The efficacy of salicylic acid peels in combination with 4% hydroquinone cream versus 4% hydroquinone cream alone in the treatment of melasma in Hispanic women

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1 Schema

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Time of Visit	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 14**
Inclusion/Exclusion Criteria	X					
Informed Consent	X					
Investigator Evaluation	X	X	X		X	X
Patient Evaluation					X	X
Dispense 4% Hydroquinone, Cleanser, Sunscreen	X					
Salicylic Acid Peel	X	X	X	X		
Adverse Events	X	X	X	X	X	X

2 Study Objectives

To assess the efficacy of salicylic acid peels every two weeks in combination with 4% hydroquinone versus 4% hydroquinone alone in the treatment of melasma in Hispanic women. This study will take place over 14 weeks in which time all patients will use 4% hydroquinone cream to the affected areas twice daily, but half the face will receive four salicylic acid peels every two weeks. End points include change in pigmentation of skin affected by melasma compared to normal skin measured objectively with a mexameter and subjectively by the MASI score, the melasma severity assessment, and the physician and patient global evaluation.

3 Background

Melasma is a common disorder of hyperpigmentation affecting the cheeks, forehead, and upper lip. It manifests as tan-brown macules/patches slowly enlarging on the face. It can affect all racial types but predominately affects women of skin types IV-VI especially those living in areas of intense UV radiation (1).

The exact etiology of melasma is unknown, but it is thought to be multifactorial. Known triggers/exacerbators include pregnancy, hormone therapy, and sunlight. Melasma can be very difficult to treat and often frustrating for the patient and physician. A recent study has shown in Hispanic women that melasma significantly affects quality of life in both personal and professional aspects (2).

Conventional treatments thus far include elimination of causative factors and a hypopigmenting agent, typically 4% hydroquinone either alone or in combination with a

retinoid, topical steroid or superficial peeling agents. In addition, patients are advised to use a sunscreen and take other sun protective measures (1).

Patients with melasma may significantly benefit from the addition of biweekly salicylic acid peels to 4% hydroquinone cream. A previous, uncontrolled study showed that salicylic acid peels of 20% to 30% at two week intervals in patients with skin types V-VI resulted in moderate-significant improvement in melasma in 4 of 6 patients with melasma (3). Although hydroquinone is the standard of care for melasma, no controlled trials have been performed comparing the efficacy of salicylic acid peels in combination with 4% hydroquinone versus hydroquinone alone.

4 Agents

The two agents used in this study will be salicylic acid 20-30% peels and 4% hydroquinone cream, both of which are FDA approved for melasma.

The 4% hydroquinone cream will be purchased as a generic cream formulation. Patients will apply this cream twice a day to affected areas on both sides of the face. Contraindications to the use of 4% hydroquinone include pregnancy, plans for pregnancy, or breast feeding (in all cases patients will be excluded from our study). Side effects can include irritation, redness, pruritus, and hypo/hyperpigmentation. One study comparing the use of 4% hydroquinone with placebo found no significant difference between the two groups in terms of incidence of side effects (4).

The salicylic acid peels will also be purchased from a medical supply company in both 20% and 30% concentrations. Patients will receive 4 peels total at 2 week intervals. The first two peels will be 20% and the last two peels will be 30%. Side effects may include redness, irritation, pruritus, skin peeling, and hypo/hyperpigmentation. One study looked at the safety and efficacy of salicylic acid peels in darker racial-ethnic groups and found the above mild side effects to occur in ~16%, all of which were transient, resolving in less than two weeks (3).

5 Eligibility Criteria

Consenting Hispanic women with bilateral moderate-severe epidermal or mixed melasma will be enrolled in this study. This study will be limited to only Hispanic women due to the high frequency of melasma in this population and in order to study a uniform population. Spanish

speaking patients will be eligible for this study and a Spanish consent/HIPAA forms will be provided to them. In addition, someone who speaks Spanish will always be available to answer questions. Key exclusion criteria include pregnancy, breastfeeding an infant, use of 4% hydroquinone cream within three months of the study, and history of chemical peels, microdermabrasion, or facial laser treatment within 9 months of the study.

