DOI: https://doi.org/10.54393/pjhs.v5i03.1284

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 3 (March 2024)

Original Article

Comparison Between Efficacy of Serial Glycolic Acid Peel with Modified Kligman's Regimen versus Modified Kligman's Regimen Alone in Epidermal Melasma

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ARTICLE INFO

Keywords:
Epidermal Melasma, Modified Kligman's regimen, Glycolic Acid Peel, MASI Score.

How to Cite:
Akhtar, N., Hassan, T., Shahzad, M. K., Aliya, N., Yousaf, S., & Anwar, M. (2024). Comparison Between Efficacy of Serial Glycolic Acid Peel with Modified Kligman's Regimen versus Modified Kligman's Regimen Alone in Epidermal Melasma : Efficacy of Serial Glycolic Acid Peel. Pakistan Journal of Health Sciences, 5(03). https://doi.org/10.54393/pjhs.v5i03.1284

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Received Date: 24th January, 2024
Acceptance Date: 14th March, 2024
Published Date: 31st March, 2024

ABSTRACT

The background of melasma involves its psychological impact and multifactorial etiology, encompassing genetic, hormonal, and environmental factors. Management strategies include sun protection and targeted treatments like glycolic acid peels and the modified Kligman's regimen to mitigate hyperpigmentation. **Objective:** To compare the clinical outcome specifically in terms of MASI score in epidermal melasma patients treated with the Modified Kligman's regimen alone versus combined with 35% Glycolic acid peels. **Methods:** In this randomized controlled trial, a total of 90 patients of epidermal melasma (with MASI score over 10) aged 18-55 years, visiting out-patient Dermatology department of Sheikh Zayed Hospital, Rahim Yar Khan were enrolled via non-probability consecutive sampling. The patients were divided into two groups (group A and group B), each having 45 patients. Patients in group A received the Modified Kligman's regimen (hydroquinone 4%, 0.05% tretinoin, and fluocinolone acetonide 0.01%), and those in group B received serial 35% Glycolic acid peels plus Modified Kligman's regimen over 3 months. Outcomes were measured at 4, 8, and 12-weeks post-treatment in terms of the MASI score. **Results:** Most of the patients i: e.75.5 % in group B showed moderate clinical improvement while most of the patients in group A i: e. 53.3% observed only mild improvement. In terms of the mean MASI score improvement, the Group B patients exhibited a significantly greater reduction from baseline compared to the Group A (8.91±2.42 vs. 7.05±4.05, p=0.010). **Conclusions:** The combination of Glycolic acid peels plus Modified Kligman's regimen is relatively more efficacious as compared to Modified Kligman's regimen alone.

INTRODUCTION

Melasma, characterized by hyperpigmented patches, often affects sun-exposed skin areas like forehead, cheeks, upper lip, and chin. This condition can have significant emotional and psychological impacts, particularly in societies where physical appearance is emphasized, leading to issues like low self-esteem and, in some cases, anxiety and depression [1-3] Women, facing social beauty standards, may experience exacerbated psychological distress [4]. Etiology of melasma is multifactorial, involving genetic predisposition, hormonal factors, sun exposure, and certain medications [5]. Effective management of melasma involves avoiding risk factors, stringent sun protection, and using hypo pigmenting agents. Essential preventive measures include minimizing sun exposure and regular use of broad-spectrum sunscreens. [6,7] A strategic use of hypo pigmenting agents, such as azelaic acid, kojic acid, retinoids, mequinol, and arbutin, which inhibit melanin production or transport, is a cornerstone of effective treatment [8]. Glycolic acid peels, a type of alpha-hydroxy acid, are effective in treating various skin conditions, including melasma, by promoting skin exfoliation and collagen synthesis [9-11]. Alternatively, the modified Kligman's regimen combines hydroquinone, tretinoin, and fluocinolone acetonide. Hydroquinone inhibits melanin production, tretinoin increases skin turnover, and fluocinolone acetonide reduces inflammation, thereby collectively lightening hyperpigmented areas [12-14].

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Given the persistent challenge posed by melasma and the varied response to currently available treatments, there is a need to better understand the comparative effectiveness of commonly used modalities. This study aims to directly compare modified Kligman's regimen alone and combination with 35% serial glycolic acid peels, with the goal of providing valuable insights that could refine treatment strategies and enhance patient outcomes in the management of melasma. It seeks to understand whether the addition of glycolic acid can enhance the treatment's efficacy without adding significant side effects. The comparison's central premise is built on the understanding that while the modified Kligman regimen targets melanin synthesis, glycolic acid works at the skin's surface, possibly leading to a more synergistic and rapid effect. Such an approach might provide a more comprehensive treatment strategy for patients struggling with this persistent and often recalcitrant disorder.

