Evaluating the Efficacy of Kligman Plus Modified Kligman Formula Versus the Same Treatment Combined with Kojic Acid, Vitamin C, Glycolic acid and Glutathione Mesotherapy in the Treatment of Melasma

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ABSTRACT:
BACKGROUND:
Melasma is a common hyperpigmentation disorder. It is therapeutically challenging, with a high relapse rate.

OBJECTIVE:
To evaluate the efficacy of Kligman formula versus the same formula combined with mesotherapy for treating melasma.

PATIENTS AND METHODS:
This is an interventional controlled comparative study conducted at the Center of Dermatology and Venereology, Medical City, Baghdad, and a private clinic in Baghdad, during the period from May 2020 to June 2021. Twenty-four patients with melasma were divided into 2 groups. Group A consisting of 13 patients were treated with Kligman formula for two months. Group B consisting of 11 patients were treated with the same formula plus two weekly sessions of mesotherapy for a total of two months. Response to treatment was assessed using the Melasma Area and Severity Index (MASI) score at the baseline and at the end of the two months treatment period.

RESULTS:
The mean MASI score for group A before treatment was 10.7 ± 2.6, and decreased to 4.6 ± 1.4 after treatment. Regarding group B, the mean MASI score before treatment was 9.8 ± 1.7 and decreased to 3.7 ± 1.5 after treatment, with statistically significant reduction in MASI score (P value <0.001) for both groups. There was no statistically significant difference in percent of change in MASI scores between the two study groups (P = 0.321).

CONCLUSION:
The use of Kligman formula is still effective in the treatment of melasma, and the addition of mesotherapy has not resulted in statistically significant improvement in MASI score in melasma patients.

KEYWORDS: Melasma, Kligman formula, Mesotherapy.

INTRODUCTION:
Melasma is a common hyperpigmentation disorder that presents with macules and patches of brown color with irregular borders distributed bilaterally on photo-exposed areas of the face. It most commonly affects females with darker skinned photo-types (Fitzpatrick skin types III-IV). There is a number of exacerbating factors, the most important of which is sun exposure. Female hormones also play an important role, as well as genetics (1). protection with the use of sunscreens. Their use should be continued even after completing therapy to prevent relapse. The most important aspect of treatment is sun Sunscreen should be broad-spectrum blocking both UV A and B. There are two types of sunscreen, either chemical or physical, with the latter containing either zinc oxide or titanium dioxide(2). There are different agents available for treating melasma. The combination with the most widely usage is called Kligman formula. This formula is composed of hydroquinone plus tretinoin plus corticosteroid. Hydroquinone is known for its depigmenting effects by inhibiting the enzyme tyrosinase. Retinoids play a role in inhibiting melanin synthesis and enhancing keratinocyte turnover. Corticosteroids help to reduce the irritation of the other two agents in the formula(3).

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One of the modalities for treating melasma is mesotherapy. It is an intervention with minimal invasiveness that delivers one or several substances into the dermis by using the technique of microinjection or microneedling. The choice of the technique as well as the agents used is of importance in affecting the results obtained with this modality. There are several agents that aid in lightening the skin by acting as antioxidants, for example, glutathione with its free radical scavenging properties, helps to repair the damage caused by reactive oxygen species. Vitamin C is another antioxidant and anti-inflammatory agent, has been widely used for treating patients with melasma. Both agents are used as mesotherapy components, with the advantage of avoiding the side effects associated with systemic administration of the drug. Additionally, this technique allows the drug to be delivered locally to the treated area for maximum effects and the possibility of treating any localized affected area of the skin.

Another inhibitor of tyrosinase enzyme is kojic acid. Copper is required for tyrosinase functioning, and kojic acid chelates copper at the enzyme’s binding sites interfering with melanin synthesis. Glycolic acid as well has been shown to have a direct effect in inhibiting melanin formation in melanocytes, and when applied topically, it will induce remodeling and desquamation of keratinocytes.

