CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3484541

Available online at: http://www.iajps.com ***Research Article***

COMPARISON OF EFFICACY OF TOPICAL 4% HYDROQUINONE WITH TOPICAL 2% ALPHA ARBUTIN IN EPIDERMAL MELASMA

Dr.Ramla Kazmi[1], Dr. Zia ul Mustafa[2], Dr. Muhammad Zeb Khan[3], Dr. Saadia Khaleeq [4], Dr. Daniyal Raza[5], Dr. Maheen Fawad[6]

Department of Dermatology[1], Sahara Medical College, Narowal. Department of Medicine[2], Sahara Medical College, Narowal. Department of Orthopedics[3], Sahara Medical College, Narowal. Department of Anesthesia[4], Junior Trainee Medical Unit Sughra Shafi Trust Hospital Narowal[5-6]

Article Received: August 2019 **Accepted:** September 2019 **Published:** October 2019

Abstract:

Background: *Several methods of treatment exist for melasma but the condition is chronic and relapsing. Research is on to discover the most efficacious and safest treatment option for the condition.*

Objective: *To compare the efficacy and safety of topical 4% hydroquinone and 2% alpha arbutin in the treatment of Epidermal Melasma*

Subjects & Methods: *This was a comparative interventional study. After history taking and clinical examination, even number patients (Group A) we retreated with topical 4% hydroquinone while odd number patients(Group B) were treated with topical 2% arbutin. Topical sunscreen of SPF-30 in cream base was applied to both groups at 4 hourly intervals from morning till evening. Six visits, at intervals of 4 weeks each, were carried out in each patient for both procedures. Severity of melasma was assessed by MASI score. Patients were photographed before and after treatment also they were assessed for side effects and clinical improvement.*

Patients were inquired about side effects of treatment such as burning, erythema and scaling on each visit. In case of side effects of treatment, it was stopped for two weeks to manage the side effects and was restarted after that. Follow-up was done for 2 months after the last session.

Results: *From 4th week till 32th week follow up time period, it was observed that as per MASI scoring patients in Group-B had significantly excellent results as compared to patients in Group-A. Patients treated with hydroquinone experienced redness, burning, tingling, hypo-pigmentation in one patient only at 28th week post-treatment and swelling during their course of treatment. However, these adverse effects were significantly more frequent with hydroquinone.*

Conclusion: *As per findings of this study clinical efficacy and safety of topical 2% alpha arbutin is higher than the gold standard, 4% hydroquinone in treating epidermal melasma patients.*

Key Words: *Epidermal melasma, Topical 4% hydroquinone, 2% alpha arbutin, MASI score.*

Corresponding author:
Ramla Kazmi,
Department of Dermatology

QR code

Please cite this article in press Ramla Kazmi et al., ***Comparison of Efficacy of Topical 4% Hydroquinone with Topical 2% Alpha Arbutin in Epidermal Melasma.,*** *Indo Am. J. P. Sci, 2019; 06(10).*

INTRODUCTION:

Melasma is an acquired disorder characterized by hyper pigmentation, caused by lesions consisting of light to dark-brown macules and patches due to deposition of melanin, typically on the sun exposed areas of the face [1]. There are three histological types of melasma; dermal, epidermal and mixed. In epidermal type, melanin is deposited mainly in basal and suprabasal skin layers. A recent study of patients with melasma has shown that a higher amount of epidermal melanin is the result of increased melano genesis and melanocytosis going on in the epidermal melanocytes [2].

Wood's light examination was a reliable instrument to know the depth of pigmentary lesions during treatment. However, recent studies suggest a poor relation between the classifications based on Wood's light examination and biopsy skin samples using light microscope[3].

The Melasma Area and Severity Index (MASI) was initially developed and explained by Kimbrough-Green et al for the assessment of melisma [4]. According to this index, severity of melasma is based on three determinants: percentage of total Area involved (A), Darkness (D) and Homogeneity (H). To calculate MASI, face is divided into four regions: the forehead (30%), right malar region (30%), left malar region (30%), and the chin (10%). Darkness of pigment when compared with normal skin is graded from 0 to 4. Homogeneity of the pigment is also graded from 0 to 4 [5].

