Title : Micro needling-Assisted Topical Tranexamic Acid Solution versus 4% Hydroquinone for Treating Melasma: A Split-Face randomized study

Abstract

Background Melasma, also known as chloasma or mask of pregnancy, is a common, acquired, hyperpigmentary disorder usually affecting females. Tranexamic acid (TA), a derivative of amino acid lysine has shown promising results over the past few years when used along with other therapies as well as when used as a stand-alone therapy. **Aim of the Work** In this study, we aimed to evaluate and compare the effectiveness of topically applied tranexamic acid after microneedling versus topically applied hydroquinone 4% alone in patients with melasma. **Patients and Methods** Fifty selected patients were divided randomly according to the random number allocation method into two groups (25 patients each) of A (topical 4% hydroquinone, nightly application) and B (microneedling + topical 4% TA, every other week). **Results** After Eight weeks of treatment, the mean modified MASI score of the HQ treated side changed from 6.604±4.02 to 3.032±1.19 with a mean decrease percentage of 54.8%±19.4%. This reduction in modified MASI score was found to be statistically significant, ($p<0.001$). MASI score of group B (TA + microneedling) changed from 6.348±3.84 to 3.712±1.19 with mean decrease percentage of 57.4%±23.4% which was also statistically significant, ($p<0.001$). **Conclusion** We demonstrated safety and efficacy

of both used modalities and with minimal side effects. Topical HQ application achieved minimal non significant higher satisfactory results among raters and subjects

Key words: Melasma, microneedling, tranexamic acid, hyroqunione

Introduction

Melasma, also known as chloasma or mask of pregnancy, is a common, acquired, hyperpigmentary disorder usually affecting females.[1] Though the exact pathomechanism of melasma is unknown many etiological factors have been implicated in its causation as well as aggravation. Though asymptomatic, the overwhelming cosmetic impact for many patients leads to tremendous emotional and psychosocial distress which results in their seeking treatment. Despite the availability of a wide variety of therapeutic options its treatment remains challenging as pigmentation may fade but often recurs.[2]

Tranexamic acid (TA), a derivative of amino acid lysine, was synthesized in 1962 by the Japanese researchers, Shosuke and Okamoto. The antifibrinolytic activity of the trans-isomer of TA was first described in 1964 and since then it has been used in a variety of clinical settings and also to reduce blood loss during various surgeries.[3]

TA in all forms (oral, topical) has shown promising results over the past few years when used along with other therapies as well as when used as a stand-alone therapy.[4] Transdermal delivery has become a popular route of drug delivery in recent years. Microneedle technology involves the creation of micron-sized channels in the skin, which can allow the delivery of hydrophilic molecules including large proteins that do not pass the skin barrier passively.[5]

In this study, we aimed to evaluate and compare the effectiveness of topically applied TA after microneedling versus topically applied HQ 4% alone in patients with melasma.

Patients and Methods

A prospective, randomized study was conducted on 50 female patients with melasma. They were selected from the Dermatology out-patient clinic and an informed written consent was obtained from each patient to be enrolled in the study and to be photographed after full explanation of the procedure. The study was approved by the Research Ethics Committee

Only epidermal (n=48) and dermal (n=2) cases of melasma were included. Patients were excluded if they had a history of recurrent herpes

infection, dermatitis on the face or keloidal tendency. Pregnant women or patients with bleeding disorders or immuno-compromising diseases and those using treatment for melasma (bleaching agents, laser, dermabrasion, chemical peels), anticoagulant therapy, chemotherapy, radiotherapy, all types of hormonal contraception or systemic steroids within 6 months before starting the study were also excluded.

The selected patients were divided randomly according to the random number allocation method into two groups (25 patients each) of A (topical 4% hydroquinone, nightly) and B (microneedling + topical 4% TA, every other week). All patients were subjected to full history taking and dermatological examination. Wood's light was used to determine the pattern of melasma (epidermal or dermal). Photographing of the face was done at baseline, before every session and 2 weeks after the last session.

Treatment protocol and postoperative care

In group A, patients were instructed to apply 1 finger unit of topical 4% HQ (Meloquin 4, Biopharm) every night. In group B topical anesthetic cream (Prilocaine, Global Napi Pharmaceutical Co.) was applied for 45–60 minutes on the treatment site and skin microneedling was performed using dermapen (Dr. Pen Ultima A6 Professional Microneedling Pen ;

Bjheyetec Electronic Technology Co., Guangzhou, China) that consisted of a hand piece, recharging battery and needle tips (36 needles) with adjustable needle length of 1.5 mm. The microneedling was carried out in four different directions (horizontally, vertically, and diagonally right and left) for about four to five times. The end point was the appearance of erythema with pinpoint bleeding points. After microneedling, 4% solution of TA (100mg/ml) (Kapron, Amoun Pharmaceutical Co) was applied on the treatment area. The maximum dose of TA per session was 8 mg. This procedure was performed every other week and for 4 times. Patients in group B were instructed to apply 1 finger unit of topical 4% HQ every night. Participants in both groups were instructed to apply sun block cream (with no pigment) with SPF 50 every 4 hours during the day. Photographs of all of the participants were taken before and after the treatment.