METHODS

This randomized controlled trial was conducted over six months, from January to June 2023, in the Dermatology Department of Sheikh Zayed Hospital, Rahim Yar Khan. Ninety patients were selected using a non-probability consecutive sampling technique. The sample size was based on a 95% confidence level and 90% power, anticipating a significant difference in clinical improvement between the two groups. Informed written consent was obtained from all participants in line with ethical standards. Study was approved by CPSP on dated December 15, 2022 (Ref No: CPSP/REU/DER-2021-110-1399). The study included men and women, aged 18 to 55, diagnosed with epidermal melasma with a Melasma Area and Severity Index (MASI) score over 10 .The diagnostic process entailed an intensive clinical examination paired with a Wood's lamp examination, specifically designed to differentiate between epidermal, dermal and mixed patterns of melasma. Exclusion criteria were pregnancy, lactation, oral contraceptive use, hypersensitivity to treatment components, other melasma treatments, keloidal tendency, concurrent skin conditions, unrealistic expectations and inability to avoid sun exposure or use sun protection. Participants' demographic data, disease history, and past treatments were documented. They were then assigned to Group A (Modified Kligman's regimen) or Group B (Glycolic acid 35% peel plus Modified Kligman's regimen. In Group A, after face washing and drying, patients were instructed to use Modified Kligman's regimen comprised of hydroquinone 4%, 0.05% tretinoin, and fluocinolone acetonide 0.01% at night, daily for 3 months. Group B received the same regimen in addition to serial sessions of 35% glycolic acid peels once in every four weeks for the period of 3 months. Initially a post auricular test peel was administered, left for 15-20 minutes, to ensure there was no hypersensitivity reaction to the components of the peeling agent .Before performing the peel, the patient was advised to wash his/her face with soap and water. After patting the face dry, cleansing was done with methyl alcohol and acetone-soaked swabs. 35% glycolic acid solution was applied with a cotton tipped applicator .The time for each session was 3 minutes. It was neutralized with 10% sodium bicarbonate solution at the end-point, followed by rinsing with water. Mild emollient and sunblock were applied after drying the face. Participants were instructed to stop their topical regimen two days before each session (restarted after 3 days of peel) and avoid cosmetic procedures for a week prior. They were also advised to avoid sun exposure and use SPF 50 sunscreen, and men were asked not to shave on treatment days. Post-treatment evaluations occurred at 4, 8, and 12 weeks. Clinical improvement was assessed using the MASI score, with categories ranging from no significant improvement (<25%) to very marked improvement (>75%). Adverse effects were also documented. The MASI score was calculated as a sum of the scores for the forehead, right malar, left malar, and chin, each graded for darkness and homogeneity from 0 to 4, and the percentage area affected from 0 to 6. Total score ranged from 0-48

RESULTS

A total of 90 patients were selected and the mean age of the patients was 34.88 ± 10.27 years.

The baseline characteristics of melasma patients were analyzed and compared between those treated with Modified Kligman's formulation alone (Group A) and those receiving the formulation plus 35% Glycolic Acid peel (Group B). Significant differences were noted in age distribution (p=0.048), with Group A having 9 patients aged 18-25years, 21 patients aged 26-35 years, 9 patients aged 36-45 years, and 6 patients aged 46-55 years. In contrast, Group B had 10 patients aged 18-25, 9 patients aged 26-35, 17 patients aged 36-45, and 9 patients aged 46-55. Gender distribution did not show a significant difference (p=0.67), with 14 males and 31 females in Group A, and 7 males and 38 females in Group B. The distribution of melasma patterns such as Centro-facial, mandibular, and malar also showed no significant difference (p=0.467), with Group A having 13, 14, and 18 patients respectively, compared to 14, 9, and 22 in Group B. The duration of the disease was similar across the groups (p=0.518), with Group A and Group B having an equivalent number of patients across the different durations. Similarly, previous medication history was not significantly different (p=0.194), with 25 patients in Group A and 30 in Group B reporting past medication use. Etiological factors, including sun exposure, drugs, pregnancy, hormonal influence, cosmetics, and idiopathic

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causes, were not significantly different between the groups, though sun exposure was slightly more prevalent in Group B (14 patients) than in Group A (8 patients), but not to a significant degree (p=0.124). These findings suggest a well-matched patient population in both groups for subsequent outcome comparison (Table 1).