Clinical studies hardly predict any response of melasma to the treatment using Wood's light examination[6]. For this reason, Wood's light examination is not considered as a perfect tool for assessing the depth of pigmentary lesions. However, skin biopsy can be an absolute option assessing the depth of melanin pigmentation.

Physician and dermatology patients are all searching for new and improved long-term topically applied skin care solutions for the treatment of hyper pigmented skin conditions.

The mainstay of the treatment is protection from the ultraviolet radiations of sun [3]. The epidermal and dermal types can be treated with topical applications such as hydroquinone, arbutin, kojic acid, tretinoin, azelaic acid and other treatments.

Hydroquinone remains the gold standard [7] by which other treatments are usually compared. However, its prolonged use is harmful because of its potential adverse effects like free radical generation, local irritation, ochronosis, permanent skin depigmentation and even cataract formation.

Arbutin, a botanical extract, is safer to be used on the skin as a cosmetic component [7]. It is a derivative of hydroquinone which has gained popularity owing to its less irritant nature and equal or even more efficacy [8].The mode of action of arbutin is through inhibition of tyrosinase activity without affecting its mRNA expression, and also to inhibit DHICA polymerase activity. It is metabolized to hydroquinone in the gastrointestinal tract with most of the byproducts being cleared by the kidneys [9].

Arbutin is commonly added to cosmetic preparations. It is capable of producing desired skin depigmentation without causing significant melanotoxicity. This study is, therefore, being conducted to compare the efficacy and safety of 4% hydroquinone and 2% alpha arbutin in our patients.

MATERIAL AND METHODS:

Study Design: Comparative Interventional Study
Place and Duration of Study: Study was conducted in the Dermatology Department Unit-1, KEMU/ Mayo Hospital, Lahore. Duration was one year
Sample Size: Determined statistically to be 55 in each group
Subjects:
Inclusion Criteria:

- Patient of either sex
- Age group 18-50 years
- Epidermal melasma

Exclusion Criteria:

- Dermal or mixed varieties of melasma
- Patients already receiving topical/oral therapy for melasma for the last one month at the commencement of treatment
- Patient on drugs like anti-tuberculous drugs, hormonal replacement therapy, oral contraceptive pills, oral retinoids or glucocorticoids
- Patients with haemoglobin levels <10g/dl
- Patients with any systemic disease e.g. liver or kidney diseases
- Pregnancy

Data Collection Procedure:
Data was collected using a well-designed proforma annexed at the end. Informed written consent was taken from the patient before enrollment in the study.

History was taken and clinical examination was performed on first visit. The clinical pattern of melasma was assigned to each patient on 1st visit. Every even number was treated with topical 4% hydroquinone while every odd number was treated with topical 2% arbutin.

Topical sunscreen of SPF-30 in cream base was applied to both groups at 4 hourly intervals from morning till evening. Six visits were carried out in each patient for both procedures. Time period between 2 visits was 4 weeks. Severity of melasma was assessed by MASI score (Annexture A) on first and every subsequent visit. Patients were photographed before and after treatment and assessed for side effects and clinical improvement at every visit.

Patients were inquired about side effects of treatment such as burning, erythema and scaling experienced on each visit. In case of side effects of treatment, the treatment was stopped for two weeks to manage the side effects and was restarted after management of the side effects. Follow-up was done for 2 months after the last session.

Assessment Criteria:
Assessment of the patient was clinical. Response to each treatment modality was graded according to improvement in MASI score and corroborated by pre- and post- treatment photographs comparison.

Data Analysis Procedure
Collected information was transferred to SPSS 20 computer software programmer and was analyzed accordingly. Output was presented in the form of graphs and tables for categorical variables. Mean, median and standard deviation was used to represent the quantitative variables. Repeated measure ANOVA was used to see the MASI score in both treatment groups from baseline till last follow up. Chi-square test was used to see the association between qualitative variables. P-value <0.05 was taken as significant.