Clinical evaluation

The modified MASI score was calculated by a blinded dermatologist at baseline and at every other week till the end of the study duration. Full face frontal and lateral photos were taken for each patient using Sony digital camera (20.1 mega pixels) at baseline (before starting sessions) and at the last microneedling session. Photographs were evaluated by two

other blinded dermatologists and rated on a 4 point scale. Grades of improvement were excellent (if more than 75% of lesions were resolved), good (if 50% -75% of lesions were resolved), fair (if less than 50% of lesions were resolved), and poor (if there was no improvement or exacerbation of the original disease).

Blinded clinical assessment of the changes in melasma area and severity index (MASI) score was done and rated by two blinded independent dermatologists (photographic assessment) to grade the severity of melasma for both groups at baseline and after last session. Then, the reduction percentage was calculated with grading as follows: mild (0–25%), moderate (26–50%), good (51–75%), and excellent (76–100%). Adverse effects, including erythema and pigmentation abnormalities, were assessed every session and at 2 weeks after the last treatment.[6]

Results

The study included 50 melasma patients. By the end of sessions 27 patients completed the study with a mean age of 31.16±19.16 years. All patients were females and twenty six (52%) of them were working with daily exposure to sun light. Thirty (60%) of them were living in rural areas. All patients had exposure to the sunlight with the majority (86%)

exposed for more than 90 minutes of daily sunlight. Cosmetics were used by (n=23) of the patients (46%). Thirty three patients (66%) had family history for melasma. The majority of patients (76%) had Fitzpatrick skin types III and IV. None of the included patients were smokers.

The mean modified MASI score of group A (HQ 4%) was 6.604±4.02 at baseline while the mean modified MASI score of group B (microneedling + TA) was 6.348±3.84 at baseline. This difference was not statistically significant, (p=0.328). **(Table 1)**

After Eight weeks of treatment, the mean modified MASI score of the HQ treated side changed from 6.604±4.02 to 3.032±1.19 with a mean decrease percentage of 54.8%±19.4%. This reduction in modified MASI score was found to be statistically significant, ($p<0.001$). MASI score of group B (TA + microneedling) changed from 6.348±3.84 to 3.712±1.19 with mean decrease percentage of 57.4%±23.4% which was also statistically significant, ($p<0.001$). By the end of the study, the miconeedling-TA -treated side of the face showed a slightly lower mean modified MASI score than the HQ 4% treated side of the face; however this difference was not statistically significant, (p=0.405) **(Table 2) (figs1-2)**.

Regarding Patients' satisfaction, no significantly different degree of improvement was found between both treatments. The majority of patients saw that the degree of improvement on both sides of the face was good to excellent. According to the two blinded observers there was no statistically significant difference in the degree of improvement between the HQ 4% treated and microneedling + TA treated sides of the face (p=0.252; p=0.327 respectively). **(Table 3)**

Assessment of side effects

Post inflammatory hyper pigmentation was higher in group A (HQ 4%) (n=3; 12%) than group B (n=1; 4%), the difference was not statistically significant ($P = .33$). Rate of erythema was significantly higher in group B (n =25; 100%) than in group B (n =3; 12%; $P < .01$), but it only lasted for a maximum of up to 72 hours.

Discussion

Tranexamic acid (TA) was accidently found to clear areas of melasma when used earlier in 1979 as a treatment for chronic urticaria.[7] The severity of melasma demonstrated a significant decrease when used continuously for 3 weeks by 12 patients and at a daily dose of 1.5mg.

Tranexamic acid is thought to affect melasma in multiple ways. Firstly it inhibits urokinase type plasminogen activator; a keratinocyte derived product that increases the activity of melanocytes.[8] Secondly TA is thought to inhibit angiogenesis by inhibition of vascular endothelium growth factor (VEGF). Moreover, TA and by suppressing the production of prostaglandins, reduces melanocyte tyrosinase activity and is able to improve melasma.[9]

In this study, we aimed to evaluate and compare the effectiveness of topically applied TA after microneedling versus topically applied HQ 4% alone in patients with melasma.Our demographic data were in line with a number of previous studies.[10]

Our study was in line with another split face study comparing 5% TA and topical 2% HQ regarding the efficacy and adverse effects.[11]Another recent study, the combination of microneedling with tranexamic acid did not differ from 4% hydroquinone in the treatment of melasma. [12]

