

Successful Short-Term and Long-Term Treatment of Melasma and Postinflammatory Hyperpigmentation Using Vitamin C With a Full-Face Iontophoresis Mask and a Mandelic/Malic Acid Skin Care Regimen

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ABSTRACT

Background: Treatment of melasma and postinflammatory hyperpigmentation is often challenging. No ideal short-term and long-term treatment is available. Vitamin C alone and in combination with iontophoresis has been studied and found to be useful; however, no long-term studies have been published.

Methods: In this study, 35 patients (34 female, 1 male) were treated with a novel full-face iontophoresis mask (FFIM) and a proprietary vitamin C (ascorbyl glucoside) preparation. Patients received one in-office treatment and 12 to 24 at-home treatments over 1 to 2 months in conjunction with a strict maintenance regimen consisting of a mandelic/malic acid skin care regimen, broad-spectrum ultraviolet A/ultraviolet B sunblock, a wide-brimmed hat, and sun-avoidance behavior. Follow-up after the initial in-office treatment ranged from 1 to 54 months (mean, 26 months). Four independent observers graded improvement of melasma and PIH using a 4-point scale. Before the study, high-performance liquid chromatography was used to verify iontophoretic penetration of vitamin C into the skin to a level of 0.2 cm in healthy volunteers (2 male, 2 female).

Results: A mean 73% improvement in abnormal pigmentation was observed at the end of FFIM/vitamin C treatment. Greater than 25% improvement was observed in 32 of 35 patients, and greater than 50% improvement in 22 of 35 patients. Melasma Area and Severity Index scores demonstrated substantial improvement from baseline for all patients, with a mean improvement of 15.7.

Conclusions: Full-face iontophoresis of vitamin C appears to be an effective short-term treatment for melasma and postinflammatory hyperpigmentation. A protocol of strict sun avoidance in combination with a mandelic/malic acid skin care regimen appears to be useful in maintaining the improvement.

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INTRODUCTION

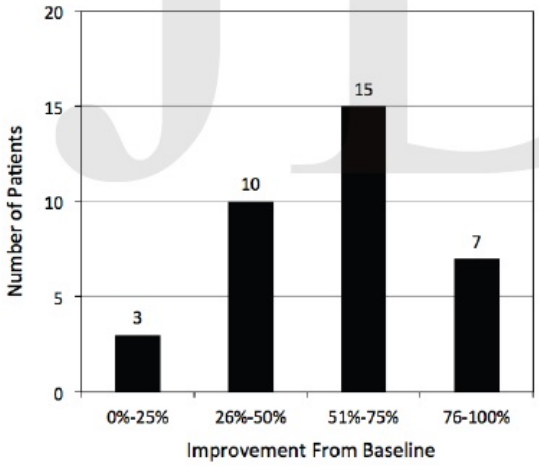
Melasma is a disorder of symmetrical hyperpigmentation predominantly affecting the faces of women with Fitzpatrick skin types III and IV. Sun exposure and hormone stimulation of localized hyperpigmentation are considered to be exacerbating factors.[1-5] A comprehensive review of melasma etiopathogenesis and treatment has recently been published.[6,7] Postinflammatory hyperpigmentation (PIH) is abnormal pigment darkening in areas of trauma, inflammation, and irritation.[8] Melasma and PIH are more common in skin of color than in white skin.

The most common treatment for melasma and PIH is the topical application of hydroquinone, alone or in combination with other ingredients such as tretinoin and a corticosteroid. Other topical agents used to treat melasma include retinoids, azelaic acid, kojic acid, α-hydroxy acids, β-hydroxy acids, beta carotene, mequinol, arbutin and deoxyarbutin, licorice extract, rucinol, resveratrol, 4-hydroxyanisole, 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone, *N*-acetylglucosamine, soybean trypsin inhibitor, and tranexamic acid.[6,7] Superficial and deep chemical peels, lasers, and intense pulsed light have all been used with mixed success.[6,7] Vitamin C is an excellent agent for the treatment of abnormal pigmentation; however, its instability and lack of penetration into the skin prevent it from being a highly effective means of treating melasma and PIH.[9-12] None of the aforementioned treatments provide an ideal short-term and long-term solution for melasma and PIH.