6 Material and data to be accessioned

Thirty adult Hispanic women with moderate to severe melasma, diagnosed by clinical criteria, will be recruited to participate in this study. Accounting for ~ 10 screening failure, we hope 20 patients will be able to complete this 14 week prospective investigator blinded, split-face trial of biweekly salicylic acid peels in combination with 4% hydroquinone versus 4% hydroquinone alone.

At the initial visit, patients will be asked for their past medical history, current medications, and will undergo a urine pregnancy test. Once it is determined that patients are eligible for the study, they will be asked to give informed written consent and sign a HIPAA authorization. Next they will undergo evaluation of their melasma by the study investigator which includes an objective measurement of the darkness of their melasma by mexameter (an electronic device which painlessly measures skin pigmentation, 0-white, 1000-black, by placing a probe on the skin) compared to nearby normal skin. In addition, a MASI score will be calculated (a subjective score based on darkness, area of involvement, and homogeneity of the pigment). A melasma severity assessment will also be performed by the physician which rates the severity of the melasma on each of side of the face according to the following numerical scale: 0 for clear, 1 for mild, 2 for moderate, 3 for severe. Standard and polarized photographs (a specialized photograph that enhances the appearance of hyperpigmentation) will also be taken. Patients will then undergo a 20% salicylic acid peel to half the face (side to be peeled will be determined by a computer generated randomization code). In addition they will be given 4% hydroquinone to use on the affected areas twice a day (X 14 weeks) and a cleanser and sunscreen to be used daily. No other medications for melasma will be allowed during the study period.

At week 2, patients will undergo another 20% salicylic acid peel to half the face. They will be asked to report any adverse events from the salicylic acid peels or the hydroquinone. Prior to the peel a mexameter reading will be taken and the MASI score calculated for each side of the face.

At week 4 and 6 patients will undergo 30% salicylic acid peels and be asked to report any adverse events. In addition, the study investigator will take mexameter readings from the peeled/unpeeled sides and calculate a MASI score on both the peeled/unpeeled sides at week 4 (investigator will be blinded as to which side was peeled). At weeks 8 and 14, patients will report any adverse events and the study investigator will take mexameter readings and calculate a MASI score as above. The physician will also perform a melasma severity assessment for each side of the face at weeks 8 and 14. In addition, at 8 and 14 weeks, both the physician and patient will perform a subjective global evaluation of which side, if any, had more improvement in the following terms: no change/slight/moderate/marked.

Visit Schedule and Assessments

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
Time of Visit	**Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 14**
Inclusion/Exclusion Criteria	X					
Information & Informed Consent	X					
Investigator Evaluation	X	X	X		X	X
Patient Evaluation					X	X
Dispense Hydroquinone 4%, cleanser, sunscreen	X					
Salicylic Acid Peel	X	X	X	X		
Adverse Events	X	X	X	X	X	X

7 Treatments

Investigational Therapy and Reference Therapy

Investigational Agent – salicylic acid peels (20-30%) applied every two weeks for a total of four peels

Reference Therapy – hydroquinone 4% cream applied BID X 14 weeks.

Treatment Assignment, Blinding, and Randomization

Patients will all be given 4% hydroquinone to use on the affected areas for 14 weeks. In addition, each patient will receive biweekly salicylic acid peels to half of the face for a total of four peels (at week 0, 2, 4, 6). The first two peels will be 20% salicylic acid and the last two peels will be 30% salicylic acid. The side to be peeled will be determined by a computer generated randomization code. Only the investigators will be blinded in the study, due to the

nature of the treatments it will not be possible for the patients or the nurse performing the peels to be blinded.

No concomitant therapy will be allowed for the duration of the study. Patients who were already on an oral contraceptive pill will be allowed to continue the pills during the study, but oral contraceptive pills may not be introduced during the study.

Interruption or Discontinuation of Treatment

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her well being. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation will be recorded.

Treatment Compliance

Patients will be asked to return all unused medication at the end of the study and the quantity of returned medication will be documented.

