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Original Article

Comparison of Metformin plus Nicotinamide Solution with Kligman formula in the management of Melasma- a Clinical Trial in a Tertiary Care Hospital

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ABSTRACT

Objective: To compare 30% Metformin plus 2% Nicotinamide solution with Kligman formula in the management of melasma in patients managed at tertiary care hospital of Rawalpindi.

Study Design: Randomized controlled trial (ClinicalTrials.gov: NCT 05790577).

Place and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Feb 2022 to Feb 2023.

Methodology: A total of eighty-eight patients of melasma were recruited for this trial and allocated randomly into two groups: A and B. Group-A received the 30% metformin plus 2% nicotinamide solution while Group-B received the Kligman formula (fluocinolone acetonide 0.01%+ tretinoin 0.025% + hydroquinone 2%). Both groups were followed up for 12 weeks to look for response which was assessed on Melasma Area and Severity Index (MASI). MASI was calculated at the start of treatment, and at 4, 8 and 12 weeks. Adverse events such as itching and burning were noted and addressed at each visit.

Results: Out of eighty-eight patients, 66(75.0%) were females while 22(25.0%) were males. Mean age of the study participants was 30.93±7.94 years. Out of 44 patients in Group-A, 13(29.0%) showed mild improvement, 21(47.0%) patients showed moderate while marked improvement was seen in 4(9.0%) patients. In Group-B, out of 44 patients grade 1, 2, 3 and 4 improvements were seen in 14(31.81%) mild, 26(59.0%) moderate, 03(9.0%) marked and total improvement in one patient, respectively. Adverse effects were noted in 2 patients (dryness and irritation) in Group-A and 5 patients (redness and burning sensation) in Group-B.

Conclusion: Both the treatment options used, 30% metformin with 2% nicotinamide solution and Kligman formula were equally efficacious in management of melasma at the completion of 12 weeks treatment.

Keywords: Melasma, Metformin, Nicotinamide.

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INTRODUCTION

The disorders of pigmentations have significant impact on physical as well as psychological impact on patients and, most studies have previously have reported that disorders of pigmentation may cause a significant negative impact on quality of life.[1] These disorders commonly effect the central and malar areas of the face.[2] Overall, the prevalence of melasma is 8.8% depending on the geographical area.[3] The management options which are available for melasma are topical steroids, dermabrasion and chemical peels.[4] Melasma is considered chronic disease with frequent relapses. Darker skin types (Fitzpatrick skin types IV to VI) are difficult to treat due to the higher risk of post-inflammatory hyperpigmentation. There is no single treatment option available which is efficacious universally. Thus, different combination treatment is considered to be the best approach for resistant and difficult cases.[5]

There is extensive literature available regarding safety and efficacy of the available topical agents in treating the melasma.[6] Topical metformin for the treatment of melasma is a new, safe, and almost as effective treatment option as triple combination therapy.[7] Literature on use of topical nicotinamide in melasma is sparse, although Rolfe et al. in 2014 published a review article and discussed the topical use of nicotinamide in treatment of atopic dermatitis, rosacea and acne vulagaris.[8]

Despite heavy burden of this disease, limited local data is available regarding the use of various topical agents for the treatment of melasma. In our hospital, this combination of 30% metformin plus 2% nicotinamide solution has not been used, we therefore designed this study with the rationale to compare 30%

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metformin plus 2% nicotinamide solution with Kligman formula for managing melasma in patients at a tertiary care hospital in Rawalpindi.

METHODOLOGY

This randomized controlled trial (ClinicalTrials.gov, ID: NCT 05790577) was conducted at the Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from February 2022 to February 2023. Ethical approval (letter no: A/28/EC/42/2022) was sought from the Institutional Ethical Review Committee prior data collection.

Inclusion Criteria: Patients of either gender with Fitzpatrick skin types III-VI and between the age of 18 and 60 years diagnosed clinically with melasma presenting to the dermatology department were included.

Exclusion Criteria: Patients with multiple dermatological conditions like acne vulgaris, rosacea, pregnant or lactating women, those using systemic medication for melasma were excluded.

The sample size was calculated using the WHO calculator with the reference prevalence of melasma as 1% [6]in general population, which came to 88. Non-probability consecutive sampling technique was used to collect the sample for this study, and data was collected after taking informed consent.

