
Treatment of Melasma Using Kojic Acid in a Gel Containing Hydroquinone and Glycolic Acid

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BACKGROUND. Melasma is difficult to clear. Many agents have been used, such as hydroquinone, and glycolic acid and glycolic acid peels, kojic acid, a tyrosinase inhibitor in the fungus *Aspergilline oryzae*.

OBJECTIVE. To see if the addition of 2% kojic acid in a gel containing 10% glycolic acid and 2% hydroquinone will improve melasma further.

METHODS. Forty Chinese women with epidermal melasma were treated with 2% kojic acid in a gel containing 10% glycolic acid and 2% hydroquinone on one half of the face. The other half was treated with the same application but without kojic acid. The side receiving the kojic acid was randomized. Determination of efficacy was based on clinical evaluation, photographs and self-assessment questionnaires at 4 weekly intervals until the

end of the study at 12 weeks. The non-parametric Wilcoxon's rank sum test was used for statistical analysis.

RESULTS. All patients showed improvement in melasma on both sides of the face. The side receiving the kojic acid did better. More than half of the melasma cleared in 24/40 (60%) patients receiving kojic acid compared to 19/40 (47.5%) patients receiving the gel without kojic acid. In 2 patients, there was complete clearance of melasma, and this was on the side where kojic acid was used. Side effects include redness, stinging, and exfoliation. These were seen on both sides of the face, and they settled by the third week.

CONCLUSION. The addition of kojic acid to a gel containing 10% glycolic acid and 2% hydroquinone further improves melasma.

TREATMENT OF melasma poses a therapeutic challenge among dermatologists and nondermatologists. This is especially so among the Chinese population in Singapore, where a fair flawless skin is the epitome of beauty, and the presence of melasma or any facial pigmentation is considered by some to be "bad luck." It is no wonder that there are many creams available over the counter purporting to treat melasma.

Some of them contain kojic acid, a compound present in the fungus *Aspergilline oryzae*. Kojic acid inhibits tyrosinase, the enzyme that converts tyrosine to melanin. Garcia and Fulton showed that kojic acid is able to reduce the pigment in melasma patients.¹

Among dermatologists, hydroquinone is the most common agent used to treat melasma. Recently, glycolic acid and glycolic acid peels have been added to the treatment regime to enhance the effectiveness of hydroquinone.² This study was undertaken to see if the addition of kojic acid to the existing regime (2% hydroquinone and 10% glycolic acid) will further improve the lightening of melasma.

Materials and Methods

This is a double blinded right/left comparison study involving 40 Chinese women with epidermal melasma (confirmed

by Wood's light). Patients with dermal melasma, mixed melasma, or acquired naevus of Ota were excluded from the study. Two sets of treatment gels were used—one containing 2% hydroquinone and 10% glycolic acid and the other containing 2% kojic acid in the same formulation (ie., 2% hydroquinone and 10% glycolic acid).

Both gels were prepared by Dermatologic Cosmetic Lab (East Haven, CT) and stored in glass bottles. Each patient had to use the gels twice a day, one on each side of the face. The side receiving the kojic acid was randomized. The patient had to use a physical sunblock containing titanium dioxide SPF 15 over the gels daily. The duration of the study was 12 weeks.

The gels were identical in appearance and consistency and labeled A and B. The identity of the gels was made known after the clinical results. Photographic and statistical analysis were done.

Patients on oral contraceptives or hormone replacement therapy were excluded from the study. None of the patients engaged in regular outdoor activities, nor could they have received any treatment for melasma at least 4 weeks prior to the study. The duration of melasma, family history, presence of aggravating factors, and distribution of melasma were noted. Determination of efficacy was based on clinical evaluation, photographs, and self-assessment questionnaires. Clinical evaluation was done at 4 weekly follow-ups until 12 weeks. The reduction in area of melasma and degree of lightening was noted. Improvement was assessed as 0–25%, 25–50%, 50–75%, more than 75%, and clear, and given scores of +1, +2, +3, +4, and +5, respectively. Photographs were obtained at enrollment into the study and again

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Table 1. Patients Showing Improvements in Melasma During the Study on the Sides with or without Kojic Acid

Improvement in melasma	With kojic acid			Without kojic acid		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
0	1	0	0	1	0	0
0–25%	18	7	2	19	10	1
25–50%	16	22	14	19	20	20
50–75%	5	8	15	1	10	14
75–99%	0	3	7	0	0	5
Clear	0	0	2	0	0	0
Total	40	40	40	40	40	40

at the end of the study at 12 weeks. The nonparametric Wilcoxon’s rank sum test for paired samples was used for statistical analysis.

Results

Three patients developed redness and irritation, and asked to be taken off the study. They were replaced by 3 others. In all, 40 patients completed the study. They were all Chinese women with epidermal melasma. The ages ranged from 32 to 58 years with a mean of 42.5 years and a median age of 42 years. All had malar melasma with 3 having melasma on the forehead and chin as well. They had their melasma for 2 to 10 years, the majority having had the condition for more than 5 years. All had previous treatments with hydroquinone but not kojic acid or glycolic acid. All had stopped treatments at least 4 weeks prior to the study. Sunlight aggravated melasma in all patients; 21 out of 40 (52.5%) had a family history of melasma.

