	2.8	1.46
%	100	**-47.85**

Conclusion: After completing the series of peeling sessions using the JET PEEL system, the patients demonstrated expressed correction of mimic and age-related wrinkles, as well as an average 48% decrease in depth and width of wrinkles.

Conclusion:

The use of the JET PEEL medical system manufactured by TavTech Ltd (Israel) for application in Dermatology and Beauty Therapy according to its operator's manual proves its safety and efficiency.

The irritation effect in the form of a slight or a moderately expressed erythema, a slight swelling as well as of a burning sensation and "prickly" skin of various intensity

depending on the skin type, its condition, is adjusted automatically. Typically, it is corrected within 3 hours, and cannot be considered a negative impact of the use of the said system.

The application of the system didn't result in any allergy-induced response in any of the patients.

The results of the correction of beauty defects—hyperkeratosis, local and diffuse hyperpigmentation, wrinkles of various degrees of prominence—as established during the clinical trials and study, prove the high effectiveness of the said method.

During the course of treatment sessions, skin demonstrated adaptation towards active impact of physical and chemical factors of the system that were demonstrated in the less expressed irritation effect with every treatment session.

The active physiological regeneration of tissues was noted during the analysis of skin of the volunteers that were subjected to the peeling sessions that engaged skin's papillary layer.

Visual control and functional methods of diagnosis of skin demonstrated the need to combine the peeling procedures with the use of the JET PEEL system with intensive sessions that are directed at the restored aqua-lipid layer of epidermis.

The system is fairly physiologic, simple to use, and the saline solution that is ended for the treatment is economically affordable.

With certain skills, this system would allow the professional to control the intensity of the effect on skin, i.e. depth of peeling, in other words:

a. allowing for the individual regime of treatment courses for every patient with the obtained desired results;
b. using the JET PEEL system to solve a wide range of beauty therapy problems.

Exponents:

N.V. Sudarikova, PhD

Responsible: **M.V. Tursunova** MD, PhD. Dermatologist

Instrumental Cosmetology

COSMETIC TECHNOLOGIES: GAS-LIQUID PEELING

By:
Mergen Antonov,
Dermatocosmetologist
Vera Kiryanova,
M.D., Professor
Marina Kiyashko,
M.D., Physiotherapist

Tsiolkovsky – Rocket – Jet engine. We have all known about it since childhood. But just a few of us know that a flying vehicle leaves deep erosions on the ground after its launch. This "headache" has become a basis of… a new medical technology.

Skin treatment by gas-liquid jet, as has been proposed by Israeli experts, belongs to mechanical polish techniques. It was developed on the base of superficial hydro-oxygen treatment of trophic ulcers, which is widely used in medical practice. This method calls for the use of unique abrasive properties of a high-speed two-phase stream of fine-dispersed liquid and gas. When microdrops are contacting the skin surface, it develops microerosions. To better understand this technology, we will first consider its physical and technical aspects.

Technique

How is a liquid-gas jet formed? A standard medical device has a distribution block to ensure 6.8 atm working pressure of a gas and special-purpose headpieces. The device is connected to a gas tank and sterile solution container (normally saline solution).

Compressed gas (oxygen or carbon dioxide) speeds up to supersonic velocity by means of a tiny nozzle which is built in the headpiece. While moving from the source to the headpiece, the gas jet sucks in the liquid from a separate tank, like a water-jet pump. This liquid is fed to the acceleration zone through microneedles, which are installed along the axis of the micronozzle. Drops are detached from the needle by ultrasonic gas jet and speed up to 200 m/sec. The drop diameter is 1-5 μm, their inside pressure reaches 1,000 atm due to capillary force. While possessing a huge kinetic energy, these drops act as solids when contacting the skin and exert a marked abrasive effect (see Fig. 1).

Skin develops a dimple, with erosion formed in the bottom due to scarifying and layer-by-layer removal of epidermal cells under the action of the jet. The depth of the erosion (and respectively exfoliation) is basically determined by nozzle position relative to skin surface and by the time of exposure. Favorable aerodynamic conditions allow removal of peeled cells from the dimple.

Nozzles of the headpiece 3 are arranged in-line with each other and on the same surface, and a professional can adjust the nature and level of exposure by varying the jet position relative to the skin surface. Cumulative effect is enhanced at repeated consecutive treatment of the same area. Concurrently, deep skin layers are impregnated with gas and liquid. Static pressure and cold around the jet help alleviate the pain.

Active factors of gas-liquid jet are therefore the following:

- Static pressure;
- Low temperatures around the jet area due to a rapid gas expansion;
- High-speed flow of microscopic drops.

Gas-liquid exfoliation surely belongs to efficient mechanic peeling techniques, because it can be widely applied in cosmetology. Along with abrasive applications, gas-liquid skin treatment is used for intracutaneous injections of liquids (and agents dissolved therein) and gases.

Figure 1. Jet peeling technology:
Gas-liquid mixture is sprayed through a special nozzle (headpiece)
Liquid drops are speeded up to supersonic velocity
High-speed jet removes subjacent skin layers

This phenomena is sufficiently described by the term of "barophoresis": when skin is deformed by the jet, micropores are formed and expanded in the epidermis (wedge-like effect) to be used for conveying jet components, with gas and liquid vacuoles created in the tissues (see Image 1). Any of the active components (regardless of their molecular mass) can be brought inside the skin through the expanded channels, including gas, e.g., oxygen (in 100% concentration in case of compressed oxygen, and in 20% concentration in case of air), by means of pressure gradient.

Technology

Gas-liquid peeling requires no special skin preparations, except that skin must be clean, dry and inflammation-free.

The procedure consists in smooth "scanning" the skin areas to be peeled. By varying the working headpiece distance from the skin, various effects can be achieved. While moving the headpiece over 1.5-2 cm above the skin surface, the skin is being massaged, its blood circulation improved and lymphatic drainage provided. This can be used either as an independent rejuvenating procedure or to prepare the skin for a more comprehensive exposure.

When the working headpiece is at a 7±2 mm distance from the skin surface, kinetic energy of the drops grows making them acquire the abrasive properties with the concurrent barophoresis effect.

At repeated consecutive treatment of the same area:

- Skin turns pink during superficial peeling due to initial irritation (epidermal exposure);
- Then, skin turns pale due to vascular ischemia under high pressure (compression);
- The first dew-like blood drops appear, and that attests to a certain depth of the exposure (papillary derma is affected). This pattern is indicative of a medial peeling;
- When the procedure is over, skin color is gradually resumed, since vascular constriction is replaced with vascular dilatation (with vascular lumen restored to normal).

Mechanic skin polishing professionals can be pretty amazed by what they see, because they are used to more ample bleeding. Everything happens for a reason, however: at the point of skin contact, the two-phased jet is inhibited, static pressure at the treated area grows, and local ischemia prevents bleeding.

It is equally important that creation of high pressure zone in the exposure area will increase pain threshold, and the procedure therefore is almost painless. This is furthered by jet cooling (by 10°C versus ambient temperature), when compressed gas is rapidly expanded at the nozzle outlet. This fact rules out the necessity of preliminary anesthesia, no matter how deep the peeling may be.

The use of oxygen as a carrier gas not only allows an efficient sanitation of exposure area, but ensures a long-term protection by means of barophoresis. Therefore, infectious complications are hardly probable, no matter how deep the peeling may be.

A complete or partial polishing of facial area (periorbital area, around the lips, cheeks, nasolabial folds, and bridge of the nose) will cause a minor erythema or no erythema at all. Swelling ceases within 24 hours, crust will persist for 3-7 days and requires no special treatment. This sparing rehabilitation period is attributed to physiological nature of the exposure: minor bleeding, no skin dehydration which is characteristic of any peeling, and extra skin impregnation with liquid (including the deepest layers).

The procedure can be performed for all parts of face and body, including décolleté, chest, stomach, backside of arms, and scalp.

Indications to gas-liquid massage and peeling are:

- Skin ageing, such as dry skin, hyperkeratosis, atonia, wrinkles (that requires massage and superficial peeling – Beauty Flash or median peeling);
- Hyperpigmentation;
- Acne, including noninflammatory elements;
- Correction of scars (see Image 2) – atrophic, hypertrophic, post-acne, stretches;
- Seborrhea;
- Cellulite;
- Local fat deposits on cheeks, stomach, gills.

Complex nature of jet exposure (MASSAGE + ABRASION + BAROPHORESIS) will ensure a long-term physiological effect.

Such focused gas-liquid jet treatment can be combined with the use of cosmetic and dermatological agents (a preliminary physical action promotes better permeability of skin), as well as electrical methods, ultrasound therapy, and photo rejuvenation of skin.

Image 1. Biological effects of gas-liquid peeling
Immediately after the procedure: epidermis removed, deep tissues impregnated with oxygen and water
Long-term effect – synthesis of neocollagen (1 week after the procedure)
Long-term effect – synthesis of neocollagen (3 weeks after the procedure)

Example:
A 50 year aged woman complains of skin ageing in the form of superficial "purse-string" wrinkles above upper lip, well marked nasolabial folds, and acne complications (such as atrophic scars and hyperpigmented areas in the lower cheek, enlarged pores in the chin area).

Procedure: makeup removal and skin cleansing were followed by gas-liquid polish with Jet Peel-2. Uniform treatment of the entire facial area was lasting for 20 minutes. Polish depth in the problem areas was according to "blood dew" sign. Following the procedure, dexapanthenol-containing regenerative cream was applied on the skin. Re-examination was scheduled a month later.
Skin wrinkles and folds (before the GLP procedure, immediately after, and 1 month later).

Clinical Testing of the Proposed Method

Safety and efficiency of gas-liquid peeling has been studied at several sites.

Zhukovsky Beauty Center

Within February – November 2005, 170 patients aged 19-65 have undergone gas-liquid procedures.
Equipment applied: Jet Peel 2 (TavTech, Israel). The apparatus was connected to medical oxygen tank (maximum gas operating pressure – 6 Bar) and a bag containing sterile normal saline solution.

All patients were interviewed before the procedure to identify their complaints, study their medical and life history, and discuss esthetic problems. Objective and local status were determined by visual examination. Scars were evaluated both visually and palpatory.

The first subgroup included 100 subjects complaining of skin ageing: wrinkles around the mouth, in the eye area, and in the forehead, hyperpigmented areas, poor skin elasticity, dry skin in the face and neck area. They have all undergone 5 superficial or median peeling procedures, every 2-3 weeks each. Procedures were focused on the problem areas (hyperpigmented areas, deep wrinkles, lines, marked ptosis zones). Headpiece – skin distance was 7±2 mm.

After the treatment program, both patients and professionals have noticed a better skin tonus, reduced depth and length of wrinkles, lifting effect in the periorbital area, improved complexion, and whitening of hyperpigmented areas. Nearly all of the patients have felt refreshed. Several patients showed significant improvement in gills and slack cheeks. However, a general lifting effect was moderate. According to the doctors and patients opinion, improved skin relief was maintained for 7-9 months.

The second subgroup (51 subjects) included patients with acne of various severities. Skin rash was basically noninflammatory. Nearly all of the patients were having atrophic post-acne scars, and hyperpigmented areas. All patients were having combined skin.

Patients have undergone 7-10 superficial gas-liquid peeling procedures, every 1-2 weeks each. An adequate skin care at home was prescribed to all of them.

Reduced rash, smaller skin pores, and lower sebum production were observed after the first treatment sessions. Atrophic spots were disappearing relatively fast. Dryness and irritation have disappeared in several patients. Nearly all of the patients exhibited a uniform complexion.

Focused treatment of atrophic scars was performed until onset of point bleeding. Patients were warned of the damage of crust removal. A pronounced improvement was observed after 2-3 treatments.

It should be emphasized that all of the patients have been fully cooperating with the doctor and were satisfied with the results. They have all marked a pronounced improvement and feeling of comfort during the procedures.

The third subgroup (15 subjects) included patients with stretched skin in the stomach and hips area, "orange peel" effect, and local fat deposits. Stretches (aged 2-8 years) were polished by gas-liquid jet (the scar and adjacent areas). Treatment sessions were performed weekly (5 sessions per treatment cycle). Marked positive changes were observed after the end of therapy: stretches have been lifted to the skin level, slackness reduced. After cellulite treatment, the skin became smoother, its elasticity increased. Fat deposit areas (stomach and sides) have slightly shrinked.

Patients in the fourth subgroup (4 subjects) were having posttraumatic and postsurgical atrophic and hypertrophic scars aged 1 year and more. Treatment sessions were performed weekly (about 5 sessions per treatment cycle). In two cases of hypertrophic scars polishing (facial – aged 1.5 years, and on the stomach – aged 8 years), the scar was reduced after the very first procedure. In general, all of the patients exhibited good and satisfactory results (improved elasticity of scarred tissue and smoothing effect).

While analyzing the first clinical tests, it should be noted that all of the patients have duly appreciated high comfort and efficiency of the proposed therapy. They were thrilled to notice positive changes after the very first procedure. No side effects were observed.

Several patients exhibited a marked improvement of telangiectasia (kuperosis), reduced and "dried up" papillomas on the neck (unexpected positive effects).

MAPO Physiology and Balneology Chair (St. Petersburg)

Gas-Liquid jet affects all skin layers: epidermis, derma, and subcutaneous fat. The use of oxygen as a gas component produces various clinical and physiological effects, including bioenergetic (intensified oxidative phosphorylation), detoxicating, antibacterial (including against various strains of Propionobacterium), and immune corrective actions. The use of carbon dioxide by increasing its skin level stimulates local circulation, increases partial pressure of oxygen (!) in tissues, and initiates lipolysis. Lymphatic drainage is attributed to a short-term compression of veins and lymphatic vessels, and lymph displacement towards large collectors.

Since facial skin is a receptive field, jet-induced efferent input reaches cerebral cortex and subcortical structures, including vegetative centers. The vegetative index of Kerdo have showed two trends of using Jet Peel: harmonization of initial vegetative tonus, and shift towards parasympathetic effects that helps normalize trophic processes. This trend was further supported by dopplerography data ("Minimaxdoppler-K"). A 2.5-fold acceleration of linear blood flow was fixed after the procedure.

Gas-liquid treatment can be used in various applications: peeling, massage, needleless injections, local gas injections (as a part of gas therapy). It stimulates microcirculation, and exerts a trophic stimulating effect by activating parasympathetic nervous system.

JET PEEL SYSTEM

Jet Peel is a unique development of Israeli researchers, which is comprised of a device and a unique headpiece to transform high oxygen pressure and liquid into two-phased ultrasonic jet.

Due to its multi-purpose nature, the device is used for **painless** treatment of a broad spectrum of skin problems:

- Rejuvenation of skin
- Age-specific spots and spots caused by sun exposure
- Fast improvement of skin
- Improved permeability of skin due to opening of pores
- Skin smoothing and polishing
- Postacne scars
- Décolleté and hands care
- Treatment of scars and stretches
- Anticellulite treatment
- Painless delivery of active components to derma (needleless injections)

Rejuvenating effect is attributed to the use of oxygen and water, which are the most important sources of life on the Earth!