8 Evaluation Criteria

Patients satisfying inclusion criteria will be chosen to participate in the study. The degree of pigmentation will be noted at baseline by mexameter readings taken on both sides of the face on affected skin and also nearby normal skin. Additional mexameter readings will be taken at weeks 2, 4, 8, and 14. In addition standard and polarized photographs will be taken at baseline and at weeks 8 and 14. A MASI score will also be calculated at baseline and at weeks 2, 4, 8, and 14. A melasma severity assessment will be performed by the physician at baseline and at weeks 8 and 14. A physician and patient global assessment will be performed at weeks 8 and 14, a subjective measure of which side, if any, improved more and to what degree (no change/slight/moderate/marked). Primary efficacy assessment will be improvement of melasma using mexameter readings while secondary assessment will be improvement in MASI scores, melasma severity assessment, and physician and patient global improvement compared with the opposite side.

9 Off-study criteria

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events. An adverse event is any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment. As this study only involves topical therapy, the most likely adverse events are

minor and may include irritation, redness, burning, skin peeling, and hyper/hypopigmentation. These adverse events will be specifically monitored for by using investigator observed evaluation and patient reporting. The patient will be specifically queried upon each visit regarding adverse events from the salicylic acid peels and/or the 4% hydroquinone cream. A patient has the right to discontinue participation in the study at any time. The study investigator also has the right to discontinue the patient's participation in the study should the patient's condition worsen, they are unable to follow the treatment schedule, or the patient has unexpected side effects from the study medications.

A serious adverse event is an undesirable sign, symptom or medical condition which: 1) is fatal or life-threatening, 2) requires or prolongs hospitalization, 3) results in persistent or significant disability/incapacity, 4) constitutes a congenital anomaly or a birth defect, or 5) is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All adverse events will be reported to the principal investigator. All unexpected or serious adverse events will also be reported to the IRB.

10 Registration and study monitoring

Once patients are recruited into the study and complete their initial evaluation, they will be given a schedule of follow up visits. As indicated in the schedule above, at each subsequent visit, they will be asked about adverse events, and they will be evaluated by a study investigator. All information will be recorded in the study report forms. All adverse events will be reported to the principal investigator, and all unexpected or serious adverse events will also be reported to the IRB.

11 Statistical Considerations

Investigators will enter the information required by the protocol into the Study Report Forms (SRFs). Additionally, a series of standardized photographs will be taken of each patient at baseline and 14 weeks to provide permanent documentation.

The objective of this trial is to study the efficacy and tolerability of salicylic acid peels in the treatment of melasma in Hispanic women. The data will be summarized with respect to efficacy and safety observations. Data will be presented for the complete intent-to-treat population (all patients having taken at least one dose of study medication) as well as the per-protocol population (all patients who completed the study without major protocol deviations).

The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. Adverse events will be summarized by presenting for each treatment group the number and percentage of patients having any adverse event, having an adverse event in each body system, and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Efficacy will be primarily assessed by comparing delta mexameter readings (affected skin-nearby normal skin) on the peeled versus unpeeled side. This data will be analyzed using a two factor repeated measures analysis of variance. Efficacy will be secondarily assessed by change in MASI score on the peeled versus unpeeled side also using the repeated measures analysis of variance. Another secondary measure of efficacy will be the melasma severity assessment of the peeled versus unpeeled side also using the repeated measures analysis of variance.

A McNemar chi-squared test will be used to determine if there is agreement between the Physician and Patient Global Assessment of Improvement at 8 and 14 weeks as to which side appears more improved. For those in which there is agreement, we will further look at the degree of agreement and use the McNemar chi-squared test to see how well they correlate. The critical value for all efficacy, tolerability, and subject satisfaction survey analyses will be 0.05.

A previous study has shown that using 4% hydroquinone cream alone results in total improvement in melasma in ~40% of patients (4). However, the assessments of melasma improvement were more subjective than objective in nature and differ from the end points we are using in our study. Furthermore, it is unclear how much more improvement we may see with the addition of the salicylic acid peels. Since we do not know how much improvement to expect given our efficacy endpoints, we will be performing a pilot study recruiting ~20 patients.

12 References

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