Table 1: Comparison of baseline characteristics of patients in study groups.

Baseline parameters		Study Groups		p-value
		Modified Kligman's Formulation Alone (Group A)	Modified Kligman's Formulation + Glycolic Acid Peel (Group B)	
		N	N	
Age group	18-25	9	10	0.048
	26-35	21	9	
	36-45	9	17	
	46-55	6	9	
Gender	Male	14	38	0.67
	Female	31	14	
Pattern	Centro-facial	13	9	0.467
	Mandibular	14	9	
	Malar	18	22	
Disease Duration	< 1 years	6	3	0.518
	1-3 years	18	15	
	4-7 years	15	21	
	> 8 years	6	6	
Medication History	Yes	25	30	0.194
Etiology	Sun Exposure	8	14	0.124
	Drugs	8	9	
	Pregnancy	6	6	
	Hormonal Influence	4	2	
	Cosmetics	12	3	
	Idiopathic	7	11	

In the evaluation of adverse effects between the two study groups, there was no statistically significant difference in the incidence of burning, erythema, scarring, crusting, or hyperpigmentation. Specifically, burning was reported by 9 patients in Group A and 11 in Group B out of 20 cases (p=0.400). Erythema was reported by 14 patients in Group A and 19 in Group B out of 33 cases (p= 0.191). Scarring was infrequent, with 1 case in Group A and 2 in Group B, totaling 3 cases (p=0.500). Crusting was reported by 4 patients in Group A and 6 in Group B, out of 10 cases (p=0.370). Hyperpigmentation was reported only in Group B by 2 patients (p=0.247). These findings indicate that the addition of 35% Glycolic Acid peels to the Modified Kligman's regimen did not significantly increase the risk of adverse effects (Table 2).

Table 2: Comparison of adverse effects between two groups.

Adverse Effects	Group A (N)	Group B (N)	Total (N)	p-value
Burning	9	11	20	0.400
Erythema	14	19	33	0.191
Scaring	1	2	3	0.500
Crusting	4	6	10	0.370
Hyperpigmentation	0	2	2	0.247

The clinical improvement among melasma patients reveals a significant difference between the two treatment groups. Group A's patients had 6 instances of non-significant improvement (<25%), compared to none in Group B. Mild improvement (25-50%) was observed in 24 patients in Group A, while Group B had 5. A more pronounced difference was seen in moderate improvement (>50 <75%), with Group A reporting 14 patients and Group B 34. For good improvement (>75%), Group A had 1 patient, and Group B had 6, indicating a more favorable outcome for the combined treatment group. These results suggest a substantial enhancement in clinical improvement when the Modified Kligman's regimen is supplemented with 35% Glycolic Acid peels (Table 3)

Table 3: Comparison of clinical improvement in both treatment groups.

Clinical Improvement	Group A (N)	Group B (N)	Total (N)	p-value
Non-significant (<25%)	6	0	6	0.000
Mild (25-50 %)	24	5	29	
Moderate	14	34	48	
(>50 <75 %)	-	-	-	
Good (> 75%)	1	6	7	

The comparison of the Mean Melasma Area and Severity Index (MASI) scores at various time intervals between the two treatment groups indicates statistically significant differences. Initially, Group A had a baseline MASI score of 16.13 ± 3.8, which is slightly higher than Group B's score of 14.76 ± 2.37 (p=0.044). After 4 weeks, Group A's mean MASI score decreased to 13.56 ± 3.4, while Group B saw a greater reduction to 9.30 ± 3.22 (p=0.000). This trend continued at 8 weeks with Group A at 10.65 ± 3.02 and Group B at 7.26 ± 1.84, and at 12 weeks with Group A at 9.08 ± 3.1 and Group B at 5.85 ± 1.6, both with a p-value of 0.000, indicating significant improvement in Group B. The mean difference in the MASI score after 12 weeks from the baseline also favored Group B with an 8.91 ± 2.42 reduction compared to Group A's 7.05 ± 4.05, with a p-value of 0.010, which again underscores the enhanced effectiveness of the combined treatment with 35% Glycolic Acid peels over the Modified Kligman's regimen alone. These findings demonstrate a statistically significant greater improvement in MASI scores for Group B across all time intervals measured (Table 4).