Short review on face rejuvenation procedures: focus on preoperative antiseptic and anesthetic delivery by JetPeel™-3 (a high pressure oxygen delivery device)

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SHORT REVIEW ON FACE REJUVENATION PROCEDURES: FOCUS ON PREOPERATIVE ANTISEPTIC AND ANESTHETIC DELIVERY BY JETPEEL™-3 (A HIGH PRESSURE OXYGEN DELIVERY DEVICE)

T. IANNITTI, S. CAPONE, B. PALMIERI

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Short review on face rejuvenation procedures: focus on preoperative antiseptic and anesthetic delivery by JetPeel™-3 (a high pressure oxygen delivery device)

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Aim. **Nowadays there is great attention in trying to slow and reverse the facial aging process. Esthetic medicine has been primarily based on the surgical approach for many years, but now, in order to solve the problem of aging skin, there is an increasing interest into non-invasive, possibly painless, procedures that can guarantee the patient a quick recovery. In this perspective the use of chemical peeling and dermabrasion, to achieve skin rejuvenation, is growing worldwide. These techniques are also relevant to treat skin pigmentation irregularities and to remove keratoses, lentigines, acne and other skin related conditions. One of the most interesting, safe and painless devices, useful for the effective antiaging face treatment, is JetPeel™-3. The aim of this study was to assess the device efficacy starting from a short review on face rejuvenation procedures.**

Methods. **The basic action mechanism of this medical device is a constant high pressure air flux delivery, including oxygen, mixed with different chemical compounds such as peeling molecules, antioxidants, vitamins and hyaluronic acid, which are mechanically forced across the skin surface. Here we report a new approach in the clinical use of JetPeel™-3, tested in 20 adult volunteers, consisting in the addition to the standard protocol of an anesthetic, carbocaine and a sterilizing and disinfectant agent, that is chlorexidine. In fact disinfection and sterilization of the skin surface is a peculiar step for every antiaging or therapeutic procedure. The procedure has been completed with multiple hyaluronic acid injections of the skin in order to achieve face rejuvenation. The anesthetic power of the JetPeel™-3-carbocaine protocol has been compared to the Emla cream one.**

Results. **The spontaneous pain sensation perceived by the patients in the hemiface treated with JetPeel™-3 was significantly lower compared to the hemiface treated with Emla cream ($P<0.001$) showing, consequently, that JetPeel™-3-carbocaine protocol had the best anesthetic performance either in dermal, subdermal or subcutaneous injections compared with Emla cream.**

Conclusion. **JetPeel™-3 has proved to be a good non-invasive approach and its use is recommended since it induces local anesthesia in a short time.**

Key words: **Rejuvenation - Keratolytic agents - Pain.**

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Facial aging is the result of intrinsic or genetically determined and extrinsic factors including sun exposure, smoking, diet, and general lifestyle leading to loss of skin elasticity, lines, wrinkles and dyspigmentation.[1-4] Furthermore, face aging is the result of interactions, at different anatomical levels, *i.e.*, skin, subcutaneous fat, muscle and bone and it is characterized by atrophy of subcutaneous fat pads and the overlying skin droops due to loss of the underlying support which may be exacerbated by cutaneous photodamage.[5-14] In particular UV irradiation is considered to be the primary environmental factor which causes skin aging.[1] The interest to reverse the signs of aging, caused by photodamage, is rising leading to the growing of the use of several procedures for facial skin rejuvenation to try to minimize the erythema, dyspigmentation, and rhytides associated with photoaging.[5] Among these procedures, the percutaneous collagen induction (PCI) therapy (skin needling) can be used to treat photoaged skin without the risk of skin dyspigmentation;[1] the ablative laser resurfacing is the most precise and important technique for facial skin rejuvenation, although it is associated with significant patient downtime and risks of adverse effects such as scarring and dyspigmentation; the intense pulsed light is a non-ablative procedure that targets dermal collagen without damaging the epidermis and effectively targets both the erythema and dyspigmentation seen in photoaging minimizing side effects and patient downtime although it does not match the results seen in fully ablative procedures; the fractional laser technologies, first non-ablative and more recently ablative, represent the most recent attempt to match the results seen in fully ablative procedures with less patient downtime.[5] The aging of the skin can be counteracted by means of cosmeceuticals, laser rejuvenation, chemical peels, and microdermabrasion.[2] For many years surgery has been the key resource in esthetic medicine to try to rejuvenate skin, but nowadays the non-surgical procedures are the treatment of choice due to their low invasiveness and shorter recovery time for the patient.[7] An example is given by a non-ablative treatment modality, called radiofrequency (RF) tissue tightening. This technique has been developed to create thermal effects in the dermis without external cutaneous wounding to respond to the growing of rhytides, wrinkles, and other signs of photoaging due to a greater sun exposure, phototoxic drugs, and demographic changes.[7] Among the minimally invasive techniques, used to fight against the aging process, we can also find botulinum toxin (BTX), intradermal fillers and chemical peels.[14] The first documented use of peeling by a physician is found in the Egypt-Ebers papyrus (1560 B.C.) where it is described its use to remove wrinkles as well as in other cosmetic treatments.[6] Peeling techniques can be either chemical or mechanical: 1) chemical peeling consists in applying a chemical solution to the face in order to cause controlled peeling of the superficial layers of the skin; 2) dermabrasion is obtained by means of a mechanical device which is used to resurface the skin by removing the same layers (a variety of abrading techniques are available, the most popular one being a small rotating abrasive wheel applied to the skin.[10] Chemical peeling and dermabrasion are useful in treating uneven areas of skin pigmentation and removing keratoses, lentigines, and acne scarring, but they can also be used to alter the epidermis and dermis of the skin to slow the aging process.[9] Chemical peeling has been widely used to rejuvenate skin since it can improve damaged skin and fine wrinkles.[8] Moreover, this peeling technique may be used to treat pigmentary disorders, superficial acne scars, aging skin changes, and benign epidermal growths, although some contraindications exist and they include patients with an active bacterial, viral or fungal infection, a tendency to keloid formation, facial dermatitis, taking photosensitizing medications and unrealistic expectations.[13] This procedure has been described as a controlled chemical burn of the epidermis and/or dermis resulting in epidermal regeneration and postinflammatory collagen neoformation with remodelling of collagen and elastic fibers and deposition of glycosaminoglycans in the dermis.[13] A classification of chemical

peels, based upon the depth of the wound created by the peel, has been reported by Landau [11] who describes three categories: 1) superficial peels that penetrate the epidermis only; 2) medium depth peels that damage the entire epidermis and papillary dermis; 3) deep peels that create a wound to the level of the midreticular dermis. The same author underlines that the depth of the peels determines the patient's inconvenience during and after the procedure, the healing time, the rate of the potential side effects and the results. Several peeling methods, such as a salicylic acid derivative, beta-lipohydroxy acid and alpha-hydroxy acids like glycolic acid, have been used by demarmatologists and plastic surgeons. In particular superficial peels are an important tool to enhance treatment of clinical conditions such as acne, melasma, dyschromias, photodamage and actinic keratoses.[3]

The present preclinical study was designed to assess the effective ability of chlorexidine 2%, to sterilize the skin by means of swab culture and compare the spontaneous degree of pain, by means of the Visual Analog Scale (VAS) of Scott-Huskisson, recorded after the puncture of 10 volunteers' forearms with needles of several sizes to the degree of pain recorded after the injection following carbocaine administration. After the preclinical study, we carried out a clinical study involving 20 volunteers to assess the safety and the efficacy of the JetPeel™-3 system. It was used on the patient's half face in combination with carbocaine as a peeling modality to achieve skin rejuvenation, focusing in particular on its anesthetic power measured by Scott-Huskisson VAS and compared to Emla cream on the patient's other half face. Chlorexidine 2% was used to sterilize the skin as a preliminary step before performing any procedure.

Materials and methods

Technology and device

JetPeel™-3 (Tav Tech Inc., Yehud, Israel) is a medical device for the skin surface treatment with different claims such as surfaceal smooth dermoabrasion, blackspots skin clearing, fine wrinkles smoothing, skin cleaning and dilated pores squeezing, dermo-epidermic hydration and oxygenation, rheologic improvement of microcirculation, dermal lymph drainage and drug dermal delivery.[10]

The basic principle of this instrument is very easy and revolutionary. A mixture of saline and oxygen is forced into an open converging-diverging Venturi channel, which accelerates the droplets to a speed of 200 m/s to the output through purposely designed nozzles, thus addressing a powerful water-drug-air-oxygen microdroplet jet (diameter ranging between 5 and 200 μm) onto the skin surface.

The spray power arising from a pressurized gas source (oxygen, or nitrogen or air) is supplied at 7 atmosphere pressure and mixed with fluid on a separate disposable handpiece.

The spray flow is emitted through a tubing system and a handpiece triggered by a footswitch, while a separate suction system aspirates gas and phragments. We reasonably suggest to enclose the Jet Peel™-3 as a preliminary step in our rejuvenation protocol with fillers and/or mesotherapy cocktails for two main reasons: 1) the need to have a very clean pathogen-free and germ-free skin surface before injections, clearing out the impurities due to contaminants and removing bacteria to reduce the risk of contamination and infection rate; 2) the need to perform painless injections even in a great number, avoiding anesthetic creams (like Emla and eutectic mixture ointment of prylocaine and xylocaine) that are cumbersome and must be dispensed one hour before the needle invasive procedure. Moreover, on the other hand, truncal and cutaneous anesthesia are quite invasive and the procedure modifies the skin appearance due to the needle trauma and injected fluid volume.[15]

Preclinical study

We performed a preliminary pilot study on 10 volunteers' (females = 8; males = 2; age between 30 and 67 [44.5±3.97,

mean±SE]) forearm skin comparing the results of a skin swab culture to a second skin swab culture, performed on the same skin five minutes after administration of 1 mL of chlorexidine 2% (Johnson & Jhonson, Milan, Italy), by means of JetPeel™-3. Later on, the intensity of spontaneous pain after puncturing the subject's skin with 16-18-21-Gauge needles was compared to the intensity of spontaneous pain perceived by the same subjects receiving the same puncture with the same needles after being sprayed by means of JetPeel™-3 with 1 mL carbocaine 1% (Astra Pharmaceuticals, Milan, Italy) for five minutes over a 1.5 x 1.5 cm spot. The data, describing the intensity of pain obtained from this pre-clinical study, were compared basing on the Scott-Huskisson Visua Analog Scale (VAS) as described by Maratea *et al*.:[12]

— slight pain=values <44 mm (RANGE 1);

— moderate pain=45 mm <values >69 mm (RANGE 2);

— strong pain=70 mm <values >88 mm (RANGE 3);

— very strong pain=values >88 mm (RANGE 4).

Clinical study

The clinical study group consisted of 20 adult volunteers (females=18; males=2), aged between 32 and 75 (50±2.68, mean±SE). The protocol was based on chlorexidine 2% antiseptic solution, sprayed by means of JetPeel™-3, with oxygen for five minutes over the face surfaces to be treated (2-6 cc accordingly to the wide area), followed by carbocaine 1% (10 cc) sprayed by means of JetPeel™-3 over the same presterilized and partially desquamated area (five minutes). Each patient's half face was pretreated with JetPeel™-3 according to the chlorexidine-carbocaine protocols and the other half with simple chlorexidin embedded cotton swab followed by Emla cream (lidocaine 2.5% and prilocaine 2.5% [Astra Pharmaceuticals, Milan, Italy]). Emla cream is an emulsion in which the oil phase is an eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. After that we proceeded with the filler injections. We used Viscofill (IBSA, Lodi, Italy) and Viscoderm (IBSA). Viscofill is a polivinylsulphone crosslinked fermentative hyaluronic acid (molecular weight =10^6 Dalton) used for prolonged filling of wrinkles and Viscoderm is a non-crosslinked native hyaluronic acid (molecular weight=10^6 Dalton) used in mesotheraphy multiple injections to stimulate fibroblast dermal chemotaxis.

The needles used to perform the filler injections were sterile 31-Gauge stainless steel supplied directly in the package of the product.

Statistical analysis

Statistical analyses were performed using Minitab® (v. 15.1; UK). The data for carbocaine administration and Emla cream application were checked for normality using the Anderson-Darling test. Since these data are not normally distributed, the logarithmic transformation was applied. The spontaneous pain data, measured using the Scott-Huskisson VAS, after carbocaine administration compared to Emla cream application, were analysed using a two-sample t-test. A value of $P<0.001$ was considered significant.

Results

Preclinical trial

The administration of 2% chlorexidine showed a complete skin sterilization. The comparison of the skin swab culture, taken before and after the skin was sprayed for five minutes with 2% chloredixine, was effective in removing from the skin surface all the pathogens (Table I).

The second part of the preclinical study showed that the needle punctures (16-18-21-Gauge) were completely painless after five minute carbocaine administration by means of JetPeel™-3. In fact the recorded VAS pain sensitivity for the injection without carbocaine fell in the third range for the 16-Gauge needle, while the pain sensitivity,

TABLE I.—*Comparison of the swab culture performed before and after a 5 minute spraying of 2% chlorexidine by means of JetPeel™-3.*

Patient	Before chlorexidine	After chlorexidine
1	*Saprophyte* *Staphylococcus* *Streptococcus*	No growth observed
2	*Streptococcus epidermidis* *Sarcinae*	No growth observed
3	*Staphylococcus aureus* *Mixed gram positivebacteria*	No growth observed
4	*Proteus* *Staphylococcus* *Streptococcus*	No growth observed
5	*Candida* *Mixed cocci*	No growth observed
6	*Saccaromyces* *Staphylococcus* *Streptococcus*	No growth observed
7	*Streptococcus epidermidis* *E. Coli*	No growth observed
8	*Haemophilus* *Mixed cocci*	No growth observed
9	*Sarcinae* *AcInetobacter* *Mixed cocci*	No growth observed
10	*Mixed gram positive bacteria*	No growth observed

recorded after the carbocaine injection, fell in the first range. As for the other two needle sizes, the spontaneous pain, recorded after the injection without carbocaine fell, in the second range, while the pain, measured after the injection with carbocaine, fell in the first range. The VAS values (mean ± SE; mm) for both groups are reported in Table II.

Clinical study

The patients' admission criteria were: aging face, wrinkles and acne scars to be treated with a dermal filler.

No anxiolytic drug or any other medication had been admitted in the last 96 hours before the session. The areas to be treated

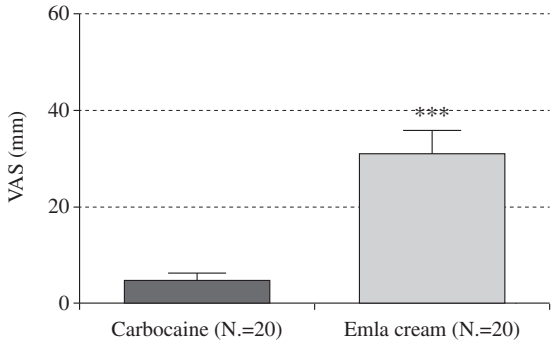

Figure 1.—Comparison between the JetPeel™-3-carbocaine protocol anesthetic power and the Emla cream one. The degree of pain was measured by means of Scott-Huskisson VAS (mean ± SE; mm).

were nasolabial folds, glabella, upper lips and filter, chin, periorbital and cheeks. Each patient's half face was pre-treated with JetPeel™-3 according to the chlorexidine-carbocaine protocols, and the other half with simple chlorexidin embedded cotton swab followed by Emla cream ointment administration and polyurethan sheet occlusion one hour before the procedure. The treated side and the control side of the face were chosen randomly in order to avoid side dominance bias. After both hemifaces had been sterilized with chlorexidine, we proceeded with the carbocaine jet by means of JetPeel™-3 on half of the face (Figure 1) and with Emla cream ointment on the other half. Then we started injecting the filler, Viscofill and subdermal Viscoderm on both hemifaces, giving to Emla cream 20 minutes to be absorbed. The injection techniques were straight subdermal along the wrinkle line, criss-cross and ferning for the polymerized hyaluronic acid and picotage for Viscoderm (Figures 2-4). Each patient received between 30 and 90 injections (55±4.47, mean±SE).