Iontophoresis is the use of a direct electrical current consisting of a negative (–) and a positive (+) charge to push an ionic molecule with the same charge (either + or –) through the epidermal barrier of the skin. Positively charged ions are driven into the skin at the anode, while negatively charged ions are driven into the skin at the cathode. Historically, iontophoresis has been used by medical professionals to deliver certain drugs through the skin to treat a wide range of conditions, including inflammation, pain, scar tissue, and calcium deposits, as well as providing dermal anesthesia.[13-15] Iontophoresis is a well-established drug delivery

FIGURE 1. The full-face iontophoresis mask (Cosmion Iontophoretic Rejuvenating Facial Mask; Cosmion LLC, Salt Lake City, UT).

FIGURE 2. Improvement in melasma pigmentation after treatment with full-face iontophoresis mask vitamin C therapy (n=35; mean follow-up 26 months).



method used primarily in the practice of rehabilitative medicine to transport charged drug ions across the skin barrier to a therapeutic level.[5] A few studies have established the utility of this means of delivery of vitamin C to effect a clinical improvement in melasma.[16,17] Vitamin C is a negatively charged ion in solution that may be transported into the skin using iontophoresis in the treatment of melasma.[2]

α-Hydroxy acids, including glycolic acid and lactic acid, have also been used in the treatment of melasma with some benefit.[3-7] One of the authors (M.B.T.) has extensive experience using other α-hydroxy acids, including mandelic and malic acid, in the treatment of melasma. Mandelic acid is an aromatic α-hydroxy acid with the molecular formula $C_6H_5CH(OH)CO_2H$. Malic acid is an organic compound with the formula $HO_2CCH_2CHOHCO_2H$. Both mandelic and malic acid are longer-chain α-hydroxy acids than glycolic or lactic acid and are less likely to cause irritation and PIH than glycolic acid (M.B.T., unpublished data, 2002-2008). Mandelic acid is widely recommended as an over-the-counter therapy for the treatment of melasma.[18,19]

We evaluated the treatment effect of vitamin C delivered via full-face iontophoresis mask (FFIM) combined with a mandelic/malic acid skin care regimen in patients with melasma or PIH.

METHODS

Patient Population

We initially evaluated the use of FFIM with vitamin C preparation in 101 patients with recalcitrant melasma or PIH receiving care at an aesthetic dermatology clinic. Patients verbally consented to have their data collected as part of this research study. There were no restrictions on the type of skin care products that patients could use for daily skin maintenance.

During the study, it was noted that patients using the FFIM vitamin C therapy and a certain daily skin care regimen consisting of a 6% to 10% mandelic/6% to 10% malic acid (M2; MCK Laboratories, Salt Lake City, UT) showed the greatest sustained improvements in pigmentation. This report describes the outcomes for the 35 patients who used the FFIM vitamin C therapy in conjunction with the mandelic/malic acid skin care regimen.

