

Original Article

Efficacy and Safety of Hydroquinone, Kojic Acid and Glycolic Acid Combination in the Treatment of Melasma

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Abstract

Background & Methodology: It was an opened clinical trial. The study was carried out from March 2009 to February 2011, in the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh to evaluate the efficacy and side effects of the combination therapy of hydroquinone(HQ), kojic acid(KA) and glycolic acid(GA) for the treatment of melasma. Patients suffering from melasma were selected as study population. Within the period of data collection, thirty patients of melasma were assigned purposively. The efficacy was evaluated using Melasma Area and Severity Index (MASI) Score. The severity of melasma of each of the four regions (forehead, right malar region, left malar region and chin) are assessed based on three variables, percentage of the total area involved (A), darkness (D) and homogeneity (H). **Results:**The study showed that majority (30%) of the cases were between 20 to 25 years, majority (77%) of patients were female, (50%) patients were housewives, (50%) were in graduation level of education, (50%) of patients was found as upper class and negative family history was present in majority (80%) of cases. It was seen that highest (93%) number of patients were malar type and 7% were centro-facial type. The study showed the change in MASI Score after treatment with combination therapy (GA 2%, HQ 2% and KA 1%). After 12 weeks of treatment, the average MASI score was decreased by 24.20% indicating mild reduction of the severity of melasma and 18%, 18%, 9% and 55% patients developed side -effects like itching, burning sensation, scaling, and erythema respectively. **Conclusion:** Combination therapy (GA 2%, HQ 2% and KA 1%) has a few lightening effect on melasma, with no remarkable side effects. Further study should be conducted with large number of sample and longer follow up.

Key words: Efficacy, Safety, Hydroquinone, Kojic Acid, Glycolic Acid, Melasma

Introduction

Melasma is a symmetric, progressive hyperpigmentation of facial skin that has a predilection for darker skin phenotypes¹. Melasma has been associated with hormonal imbalance, sun damage and genetic predisposition². Melasma has been considered to arise from pregnancy, oral contraceptives, endocrine dysfunction, genetic factors, medications, nutritional deficiency, hepatic dysfunction, and other factors.³ It is a macular hyperpigmentation and generally involves sun exposed area of the cheeks, upper-lips, chin and forehead¹. Although melasma may affect

any race, it is much more common in constitutionally darker skin types (Skin type IV - VI) than in lighter skin types. It is most common pigmentary disorder among Indians⁴. Women are mostly affected during the reproductive years.² By causing cosmetic disfigurement of the face, it is frequently associated with a significant emotional effect. There is no universally effective specific therapy for the disease - existing agents have varying degrees of effectiveness, and the condition, more often than not, relapses.⁵ Multiple factors have been postulated to evolve the etiology and pathogenesis of melasma.⁶

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Treatment of melasma remains a challenge and difficult to treat specially in dark skinned patient. 7 Treatment with demelanizing agents must be continued for several months before significant clinical benefits become noticeable. 8 Treatment of melasma involves the use of topical hypo-pigmenting agents, laser therapy and dermabrasion. 9,10. Combination treatment of kojic acid (1%), glycolic acid (2%) and hydroquinone (2%) have shown good results in several studies. 11 Powerful depigmenting agent (hydroquinone & kojic acid) comprehensively inhibits melanogenesis, thus effectively brightens and whitens the skin. Presence of glycolic acid serves to remove the outer layer of dull skin and thus leave skin with a rejuvenated appearance with smoother look. Components of hydroquinone(HQ) have potent antioxidant abilities 12. It causes reversible inhibition of cellular metabolism by affecting both DNA and RNA synthesis. Hydroquinone can be considered as a potent melanocyte cytotoxic agent and is also a poor substrate of tyrosinase, thereby competing for tyrosine oxidation in active melanocyte and inhibit conversion of tyrosine to melanin in the skin. 13 Kojic acid (KA) is a fungal metabolic product of *Aspergillus oryzae* fungus, inhibits the catecholase activity of tyrosinase which is the rate limiting, essential enzyme in the biosynthesis of the skin pigment melanin. 3 Glycolic acid (GA) is a natural product, derived from sugarcane and citrus fruits and is considered as one of the mildest acids to be used in chemical peels. 14 The main benefit of using this is that it helps to get a younger looking skin by diminishing the appearance of wrinkles and fine lines. The glycolic acid (GA) decreases the stratum corneum barrier function and accelerates the turnover of skin. So basically acts as an exfoliating agent. A therapeutic option for melasma is limited and the results are somewhere not satisfactory to some extent. 15 Here an endeavor had been made to evaluate the efficacy and side effects of the combination therapy for the treatment of facial melasma.