TABLE II.—*Preclinical trial. Normal injection versus post-carbocaine injection (needles of three different sizes have been used). The degree of pain was measured by means of Scott Huskisson VAS (mean ± SE; mm).*

Normal injection (N.=10) - 16-Gauge needle (mean ± SE)	Injection after carbocaine jet (N.=10) – 16-Gauge needle (mean ± SE)	Normal injection (N.=10) – 18-Gauge needle (mean ± SE)	Injection after carbocaine jet (N.=10) – 18-Gauge needle (mean ± SE)	Normal injection (N.=10) – 21-Gauge needle (mean ± SE)	Injection after carbocaine jet (N.=10) – 21-Gauge needle (mean ± SE)
88±3.26	2.5±1.11	65±6.05	1±0.66	52.6±4.83	1±0.66

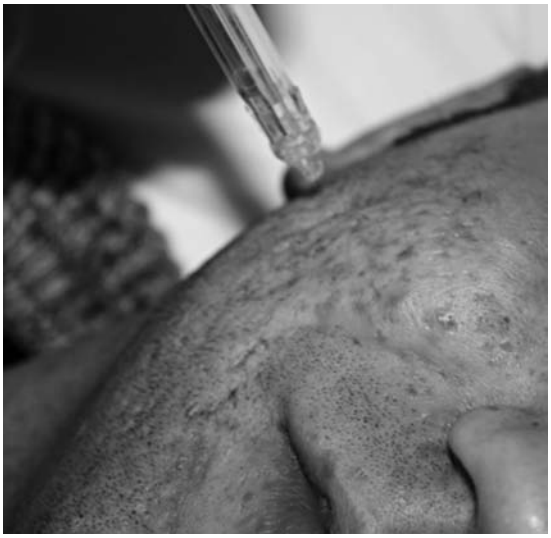

Figure 2.—Carbocaine perfusion by means of JetPeel™-3.

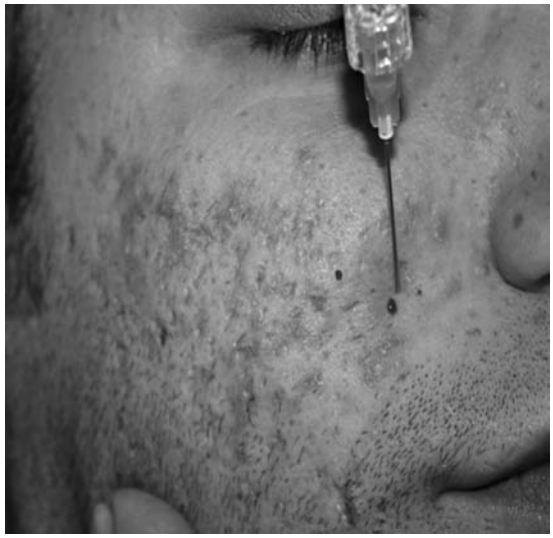

Figure 4.—Painless injection of hyaluronic acid by means of a 23-Gauge needle.

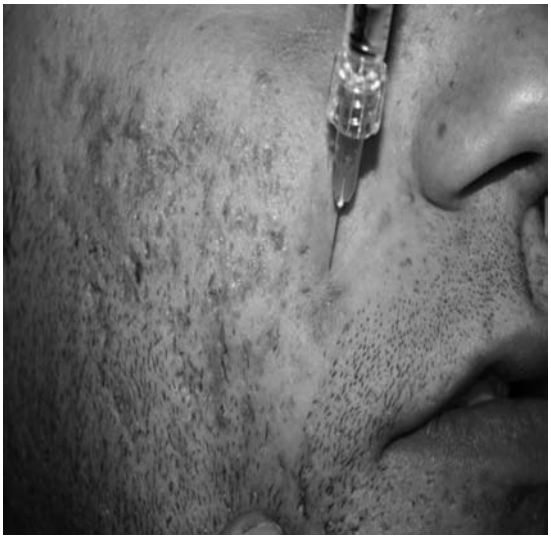

Figure 3.—Painless injection of hyaluronic acid with a 18-Gauge needle.

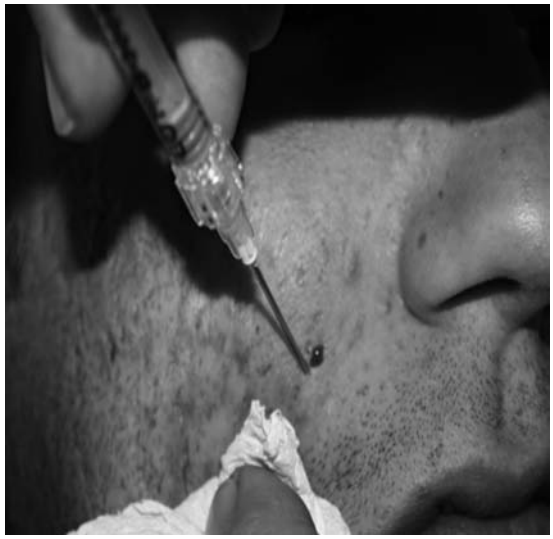

Figure 5.—Painless injection of hyaluronic acid by means of a 21-Gauge needle.

Immediately after the injection on each hemiface, the intensity of the overall tolerated pain was assessed for each individual patient by means of Scott-Huskisson VAS. All the patients completed the trial and no dropout, due to discomfort or pain, was recorded. The spontaneous pain sensation perceived by the patients in the hemiface treated with JetPeel™-3-carbocaine was significantly lower compared to the hemiface treated with Emla cream ($P<0.001$; Figure 5) showing, consequently, that JetPeel™-3 had the best anesthetic performance either in dermal, subdermal or subcutaneous injections compared with Emla cream. As a matter of fact Emla anesthesia was almost surfaceal. Especially along horizontal needle tracks, in the very sensitive areas (lipo contour, perirobital wrinkles, glabella), the patients

TABLE III.—*Pain sensitivity measured by Scott-Huskisson VAS (mean ± SE; mm).*

Treatment	Scott-Huskisson VAS(mm; mean ± SD)
Carbocaine (N.=20)	4.70±1.406
Emla cream (N.=20)	30.95±4.84

showed some, even if inhibited and self-controlled, muscular reactions. The pain sensitivity data measured by Scott-Huskisson VAS (mm) are reported in Table III.

Conclusions

This study shows an approach to face rejuvenation by means of JetPeel™-3. This instrument is effective in terms of skin preparation and anesthesia when we choose multiple injections or sequential mesotherapy as a treatment. This study shows its effectiveness if either cross-linked or natural hyaluronic acid are injected contemporarily to achieve the best cosmetic effect.

JetPeel™-3 is a very easy and original tool to achieve an ideal skin-drug interaction and penetration if the molecular weight of the delivered compound is not too much heavy to be transferred accross the healthy skin layers and if the electric charges (hydrophobicity *versus* hydrophilia) do not inhibit absorbtion.

As to the dynamic jet pressure of the gas, it helps the liquid droplets to release the squamous layers sheets of the skin with a kinetic energy that is related to the square of its mass and to the impact velocity. Thereafter the drug molecules are released and partially swept off on the surface, partially penetrate into the skin texture down to the dermal papillae and potentially to the blood stream through dermal microcirculation.

In our protocol the second step of carbocaine administration, after the first sterilizing and peeling washout, enhances the anesthetic compound uptake due to the horny layer and the epidermal thickness partial reduction achieved in the first part of the procedure.

In this study we show that JetPeel™-3 mediated anesthesia is superior to Emla cream administration. In fact its penetration is due to simple skin diffusion and not actively pushed by jet force.

In our labs ongoing studies will involve vasoconstrictor (adrenaline) synergistic penetration with JetPeel™-3 and comparisons of different local anesthetic compound effectiveness.

We believe that JetPeel™-3 induced local anesthesia is, at the moment, among the best non-invasive approach to people, especially children with fear of the needles, or in cases, like rejuvenation procedures and mesotherapy, where multiple injections are required. In this specific field our protocol is extremely safe and effective as it is also able to prevent the infection risk. In the surgical area JetPeel™-3, both skin cleaning and anesthesia are very helpful especially for the lasers, cavitation and intense pulsed light instrument procedures as it withdraws the need of cooling the skin with some possible bias due to the impact between epidermal low temperature and the vaporizing and heating beam. We believe that in treatment of teleangiectasia, angiomas and melanin spots, and specifically in the pediatric area, JetPeel™-3 can be the gold standard procedure.

Riassunto

Procedure cosmetiche di ringiovanimento facciale: focus sull'effetto preoperatorio antisettico e anestetico del JetPeel™ -3 (device a rilascio di ossigeno ad alta pressione)

Obiettivo. Oggigiorno c'è un grande attenzione nel tentare di rallentare il processo di invecchiamento facciale. La medicina estetica si è basata per molti anni su un approccio di tipo chirurgico, ma adesso, per correggere il problema dell'invecchiamento, l'interesse si è spostato verso l'utilizzo di tecniche non invasive, possibilmente indolori, che possano garantire al paziente un recupero veloce dopo la procedura. In questa prospettiva è in evidente aumento l'utilizzo di peeling chimici e della dermoabrasione per migliorare il ringiovanimento cutaneo. Queste tecniche sono anche utili per trattare le irregolarità della pigmentazione cutanea e

rimuovere cheratosi, lentiggini, acne e altre condizioni cutanee. Uno dei più interessanti sistemi, sicuro e indolore, utile per il trattamento del viso, è JetPeel™ -3. Scopo dello studio era verificare l'efficacia di questo strumento.

Metodi. Il meccanismo d'azione di questo dispositivo medico è basato sul rilascio di un costante flusso d'aria ad alta pressione, incluso ossigeno, insieme ad altri differenti composti chimici come molecole per peeling, antiossidanti, vitamine e acido ialuronico, che sono forzate meccanicamente attraverso la superficie cutanea. In questo studio riportiamo un nuovo approccio all'uso clinico di JetPeel™ -3, testato in 20 volontari adulti, consistente nell'aggiunta al protocollo standard di un anestetico, la carbocaina, e di un agente disinfettante e sterilizzante, la clorexidina. Infatti la disinfezione e la sterilizzazione della superficie cutanea sono uno step peculiare per ogni procedura antiaging e terapeutica. La procedura è stata completata con iniezioni multiple di acido ialuronico, per migliorare l'aspetto della cute. Il potere anestetico della carbocaina, veicolata con JetPeel™ -3 è stato paragonato con quello della crema Emla (P<0.001).

Risultati. La sensazione di dolore, percepita dai pazienti nella parte del viso trattata con il protocollo JetPeel™ -3-carbocaina, era significativamente più bassa rispetto a quella percepita nella parte del viso trattata con la crema Emla (P<0,001). Ciò dimostra che tra i due, JetPeel™ -3 ottiene i risultati anestetici migliori sia nelle iniezioni subcutanee che in quelle subdermali e dermali.

Conclusioni. Questo studio dimostra che JetPeel™ -3 rappresenta un ottimo approccio non-invasivo e il suo uso è raccomandato per indurre anestesia locale in breve tempo.

Parole chiave: Ringiovanimento cutaneo - Agenti cheratolitici - Dolore.

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Hydroporation with Jetpeel Dermalinfusion – an analysis of efficacy

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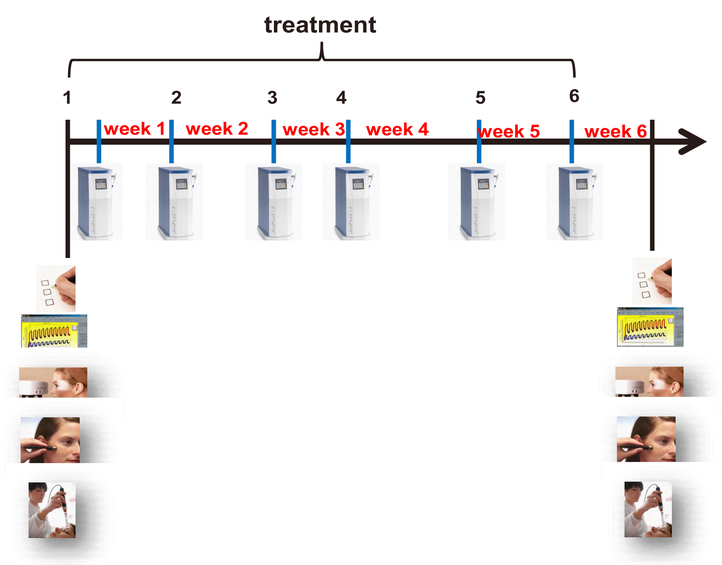
Introduction

Beautyful skin causes in physical attractiviness. Therefore cosmetic procedures should optimize parameters like skin glow and elasticity.
Jetpeel is a device for cosmetic resurfacing of the facial skin. It is based on a technology of a 2-phase stream that creates a jet composed of high pressure air flux delivery, including oxygen, mixed with different chemical compounds sucand microdroplets of saline or for example antioxidants, vitamins and hyaluronic acid accelerated to supersonic velocities. This jet impacts the skin, causing gentle and accurate cosmetic peeling.
In this half side, randomized controlled split face trail we evaluated the effects of a new hydroporation method.