Improvement in melasma was seen at week 4, and this continued throughout the study (Table 1). At the end of the study, all patients showed improvement in their melasma, regardless of whether kojic acid was used or not. The overall reduction in melasma varied from 25% to 100% or from a score of +1 to +5. Only two patients had complete clearance of their melasma, and this was on the side where kojic acid was used. Table 2 showed that more than half of the melasma was cleared in 24 out of 40 (60%) patients using kojic acid in 2% hydroquinone and 10% glycolic acid gel compared with 19 out of 40 (47.5%) patients using the same gel (2% hydroquinone and 10% glycolic acid) without kojic acid. Figures 1A–D show a patient with improvement in

melasma after applying the gel with kojic acid to one half of the face and the same gel without kojic acid to the other half of the face.

Table 3 shows the improvement seen on each half of the face. Seventeen out of 40 (42.5%) patients had

Table 2. Patients Showing More than 50% Improvement in Melasma at the End of the Study (12 Weeks)

Improvement in melasma	With kojic acid	Without kojic acid
Less than 50%	16 (40.0%)	21 (52.5%)
More than 50%	24 (60.0%)	19 (47.5%)
Total	40 (100.0%)	40 (100.0%)



Figure 1. A) Side receiving gel with Kojic acid at week 0. B) Side receiving gel without Kojic acid at week 0. C) Side receiving gel with Kojic acid at week 12. D) Side receiving gel without Kojic acid at week 12.

Table 3. Improvement in Melasma Comparing the Side with Kojic Acid and the Side without Kojic Acid

Improvement	With kojic acid	Without kojic acid
More effective	17 (42.5%)	5 (12.5%)
No difference	18 (45.0%)	18 (45.0%)
Less effective	5 (12.5%)	17 (42.5%)
Total	40 (100.0%)	40 (100.0%)

a more dramatic reduction in melasma on the side receiving kojic acid (in 2% hydroquinone and 10% glycolic acid and gel) and 5 out of 40 (12.5%) patients had a more dramatic reduction in melasma on the side receiving the hydroquinone-glycolic acid gel without kojic acid. In 18 out of 40 (45.0%) patients, there was an equal reduction in melasma on both sides, regardless of whether kojic acid was used or not.

Table 4 compares the doctor's assessment with that of the patients. Both concurred that kojic acid did not worsen the melasma. Instead, addition of kojic acid either improved the melasma further or made no difference in the final result.

All patients experienced redness, stinging, and mild exfoliation. Side effects were seen on both halves of the face regardless of whether kojic acid was added or not. These settled by the third week. Three patients (7.0%) asked to be withdrawn from the study because of side effects, and they were not included in the analysis. They had redness and peeling, and were not keen to continue the gel beyond 2 weeks. One patient had itch with the gel but again this settled by the fourth week.

Discussion

In the study by Garcia and Fulton,¹ kojic acid is as effective as hydroquinone in reducing the pigment in melasma. However, neither was effective in clearing the

Commentary

Melasma continues to be a difficult problem. The pathogenesis of melasma is not fully understood, but pregnancy, estrogen ingestion, UV light exposure, and family history are well recognized. Although hydroquinone is effective and has been available for years, a new product, kojic acid, has increasingly been used as a skin-depigmenting agent.

Kojic acid (5-hydroxy-2-(hydroxymethyl) 4-pyrone), a fungal metabolic product, of high purity (>99%) made by a certain pharmaceutical manufacture, is obtained from *Aspergillus*, being used for topical application. Current evidence suggests that kojic acid induces skin depigmentation through suppression of free tyrosinase, mainly due to chelation of its copper,

Table 4. Improvement in Melasma as Assessed by Doctor and by Patients

	With kojic acid		Without kojic acid	
	Better	Same	Better	Total
Doctor	17 (42.5%)	18 (45.0%)	5 (20.0%)	40
Patient	18 (45.0%)	19 (47.5%)	3 (17.5%)	40

melasma completely. By using both agents together in a gel containing glycolic acid, there was clearance of melasma in 2 patients and a more dramatic reduction in 17 out of 40 (42.5%) patients. However, this improvement is statistically not significant ($p = 0.9$), probably due to the small sample size.

Side effects experienced were acceptable by most patients, and these disappeared by the first month. Addition of kojic acid did not cause more irritation. Of the 3 patients who dropped out of the study, the irritation was seen equally on both sides of the face, suggesting that this could be due to either the gel or the glycolic acid or hydroquinone or all three and not due to kojic acid alone.

Both kojic acid and hydroquinone are tyrosinase inhibitors preventing the conversion of tyrosine to melanin. The combination of both agents augment this inhibition further. Hence in patients whose melasma do not respond to either hydroquinone or glycolic acid or both, Kojic acid could be added to the treatment regime. The addition of glycolic acid enhances penetration of both agents and hence promotes efficacy.

References

- Garcia A, Fulton JE. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg* 1996;22:443-7.
- Lim JTE, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. *Dermatol Surg* 1997;23:177-9.

and it has been demonstrated to be responsible for therapy and prevention of pigmentation, both *in vitro* and *in vivo*.

Both formulas in this study by Dr. Lim are effective in the reduction of the pigmentation from melasma. The availability of both formulations allows the dermatologist to have an alternative. It would be encouraging to see more articles and studies presented that expand the use and effectiveness of kojic acid in the future.

Caution must be exercised when using kojic acid, however, as it is considered to have high sensitizing potential.

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