Materials and Methods

It was an opened clinical trial study. The study was carried out for a period of 2 years from March 2009 to February 2011, in the outpatient to department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Patients suffering from melasma were selected as study population. Purposive type of non-probability sampling technique was followed. Data were recorded on pre designed data col-

lection sheet. Within the period of data collection, 30 patients of melasma were assigned purposively considering exclusion and inclusion criteria of patient selection.

Inclusion Criteria

1. Patient of 15 to 50 years of age group
2. Both male and female of above age group
3. Female not taking oral contraceptive pill
4. Patient taking no other medication for melasma treatment

Exclusion Criteria

1. Patient unwilling to give informed consent to take part in the study
2. Pregnant woman
3. Patient suffering from any endocrine disorder
4. Patient suffering from any liver disease
5. Patient taking oral contraceptive pill, phenytoin, mephenytoin
6. Known hyper sensitivity to HQ, KA and GA.

Procedure of study

Informed consent was sought from the patients to take part in the study. At the baseline visit, history of melasma regarding length of time present, relationship to pregnancy, oral contraceptive, drug history were taken. Patients were asked about previous use of any other medications and any hypersensitivity to those agents. Patient were advised to apply the above mentioned combination therapy over the melasma once daily in the night and the patient were asked to report on 4th , 8th , 12th weeks for evaluation. The efficacy was evaluated using Melasma Area and Severity Index (MASI) Score as proposed by Kimbrough-Green et.al. At each visit, side effects were determined in the treatment area.

MASI Score

Melasma area severity index (MASI) is developed by Kimbrough-Green et al¹⁶ for the assessment of Melasma. The severity of melasma of each of the four regions (forehead, right malar region, left malar region and chin) are assessed based on three variables:

Percentage of the total area involved (A), darkness (D) and homogeneity (H).

A numerical value assigned for the corresponding percentage area involved is as follows:

- 0 = No involvement
- 1 = < 10% involvement
- 2 = 10% - 29% involvement

- 3 = 30% - 49% involvement
- 4 = 50% - 69% involvement
- 5 = 70% - 89% involvement
- 6 = 90% - 100% involvement

The darkness of melasma (D) is compared to the normal skin and graded on scale of 0 - 4 as follows:
0 = normal skin color without evidence of hyperpigmentation

- 1 = barely visible hyperpigmentation
- 2 = mild hyperpigmentation
- 3 = moderate hyperpigmentation
- 4 = severe hyperpigmentation

Homogeneity of hyperpigmentation (H) is also graded on scale of 0 - 4 as follows

- 0 = normal skin color without evidence of hyperpigmentation
- 1 = specks of involvement



Photograph A: showing regions of severity of involvement of melasma

A = Area involvement, 0 = 0%, 1 = 10%, 2 = 10% - 29%, 3 = 30% - 49%,
4 = 50% - 69%, 5 = 70% - 89%, 6 = 90% - 100%
D = Darkness, 0 = absent, 1 = slight, 2 = mild, 3 = marked, 4 = severe
H = Homogeneity, 0 = absent, 1 = slight, 2 = mild, 3 = marked, 4 = severe

- 2 = small patchy area of involvement < 1.5 cm diameter
- 3 = patches of involvement > 2 cm diameter
- 4 = uniform skin involvement without any clear areas

To calculate the MASI score, the sum of severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10%-30%)

$$\text{Total MASI score} = 0.3(\text{DF}+\text{HF})\text{AF} + 0.3(\text{DMR} + \text{HMR})\text{AMR} + 0.3(\text{DML} + \text{HML})\text{AML} + 0.1(\text{DC} + \text{HC})\text{AC}$$