Methods & material

In this randomized, double-blind, half-side comparison of 6 weeks duration 20 healthy females (aged 20 - 45 years) with signs of skin aging were randomized to receive a treatment with a hyaluronic acid solution applied with the Jetpeel (figure 2) at one side of the face and a saline peeling at the contralateral side.
Efficacy was assessed at baseline and after treatment using a subject questionnaire. Additionally biophysical assessments of surface topography (Primos®, GFMesstechnik GmbH, Berlin, Germany), skin elasticity (Cutometer® MPA 580) and skin hydration (Corneometer® CM 825) were also performed. To evaluate the tolerance of the treatment pH-value (Skin-pH-Meter® PH905), transepidermal waterloss (Tewameter® TM 300, all Courage & Khazaka, Cologne, Germany) were performed and furthermore subjects were asked to keep a project diary. Pictures were performed by using Visia System (Canfield, Fairfield, USA)

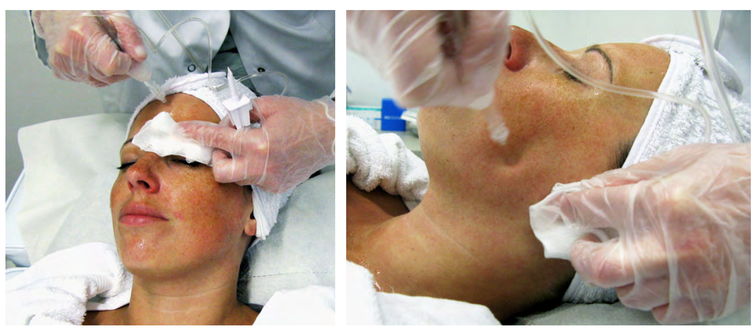
Study design



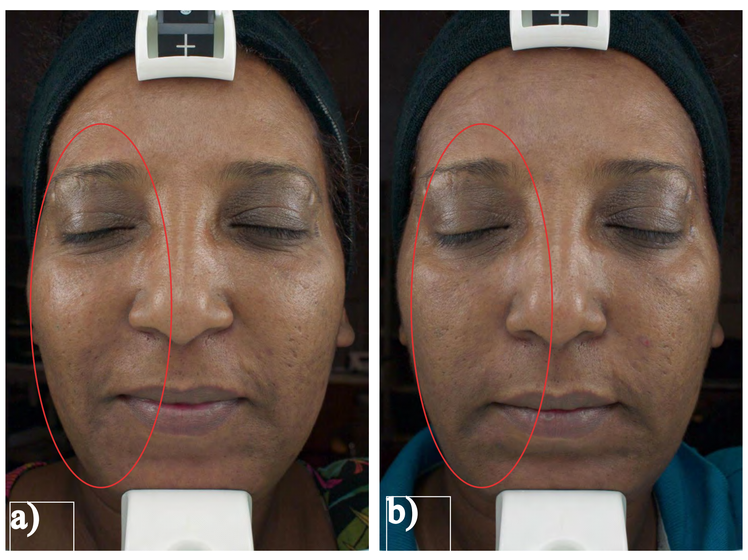
▲Fig. 1: Treatment and evaluation course

Results

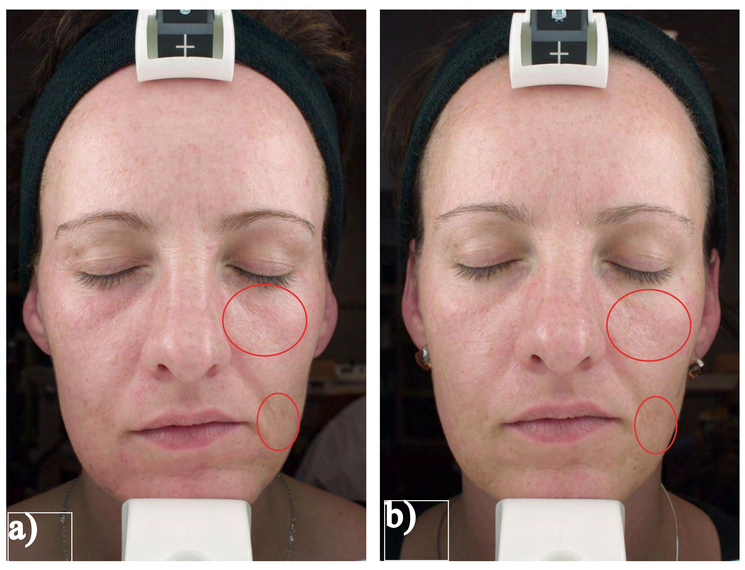
After 6 treatments using saline solution and delivering by hyaluronic acid with Jetpeel skin quality improved in all subjects. There was a clinical improvement of wrinkle severity according to the evaluation of skin topography. Skin netto elasticity increased by 14,8%, brutto elasticity by 4,8%. Skin surface hydration evaluated by corneometry improved from 63,64 to 65,05. Results of the subject questionnaire showed a significant time effect for skin sensation ($p = 0{,}005$), skin glow ($p \leq 0{,}001$), skin smoothness ($p = 0{,}02$) and skin hydration ($p = 0{,}001$). 95% of subjects were delight with the treatment. There were no reported side effects, moreover pH value and transepidermal waterloss remained in physiological range over the entire study period.



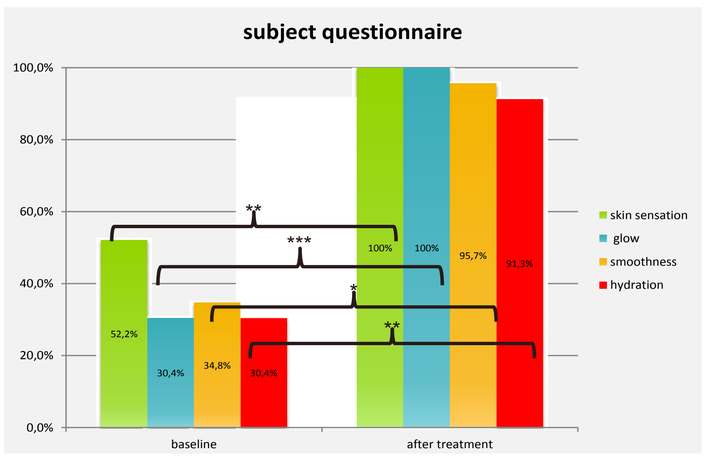
▲Fig. 2: Treatment with Jetpeel



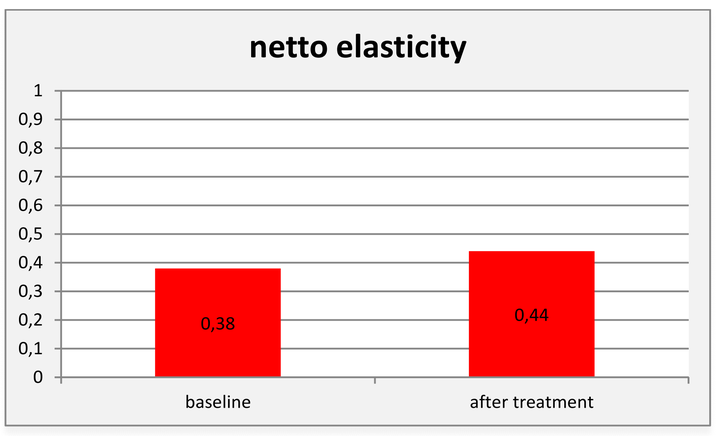
▲Fig. 3: standadized fotography at a) baseline and b) after a six week treatment wih Jetpeel



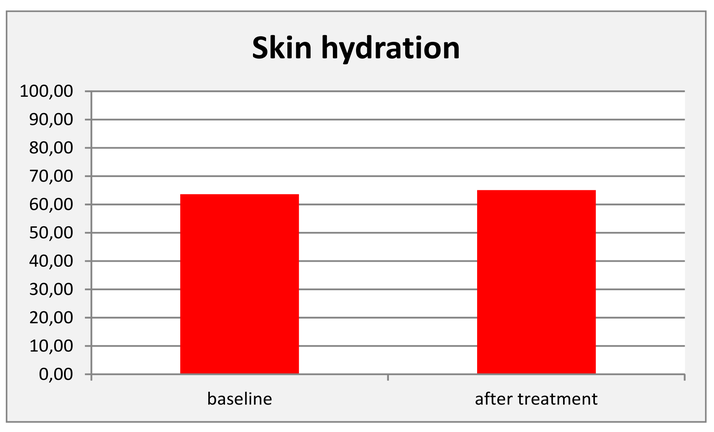
▲Fig. 4: standardized photography at a) baseline and b) after a six week treatment wih Jetpeel



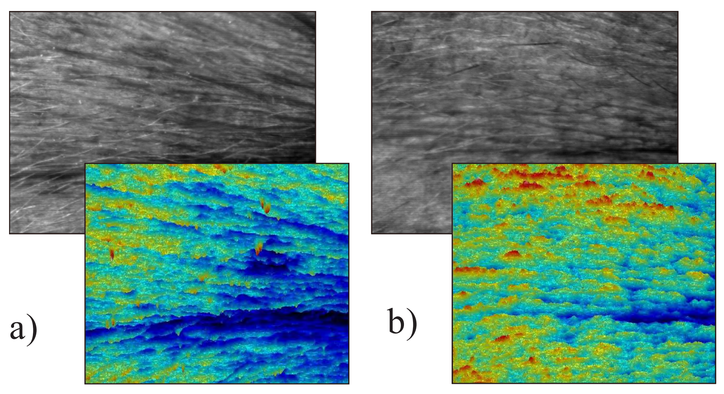
▲Fig. 5: Results of facial appearance self-perception questionnaire (* p<0.05, **p<0.01, ***p<0.001)



▲Fig. 6: Results of skin elasticity (arbitrary values)



▲Fig. 7: Results of corneometry (arbitrary values)



▲Fig. 8: Results of skin topography a) at baseline, b) after six week of treatment

Conclusion

The evaluated cosmetic procedure proved to be an effective option for non-invasive application of hyaluronic acid. It impoves skin glow, smoothness and hydration and is accombiened with a high subjects` satisfaction. Furthermore it s well tolerated.

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Drug Design, Development and Therapy

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ORIGINAL RESEARCH

A preliminary study of painless and effective transdermal botulinum toxin A delivery by jet nebulization for treatment of primary hyperhidrosis

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Background: Hyperhidrosis is a chronic disease characterized by increased sweat production. Local injections of botulinum toxin A (BTX-A) have been extensively used for treatment of primary hyperhidrosis (idiopathic). The current treatment for this condition involves several intradermal injections, resulting in poor patient compliance due to injection-related pain. Therefore, new protocols, including an improved anesthetic regimen, are required.

Aim: We designed the present study to determine whether JetPeel™-3, a medical device used for transdermal delivery of drugs by jet nebulization, could be used to deliver lidocaine prior to the standard multiple BTX-A injections or deliver lidocaine together with BTX-A in order to determine the protocol giving better results in terms of procedure-related pain, sweating, and patient satisfaction in subjects affected by primary axillary, palmar or plantar hyperhidrosis.

Materials and methods: Twenty patients with a visual analog scale (VAS) sweating score ≥ 8 cm were randomized to receive lidocaine 2% (5 mL) delivered by JetPeel™-3 followed by multiple injections of BTX-A (100 units) or lidocaine 2% (5 mL) and BTX-A (50 units) delivered together by JetPeel™-3. Effect of treatment on sweating was measured by VAS (0= minimum sweating; 10= maximum sweating) at 3-month follow-up. Pain induced by the procedure was assessed by VAS (0= minimum pain; 10= maximum pain) immediately after the procedure. Patient satisfaction was assessed at 3-month follow-up using a 5-point scale (1= not at all satisfied; 2= not satisfied; 3= partially satisfied; 4= satisfied; 5= highly satisfied).

Results: Both treatment modalities reduced sweating at 3-month follow-up, if compared with baseline (all $P<0.001$). Delivery of lidocaine and BTX-A by JetPeel™-3 resulted in lower procedure-related pain and reduced sweating, if compared with lidocaine delivered by JetPeel™-3 followed by multiple BTX-A injections (all $P<0.001$). Patient satisfaction with the procedure was higher in the group receiving lidocaine and BTX-A treatment by JetPeel™-3, if compared with lidocaine delivered by JetPeel™-3 followed by multiple BTX-A injections ($P<0.001$). No side effects were observed in both groups.

Conclusion: Lidocaine and BTX-A can be safely delivered together by JetPeel™-3 to treat primary palmar, plantar and axillary hyperhidrosis, resulting in lower procedure-related pain, improved sweating and higher patient satisfaction, if compared with lidocaine delivered by JetPeel™-3 followed by standard BTX-A injection therapy. Our protocol delivering lidocaine and BTX-A together by JetPeel™-3 requires a reduced quantity of BTX-A, further supporting the use of the transdermal drug delivery by jet nebulization over standard injection therapy for treatment of primary hyperhidrosis.

Keywords: hyperhidrosis, JetPeel™-3, botulinum toxin A, anesthesia, pain, sweating, transdermal drug delivery, jet nebulization

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Introduction

Hyperhidrosis

Hyperhidrosis is an eccrine sweat gland disorder resulting in an increase in sweating which goes beyond what is physiologically appropriate for temperature regulation, and can affect hands, palms, feet soles, axillae, face, and head.[1] Primary hyperhidrosis is a disorder of unknown cause (idiopathic) but may be exacerbated by stress.[1,2] It affects both men and women equally (2.8% of the general population in the United States),[3] and can be extremely socially debilitating, interfering with work activities and negatively affecting the patients' quality of life.[4,5]

Management of hyperhidrosis

The management of hyperhidrosis includes the use of topical antiperspirants such as aluminum chloride or tannic acids, oral anticholinergic medications such as glycopyrrolate and propantheline or iontophoresis.[6] Local injections of botulinum toxin A (BTX-A) are effective in treating primary hyperhidrosis, because BTX-A blocks the release of acetylcholine from the presynaptic nerve terminal with a temporary and reversible local chemodenervation.[7–14] However, as a great number of painful intradermal injections are required, many patients complain of pain during injections, causing poor compliance in the regular re-injection follow-up. Unfortunately, commonly used pain relief methods such as topical anesthesia, cooling of the skin and use of needles of reduced size[15,16] have proven unsuccessful, requiring the design of new protocols.

A previous study in our laboratories showed that JetPeel™-3 (TavTech Ltd., Yehud, Israel) can be used successfully to deliver lidocaine with an anesthetic power superior to topical anesthetic cream in the aesthetic medicine setting.[17] In the present study, JetPeel™-3 was used to deliver lidocaine prior to standard multiple BTX-A injections or to deliver lidocaine plus BTX-A, in order to determine the protocol giving better results in terms of procedure-related pain, sweating, and patient satisfaction.

Materials and methods

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at the Poliambulatorio del Secondo Parere (Modena, Italy), where the study was performed.

Patients

Twenty patients (13 women and 7 men) aged 39±2.63 years (mean ± standard error of the mean), were enrolled in this study. All patients signed the informed consent. Only patients affected by primary axillary, palmar or plantar hyperhidrosis with a visual analog scale (VAS) sweating score ≥ 8 cm participated in this study. Exclusion criteria were neuromuscular disease, concomitant drug treatment interfering with neuroglandular transmission, infections, dermatitis or other skin diseases, allergy or sensitivity to the study medication, previous treatment with BTX-A in the 12 months preceding the study, pregnancy and breastfeeding.

JetPeel™-3

JetPeel™-3 is a medical device which can be used for dermoabrasion, dark spot removal, fine wrinkle smoothing, skin cleansing, squeezing of enlarged pores, dermoepidermal hydration and oxygenation, improvement in microcirculation rheology, dermal lymph drainage and transdermal drug delivery by jet nebulization. Moreover, it can be used to achieve effective skin disinfection and/or sterilization and induce local anesthesia, avoiding the use of needles.[17] The basic principle of JetPeel™-3 can be described as follows: a mixture of saline and oxygen is forced into a channel, which accelerates the droplets (200 m/sec) outside through a specific nozzle, delivering a powerful jet of microdroplets containing water, drug, air and oxygen (diameter 5–200 μm) onto the skin surface.