**PATIENTS AND METHODS:**

This is an interventional controlled comparative study conducted at the Center of Dermatology and Venereology, Medical City, Baghdad, and a private clinic in Baghdad. The period of the study was from May 2020 to June 2021.

A detailed history was taken from the patients, including the duration of melasma, sun exposure, drug history, and any previous treatments used. Informed consents were obtained from all the patients. Pregnant, lactating females, females on contraceptive pills, and patients on concurrent treatment with other depigmenting agents were excluded from the study. The patients were examined carefully, and the site, color, homogeneity, and the surface area of their melasma were documented. The type of melasma (epidermal, dermal, or mixed) was determined by using a Wood’s lamp. Thirty-five patients were included in the study, and were divided into two groups.

**Group A:** This group consisted of eighteen patients; all of them were treated and followed at the Center of Dermatology and Venereology. Patients were instructed to use Kligman formula (combination of hydroquinone 2% cream, tretinoin 0.025% cream, and mometasone furoate 0.1% cream) applied at night over the melasma area for 2-3 hours then washed, followed by overnight application of a combination of hydroquinone 4% cream with hydrocortisone 1% cream. The total duration of treatment was two months. Strict use of sunscreen was recommended.

**Group B:** This group consisted of seventeen patients; all of them were treated and followed at a private clinic. Patients were treated with the same combination as the first group. Additionally, they were treated with two weekly sessions of mesotherapy injected to the area of melasma. Mesotherapy solution used consists of a combination of kojic acid, vitamin C, glycolic acid, and glutathione (BCN MELANO). The solution was injected with a mesotherapy needle gauge 30 having a length of 4 mm (intradermal injection). For each session, 1 ml of mesosolution was used, diluted with 2ml of lidocaine hydrochloride 2% solution. Multiple intradermal injections (with blebbing) were given to cover the area of melasma.

**Follow up:** The patients were followed every two weeks to evaluate the response to treatment, record any side effects, and to calculate the MASI score, then the patients were seen monthly for further two months to assess for relapse.

**RESULTS:**

**Group A**

**Patient’s data:** Eighteen patients were included in group A, five patients defaulted from the study. Thirteen patients completed the study, with a mean age of 29.2 ± 6.8 years (range: 18-42 years). Eleven patients were females (84.61%), and two were males (15.38%). The duration was between 1 to 7 years with a mean ± SD of 4.1 ± 2 years. Eight patients had epidermal type, and five patients had mixed type.

**Clinical results:** The mean MASI score before treatment was 10.7 ± 2.6, and decreased to 4.6 ± 1.4 after treatment, the average decrease in MASi was 6.1 ± 2 (56.8% ± 9.7%), and it is statistically significant (P value <0.001). Five patients had relapsed within 1 month after completing therapy. Four patients developed slight erythema and burning sensation (after applying Kligman formula, fading within an hour) for the first few days of
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treatment. This was reduced with continuous treatment.

**Group B**

**Patient’s data:** Seventeen patients were included in group B, six patients defaulted from the study. Eleven patients completed the study, with a mean age of 32.3 ± 7.5 years (range: 23-42 years). All patients were females. The duration was between 2 to 7 years with a mean ± SD of 4.2 ± 1.9 years. Nine patients had epidermal type, and two patients had mixed type.

**Clinical results:** The mean MASI score before treatment was 9.8 ± 1.7 and decreased to 3.7 ± 1.5 after treatment, the average decrease in MASI was 6.1 ± 1.9 (62% ± 15.1%), which is statistically significant (P value <0.001). Four patients had relapsed within 1 month after completing therapy. Three patients developed burning sensation and erythema (after applying Kligman formula, fading within an hour) for the first few days of treatment, which was reduced with continuous treatment. Three patients developed mild bruising after the session of mesotherapy, for which they were instructed to apply icepacks to the area treated. There was no statistically significant difference in percent of change in MASI scores between the two study groups, as it was 56.8% ± 9.7% in group A, compared to 62% ± 15.1% in group B, with only 5.2% difference in percent of change (P = 0.321).