Treatment and Assessment

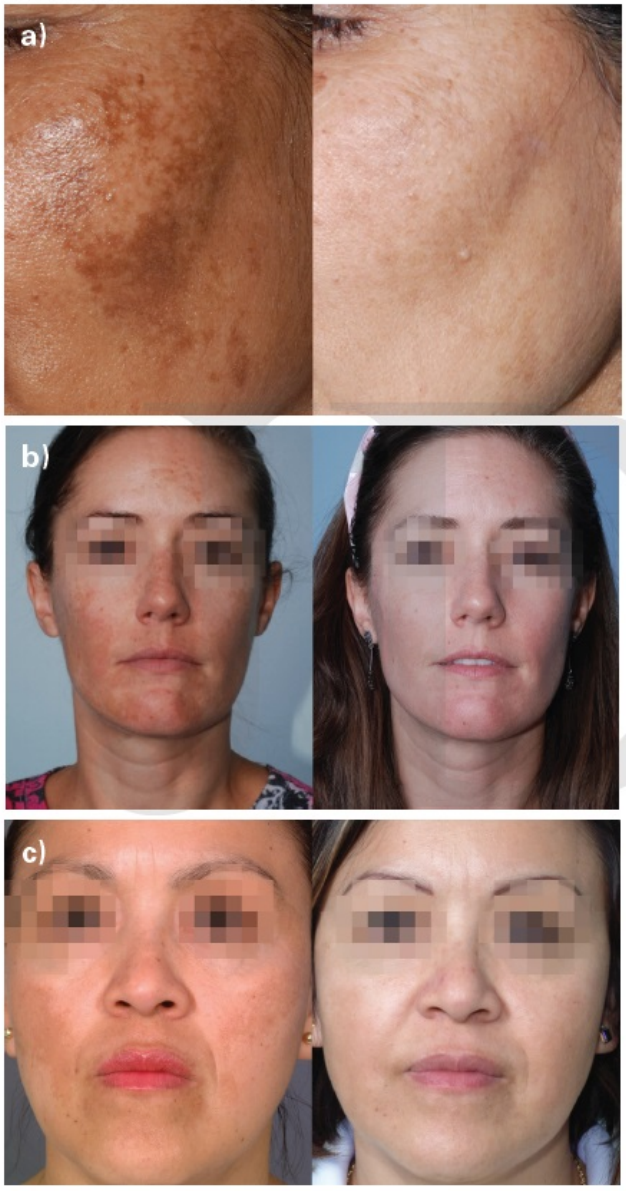
After screening and informed consent, patients were instructed in proper application and use of the FFIM and vitamin C preparation containing 20% ascorbyl glucoside. FFIM vitamin C treatments consisted of a 1-hour application 3 times each week for 1 to 2 months.

Photos were taken of each subject before and after (ie, last follow-up appointment) treatment using the Canfield Mirror Suite photographic system (Canfield Scientific, Inc, Fairfield, NJ) and a Nikon D-80 digital camera (Nikon Corporation, Tokyo, Japan). Photographs were judged by 4 independent observers, who graded the improvement of melasma and PIH on the following quartile scale: 1 = slightly better, 2 = moderately better, 3 = much better, and 4 = clear or almost clear. Response to treatment was also graded with the Melasma Area and Severity Index (MASI), which assesses severity in each of the 4 regions (forehead, right malar region, left malar region, and chin) as a percentage of the total area of involvement (A), darkness (D), and homogeneity (H).[20]

Full-Face Iontophoresis Mask (FFIM)

The FFIM utilized in this study was the Cosmion Iontophoretic Rejuvenating Facial Mask (Cosmion LLC, Salt Lake City, UT; Figure 1). This FFIM is constructed of medical-grade materials,

FIGURE 3. Photographs of patients before and after full-face iontophoresis mask vitamin C therapy.



including biocompatible gels and adhesive backing. The device utilizes a 6-volt power source, has a mask delivery area of 331.29 cm², and a mask area power output of 1.8 µAm per cm². The ground area power output is 14.14 µAm per cm².

Penetration of Vitamin C

Before conducting the current study, an experiment was performed to measure the depth that vitamin C penetrates into the skin when delivered via an iontophoresis patch identical in materials and construction to the FFIM. Three investigators (D.O.D., J.C.S., and M.C.) studied iontophoresis of vitamin C in 4 subjects (2 male, 2 female; mean age, 21.75 ± 2.63 years) recruited by classroom volunteer. Each subject had <5 mm of adipose tissue in the treatment area and was free of any injury, swelling, or infection for at least 3 months before the study. Under sterile conditions, an intramuscular microdialysis probe was inserted at the musculotendinous junction of the gastrocnemius muscle at a depth of 0.2 cm with a 27-gauge needle used as a guide cannula. The entrance and exit sites of the skin were separated by at least 2.5 cm. The guide cannula was inserted horizontally in the dermis, and the microdialysis probe was fed through the guide cannula. The cannula was removed, and the probe left in place. Doppler ultrasound was used to verify the depth of the microdialysis probe.