Experimental procedure

Patients were randomized to receive a single session of 1) lidocaine 2% (Astra Formedic, Milan, Italy; 5 mL) delivered by JetPeel™-3 and subsequent multiple BTX-A (100 units (U); Bocouture®, Merz Aesthetics, Frankfurt am Main, Germany; BTX-A was reconstituted in 5 mL of saline solution) injections in the area affected by hyperhidrosis (group A [n=10]) or 2) lidocaine 2% (5 mL) and BTX-A (50 U diluted in the lidocaine for each palm, axilla, or foot)

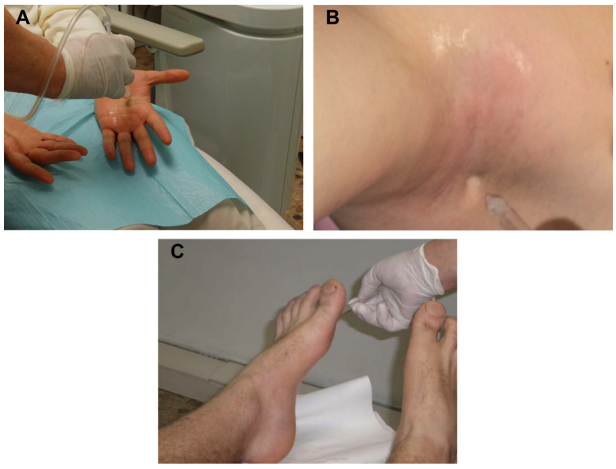

Figure 1 Treatment of primary palmar (**A**), axillary (**B**), and plantar (**C**) hyperhidrosis with lidocaine and botulinum toxin A delivered by JetPeel™-3.
Note: JetPeel™-3 is manufactured by TavTech Ltd., Yehud, Israel.

administered together by JetPeel™-3 (Figure 1) over the area affected by hyperhidrosis (group B [n=10]). In patients affected by axillary hyperhidrosis, the area was shaved 2 days before the procedure. Patients were instructed not to use antiperspirants or deodorants for at least 24 hours prior to treatment. Patient follow-up to assess patient satisfaction with the procedure and improvement in sweating was performed at 3 months.

Measurement of procedure-related pain, sweating, and patient satisfaction

Procedure-related pain was rated by the patients using a VAS (0= minimum pain; 10= maximum pain) immediately after the procedure. The patients were asked to quantify the intensity of sweating using a VAS (0= minimum sweating; 10= maximum sweating) before and after treatment. Patients' satisfaction with the procedure was assessed at 3-month follow-up using a 5-point scale (1= not at all satisfied; 2= not satisfied; 3= partially satisfied; 4= satisfied; 5= highly satisfied).

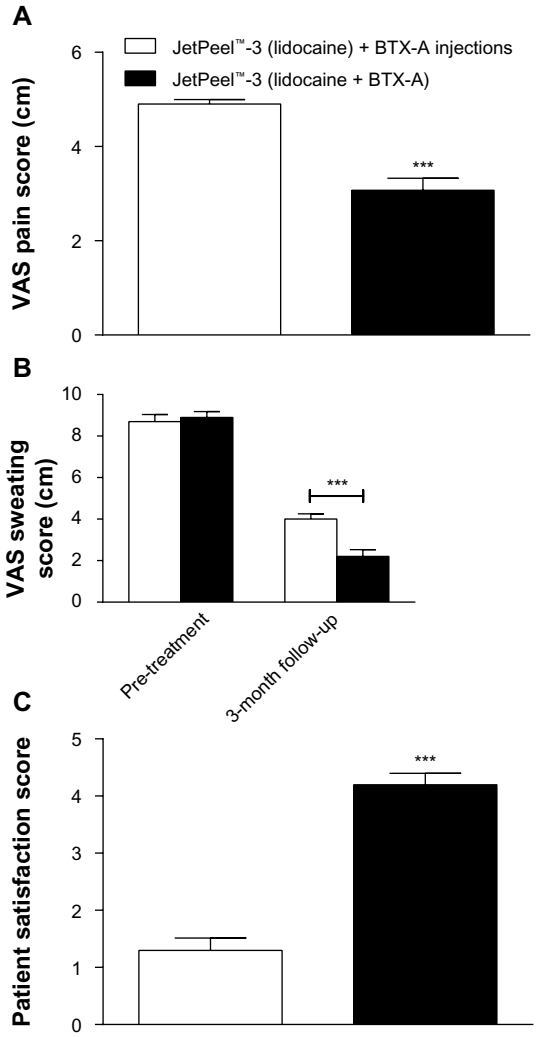

Figure 2 (**A**) Delivery of lidocaine and BTX-A by JetPeel™-3 results in lower procedure-related pain versus delivery of lidocaine by JetPeel™-3 followed by BTX-A injections; (**B**) delivery of lidocaine and BTX-A by JetPeel™-3 decreases sweating at 3-month follow-up versus lidocaine delivered by JetPeel™-3 followed by multiple BTX-A injections; (**C**) patients are more satisfied with the protocol based on delivery of lidocaine and BTX-A by JetPeel™-3, if compared with the procedure based on delivery of lidocaine by JetPeel™-3 followed by BTX-A injections.

Notes: Data are presented as the means ± standard error of the mean. ***$P<0.001$. JetPeel™-3 is manufactured by TavTech Ltd., Yehud, Israel.

Abbreviation: VAS, visual analog scale.

Statistical analysis

Data were analyzed using GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA). All data are presented as the means ± standard error of the mean and were first checked for normality using the D'Agostino-Pearson normality test. A two-sample unpaired Student's *t*-test was applied to analyze differences in VAS pain score and patient satisfaction score between the two treatment groups. A paired Student's *t*-test was used to compare changes in VAS sweating score at follow-up versus baseline for each treatment modality. Difference in VAS sweating score between the two drug delivery modalities at follow-up was analyzed using a two-way analysis of variance (ANOVA) followed by Sidak's multiple comparisons test.

Results

In group A, three patients had axillary hyperhidrosis, three had plantar hyperhidrosis and four had palmar hyperhidrosis. In group B, two patients had axillary hyperhidrosis, four had plantar hyperhidrosis and four had palmar hyperhidrosis. Both treatment modalities reduced sweating at 3-month follow-up, if compared with baseline (all $P<0.001$). Sweating decreased from a baseline value of 8.7±0.3 cm to 4±0.2 cm in the group receiving lidocaine by JetPeel™-3 and multiple BTX-A injections. Sweating decreased from a baseline value of 8.9±0.2 cm to 2.2±0.3 cm in the group receiving lidocaine and BTX-A by JetPeel™-3. Delivery of lidocaine and BTX-A by JetPeel™-3 resulted in lower procedure-related pain, as assessed immediately after the procedure, and reduced sweating at 3-month follow-up, if compared with lidocaine delivered by JetPeel™-3 followed by multiple BTX-A injections (all $P<0.001$; Figure 2A and B). Patient satisfaction with the procedure was higher in the group receiving lidocaine and BTX-A treatment by JetPeel™-3, if compared with the group receiving lidocaine by JetPeel™-3 plus multiple BTX-A injections ($P<0.001$; Figure 2C). Cold-related pain was observed in a patient affected by axillary hyperhidrosis after BTX-A injections. However, the patient completed the procedure successfully and the pain resolved within 20 minutes without treatment. No side effects were observed in both groups.

Discussion

Hyperhidrosis is overproduction of sweat by the exocrine sweat glands and is characterized by enormous psychosocial stress.[18,19] We found that combined delivery of BTX-A and lidocaine by JetPeel™-3 resulted in lower procedure-related pain, improved sweating and higher patient satisfaction, if compared with lidocaine delivered by JetPeel™-3 followed by multiple BTX-A injections into the dermis. The protocol delivering the anesthetic together with BTX-A using JetPeel™-3 required a reduced quantity of BTX-A, further supporting the use of transdermal drug delivery by jet nebulization over standard injection therapy for treatment of hyperhidrosis. This evidence suggests a more direct penetration of the drug when using JetPeel™-3. Many studies have investigated the persistence of BTX-A injection efficacy in patients affected by hyperhidrosis. For example, Naver et al[20] reported a median duration of treatment of 10 months after injecting BTX-A in 170 patients affected by palmar and axillary hyperhidrosis. Furthermore, Schnider et al[21] injected BTX-A in 13 subjects affected by axillary hyperhidrosis and observed a significant reduction in sweat production over a period of 13 weeks. In a further clinical study[22], Xeomin®, a type of BTX-A, was injected into patients affected by axillary hyperhidrosis, while patients affected by palmar hyperhidrosis, were injected with Xeomin® and Neurobloc®, a type of BTX-B. At the 3-week follow-up, all patients, treated for axillary and palmar hyperhidrosis, reported a significant improvement in Dermatology Life Quality Index (DLQI) score. Andrade et al[23] found two efficient non-invasive methods, iontophoresis and phonophoresis, to administer BTX-A in patients with bilateral primary palmar hyperhidrosis. In this study, BTX-A efficacy lasted over 16 weeks after the end of treatment.

Conclusion

The present study shows that JetPeel™-3 can be efficiently and safely used to treat primary palmar, plantar and axillary hyperhidrosis, delivering both anesthetic and BTX-A at the same time. This protocol results in lower procedure-related pain, improved sweating and higher patient satisfaction, if compared with lidocaine delivered by JetPeel™-3 followed by standard BTX-A injection therapy, also requiring a reduced quantity of BTX-A used. A limitation of our study is the small number of patients involved. Therefore studies in larger cohorts of patients are required.

Acknowledgments

The authors contributed equally to this work. The authors hereby certify that all work contained in this article is original. The authors claim full responsibility for the content of the article.

Disclosure

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in this article.

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EPIDERMAL AND DERMAL HISTOLOGICAL CHARACTERISTICS IN RESPONSE TO HYDROPORATION

Epidermale und dermale Hydroporation histologisch charakterisiert

UWE PAASCH[1]

KEY WORDS: Hydroporation, histology, wound healing, drug delivery, fractional laser

SUMMARY

BACKGROUND: Targeted drug deliver through an intact epidermal barrier is of interest in order to treat various skin conditions and diseases. Among many available methods hydroporation has already been shown to be effective for controlled skin rejuvenation by localized epidermal ablation. Therefore the concept might also be suitable to be used to trans-epidermal scarless deposition of substances, drugs or molecules using recently developed handpieces having nozzles smaller than 120 µm. However systematic studies investigating the tissue effects on those hydroporation systems are lacking.

OBJECTIVES: The aims of this in vitro study were (1) to prove the ability of the hydroporation system to penetrate the epidermal compartment and (2) to be able to deposit liquids (NaCl, vitamin a and c solutions), viscous substances (hyaluronic acid), crystalloid suspensions (triamcinolone, 40 mg/ml), and molecules of higher molecular weight like antibodies (IgG-FITC), PEG's (FITC-PEG's) and sugars (Dextrane-FITC) into the dermis using an skin explant model with and without AFXL pre-treatment using two different types of ablative fractional lasers.

MATERIALS AND METHODS: Skin explants were subjected to hydroporation using alcian blue inked 0.9 % NaCl, unstained 0.9 % NaCl applications for 10 s, 30 s, 1 min, ready to use solutions containing vitamin a and c as well as hyaluronic acid crystalloid suspensions, antibodies, hetero-functionalized polyethylene glycol and sugars to investigate morphological tissue changes and to measure distribution within the epidermis and the dermis. To test the potential synergistic effect of fractional ablative laser pre-treatment in conjunction with hydroporation to apply molecules of higher molecular weights two laser systems have been used.

RESULTS: The hydroporation system has been tested for effective deposition of low molecular weight particles in a homogenous distribution up to a dermal depth of 1436 µm. Furthermore hyaluronic acid of low viscosity and crystalloid suspensions could be placed into the dermis of normal skin. In cases of dense collagen fibers as seen in scars deposition was limited. The transport of high molecular weight substances (2, 70, and 150 kDa) was possible through the nozzle of a standard handpiece, however epidermal penetration was limited. Pre-treatment with either a fractional ablative CO_2- or Er:YAG-laser enabled deep dermal deposition of those molecules.

CONCLUSION: This in large vitro study clearly demonstrated that the hydroporation concept can be applied to human skin in a safe and effective manner not only for controlled ablation but also for scarless dermal application of low molecular weight molecules in liquids of low and medium viscosity. The application of high molecular weight compounds was made possible by pre-treating the skin with fractional ablative lasers.

SCHLÜSSELWÖRTER: Hydroporation, Histologie, Wundheilung, transdermal, fraktionale Laser

ZUSAMMENFASSUNG

HINTERGRUND: Die gezielte intra- und transepidermale Bereitstellung von Therapeutika ist von jeher zur topischen Therapie jedweder Erkrankung von hohem Interesse. Bisher wurden zahlreiche Konzepte entwickelt, unter denen die kontaktfreie Hydroporation bereits zur Hauterneuerung und ablativen Therapie eingesetzt wurde. Das theoretische Potential dieser Technik schließt die narbenfreie trans-epidermale Deposition von Substanzen, Arzneimitteln oder Molekülen bei der Verwendung neuer Applikatoren mit Strahldiametern von nur 120 µm ein. Allerdings fehlen systematische Studien zu Gewebepenetrationscharaktersitka und – interaktionen.

ZIEL: Ziel der Studie war es (1), die Penetrationsfähigkeit von Epidermis und Dermis qualitativ und quantitativ zu erfassen (2) den Depositionseffekt von Fertiglösungen (NaCl, Vitamin A und C), viskösen Substanzen (Hyaluronsäure), kristalloiden Substanzen (Triamcinolon, 40 mg/ml), und Molekülen mit hohem und höherem Molekulargewicht wie Antikörper (IgG-FITC), PEG's (FITC-PEG's) und Zucker (Dextran-FITC) in der Dermis anhand eines Explantatmodels mit und ohne Vorbehandlung mittels zweier faktional ablativer Laser zu untersuchen.

MATERIAL UND METHODEN: Hautexplantate wurden in-vitro mit gefärbter (Alcianblau) und ungefärbter 0,9 % NaCl für 10 s, 30 s und 1 min, Fertiglösungen von Vitamin A und C, Hyaluronsäure, Triamcinolonsuspension, Antikörpern, hetero-funktionalisiertem Polyethylenglycol und Dextran hydroporiert und mikroskopisch die Gewebeinteraktion erfasst. Der Einfluss fraktional ablativer Laser auf das Penetrationsverhalten hydroporierter Moleküle hohen Molekulargewichtes wurde mittels CO_2- und Er:YAG-Laser ermittelt.

ERGEBNISSE: Die Hydroporation niedermolekularer Substanzen konnte bis zu einer Tiefe von 1436 µm nachvollzogen werden. Hyaluronsäure niedriger Viskosität sowie kristalloide Suspensionen konnten ebenfalls nach Hydroporation mikroskopisch dermal visualisiert werden. Im Falle von Narbengewebe war die Deposition jedoch limitziert. Die Applikation hochmolekularer Substanzen war ebenso mit den verwendeten Handstücken möglich, jedoch die Penetrationskapazität ohne Vorbehandlung limitiert. Ein fraktional ablative Vorbehandlung führte zur Verbesserung der Penetrationsleistung.