After diagnosis of patient and fulfillment of ethical process and consent, patients were randomly divided into two groups (Figure). Research team used lottery method to allocate patients into two groups of 44 patients each. For patients in Group-A, 30% metformin plus 2% nicotinamide solution was prepared and dispensed in amber colored glass bottle as 25 mL. Patients were advised to apply very small amounts of lotion at night, with sunscreen application in the morning. Similarly, 44 patients of Group-B were advised to apply Kligman formula and were also advised to wash face with tap water and apply a very thin layer of cream over area which is affected on face at night, with the use of a sunscreen of SPF 50 plus in the morning, for a period of 12 weeks.

Before commencing the treatment, a detailed history of patients was obtained, and clinical examination was performed. At the start of treatment clinical photographs were also taken and the severity of melasma was evaluated by MASI scoring system.[9]

Grading was done by improvement percentage according to the scale of global improvement as grade 0 (no improvement), grade 1 (mild improvement), grade 2 (moderate improvement), grade 3 (marked improvement) and grade 4 (near total/total improvement) and expressed in percentage as (1%-25%), (25%-50%), (>50%-75%) and (>75%) respectively.[10]

All statistical data was assessed by using Statistics Package for Social Sciences (SPSS) version 29. (SPSS-29.0). Percentage and frequency were calculated for qualitative variables like presence or absence of good response, gender of study participants and presence of comorbid medical conditions. The Independent sample t-test was applied for age. For the variable of gender chi-square was applied and we compared median MASI score using Mann- Whitney U test. A *p*-value less than or equal to 0.05 was considered significant for establishing the association.

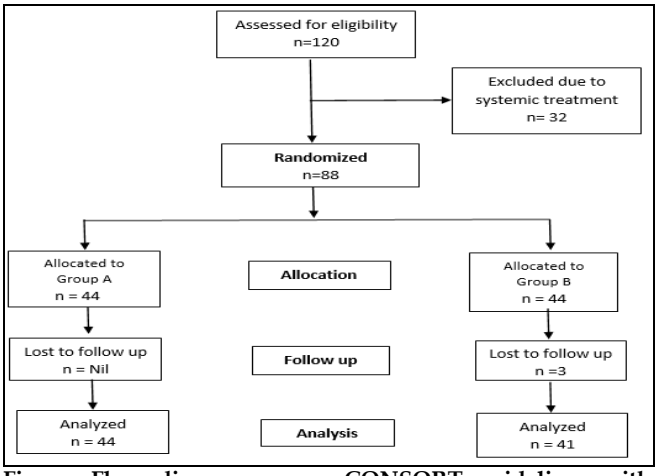

Figure: Flow diagram as per CONSORT guidelines with details of selection of patient participants (n=88)

RESULTS

Out of Eighty-eight patients of melasma, 66(75.0%) were females while 22(25.0%) were males. Mean age of the study participants was 30.93±7.94 years. Out of 44 patients in Group-A, 13 showed grade 1 (1% to 25%), improvement 21 patients showed grade 2 improvement (25% to 50%), while grade 3 improvement was seen in 4 patients (50% to 75%). In Group-B 34(77.2%) were female and 10(22.8%) males. In Group-B, grade 1, 2, 3 and 4 improvements were seen in 14, 26, 3 and one patient, respectively. Three patients lost follow up. Adverse effects were noted in 2 patients of Group-A, and 5 patients in Group-B. Both groups were followed-up after every 4 weeks for the assessment of percentage of improvement and adverse effects were also noted. After each visit MASI score

and improvement in term of percentage was calculated. The median MASI score in Group-A was reduced significantly from the baseline value of 11.55 (12.67-8.90) to 8.50 (10.25–7.20) after completion of 12 weeks treatment. Similarly, Group-B showed reduction from 10.35 (12.50–8.40) at baseline to 8.00 (9.20–6.00) after 12 weeks of treatment. But there was no statistically significant reduction found between the two groups (p=0.11). The statistical difference between the Group-A and Group-B with respect to duration, gender, age, and mean MASI score at the start of the treatment was not significant as depicted in Table.