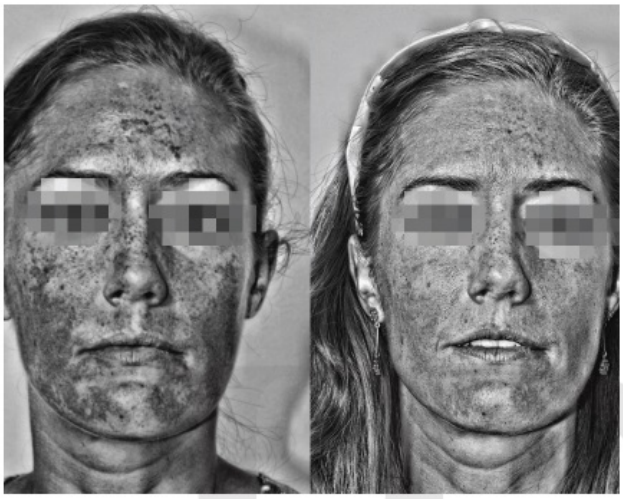
TABLE 1.

Patient Age, Skin Type, and Duration of Follow-up (n=35)	
Gender, n	
Female	34
Male	1
Age (y)	
Mean ± SD	47.6 ± 8.3
Min, max	36.0, 68.0
Fitzpatrick Skin Type, n	
Type II	1
Type III	13
Type IV	10
Type V	9
Type VI	2
Follow-up (mo)	
Mean ± SD	26.0 ± 16.2
Min, max	1.0, 54.0

SD, standard deviation.

After placement, the probe was perfused with 0.9% saline at a rate of 0.6 mL/hr with a Harvard infusion pump and the perfusate was collected in an Eppendorf container taped to the lateral portion of the leg. A 60-minute flush and recovery period was performed to allow local skin blood flow to return to baseline. Following the recovery period, the Eppendorf container was removed and replaced with a new one. A small amount of vitamin C solution was applied to the skin on the treatment site directly over the microdialysis probe. The battery-powered iontophoresis patch was placed with the negative pad directly over the microdialysis probe. Once the pad comes in contact with the skin, the current begins to flow. The treatment duration was 30 minutes, during which the 0.9% saline continued to flow through the probe at a rate of 0.3 mL/hr, pushing any vitamin C that penetrated the skin into the Ep-

FIGURE 4. Ultraviolet photo showing improvement in pigment before and after full-face iontophoresis mask vitamin C therapy. The patient reports her skin is still clear 3 years later.



pendorf container. At the conclusion of the treatment, the patch was removed and any adhesive from the electrodes left on the dermis was cleaned. The intramuscular microdialysis probe was removed, and portal sites within the tissue were treated with triple antibiotic ointment and covered with a sterile bandage.

A 20-µL sample was taken from each perfusate and analyzed using high-performance liquid chromatography (HPLC). A 2% diluted sample of the vitamin C solution in HPLC revealed 1 peak at 2 minutes, which was used as the standard to identify the vitamin C in the perfusate samples (D.O. Draper et al, written communication, 2008). The quantity of vitamin C was measured as an area under the curve in mAU*s, the ultraviolet (UV) detector's electronic absorption units. The HPLC results for subjects 1 through 4 were as follows: 41.71, 30.99, 49.23, and 29.02 mAU*s. These results demonstrate that the vitamin C solution delivered via iontophoresis penetrated the skin to a depth of 0.2 cm.

RESULTS

As shown in Table 1, 34 of the 35 patients were women. The mean patient age was 47.6 years. The majority of patients (32 of 35) had Fitzpatrick skin types III, IV, and V. After FFIM vitamin C treatment, patient follow-up varied from 1 to 54 months, with a mean follow-up duration of 26 months. Patients tolerated the treatment well. The only adverse event reported was a minor acne breakout following one of the early treatments, which may or may not have been related to the FFIM vitamin C treatment.

The mean improvement in melasma pigmentation from baseline was 73%. Greater than 25% improvement was observed in 32 of 35 patients, and greater than 50% improvement noted in 22 of 35 patients (Figure 2). Mean improvements in skin texture and wrinkles were 62% and 39%, respectively. As shown in Table 2, MASI scores also demonstrated substantial improvement from baseline for all patients (mean improvement, 15.7). Before and after treatment photos of 3 patients are shown in Figures 3 and 4.