ZUSAMMENFASSUNG: Die Hydroporation niedrigmolekularer und auch höhermolekularer Substanzen in die Haut kann reproduzierbar und effektiv mit flüssigen und niedrigviskösen Systemen erfolgen. Die Applikation hochmolekularer Substanzen ist per se limitiert kann jedoch mit einer fraktional ablativen Vorbehandlung verbessert werden.

TAB. 1: OVERVIEW OF CURRENT TECHNOLOGIES TO PENETRATE THE EPIDERMAL BARRIER [13].

Designed topicals	Chemical & mechanical penetration	External forces	TOR – Temporarily opened epidermal barrier
Supersaturation Penetration enhancer Encapsulation Nanocarriers	Syringes Suction blisters Dermabrasio Peeling	Iontophoresis Sonopheresis Electroporation Photomechanical waves Hydroproration Laser microjet	Dermaroller Fractional ablative Laser & RF-devices Fractional non-ablative qs Laser
High limitation to size of compound & transport capacity	Limitation to area and depth of penetration & transport capacity	Limitation to size of compound & transport capacity	50 % of skin can be opened without scar formation for 24h Potentially high capacity but inside out pressure gradient

INTRODUCTION

The human skin, the largest organ surface wise has been attractive for topical and transdermal intervention since ever. However, Evolution has designed a very efficient barrier preventing human beings from water loss, penetration of germs, allergens poisons, toxins, radiation and other influences of danger in a very sufficient manner. To overcome the barrier many concepts have been developed (Tab. 1).

Recent insights to the potential of fractional skin treatments have established standard laser procedures to treat aged and sun damaged skin and scars. The biggest potential of it is foreseen with the option of a contact free temporary opening of the epidermal barrier (TOR, German: gate) to promote new and intensified treatment regimen. Fractionated laser therapies are routinely used in the clinic to treat scars and many other conditions [1]. By treating the skin with fractions, a response is initiated that involves the skin replacing itself in up to 50 % of the surface if the individual piece of skin removed is smaller than ~0.3 mm in diameter. These columns of treated skin can reach as deep as the dermal compartment and are called microscopic treatment zones (MTZ or microscopic ablation zones (MAZ)) [2–4]. In recent years, experimental in vitro and in vivo studies have proven that treatment with AFXL enhances the uptake of topically applied small molecules like photosensitizers and facilitates distribution into deep skin layers [5–9].

Among the use of external forces (Table 1) hydroporation has gained a new interest since the development of highly effective devices. It has been effectively used for lymph drainage, gentle massage and also facial rejuvenation [10]. In the latter setting the system was able to ablate of the epidermis in a controlled manner. Interestingly there were no disturbances of wound healing. However, as in traditional laser concepts aiming on full thickness epidermal ablation erythema, herpes virus infection, crusting and emphysema have been reported [10].

Hydroporation however may also ensure a contact free drug delivery approach together with the use target molecules within a jet stream at high speeds to treat large surface areas. This concept avoids epidermal ablation despite the possible application of high volumes or substance concentrations. However systematic studies investigating the tissue effects on those hydroporation systems are lacking. So far it is not known what type of penetration injury takes place and if at all a substance or drug is deposited to the

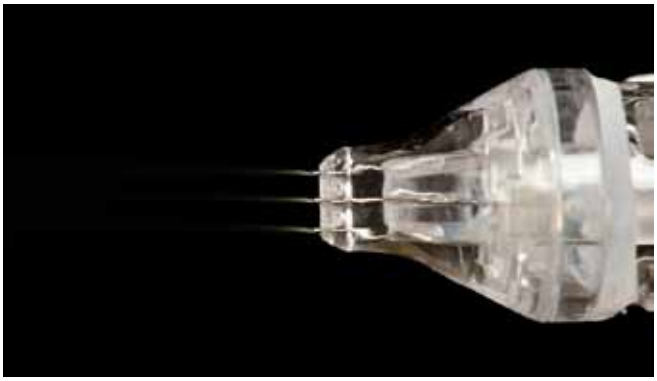

Fig. 1: The triple nose handpiece ensures a larger treatment area while dividing the fluid stream into three.

Fig. 2: The standard single outlet handpiece ensures the most powerful application mode of a stream accelerated up to app. 750 km/h.

Fig. 3: The prototype handpiece with a backpack like opening for standard vials was used to test liquids having a higher viscosity. The system displayed does also have a triple outlet.

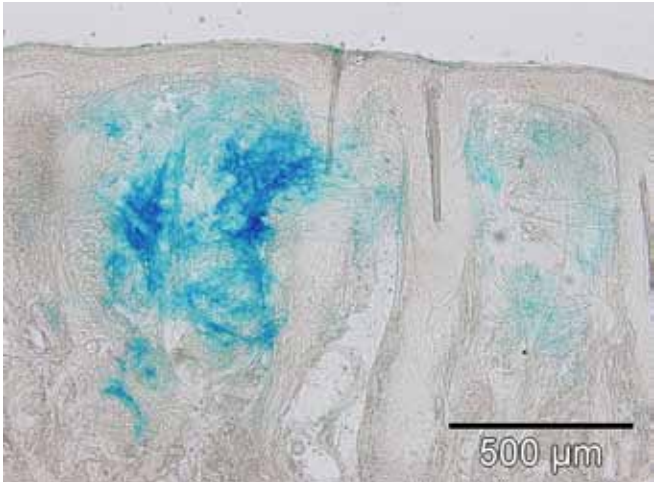

Fig. 4: Visualization of distribution type and depth of ink stained 0.9 % NaCl solution stained with blue ink (patent blue). Without displaying a gross damage on the epidermis the ink is homogenously distributed in an area of 693 µm width and up to 1024 µm depth.

deeper structures of the skin. Of importance is to know penetration depth and delivery capacities in relation to substance viscosity, molecule size and tissue properties.

The aims of this in vitro study were (1) to prove the ability of the hydroporation system to penetrate the epidermal compartment and (2) to be able to deposit liquids (NaCl, vitamin a and c solutions), viscous substances (hyaluronic acid), crystalloid suspensions (triamcinolone, 40 mg/ml), and molecules of higher molecular weight like antibodies (IgG-FITC), PEG's (FITC-PEG's) and sugars (Dextrane-FITC) into the dermis using an skin explant model with and without AFXL pre-treatment using two different types of ablative fractional lasers.

MATERIALS AND METHODS

A prospective, single-center, in vitro study was designed to examine morphological changes visible at microscopically as performed in earlier studies [11, 12]. The study protocol used a previously described model and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Skin samples, obtained at routine skin surgery, were used as skin explants. All subjects consented the use of their skin explants.

Hydroporation

Hydroporation was performed using the system JetPeel™-3 System (TavTec, Israel) in conjunction with two out of the available applicator systems (triples nose, single nose, Figure 1 and 2) and a specific prototype made for application tests (name?). The hydroporation system ensures a fluid stream accelerated up to 720 km/h.

Laser system

AFXL was performed with a 10,600 nm CO_2 laser (Exelo2, former Quantel-Derma now Alma Lasers GmbH) and a 2,940 nm Er:YAG-Laser (Burane FXL, former Quantel-Derma GmbH now Alma Lasers GmbH, optic lens array FX12).

The fractionated CO_2-laser was operated with a scanner, using a spot diameter of 250 µm. The pulse duration (exposure time) was 1 ms, and the pulse energy of 40 mJ was delivered by 1 stack and 1 pass at a density of 250 MAZ/cm^2. The average fluence in each MAZ generated by a scanner was 81.6 J/cm² (spot area 0.049 mm²; 40 mJ / 0.049 mm² = 0.04 J / 0.00049 cm² = 81.6 J/cm²). The average fluence with the treatment area is calculated as 40 mJ * 250 MAZ/cm^2 = 10,000 mJ/cm² = 10 J/cm².

The fractionated Er:YAG-laser was operated with a FX12 optic a lens array, density of 270 MAZ/cm^2, providing a spot diameter of 150 µm. The laser was set to 31.8 mJ pulse energy with a 300 ms pulse duration (exposure time), consisting of 10 stacked subpulses of 3.18 mJ each. The average fluence with the treatment area is calculated as 31.8 mJ * 270 MAZ/cm² = 8,586 mJ/cm² = 8.6 J/cm². Therefore the average fluencies in each treatment areas are comparable, despite differences in absorption characteristics.

Skin explants

Skin explants were subjected to hydroporation (JetPeel™-3 System, TavTec, Israel) using (1) alcian blue inked 0.9 % NaCl, (2) unstained 0.9 % NaCl applications for 10 s, 30 s, 1 min, (3) ready to use solutions containing vitamin a and c as well as hyaluronic acid (4) crystalloid suspensions (triamcinolone), (5) proteins (IgG-FITC, goat anti-mouse IgG-FITC, average molecular weight ~150,000, Santa Cruz Biotechnology, cat# sc-2010), (6) FITC-PEG's (Fluorescein hetero-functionalized polyethylene glycol, MW 2000, cat# PEG4-0002, mPEG-FITC, Nanocs, www.nanocs.com) and (7) sugars (Fluorescein isothiocyanate-dextrane, Dextrane-FITC, average molecular weight 70,000, Sigma cat# 46945) to investigate morphological tissue changes and to measure distribution within the epidermis and the dermis. To test the potential synergistic effect of AFXL in conjunction with hydroporation skin explants were fist subjected to AFXL as described above and then hydroporated using test substances of higher molecular weight (8) IgG-FITC, FITC-PEG's and Dextrane-FITC.

Routine pathology workup

Each skin sample was subjected to 4 % buffered formalin post intervention. Following fixation in formalin, all skin explants were

embedded into paraffin, sectioned into 4 µm to 6 µm thick slices and stained with hematoxyline and eosin and alcian according to in-house routine protocol. Only samples treated with inked NaCl were processed without H&E and alcian staining.

Immunofluorescence

The tissue sections were frozen and sectioned into 5–8 µm thick slices. Slides were the analyzed using the fluorescence microscope using different magnifications (Olympus BX41, Germany, magnification: 1.25, 4, 10, 20, 40, 60, 100x) and documented using a calibrated digital camera system (Olympus DP71, Germany) together with the software evaluation package (Olympus Cell F, Germany). Fluorescence microscopy enabled visualization of FITC-labeled antibodies, PEG's, and antibody distribution in detailed areas of skin the sections before and after hydroporation alone or following ablative fractional laser treatment.

RESULTS

The investigation of the general ability of the Jetpeel hydroporation system to interact with epidermal and dermal human structures was first tested by the application of stained 0.9 % NaCl inked with alcian blue. The test application was performed using the single outlet handpiece with a mean application time of 10 s per area of app. 1 cm^2. The histological slides reveal a homogeneous distribution of the ink which was also visible macroscopically within the upper two thirds of the dermal compartment leaving the epidermis on microscopical level intact. Interestingly only remnants of ink were detectable at the explants surface (Fig. 3).

To further test the safety and efficacy of the hydroporation system over time of application, unstained 0.9 % NaCl has been applied using the triple outlet handpiece for 10 s, 30 s and 60 s in a defined surface area of app. 1 cm^2. As control served massage application in the same area size according to the instructions of the manufacturer. H&E stained slides revealed no epidermal or dermal changes using the so called massage application. In comparison to untreated controls superficial parts of the stratum corneum only have been removed (Fig. 5). When hydroporation was done over a time period of 10 s vacuole

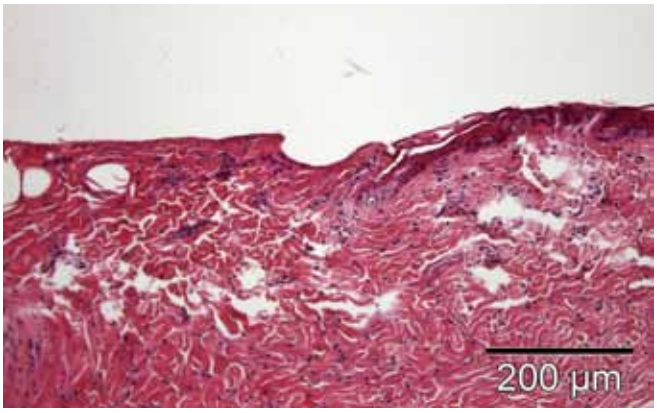

Fig. 7: Hydroporation over 60 s in a defined area led to a complete loss of the epidermis, dermal vacuole formation, and localized separation of dermal fibre bundles.

Fig. 8: Using ready to use solutions containing vitamin a provided by the manufacturer a rather uniform vacuole formation, spreading of dermal fibers within the full depth of dermis up to 1436 µm was measurable. However in some areas there was also a complete destruction of the dermal fiber structure visible.

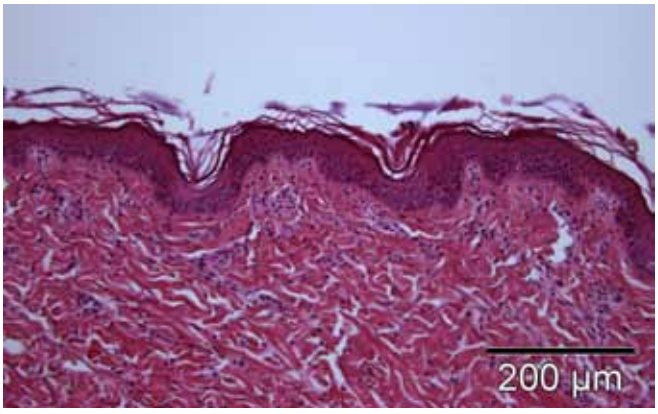

Fig. 5: Hydroporation does not lead to any morphological changes within the epidermis or dermis. In comparison to untreated controls superficial parts of the stratum corneum only have been removed.

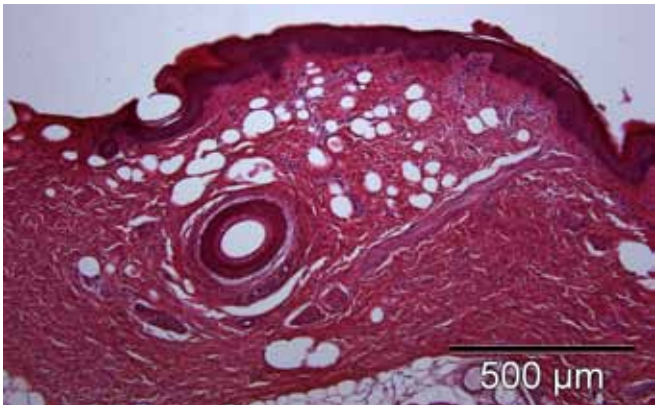

Fig. 6: Hydroporation over 30 s in a defined area led to vacuole formation, removal of the stratum corneum and circumscribed epidermal loss. Localized separation of dermal fibre bundles are visible.