RESULTS:

At baseline and 1stweek post-treatment, all patients' melasma score was poor. At 2nd week in Group-B, MASI score of 7 patients was satisfactory. However in Group-A, all patients still had a poor score. At 12th and 16th week, 12 (21.82%) and 17 (30.91%) patients in Group-A had satisfactory MASI score respectively.

In Group-B at 12th and 16th week, 12 (21.82%) and 15 (27.27%) patients had poor MASI score respectively. At 20thweek follow up, 8 patients in Group-A, and 5 in Group-B, MASI score was satisfactory and 16 (29.09%) patients each in both treatment groups had good MASI score. At 24thweek in Group-A, 22 (40%) patients had good and only 2 (3.64%) patients had excellent MASI score. In Group-B, 15 (27.27%) patients had good and 10 (18.18%) patients had excellent MASI score.

At 28th week only 10(18.18%) patients in Group-A and 18 (32.73%) in Group-B had excellent MASI score. At the last follow up time interval which was 32ndweek post-treatment, in Group-A 18 (32.73%) patients MASI score was excellent and 28 (50.91%) patients in Group-B had excellent outcome.

From 24th week till 32th week follow up time interval more patients in Group-B had excellent MASI score as compared to patients in Group-A (Table-1).

Those treated with hydroquinone experienced redness, burning, tingling, hypo-pigmentation in one patient only at 28th week post treatment and swelling during their course of treatment. However, these adverse effects were significantly more frequent with hydroquinone.

TABLE-1
SEVERITY OF PGA SCORE IN TREATMENT GROUPS DURING COURSE OF FOLLOW UP

	Week20		Week24		Week28		Week32	
MASI Score	***A***	***B***	***A***	***B***	***A***	***B***	***A***	***B***
Poor	**31(56.36%)**	**34(61.82%)**	**24(43.46%)**	**27(49.09%)**	**11(20%)**	**8(14.55%)**	**8(14.55%)**	**5(9.09%)**
Satisfactory	**8(14.55%)**	**5(9.09%)**	**7(12.73%)**	**3(5.45%)**	**4(7.27%)**	**13(23.64%)**	**4(7.27%)**	**10(18.18%)**
Good	**16(29.09%)**	**16(29.09%)**	**22(40%)**	**15(27.27%)**	**30(54.55%)**	**16(29.09%)**	**25(45.45%)**	**12(21.82%)**
Excellent	**0(0%)**	**0(0%)**	**2(3.64%)**	**10(18.18%)**	**10(18.18%)**	**18(32.73%)**	**18(32.73%)**	**28(50.91%)**
p-value	***0.660***		***0.037***		***0.008***		***0.018***	

Poor: <40%, Satisfactory: 40-59%, Good: 60-79%, Excellent: ≥80%
Group-A = 4% Hydroquinone cream
Group-B = 2% Alpha Arbutin cream

TABLE-2
COMPARISON OF ADVERSE EFFECTS IN BOTH TREATMENT GROUPS DURING

		Redness		***Burning***		***Tingling***		***Hypo-pigmentation***		***Swelling***		***Others***	
		Yes	***No***	***Yes***	***No***	***Yes***	***No***	***Yes***	***No***	***Yes***	***No***	***Yes***	***No***
24 week	***Group-A***	14	41	10	45	14	41	0	55	0	55	0	55
	Group-B	0	55	1	54	3	52	0	55	0	55	0	55
	p-value	***0.000***		***0.004***		***0.003***		-		-		-	
28 week	***Group-A***	5	50	10	45	10	45	1	54	0	55	0	55
	Group-B	1	54	0	55	3	52	0	55	0	55	0	55
	p-value	***0.093***		***0.000***		***0.038***				-		-	
32 week	***Group-A***	5	50	8	47	10	45	0	55	0	55	0	55
	Group-B	1	54	0	55	2	53	0	55	0	55	0	55
	p-value	***0.093***		***0.003***		***0.014***		-		-		-	

DISCUSSION:

Melasma is amongst the most common skin disorders encountered by dermatologists. Although it is considered amongst the commonest diseases with highly cosmetic concerns worldwide, even then there is a lack of systematic and clinically usable treatment algorithms and guidelines for melasma management[10].