The formula can be written as:

$$\text{MASI} = 0.3(\text{DF}+\text{HF})\text{AF} + 0.3(\text{DMR} + \text{HMR})\text{AMR} + 0.3(\text{DML} + \text{HML})\text{AML} + 0.1(\text{DC} + \text{HC})\text{AC}$$

Grading of Melasma Area and Severity Index (MASI)

Particulars	Factor	Area	Severity of melasma
Forehead (F)	0.3	A _F	D _F + H _F
Right Malar (MR)	0.3	A _{MR}	D _{MR} + H _{MR}
Left Malar (ML)	0.3	A _{ML}	D _{ML} + H _{ML}
Chin ©	0.1	A _C	D _C + H _C

$$\text{MASI} = 0.3(\text{DF}+\text{HF})\text{AF} + 0.3(\text{DMR} + \text{HMR})\text{AMR} + 0.3(\text{DML} + \text{HML})\text{AML} + 0.1(\text{DC} + \text{HC})\text{AC}$$

Ethical Issues

The following factors were considered during the study:

1. Patient were clearly informed about the scopes and limitations of the study
2. Written (or verbal) consent were obtained from the patient
3. Confidentiality of the patient about personal information were strictly maintained

Ethical & Legal-procedure: This Protocol was approved by department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka.

Results:

It was an opened clinical trial study. The study was carried out for a period of 2 years from March 2009 to February 2011, in the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Patients suffering from melasma were selected as study population. Figure I showed that age of the patients at onset of melasma, in majority

(30%) cases were between 20 to 25 years, 27% were between 26 to 30 years, 23% were between 31 to 35 years old, 17% were between 36 to 40 years old, 3% were between 41 to 44 years old. Figure II showed that majority (77%) of patients was female and 23% was male. Table III showed that maximum (50%) patients were housewives, 10% were students and 40% were service holders. Regarding level of education, majority of the patients were in graduation level, 10% were primary level, 20% were secondary level and 20% were higher secondary level. On the basis of socio-economic condition, patients can be divided into 50% as upper class, 43.3% as middle class and 6.7% as upper class. Regarding family history of melasma, positive history was present in 20% cases and negative history was present in majority (80%) of cases. Figure III showed that highest (93%) number of patients was malar type and 7% were centrofacial type.

Figure IV showed that change in MASI Score after treatment with combination therapy (GA 2%, HQ 2% and KA 1%). About 12 weeks of treatment the average MASI score was decreased by 24.20% indicating mild reduction of the severity of melasma (0 = No reduction, up to 25% = mild, 26-50% = moderate, above 50% = remarkable reduction). Figure V

Figure I: Distribution of the patients by age at onset (n=30)

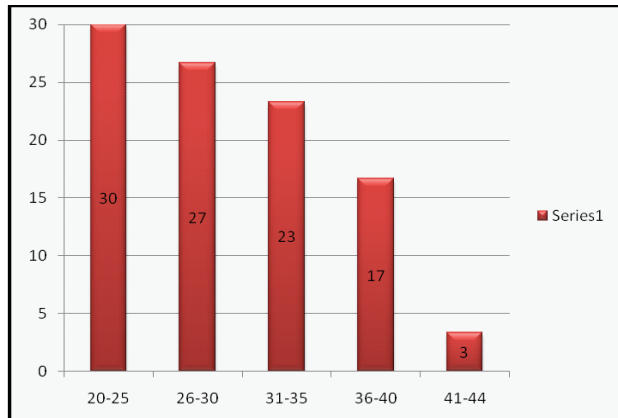


Figure II: Distribution of the patients by sex. (n=30)

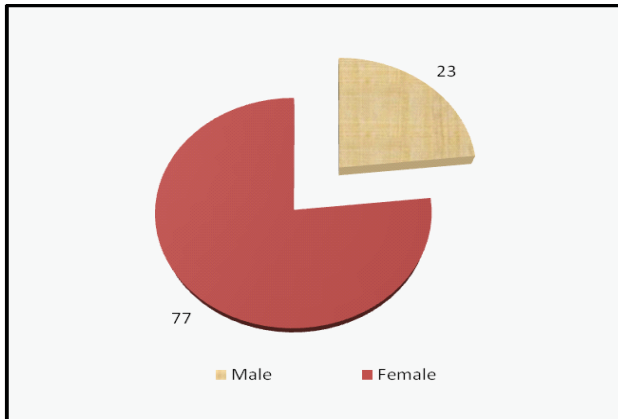


Table I: Distribution of the patient by epidemiological profile (n=30).