<table>
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<th>Variables</th>
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<th>Group B</th>
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<th>P-value</th>
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<td>Percent of change in MASI score</td>
<td>Mean± SD</td>
<td>Mean± SD</td>
<td>Mean± SD</td>
<td>0.321</td>
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<tr>
<td>Percent of change in MASI score</td>
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<td>62± 15.1</td>
<td>5.2</td>
<td>0.321</td>
</tr>
</tbody>
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![Table 1: Distribution of MASI score percent of change according to study groups.](image)

Figure 1: A 32 years old female from group A with 5 years history of melasma, with MASI score 9 before (upper photo), and a score of 3 after (lower photo) the two months treatment period.
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Figure 2: A 30 years old female from group B with 5 years history of melasma, with MASI score 10.8 before (left photo), and a score of 4.4 after (right photo) the two months treatment period.

DISCUSSION:
Kligman formula is comprised of three pharmacological agents, and they all appear to target various steps in the pathophysiologic process of melasma. Two pivotal trials involving thirteen centers were performed to compare a triple-combination composed of tretinoin 0.05%, hydroquinone 4%, and fluocinolone acetonide 0.01% with a dual-combination composed of any two of these three agents mixed together. The results showed that (26.1%) of the patients that were treated with the triple-combination formula experienced complete clearance at week 8. This was significantly different from the results obtained with any of the dual-combination formulas, P < 0.001. These results are showing that the use of these three agents combined is much more effective in achieving therapeutic success than any of the dual-combination formulas.

A study conducted in India by Puri N. et al using glutathione and vitamin C mesotherapy for the treatment of melasma. At the end of the study, results showed that there was 42.38% reduction in MASI score. In comparison to our study, group B demonstrated a percentage of reduction in MASI score of 62%. We had a smaller sample size, and a smaller number of sessions compared to the Indian study. This could explain that there was no statistically significant difference in percent of reduction in MASI score between our two study groups (Kligman formula alone versus Kligman formula plus mesotherapy).

Zohreh Tehranchinia et al performed a study comparing the use of topical hydroquinone 4% cream alone to the use of the same topical cream combined with intradermal infiltration of tranexamic acid (TA). The decline in MASI score was significant in both groups (p < 0.01), but the second group showing more significant reduction in MASI score.

A study conducted by Iraji et al, to assess the efficacy of mesotherapy using tranexamic acid and vitamin C with and without glutathione. There is significantly more reduction of mMASI score achieved by the addition of glutathione to the above combination (P-value < 0.001). Comparing the results of the aforementioned studies to our study, the addition of mesotherapy to conventional topical treatment had resulted in more significant reduction in MASI score. This reflects that mesotherapy cocktails containing tranexamic acid might be a better option for treating melasma. The method of drug delivery might be relevant as well, Budamakunta et al, compared the administration of TA by microinjection versus microneedling in the treatment of melasma. Response was better in the microneedling group, though the difference was not statistically significant. Microneedling allows uniform delivery of the drug into deeper layers of the skin.

A similar study performed by Al-Hamamy et al, using TA 4mg/ml delivered by microneedling in one group, and compared it to the use of the same concentration of TA, but otherwise injected intradermally via an insulin syringe. Both groups were treated additionally with topical hydroquinone 4% daily at night. A third group was treated with only topical hydroquinone 4% used daily at night for 3 months. Improvement was
noted in all 3 groups, but the greatest reduction in MASI score was achieved with the microneedling technique\(^{(12)}\).

**CONCLUSION:**
The use of Kligman formula is effective in the treatment of melasma, and the addition of mesotherapy has not resulted in statistically significant improvement in MASI score in melasma patients.

**REFERENCES:**