Various studies have been conducted on different hypopigmenting agents making comparison between their efficacy and safety profiles. In literature, there was not even a single study comparing both hydroquinone and arbutin for the cure of melasma. The narrow safety index of hydroquinone has made scientists work on finding alternate for hydroquinone with much broader safety index for the cure of melasma. Hydroquinone's efficacy in treating melasma, both alone and in combination with other agents is well established.

Among patients who were treated with hydroquinone among them no improvement was seen in MASI score till 8th week follow up. At 12th and 16th week 12 (21.82%) and 17 (30.91%) patients had satisfactory MASI score respectively. However at 20th week follow up time period 16 (29.09%) patients had good and at 24th week 22 (40%) had good and only 2 (3.64%) patients had excellent improvement in MASI score.

At 28th and 32nd month 30 (54.55%) and 25 (45.45%) patients respectively had good and 10 (18.18%) and 18 (32.73%) had excellent MASI scores. Both arbutin and hydroquinone showed improvement in MASI score

during the course of follow up time period but the former showed much better results as compared to the latter. Spencer[13] performed one of the first studies using hydroquinone at concentrations of 2 %, 3 %, and 5 % applied twice daily for 3 months to the dorsal surface of the hands of white men with solar lentigines. On clinical examination, a decrease in pigmentation was seen that was dose dependent, with maximum results after 2 months of treatment and once the treatment was stopped a relapse was noticed [11].

The safety of hydroquinone has always been a huge concern with its long term use. In this study adverse effects like redness, burning, tingling and hypo-pigmentation in one patient were noticed after 7 months of treatment and swelling during the course of treatment with hydroquinone. The frequency of adverse effects was found to be significantly higher with hydroquinone. However in literature it is reported that the frequency of overall adverse events with hydroquinone as 25% and 28.6% respectively [12,13].

Arbutin is a molecule whose efficiency is proven in the treatment of melasma. In a randomized, open-label study, melanins levels were significantly decreased in 10 melasma patients treated with 1% arbutin for 6 months [14].

As per study results, the patients who were treated with Arbutin showed that after 16th weeks of treatment MASI score of 15 (27.27%) patients was satisfactory. However with the passage of treatment duration progress in MASI score was seen. i.e. 20th week MASI score [Satisfactory: 5 (9.09%) & Good: 16 (29.09%)]; 24th Week: [Satisfactory: 3 (5.45%), Good: 15 (27.27%) & Excellent: 10 (18.18%)]; 28th Week: [Satisfactory: 13 (23.64%), Good: 16 (29.09%) & Excellent: 18 (32.73%)]; 32th Week: [Satisfactory: 10 (18.18%), Good: 12 (21.82%) & Excellent: 28 (50.91%)]. However from 24th week till 32th week improvement in patients treated with arbutin was much better than those treated with hydroquinone as far as MASI score is concerned.

The marked feature of arbutin as compared to hydroquinone, is its minimal adverse effects in therapeutic doses [15] and it does not cause necrotic changes even at higher concentrations of arbutin in 10% aqueous solutions. Arbutin also does not show any mutagenic or carcinogenic properties [16].

However, according to some studies, few adverse effects were noticed while treatment with arbutin containing preparations subjected to the dose administered. Arbutin causes skin irritation and hyper pigmentation when applied in higher concentrations [17].

Thanks to the studies on the biological activities of arbutin, its derivatives and arbutin-containing extracts the spectrum of their uses is broadening. The need of exploring new sources and methods of arbutin derivatives synthesis cannot be neglected.