Table: Characteristics of Study Participants (n=88)

Parameters	Study Groups		*p*-value
	Group-A (n=44)	Group-B (n=44)	
Age in years (Mean ±SD)	32.72±3.81	31.36±3.55	0.556
Gender			
Female Male	32(72.7%) 12(27.3%)	34(77.2%) 10(22.8%)	0.828
MASI Score at Baseline Median (IQR)	11.55(12.67-8.90)	10.35(12.50–8.40)	0.210
MASI Score after 12 weeks Median (IQR)	8.50(10.25–7.20)	8.00(9.20–6.00)	0.110

DISCUSSION

Management of melasma is considered as highly challenging, especially because it is prone to frequent relapses despite successful treatment.[11] Metformin is quite safe and effective in the treatment of various inflammatory dermatoses, dermatosis related to endocrine disorders, skin malignancies, melasma, skin aging and wound healing.[12] It was found that metformin reduce intracellular c-AMP which has a role in melanogenesis.[13] Topical metformin has been considered to decrease melanin synthesis by inhibiting the activity of tyrosinase, while niacinamide reduces the transfer of melanin to the skin surface. The combination of these agents has a synergistic effect in reducing hyperpigmentation.[14]

Topical 30% metformin with 2% nicotinamide solution and Kligman formula were equally efficacious in management of melasma in our study participants at the end of twelve weeks trial. Adverse effect of mild redness was noted in 2(6.8%) patients of Group-A, while 5(11.3%) patients complained of redness and burning sensation with the application of Kligman formula in Group-B. The findings of our study are consistent with previous studies, which showed the effectiveness of topical metformin and niacinamide for the management of melasma. A randomized controlled study was conducted on topical metformin in the management of melasma and found topical metformin to be a new, safe option which was almost as fruitful a treatment option as Kligman formula, and results showed mean MASI score reduction from start of the treatment after two months in metformin group and reduction of baseline MASI from 6.43±5.35 to 5.2±5.02 in Kligman group.[15]

AboAlsoud *et al.*, conducted a randomized control trial in 2022, which evaluated the safety and effectiveness of using 30% metformin cream as compared to Kligman's formula in management of melasma and study showed significant MASI score reduction after 8 weeks of treatment with a mean decrease of 55.97%±16.77% for metformin group and mean decrease of 56.50%±19.44% for group Kligman group.[16] Our study showed similar results, with mean MASI reduction from 11.23±2.11 to 8.79±2.07 after 12 weeks of treatment in Group-A and similarly reduction of mean MASI from 10.62±2.42 to 7.72±2.40 in Group-B. In both studies mentioned above, a significant difference was not observed in term of effectiveness and results were more or less same in both groups. Our study also showed the similar results.

One advantage of the metformin and nicotinamide solution over the Kligman formula is its safety profile. Hydroquinone, one of the components of the Kligman formula, has been associated with numerous adverse effects, including exogenous ochronosis, hypersensitivity reactions, and carcinogenic potential.[17] Metformin and nicotinamide, on the other hand, have been shown to be safe and well-tolerated in various clinical trials.[18]

LIMITATION OF STUDY

It was a single center trial and involved mostly entitled patients (retired military personnel) so results can't be generalized to whole population. Moreover, the efficacy was studied for a short duration of 12 weeks. Long term data is still lacking especially in case of relapse of illness if treatment is stopped. Safety was also a concern which was not addressed in this trial as main focus was on efficacy of treatment.

CONCLUSION

Both the treatment options used, 30% metformin with 2% nicotinamide solution and Kligman formula were equally efficacious in management of melasma at the completion of 12 weeks treatment.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

IA & QUD: Data acquisition, data analysis, critical review, approval of the final version to be published.