Topical TA (2%-3% solution) when used to ultraviolet exposed skin of guinea pigs prevented the pigmentation process compared to other areas where a vehicle control solution was applied. Furthermore,

histopathological examination revealed a significantly reduced basal layer melanin content.[13]

In another study, twice daily application of topical 3% TA solution for 12 weeks was as effective as the application of 3% HQ in 0.01% dexamethasone.[14]

Laser assisted delivery of TA had been studied however the most striking side effect was post treatment hyperpigmentation.[15] Different strengths of topical TA have been used ranging for 2% to 5%. One split face study compared 5% liposomal TA on one side with 4% hydroquinone on the other and found both to be effective with better results in the TA side though not statistically significant.[16]

A number of studies used oral TA as a solo treatment or in adjunction with other topical treatments for treating melasma. Moreover, TA was used in different doses and using different protocols of administration. Of those studies, two were randomized and controlled and demonstrated a good evidence base level. One evaluated the role of only oral TA 250 mg B.D in melasma without any other therapy and showed 49% improvement as compared to 18% in the placebo group.[17] The other RCT compared oral TA 250 mg B.D along with topical therapy with patients

treated with only topical therapy and showed rapid and sustained improvement in the combination therapy group.[18]

Two other studies demonstrated a significant decreased severity of melasma following either a twice daily or three times daily administration of 500 mg TA. Both studies correlated the improvement in clinical response with decreased epidermal pigmentation and decreased Melan A staining on immunohistochemistry.[19-20] Moreover, it had been revealed that different doses of not less than 500 mgs per day and up to 1500 mgs per day remain to be of sign infant value in decreasing the severity of melasma.[21]

Only few studies compared the intradermal injections of TA. A randomized, open label, comparative study of TA microinjections and HQ application in patients of melasma showed a statistically better clearance of melasma among the injection group.[22] Another study demonstrated the safety and efficacy of intradermal TA microdroplet injections in decreasing the severity of melasma.[23]

No much significant side effects were reported in this study in agreement with TA use in literature.[24] Limitations to the study included the smaller study sample as well as the type limitation of melasma to epidermal and

dermal types. Failure to histologically and immunohistochemically evaluate the pigmentary changes represent another limitation as well as the short follow up period taking into consideration the recurrent nature of melasma. .

In conclusion, we demonstrated safety and efficacy of both used modalities and with minimal side effects. Topical HQ application achieved minimal non significant higher satisfactory results among raters and subjects. More controlled larger sample trials are required to establish an optimal and effective treatment for melasma.

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Table (1) Comparison between modified MASI score of both sides before and after treatment

MASI	HQ 4%	Microneedling+TA	p-value
	Mean ± SD	Mean ± SD	
Baseline	6.604±4.02	6.348±3.84	0.328
Eigth week	3.032±1.19	3.712±1.19	0.405
Mean improvement (%)	54.8%±19.4%	57.4%±23.4%	-
p-value	<0.001**	<0.001**	-

TA: Tranexemic acid. HQ; Hydroqunione

Wilcoxon Signed Rank test showed statistically significant difference in modified MASI score before and after treatment in both sides of the face*;* MASI Modified melasma area and severity index

Table 2. Rater Dermatologists assessment of degree of improvement in both treatments

Rater's assessment		HQ 4%	Microneedling +TA	Difference (95% Confidence Interval)	p-value
1st Rater: degree of improvement	Excellent	39.3%	38.1%	18.5% (-9.8% to 44.0%)	0.265
	Good	55.1%	54.1%	3.7% (-24.4% to 31.2%)	0.999
	Excellent/Good	94.4%	92.2%	14.8% (-6.9% to 35.9%)	0.252
2nd Rater: degree of improvement	Excellent	39.9%	34.7%	14.8% (-13.8% to 40.9%)	0.407
	Good	50.0%	50.0%	0.0% (-27.1% to 27.1%)	0.778
	Excellent/Good	89.9%	84.7%	14.8% (-9.9% to 38.0%)	0.327

z-test showed no statistically significant difference between both studied methods of treatment (HQ and microneedlig + TA) regarding degree of improvement according to both raters' assessment. ($p>0.05$)

Table 3. Patient's assessment at the end of the study in both groups

Patients assessment	Study group (n=50)		P Value
	HQ 4 (%)	Microneedling + TA (%)	
Excellent	(56%) 14	10 (40%)	**0.629**
Good	(40%) 10	12 (48%)	
Poor	(4%) 1	(12%)34	

TA; Tranexemic acid. HQ; Hydroqunione ; $P<0.05$: statistically significant

Figure Legends

Fig1. Marked improvement in melasma: Baseline (A) and after (B) 8 weeks treatment with microneedling and TA

Fig 2. Marked improvement in melasma: Baseline (A) and after (B) 8 weeks treatment with Hydroquinone 4%