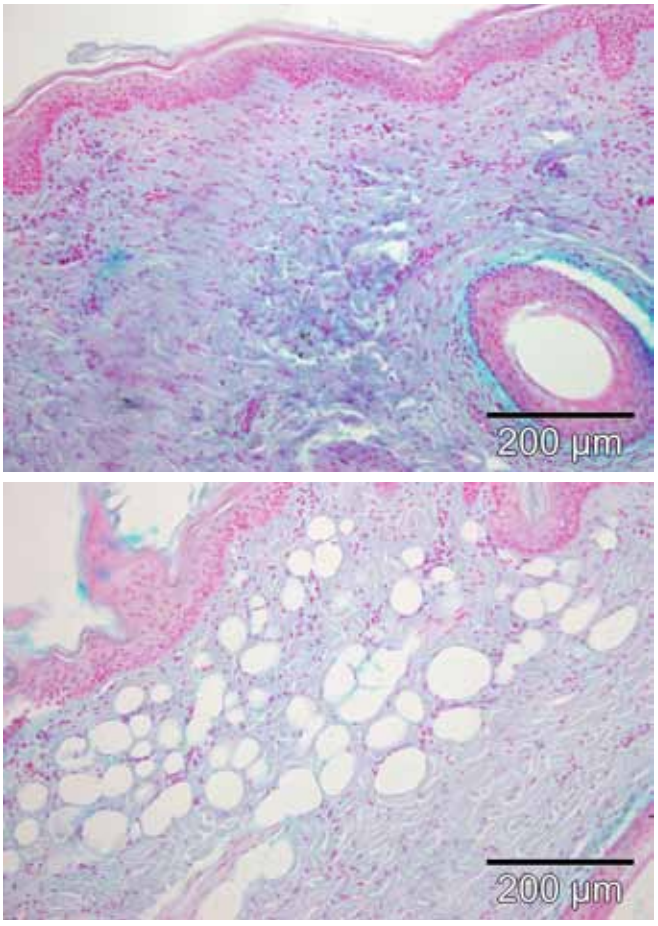

Fig. 9: If the provided hyaluronic acid in low viscosity condition as provided by the manufacturer was applied in the same way equivalent distribution pattern could be achieved as visualized in light blue color by alcian blue staining. Most probably depending on application pattern a predominant vacuole formation or a more in between the fibers deposition pattern was visible.

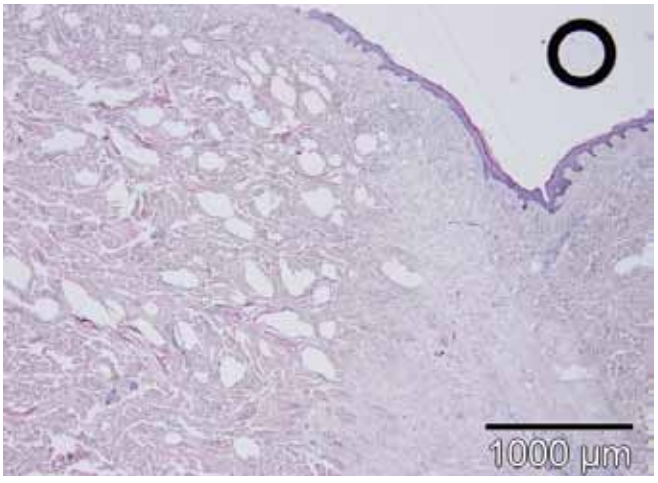

Fig. 10: Microscopy of a scarred tissue explant subjected to triamcinolone hydroporation. The tissue section reveals a homogenous deposition of the drug within the dermis. However denser scar tissue has not been penetrated (H&E). On top of this there was a higher tendency of an epidermal damage.

formation within the upper thirds of the dermal compartment appeared. Extending this time up to 30 s vacuoles increased in size (Fig. 6). Localized separation of dermal fiber bundles was visible. On top of this, in circumscribed areas there was a complete loss of the epidermis. Extending the application time to one minute revealed a total loss of the epidermal compartment (Fig. 7) as described earlier [10].

In a third step of experimentation ready to use solutions containing vitamin a and c as well as hyaluronic acid provided by the manufacturer have been applied to skin explants in order to estimate the distribution of within the dermis and to measure maximum penetration depths. Using those solutions and applying them according to the instructions of the manufacturer in skin explants after standard histology work-up a penetration up to 1436 µm was visible while there was a more or less uniform vacuole formation pattern and spreading of the dermal compartment visible (Fig. 8). There were no major differences visible if vitamin a or vitamin c solution were in use. If the hyaluronic acid of low viscosity condition as provided by the manufacturer was applied in the same way, equivalent distribution pattern could be achieved visualized by alcian staining. Most probably depending on application pattern a predominant vacuole formation or a more in between the fibers deposition pattern was visible (Fig 9 a+b). Interestingly with increasing viscosity there was no more pronounced epidermal damage visible on a microscopic level. As control a classical syringe based filler has been used. There was a clear dermal- and subdermal deposition of an opaque material visible. Volume wise the filler application was much higher than that of the hydroporation system.

To further test the limits of the system and to answer the question if the concept may be also translated into clinics a crystalloid suspension (triamcinolone) as in use for clinical scar treatment has been applied to skin explants bearing scars using the prototype handpiece. Interestingly hence the sizes of the crystals is much smaller that the nozzle size of 120 µm the triamcinolone particle could be transported via stream through the nozzle. Microscopy revealed a homogenous deposition of the drug with the dermis. However, the power of the system was clearly insufficient to penetrate the denser scar tissue (Fig. 10).

To date trans-dermal drug delivery assisted by fractional laser is of extreme importance. Therefore the ability of the system to transport fluorescence labelled molecules like antibodies (IgG-FITC), PEG's (FITC-PEG's) and sugars (Dextrane-FITC) have been tested while using the prototype handpiece. Fluorescence microscopy revealed no significant deposition of the high molecular test substances PEG and the IgG antibody using the hydroporation system only. Only some deposition was visibly applying the sugar (Fig. 11 a–c). Hence the method of AFXL is now widely used to enhance dermal drug delivery in daily clinics, two laser systems were used to facilitate the hydroporation induced uptake of high molecular substances (Fig. 12 a–c). Pre-treatment of both laser systems resulted in an enhanced deposition of all high molecular weight test molecules within the MAZ and also the coagulation zone made by the CO_2-Laser. If an Erbium laser was used the deposition within the dermis

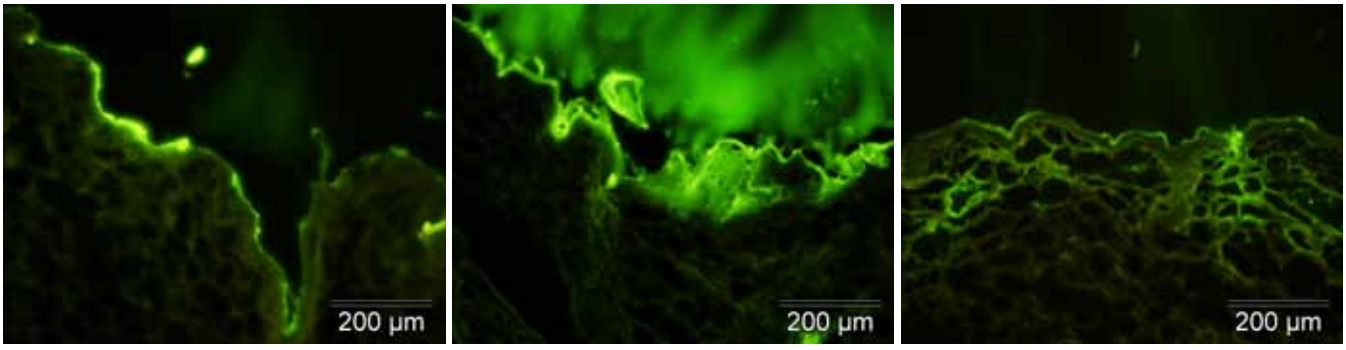

Fig. 11: Immunofluorescence of penetration capacity of hydroporated IgG-FITC (Fig 11a), FITC-PEG's (Fig 11b) and Dextrane-FITC (Fig 11c) without laser pre-treatment.

was less intense around the MAZ most probably due to the fact of a lower residual thermal damage.

DISCUSSION

The investigation of the general ability of the Jetpeel hydroporation to penetrate the stratum corneum and the epidermal compartment in order to deposit liquids and small molecules by using an jet stream of liquids accelerated by pressure up 720 km/h through an very small singular or triple nozzle revealed by using inked 0.9 % NaCl a homogenous localized dermal deposition in unstained tissue slides made of human skin explants.

Hence the amount of liquid applied to a given surface area is strongly operator dependent, the safety of the massage procedure as suggested by the manufacturer has been tested successfully. According to the H&E slides a very superficial removal of the stratum corneum was visible only. However, extended application times resulted in first vacuole formation, lateral spreading of collagen fibers and finally complete loss of the epidermal compartment as known from previous studies [10]. These findings suggest that precise operator skills are necessary for optimal effects and homogenous deposition of substances using the system. The experimental design using skin explants and inked NaCl might provide a cheap an easy training setting hence coloration is visible by the naked eye. Furthermore, states of the art of after care professional assistance of wound healing are required in case of epidermal damage. As known from laser procedures, precautions may be set in place e.g. herpes prophylaxis, sunscreen, down time and post treatment regimen.

The manufacturer does provide a variety of ready to use liquids containing for example vitamin a and c as well as hyaluronic acid of low viscosity for dermal treatments. The question arose if at all and how deep those substances may penetrate and what the distribution pattern looks like. There were no major differences of distribution type and depths visible if vitamin a or vitamin c solution were in use. The total penetration depth was measured as 1,436 µm while preventing a major epidermal collateral damage. In case of the hyaluronic acid which does certainly excels a higher viscosity similar distribution types and patterns were visible on a microscopic level.

In an experimental set-up using the prototype handpiece mounted with a matching vial containing a standard solution of triamcinolone 40 mg/ml as clinically used for scar treatments the hydroporation concept has been tested if crystalloid suspension also may be applied to healthy and scarred tissue. Microscopy revealed a rather homogenous deposition of the drug within physiological tissue while dense scar tissue was almost not penetrated. It is therefore concluded that small insoluble particles in liquid might be transported by the system, however penetration capacity is limited if texture density increases.

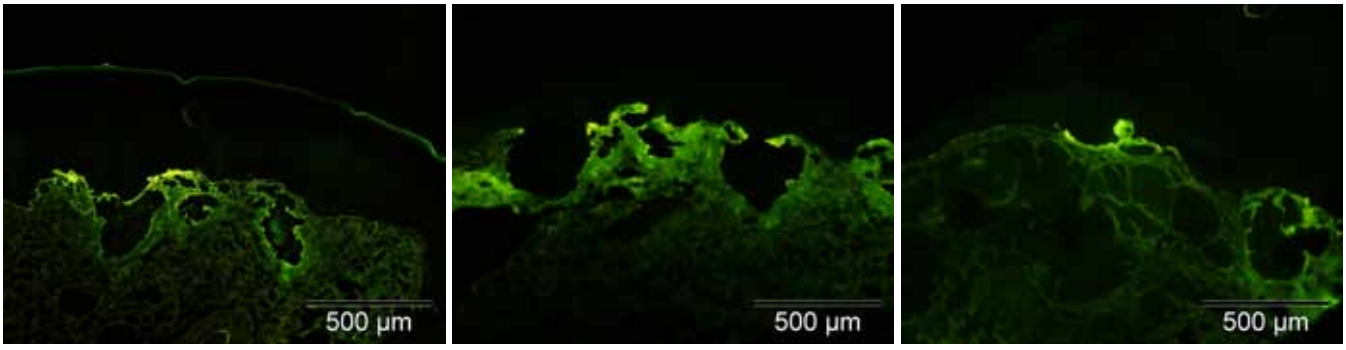

Fig. 12: Immunofluorescence of penetration capacity of hydroporated IgG-FITC (Fig 12a), FITC-PEG's (Fig 12b) and Dextrane-FITC (Fig 12c) using a CO2- ablative fractional laser pre-treatment.

Another potential limitation of the system is assumed if high molecular molecules shall be applied. Hence their application would of clinical interest three test molecules were used to test the transportation capacity and the ability to get those molecules deposited to the dermis. The experimental design was made by using fluorescent labelled antibodies, PEG's and dextrane. Using the hydroporation alone it has to be concluded although transported onto the skin surface there was a limited penetration visible for the dextrane only. Moreover in conjunction with an AFXL pretreatment however this limitation could be overcome clearly.

There are several limitations of the study that warrant attention. First those results gained in-vitro may not directly apply to clinical settings. Especially the experimental design does not allow the exact calculation of how much of the potential drugs can be transported into the skin. Finally it remains open, to test if potentially applied drugs, molecules or substances tolerate this mechanism of transportation without change or loss in function or biological properties. These might be especially the case in large size proteins like antibodies.

CONCLUSION

This in large vitro study clearly demonstrated that the hydroporation concept can be applied to human skin in a safe and effective manner as long as a well-trained operator follows the instructions of the manufacturer. Hence the jet stream is accelerated to enormous speeds liquids containing active substances as well as hyaluronic acid having a higher viscosity can be transported. Even small insoluble particles may be placed into the dermal compartment. However, penetration capacity is limited if texture density increases as it is the case in scars. Also due to the fact of the very high pressure acting on the epidermis inappropriate use of the system might lead to epidermal damage or complete loss of it resulting in wounding. Therefore appropriate after care needs to be provided. Hence hydroporation would be a very nice contact free application method in a wide clinical setting e.g. vaccination, topical biological therapy and many more the transport and deposition capacity of the system has been tested using antibodies, a PEG's and dextrane. Although still being transported via the nozzle the penetration into the dermis was limited. A second approach using two different fractional ablative laser pre-treatment protocols at standard settings revealed again a sufficient dermal deposition.

Taken together this large in vitro study clearly shows the potential and limitation of the concept of hydroporation. Further clinical trials shall be performed to confirm these in-vitro findings.

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Uwe Paasch served as consultant for Quantel-Derma GmbH, now Alma Lasers GmbH, Nürnberg, Germany.
The JetPeel V3 was loaned from Laserwelt GmbH, Berlin Germany.

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JetPeel™ a New Technology for Facial Rejuvenation

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Shaare Zedek Medical Center, Jerusalem, Israel

ABSTRACT:

JetPeel™ is a new device for cosmetic resurfacing of the facial skin. It uses a new technology of a two-phase stream that creates a jet comprised of gas (oxygen) and micro droplets of fluid (saline) accelerated to supersonic velocities. This jet impacts the skin causing gentle and accurate cosmetic peeling.

Our preclinical and clinical experience with the JetPeel™ for rejuvenation of the face is presented. In a group of 50 patients we found the JetPeel™ technology to be a safe and effective new tool for the usual indications for facial peeling. It was most useful and effective for perioral peel. JetPeel™can be used in combination with other resurfacing modalities such as chemical peeling or laser.
Further investigation is needed to explore other applications of this technology, such as using different combinations of gases and fluids, and transdermal transfer of medication dissolved in the peeling jet.