Epidemiological profile	Frequency
Occupation	
Housewife	15(50%)
Students	3(10%)
Service holder	12(40%)
Level of education	
Primary level	3(10%)
Secondary level	6(20%)
Higher Secondary level	6(20%)
Graduation level	15(50%)
Socio-economic condition	
Upper class	15(50%)
Middle class	3(43.3%)
Lower class	2(6.7%)
Family History of melasma	
Positive	6(20%)
Negative	24(80%)

Figure III: Distribution of the patients by site of involvement

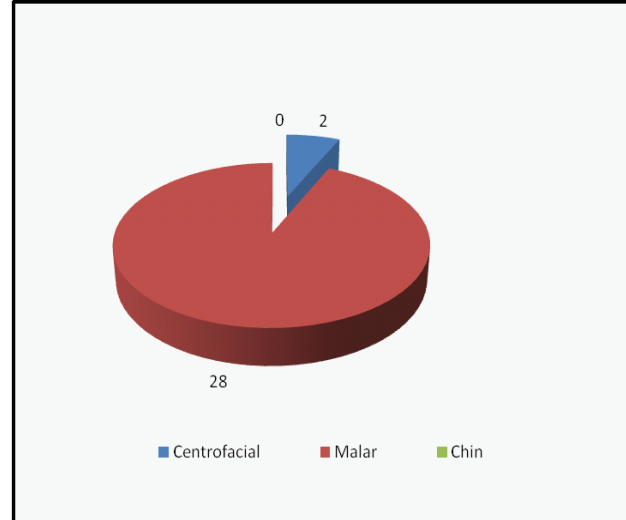


Figure IV: Distribution of the patients by change in MASI Score after treatment

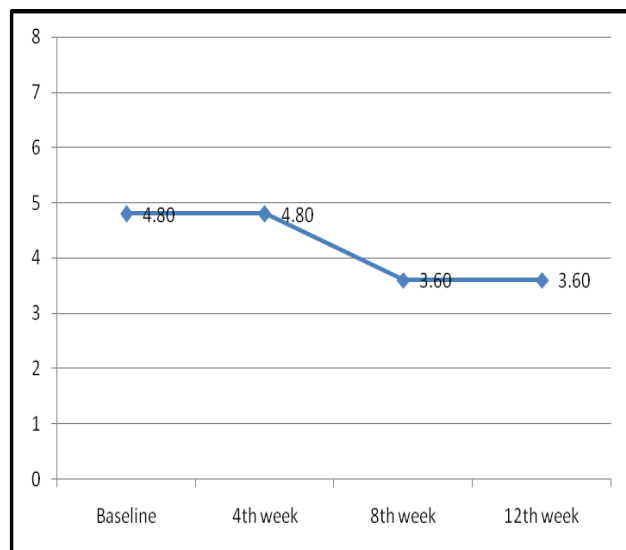
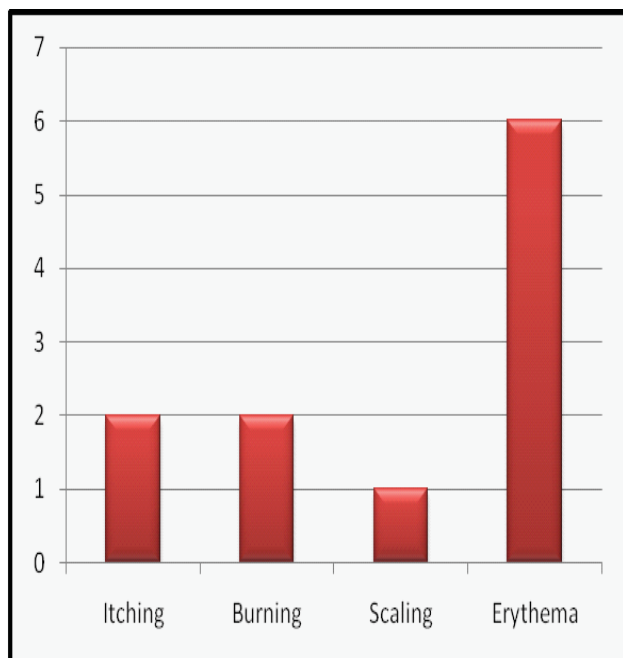