Table 4: Comparison of mean MASI score at different time intervals in both treatment groups.

MASI score	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
MASI Score at Baseline	16.13 ± 3.8	14.76 ± 2.37	0.044
After 4 weeks	13.56 ± 3.4	9.30 ± 3.22	0.000
After 8 weeks	10.65 ± 3.02	7.26 ± 1.84	0.000
After 12 weeks	9.08 ± 3.1	5.85 ± 1.6	0.000
After 12 weeks from Baseline Score	7.05 ± 4.05	8.91 ± 2.42	0.010

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DISCUSSION

Melasma, primarily affecting women, poses significant treatment challenges. Combination therapies, particularly involving hydroquinone, tretinoin, and fluocinolone acetonide, have shown effectiveness in reducing pigmentation and improving life quality across various ethnicities. [15] Additionally, chemical peels using glycolic and lactic acid have demonstrated potential in melasma treatment, though with varied success rates. Our study's demographic findings align with previous research, indicating a higher prevalence of melasma among females, who constituted 76.7% of our participants. This supports the gender-related observations in melasma prevalence reported in studies by Badabagni P *et al.*, Hussain *et al.*, Nasrollahi SA *et al.* and Modi A *et al.*, thereby reinforcing the understanding that melasma is more common in females [15-18]. The age distribution in our study, with a notable prevalence in the 26-35 years group, mirrored findings from Badabagni P *et al.* Etiological factors for melasma identified in our study included sun exposure and drug usage as major contributors, followed by cosmetics and idiopathic causes. This slightly contrasts with the study who found sun exposure as the dominant factor. [16] The malar pattern was the most prevalent form of melasma among our patients, consistent with previous studies by Badabagni P *et al.*, Basil *et al.*, though Modi A *et al.*, reported a higher prevalence of the Centro-facial pattern [16, 18, 19]. Our study's treatment outcomes revealed a mean reduction in MASI scores of 53.82% in the group treated with modified Kligman's regimen plus GA peel, in contrast to a 44.80% reduction in the group treated with modified Kligman's regimen alone. This result contrasts with Modi A *et al.*, where both groups showed similar average reductions [18]. The various categories of improvement between the two groups in our study were also notable. Non-significant improvements were less frequent in the combination treatment group, while moderate and good improvements were more common compared to the modified Kligman's regimen alone, a finding that aligns with Godse KV *et al.*, and Kamal K *et al.* [20-21]. The study demonstrated a trend towards greater efficacy with the combination treatment. In contrast, a study involving MKF and GA peel by another group found 80% of patients reporting outstanding improvement, compared to 60% in the MKF-only control group [22]. The effectiveness of the treatments in reducing MASI scores over 12 weeks was significant, with Group B showing a greater mean difference from baseline. This finding is in line with Chaudhary S *et al.* and Sarkar R *et al.*, who also observed significant differences in score reductions favoring combination therapy [23, 24]. Adverse effects were more frequent in the combination treatment group, particularly burning, erythema, and hyperpigmentation. These findings mirror those in studies by Sarkar R *et al.* and Badabagni P *et al.*, highlighting the need for careful monitoring. [16, 24] This underscores the importance of vigilant side effect management in combination therapies. The study's strengths include its well-defined participant criteria, rigorous diagnostic process, and comparison of two distinct treatment approaches for melasma. However, limitations such as the study's short duration, single-location setting, and heavy reliance on patient-reported outcomes must be acknowledged. To address these limitations, future research should focus on multicenter, longer-duration randomized controlled trials. These studies should aim to assess long-term effects, incorporate more objective measures alongside patient-reported outcomes, and explore additional potential treatment combinations.

CONCLUSIONS

The study findings indicate that both the Modified Kligman's formulation plus GA peel combination and Modified Kligman's formulation are effective in managing melasma, with a slightly higher efficacy observed for the Modified Kligman's formulation plus GA peel. These results contribute valuable evidence to guide clinical decision-making in melasma treatment. It is important to note the significance of monitoring and managing potential adverse effects and tailoring treatment approaches based on individual patient requirements.

Authors Contribution

Conceptualization: NA[1]
Methodology: NA[1], SY, MA
Formal analysis: NA[2], MKS
Writing-review and editing: TH, Na[1]

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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