INTRODUCTION:

The desire to rejuvenate the skin by resurfacing it is very old and dates back to the era of ancient Egypt. The oldest record of cosmetic therapies performed by physicians is the Ebers papyrus (1560 B.C) [1]. Early resurfacing techniques involved direct application of minerals, plant extracts, sulphur, mustard or limestone. Renewed interest for facial skin resurfacing was noted among physicians and surgeons in the early twentieth century. McKee (1903) was the first to report his experience with liquid phenol in the treatment of acne scars [2]. Kromayer (1905) is considered the first to apply mechanical dermabrasion techniques using rotating wheels and rasps for the treatment of acne scars, keratoses and pigmentation disorders [3]. After World War II lay peelers rather than physicians and surgeons developed new techniques and proclaimed to find the fountain of youth for their patients. Skepticism of the medical society gradually resolved in the 1960s with data from numerous studies showing the clinical effectiveness and histological changes in the skin associated with chemical peeling [4-9].
Traditionally peeling techniques are either chemical or mechanical. In chemical peeling the chemical solution applied to the face is designed to cause controlled peeling of the superficial layers of the skin.
In dermabrasion a mechanical device is used to resurface the skin by removing the same layers. A variety of abrading techniques are available, the most popular one being a small rotating abrasive wheel applied to the skin.

Since the early 1990s various types of lasers have been used to resurface photo aged skin. CO2 Laser was first introduced in a nation-wide presentation by Roberts in 1995 [10]. Since then, technologies have been changing and the clinical use has expanded rapidly throughout the world. Many proponents of Laser resurfacing attest to its accuracy and predictability of the clinical results obtained by experienced operators.

The various types of peeling techniques share a common denominator: they all produce a partial thickness injury to the skin. Following the controlled injury to the skin, wound healing processes ensue regenerating the epidermis, replacing and reorienting the fibres in the dermis. The effectiveness of the resurfacing technique is directly related to the depth of the controlled injury to the skin. The physiologic basis of healing following either technique rests upon the ability of the skin to regenerate its epidermal cover by epithelialization through the skin appendages, primarily the pilosebaceous unit. The result is an improved, more youthful appearance and texture of the skin.

This article introduces a novel method for skin resurfacing. The JetPeel™ device is based on a new technology derived from the world of aviation. A mixture of sterile saline and oxygen passes through an open converging-diverging venturi channel, designed to produce supersonic flow accelerating the solution droplets to approximately 200 m/sec and exits through specialized nozzles as a powerful jet directly onto the desired area of skin. This high-energy micro droplet spray gently exfoliates the skin. After removing the epidermal layer additional layers of the upper papillary dermis can be removed accurately to reach the desired end point depth as set by the operator.

STUDY OBJECTIVES:

To determine the safety and the efficacy of the JetPeel™ system as a peeling modality in a preclinical setting and to determine the clinical results and patient satisfaction with the procedure.

MATERIALS AND METHODS:

1. THE TECHNOLOGY

The idea behind the JetPeel™ is derived from the world of aviation using supersonic flow in nozzles. Liquid medium is propelled by sub-atmospheric pressure caused by the rapid flow through a parallel capillary tube. The mixture of liquid and gas is accelerated in an open converging-diverging venturi channel to reach high velocity using a two-phase stream and emits through a specially designed nozzle unit. The jet spray impacts on the skin causing shearing forces strong enough to peel the epidermal and dermal layers of skin as necessary.

2. THE DEVICE

The device used in this study is the JetPeel™ system manufactured by TavTech Ltd., (Yehud, Israel). The JetPeel™ system is a portable device, which produces a spray of liquid mixed with gas under a predetermined pressure of 7 atmospheres. The jet spray consists of liquid droplets, 5-200 m in diameter, emitted at a speed of up to 200 m/sec.

The JetPeel™ device consists of a control unit, a hand piece, a footswitch and tubing line accessories. A source of pressurized oxygen (or any other gas, e.g. nitrogen) is connected to the control unit set to yield a pressure of 7 atmospheres. A disposable solution bag supplies the sterile liquid medium needed. The mixture of gas and fluid occurs inside a sterile, disposable hand piece. A separate suction hand piece removes gas and debris.

3. PEELING TECHNIQUE

The hand piece is held by the operator at a 45o-90o angle to the skin surface and at a distance of 2-5 mm from the skin. When the footswitch is pressed the jet is released from the nozzles. Care is taken to avoid the eyes and the eyelids. When the jet is applied to the skin a blanching effect is noticed representing a momentary withdrawal of blood from the treated skin segment. This serves as an indicator for proper application of the jet. Gradually the abrasive droplet attack creates enough mechanical energy for peeling of the epidermis. Slow scanning advancement of the jet stream is then begun along a line in a forward direction, exploiting the momentum of power, creating a “front” of peeling and achieving a uniform depth of removal. Areas for which the operator wishes to increase the depth of peeling are retreated in the same manner (for example: along the wrinkle creases in the perioral area). Punctate bleeding and its intensity after discontinuing the jet serve as an indicator for the peeling depth (Figure 1).

4. PRECLINICAL STUDY DESIGN:

Since the porcine model is the most closely analogous to human skin, it was used as the preliminary in vivo model. The porcine model has been well established in the scientific literature [11].

Four porcine (sus scrofa) of a local strain of Landrace x Large Whites, aged less than 2 years and weighing about 15 kg, were used as the experimental model.

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After proper acclimatization, fasting and sedation, general anesthesia was initiated. The back and flank of the anesthetized pigs were clipped, taking care not to cause injury to the skin, and then scrubbed according to standard aseptic practices for preparation of skin (Iodine surgical scrub and Alcohol rinse). A template was used to mark the experimental windows on each side of the back and flank of the swine.

Skin peeling technique was performed using the JetPeel™ system.

Full thickness 8 mm punch biopsies were taken both immediately prior to the procedure and at 7 and 14 post treatment days during the healing phase.

Evaluation was based on gross and microscopic examinations of the biopsies. The parameters examined included peeling depth, dermal inflammation and re-epithelalization.

5. CLINICAL STUDY DESIGN:

The study group consisted of 50 healthy adult volunteers who agreed to participate in our study. The study was conducted in accordance with the Helsinki committee regulations for human experiments.

The indications for treatment were: sun damaged skin, facial rhytids, pigmentation disorders and post-acne facial scarring.

Periocular skin and eyelids were excluded from treatment.

For partial facial procedures the treatment area was anesthetized locally using 5% EMLA cream in all cases. Facial blocks using 2% Lidocaine with 1:200,000 Adrenaline were used as necessary. Full-face procedures were done under general anesthesia or IV sedation.
The skin was aseptically prepared and draped using a Betadine solution mixed with normal saline at a ratio of 1:1.

The procedure was continued until the end result as desired by the operator was reached, judged clinically by direct vision and the intensity of punctate bleeding.

At the end of the procedure petroleum jelly (Vaseline) was evenly applied to cover the entire treatment area. An open treatment regime was used postoperatively and the patients were instructed to cleanse the treated area with warm tap water and mild soap twice daily and then to apply a fresh thin layer of Vaseline.
All the patients were given oral Acyclovir 200 mg 5 times daily from a day prior to the procedure until healing was complete.

RESULTS:

PRECLINICAL:

Biopsies taken from the treated skin showed the effects of removing the epidermis and the upper dermis. Healing was uneventful, occurring from 7 to 14 days post treatment. There were no wound healing complications (e.g. infection, delayed healing, etc.). Clinical and histological examinations proved that the JetPeel™ achieved the desired peeling effect (Figure 2).

CLINICAL:

The study group consisted of 50 healthy adult volunteers, 40 females and 10 males (age 19-62; mean 38)
The indications for treatment were: sun damaged skin, facial rhytids, skin pigmentation and post-acne facial scarring.
Treatment areas were: concealed retro auricular skin in the preliminary 10 cases, partial facial areas (especially perioral) in 32 and full-face peeling in 8.
Healing course was smooth and uneventful. Re-epithelialization occurred within 7 to 9 days depending on the depth and location of the area treated. Regular follow-up visits were scheduled at predetermined intervals, the longest follow up to date being 24 months.

The overall length of treatment ranged 5-70 minutes.
The healing phase was very smooth and easy. Erythema was noted during the first 2-4 weeks post peeling. All the patients were instructed to abstain from the sun as much as possible and to use sunscreens with SPF >= 30 whenever sun exposure was inevitable.
The aesthetic results as judged both by the patients and by the medical staff were good to excellent and patient satisfaction was high (Figures 3,4).

COMPLICATIONS:

We noted only a few cases of complications, all of which were minor:
One case of Herpes Simplex Virus (HSV) infection was noted in a 40 year old female with post-acne scarring after a full-face jet peeling procedure despite preventive treatment with Acyclovir. The patient was noticed to have pain, erythema and some small vesicles on her face. The dose of Acyclovir was increased to a therapeutic level given intravenously and an antibiotic treatment was added. Healing was complete with excellent results and no scarring (figures 5 A, B).
Three cases of hyper pigmentation, presumably related to sun exposure, were treated conservatively with Hydroquinone and Isotretinoin based products with satisfactory improvement.
One case of subcutaneous emphysema of the lower eyelid was encountered when the treatment was too close to the periocular area. The emphysema, although troublesome both to the surgeon and to the patient, subsided in 2-3 hours without any sequelae.
This unique complication is due to subcutaneous penetration and dissection of the jet stream in a very loose and thin type of skin. The best way to avoid it is to exclude areas of thin skin (usually the eyelids) from treatment, and to use eye-blocking goggles as a means of protection from inadvertent passage of the jet to emphysematous prone areas.

DISCUSSION:

Whenever a new technology, method or technique is introduced it must prove itself to be superior or at least as good as older "traditional" methods. It is commonly said that a new technology is not necessarily good or better, but every good and useful technology was once new. The most appealing parameters about the JetPeel™ are its simplicity, efficacy and safety.

The results show that the JetPeel™ system is a safe and effective device that achieves mechanical peeling through natural resources such as saline and oxygen. It avoids potentially harmful processes like burns and does not create an eschar of dead tissue.
It appears to be less bloody and cumbersome as compared with traditional dermabrasion devices. The device is quite easy to operate and mandates only minimal dexterity from the operator with a short learning curve as noted by ourselves.
The resources needed for applying the JetPeel™ technology (saline and pressurized gas) aside from the JetPeel™ device itself are readily available in most medical facilities. It is an accurate tool that can be applied to the desired area without any significant collateral damage.

It is a versatile tool which allows for "fine tuning" of the peeling depth by controlling gas pressure and number of passes, thus meeting the requirements of different areas of skin simultaneously. Since the skin is actually peeled off it is not left to become necrotic and slough later. It is our clinical impression that healing is somewhat smoother and swifter as compared to other peeling modalities.
We find the JetPeel™ especially efficient in treating the perioral region. The ability to achieve different depths of penetration in this area is of significant importance.
The JetPeel™ technology can be used in combination with other peeling techniques, for example combining the accuracy of the JetPeel™ in the perioral area with the speed of a chemical peel in the rest of the face.

We believe that further applications of the JetPeel™ technology should be carefully examined. One example is the use of various combinations of liquids with gases that may prove to be superior to others. Another example is the potential transdermal transfer of medications, passing the skin barrier. This type of transdermal transfer deserves serious investigation and might be a useful vector for introduction of various medications, from vitamins to growth factors, for various therapeutic purposes.

It is possible that tissue oxygenation during the treatment with the JetPeel™ device contributes to the accelerated wound healing that was noticeable in this study.

Another application is already in use: a very superficial peeling is performed by para-medical staff for indications like post rhinoplasty intense skin treatment or post Laser eschar removal.

CONCLUSIONS:

These are the first published results from an ongoing study. We find several advantages for the use of the JetPeel™ technology as a peeling technique: it is safe, accurate and versatile. Perioral rhytids, which are numerous creeks compacted closely together, best demonstrate the advantage of JetPeel™ technology as it has the added ability to treat each wrinkle separately. The healing process was noticed to be very smooth and easy. Our patients were very satisfied with the treatment and the results.

The KISS principle (Keep It Safe and Simple) strongly applies to the JetPeel™ system. Further applications of this technology should be investigated.

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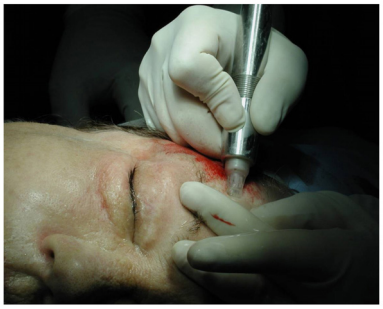
Figure 1:



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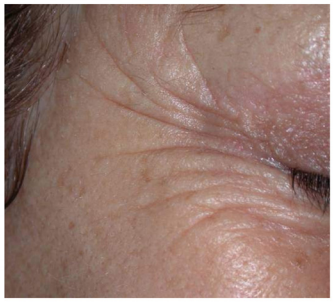

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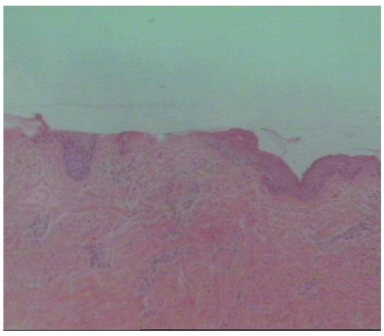

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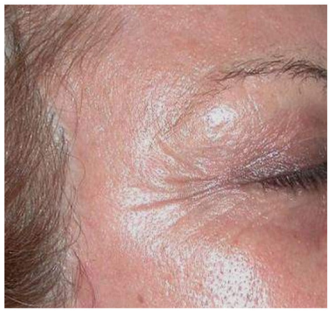

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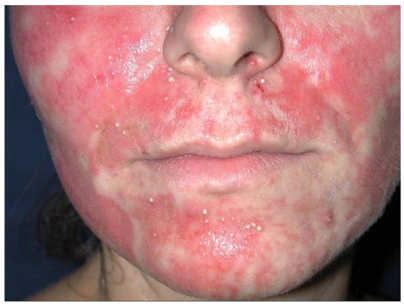

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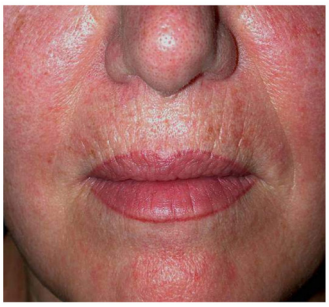

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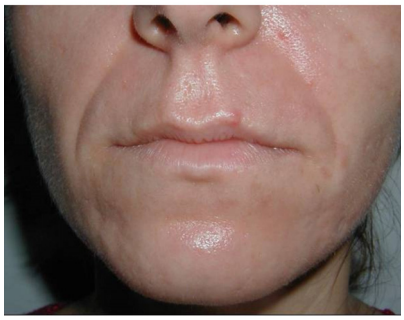

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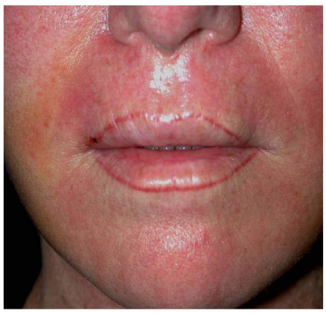

Legend to figures:

Figure 1: The technique of using the JetPeel™ system.

Figure 2: Histological examination of porcine skin treated with the JetPeel™ device. Level of peeling is at the papillary dermis (H&E X4).

Figures 3 (A, B): Treatment results of the crow's feet: A - Pre treatment, B - Post treatment.

Figures 4 (A, B): Treatment results of perioral rhytids: A - Pre treatment, B - Post treatment.

Figures 5 (A, B): Herpes Simplex Virus Infection. A - Active infection, B - Aesthetic result one month after healing was complete.