DISCUSSION

Vitamin C used in combination with a full-face iontophoretic mask produced rapid improvement in appearance of melasma and PIH within 1 to 2 months in all skin types studied. With a daily skin care maintenance regimen of mandelic/malic acid, UVA/UVB sunblock and sun-avoidance behavior, the improvements were sustained up to 54 months. The combination treatment appears to be both safe and effective in maintaining long-term improvement in the appearance of melasma and PIH.

Wrinkles, skin tone, and texture were incidentally observed to improve during the study. This is not surprising, considering the long-term use of highly concentrated vitamin C and α-hydroxy acid products. Generalized facial lightening was also observed anecdotally in many of the patients in the study; however, data were not collected on this parameter.

Vitamin C therapy delivered via FFIM for 1 to 2 months was well tolerated in this study with only one minor acne breakout possibly related to the treatment. Other long-term therapies for melasma and PIH that have been effective are associated with adverse effects. Long-term therapy with a triple combination product (hydroquinone, tretinoin, and fluocinonide) appears to be effective. However, there is a measureable risk of skin atrophy and telangiectasia.[5,21] Other hydroquinone products also have adverse effects when used long-term, including irritation, exogenous ochronosis, PIH, and instability leading to decreased efficacy.[6,7]

> "This study supports the safe and effective use of a full-face iontophoresis mask for treatment of melasma as an important method for obtaining sufficient concentrations of vitamin C at therapeutic levels and skin depth to effect a favorable clinical response."

The long-chain mandelic and malic acids skin care regimen is well tolerated long-term. (M.B.T., unpublished data, 2002-2008). The 6 % mandelic/6% malic acid product is well tolerated in sensitive and darker skin types (Fitzpatrick types V and VI) without causing PIH. In addition, patients are often able to upgrade

to the 10% mandelic/10% malic acid formula following a few weeks of conditioning with the lower concentration. The pH of both products is 3.1 to 3.3. The personal experience of one author (M.B.T.) has shown mandelic/malic acid to be a less irritating α-hydroxy acid than glycolic acid and better tolerated in PIH-sensitive darker skin types.

This study supports the safe and effective use of a full-face iontophoresis mask for treatment of melasma as an important method for obtaining sufficient concentrations of vitamin C at therapeutic levels and skin depth to effect a favorable clinical response. The long-term use of a novel mandelic and malic acid skin care regimen further supports sustained improvement (mean, 26 months) when used in combination with a strict sun-protection protocol. Compliance with a strict regimen of sun protection and avoidance is difficult to measure. It is assumed that the patients in this study were much less than 100% compliant; however, a satisfactory improvement in melasma and PIH was still achieved.

DISCLOSURES

Dr. Taylor has an equity interest in Cosmion LLC and MCK Labs. Mr. Yanaki has an equity interest in ActivaTek Inc, a manufacturer of iontophoresis products. The other authors have no relevant conflicts of interest to disclose.

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TABLE 2.

MASI Improvement After Treatment With FFIM Vitamin C Therapy (mean follow-up, 26 months)

	MASI Score		
Patient No.	Before Treatment	After Treatment	Change From Baseline
1	18	2	–16
2	20	4	–16
3	16	9	–7
4	10	6	–4
5	32	4	–28
6	40	4	–36
7	30	25	–5
8	18	10	–8
9	20	9	–11
10	18	8	–10
11	42	0	–42
12	30	0	–30
13	48	0	–48
14	24	6	–18
15	21	18	–3
16	21	3	–18
17	28	2	–26
18	7	5	–2
19	42	36	–6
20	18	15	–3
21	12	4	–8
22	12	2	–10
23	30	12	–18
24	24	4	–20
24	28	0	–28
26	24	12	–12
27	21	10	–11
28	30	8	–22
29	24	4	–20
30	12	2	–10
31	25	12	–13
32	8	4	–4
33	8	6	–2
34	20	2	–18
35	24	8	–16
Mean	23.0	7.3	–15.7

FFIM, full-face iontophoresis mask; MASI, Melasma Area and Severity Index.

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