Figure V: Distribution of the patients by adverse effects of combination therapy



Discussion

It was an opened clinical trial study. The study was carried out from March 2009 to February 2011, in the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh to evaluate the efficacy and side effects of the combination therapy of hydroquinone, kojic acid and glycolic acid for the treatment of facial melasma. Patients suffering from melasma were selected as study population. Within the period of data collection, 30 patients of melasma were assigned purposively. The efficacy was evaluated using Melasma Area and Severity Index (MASI) Score. The severity of melasma of each of the four regions (forehead, right malar region, left malar region and chin) are assessed based on three variables, percentage of the total area involved (A), darkness (D) and homogeneity (H).

Among the patients, 77% of the patients were female while 23% of the patients were male, which is accordance with the observations of many authors, which is again similar to the research work of Alicia Garcia, where 97% of the patients were female and 03% of the patients were male.¹⁵ A strong family history of melasma was present in 20% of the patient in this study and suggests an important genetic factor in the pathogenesis of this condition. With regard to the site of involvement of melasma, 93% of the

patients had malar distribution and 7% of the patients in this study had centrofacial distribution, which is similar to the research work of Alicia Garcia, where 91% of the patients had malar distribution and 9% of the patients had centrofacial distribution.¹⁵

This study showed a little reduction of the severity of melasma demonstrated by MASI score after 12 weeks of treatment with Combination therapy (GA 2%, HQ 2% and KA 1%) when compared to their baseline. The result of this indicates that daily night use of the Combination therapy (GA 2%, HQ 2% and KA 1%) has a mild lightening effect on the melasma. After 12 weeks, the average MASI score decreased by 24.20%. Cutaneous side effects noted throughout the study were itching (7%), burning sensation (7%) and scaling (3%) and erythema (20%). The skin irritation disappeared after 4 to 8 weeks of therapy. These findings are mostly in accordance with the observations of Some Recent Studies.¹⁷⁻¹⁸

Cutaneous side effects were limited to the burning sensation, itching scaling and erythema in the area of application, which subsided with continuation of therapy. As the study is a small scale one of 12 weeks duration it cannot reflect the proper efficacy and possible side effects of Combination therapy (GA 2%, HQ 2% and KA 1%) in the treatment of melasma. So large scale study with longer follow up should be under taken to find out the outcome with the combination therapy (GA 2%, HQ 2% and KA 1%) in the management of melasma.

The limitations of the study was that it was an opened, randomized and controlled clinical trial study performed on a limited number of cases. Duration of the study was limited (12 weeks), which could not reflect the proper efficacy and possible side effects of proposed therapy. As VANTEN cream is an expensive drug, I could not include many of melasma cases especially in lower and mid level due to lack of their socio economic condition.

As my study patients were mostly female and service holder, due to their lack of time and carelessness and most importantly their tendency to give more attention and priority to their family, I was unable to follow up and ensure their progress properly. Limitation of time and financial support of my study patients were my enormous restrictions.



Before treatment



After treatment



Before treatment



After treatment

An attempt was made to evaluate the efficacy and side effects of combination therapy (GA 2%, HQ 2% and KA 1%) in the treatment of melasma. The study was carried out among 30 patients, fulfilling inclusion criteria for a period of 12 weeks. So, the result of this study may not be the representative of exact evaluation. It needs further elaborate study on a larg-

er number of patients over a longer period of time. There were many limitations in this study. Still it could be concluded that combination therapy (GA 2%, HQ 2% and KA 1%) has a few lightening effect on melasma, with no remarkable side effects. Further study should be conducted with large number of sample and longer follow up.

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