UN & AS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MSK & UAA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Zhu Y, Zeng X, Ying J, Cai Y, Qiu Y, Xiang W. Evaluating the quality of life among melasma patients using the MELASQoL scale: A systematic review and meta-analysis. Plos One 2022; 17(1): e0262833. https://doi.org/10.1371/journal.pone.0262833
2. González-Molina V, Martí A, González N. Topical treatments for Melasma and their mechanism of action. J Clin Aesthet Dermatol 2022; 15(5): 19-28.
3. Neagu N, Conforti C, Agozzino M, Marangi GF, Morariu SH, Pellacani G, et al. Melasma treatment: a systematic review. J Dermatol Treat 2022; 33(4): 1816-1837. https://doi.org/10.1080/09546634.2021.1914313
4. T Jadotte Y, A Schwartz R. Melasma: insights and perspectives. Acta Dermatovenerol Croat 2010; 18(2): 124-129.
5. Mongkhon P, Ruengorn C, Awiphan R, Phosuya C, Ruanta Y, Thavorn K, et al. Efficacy and safety of metformin for melasma treatment: a systematic review and meta-analysis. Front Pharmacol 2023 14(1): 1281050. https://doi.org/10.3389/fphar.2023.1281050
6. Chang YF, Lee TL, Oyerinde O, Desai SR, Aljabban A, Bay CP, et al. Efficacy and safety of topical agents in the treatment of melasma: What's evidence? A systematic review and meta-analysis. J Cosmet Dermatol 2023; 22(4): 1168-1176. https://doi.org/10.1111/jocd.15566
7. El-Komy MH, Elnowaihy SW, Shamma RN, Bedair NI. Efficacy and safety of a novel weekly topical metformin-loaded peel-off mask in the treatment of melasma: a split-face, placebo-controlled study. Clin Exp Dermatol 2024; 49(12): 1633-1640. https://doi.org/10.1093/ced/llae274
8. Rolfe HM. A review of nicotinamide: treatment of skin diseases and potential side effects. J Cosmet Dermatol 2014; 13(4): 324-328. https://doi.org/10.1111/jocd.12119
9. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN. Topical retinoic acid (tretinoin) for melasma in black patients: a vehicle-controlled clinical trial. Arch Dermatol 1994; 130(6): 727-733. https://doi.org/10.1001/archderm.1994.01690060057005
10. Yalçın HT, Çakır DA, Yirün A, Sanajou S, Işık G, Bozdemir Ö, et al. Comparative in vitro and in silico evaluation of the toxic effects of metformin and/or ascorbic acid, new treatment options in the treatment of Melasma. Toxicol Res 2025; 14(1): tfaf025. https://doi.org/10.1093/toxres/tfaf025
11. Kwon SH, Na JI, Huh CH, Park KC. A Clinical and Biochemical Evaluation of a Temperature-Controlled Continuous Non-Invasive Radiofrequency Device for the Treatment of Melasma. Ann Dermatol 2021; 33(6): 522. https://doi.org/10.5021/ad.2021.33.6.522
12. Monte-Serrano J, Villagrasa-Boli P, Cruanes-Monferrer J, Arbués-Espinosa P, Martínez-Cisneros S, García-Gil MF. The role of metformin in the treatment of dermatological diseases: A narrative review. Aten Primaria 2022; 54(6): 102354. https://doi.org/10.1016/j.aprim.2022.102354
13. Saleh FY, Abdel-Azim ES, Mohamed ZS. Study of wood's lamp and dermoscopic features of melasma. Minia J Med Res 2019; 30(1): 66-67.
14. Rachmin I, Ostrowski SM, Weng QY, Fisher DE. Topical treatment strategies to manipulate human skin pigmentation. Adv Drug Del Rev 2020; 153(1): 65-71. https://doi.org/10.1016/j.addr.2020.02.002
15. Banavase R, Andanooru NK. Topical metformin in the treatmentof melasma: A preliminary clinical trial. J Cosmet Dermatol 2020; 19(5): 1161-1164. https://doi.org/10.1111/jocd.13145
16. AboAlsoud ES, Eldahshan RM, AbouKhodair Mohammed H, Elsaie ML. Safety and efficacy of topical metformin 30% cream versus triple combination cream (Kligman's formula) in treating melasma: A randomized controlled study. J Cosmet Dermatol 2022; 21(6): 2508-2515. https://doi.org/10.1111/jocd.14953
17. Bronzina E, Clement A, Marie B, Fook KT, Faure P, Passeron T. Efficacy and tolerability on melasma of a topical cosmetic product acting on melanocytes, fibroblasts and endothelial cells: a randomized comparative trial against 4% hydroquinone. J Eur Acad Dermatol Venereol 2020; 34(4): 897-903. https://doi.org/10.1111/jdv.16150
18. Boo YC. Mechanistic basis and clinical evidence for the applications of nicotinamide (niacinamide) to control skin aging and pigmentation. Antioxidants 2021; 10(8): 1315. https://doi.org/10.3390/antiox10081315