CONCLUSION:

As per this study, it reveals that 2% alpha arbutin is a better choice than the gold standard, 4% hydroquinone for the cure of epidermal melasma in terms of clinical efficacy as well as safety and this is the reason why Arbutin has now been an exclusive alternate for conventionally prescribed skin-lightening agents in topical skin preparations as it is more effective and safe in producing the desired effects on human skin.

REFERENCES:

1. Kang HY, Ortonne JP. What should be considered in treatment of melasma? *Annals Dermatol*. 2010;22:373-8.
2. Kang W, Yoon K, Lee ES, Kim J, Lee K, Yim H, et al. Melasma: histopathological characteristics in 56 Korean patients. *Br J Dermatol*. 2002;146:228-37.
3. Sarkar R, Puri P, Jain R, Singh A, Desai A. Melasma in men: a clinical, etiological and histological study. *J EurAcadDermatolVenereol*. 2010;24:768-72.
4. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, et al. Topical retinoic acid (tretinoin) for melasma in black patients: a vehicle-controlled clinical trial. *Arch Dermatol*. 1994;130:727-33.
5. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing Melasma Severity Index: A New, More Practical, Office-based Scoring System for Assessing the Severity of Melasma. *Indian J Dermatol*. 2016;61(1):39–44. doi:10.4103/0019-5154.174024
6. Lawrence N, Cox SE, Brody HJ. Treatment of melasma with Jessner's solution versus glycolic acid: a comparison of clinical efficacy and evaluation of the predictive ability of Wood's light examination. *J Am Acad Dermatol*.1997;36:589-93.
7. Kanthraj GR. Skin-lightening agents: New chemical and plant extracts-ongoing search for the Holy Grail. *Indian J Dermatol Venereol Leprol*. 2010;76(1):3.

8. Ortonne J, Arellano I, Berneburg M, Cestari T, Chan H, Grimes P, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. *J Eur Acad Dermatol Venereol*. 2009;23:1254.
9. O'donoghue J. Hydroquinone and its analogues in dermatology–a risk-benefit viewpoint. *J Cos Dermatol.* 2006;5(3):196-203.
10. Shankar K, Godse K, Aurangabadkar S, Lahiri K, Mysore V, Ganjoo A, et al. Evidence-Based Treatment for Melasma: Expert Opinion and a Review. *DermatolTher*. 2014;4(2):165-86.
11. Spencer MC. Topical use of hydroquinone for depigmentation. *JAMA*. 1965;194(9):962-4.
12. Ennes S, Paschoalick R, Alchorne MMDA. A double-blind, comparative, placebo-controlled study of the efficacy and tolerability of 4% hydroquinone as a depigmenting agent in melasma. *J Dermatol Treat*. 2000;11(3):173-9.
13. Haddad AL, Matos LF, Brunstein F, Ferreira LM, Silva A, Costa D. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Inter J Dermatol*. 2003;42(2):153-6.
14. Ertam I, Mutlu B, Unal I, Alper S, Kiv CA k B, Ozer O. Efficiency of ellagic acid and arbutin in melasma: A randomized, prospective, open label study. *J Dermatol*. 2008;35 (9):570-4.
15. Maeda K, Fukuda M. Arbutin: mechanism of its depigmenting action in human melanocyte culture. *J Pharmacol ExpThera*. 1996;276(2):765-9.
16. Lim Y-J, Lee EH, Kang TH, Ha SK, Oh MS, Kim SM, et al. Inhibitory effects of arbutin on melanin biosynthesis of α-melanocyte stimulating hormone-induced hyper pigmentation in cultured brownish guinea pig skin tissues. *Arch Pharmacol Res*. 2009;32(3):367-73.
17. Kim H, Choi H-R, Kim D-S, Park K-C. Topical hypo pigmenting agents for pigmentary disorders and their mechanisms of action. *Annals Dermatol*. 2012;24(1):1-6.