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ORIGINAL ARTICLE

A Prospective, Randomized and Open Label Study to Compare Efficacy, Safety and Quality of Life Impact of Topical Glutathione (2%) in Comparison to Topical Tranexamic Acid (3%) in Adult Melasma Patients

Saurabh Bijalwan, Gurpreet K. Randhawa, Tejinder Kaur*

Background: The most common cause of facial melanoses is melasma. There is no universally efficacious melasma therapy and the gold standard therapy (triple combination cream) has multiple long term adverse effects. Topical glutathione is a relatively novel drug acting on key melasma pathology features.**Objectives:**This is first study to compare efficacy, safety and quality of life (QoL) impact of topical glutathione (2%) with topical tranexamic acid (TA) (3%) in adult melasma patients.**Design:** Randomized, prospective, parallel and open label.**Methods:** This study compared topical glutathione (2%) (Group A, n = 30) with topical TA (3%) (Group B, n = 30) in 60 adult melasma patients for 3 months. Evaluation of efficacy was done through Modified Melasma Area Severity Index (mMASI score) & Physician Global Assessment (PGA) score on 30, 60 and 90 days. QoL was assessed through Melasma Quality of Life score (MELASQOL) and photographs were taken at 0 &90 days. Adverse effects were reported every 30 days.**Results:** Both groups exhibited improvement in mMASI & PGA score at 30 days, but statistically significant improvement ($p < 0.001$) was observed from 60 to 90 days. Group A was significant over Group B in improving mMASI ($p < 0.001$) and PGA score ($p < 0.001$) from 60 days to 90 days. Both groups had a comparable safety profile ($p > 0.05$) with no serious adverse effects. **Conclusion:** Topical glutathione showed better efficacy, QoL improvement and comparable safety to topical TA over 3 months in melasma.

Keywords:
Topical Glutathione , Topical TA , Melasma, Hyperpigmentation, Triple Combination Creams

Introduction

The most common cause of facial melanosis is melasma.[1]Melasma is an acquired, symmetrical, and circumscribed hypermelanosis with light to dark brown macules on face, neck and forearms. [2]Its global prevalence ranges from 1 to 50% with prominence in light brown skin, as in Indians.[3,4] There is no universally efficacious melasma therapy. [5]

Topical glutathione inhibits tyrosinase enzyme and reduces production of melanin from tyrosine. It also does free radical scavenging which affects tyrosinase activation, reduces photodamage and increases production of pheomelanin [red or yellow] from eumelanin [brown or black].[6] TA decreases tyrosinase activity, alters interaction of keratinocytes and melanocytes, and contracts dermal vasculature.[7,8]

There is aggressive global promotion of glutathione as a skin whitening agent,in spite of scarcity of data on it. [9,10] Topical TA is a first line melasma therapy.[2]

Thus, in present study, we compared the efficacy and safety of topical glutathione (2%) with topical TA (3%)

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and their effect on quality of life in adult melasma subjects over 3 months.

Material & Methods

This was a prospective, randomized and open label study.Recruitment of study subjects was started after obtaining approval of Institutional Ethics Committee. 60 melasma patients visiting OPD of Dermatology, and fulfilling inclusion criteria, were recruited in study for 90 days after taking their informed consent.

Inclusion Criteria: Melasma patients of both sexes diagnosed clinically; 18 – 60 years patients who hadn't received melasma treatment 30 days before study.

Exclusion Criteria: Patients refusing to give written informed consent; Known hypersensitivity to study drugs; Pregnancy & lactation; History of major comorbidities; Patients who had taken OCP's or hormonal medication 3 months prior from beginning of study.

Patients were randomly divided into 2 groups- A and B(30 patients each). Graph Pad software (2020 version) was used for generating random numbers.All patients were prescribed and explained standard sunscreen (SPF 30) usage and advised to minimize sun exposure.

Group A -2 % glutathione gel BD

Group B - 3 % TA gel BD

Drug Application

Patients were advised to clean affected area with soap and water, and dry it by patting with towel. Thin uniform film of drug was applied twice daily with 10 hours interval.

Coloured photographs of affected areas were taken at 0 and 90 days with a steady hand at approximately 20-centimeters in front and both sides of face. At baseline, Hemoglobin, Woods Lamp examination (for depth of pigmentation), Modified Melasma Area Severity Index (mMASI)score (indicates melasma severity) and Melasma Quality of Life Index (MELASQOL) score were assessed. From first follow-up (30 days),Physician Global Assessment (PGA) score (to assess response of treatment)and adverse effects were also studied.Follow up was done every 30 days for 90 days, but MELASQOL was followed up at 90 days only.

Melasma Severity: mMASI score is rated from 0 to 24 on basis of Area of involvement (A) and Darkness (D). Face is divided into 4 regions: [11]

i. Forehead (f) - 30% of face. Right and left forehead – 15% each
ii. Right malar (rm) - 30% of face
iii. Left malar (lm) - 30% of face
iv. Chin (c) - 10 % of face

Darkness – (compared with subject's normal skin) is rated from 0 to 4 and area from 0 to 6. The final mMASI was calculated as per:

0.3 * A(f)* D(f) + 0.3 * A(lm)*D(lm) + 0.3 * A(rm)*D(rm) + 0.1 * A (c)*D(c)

Statistical Analysis

The study used 't' test for continuous data, Chi-square test and Fischer's Exact test for categorical data, and Mann-Whitney U test and Kruskal Wallis test for ordinal data by using IBM SPSS software V21. A p value of <0.05 was considered as statistically significant.

Results

There were 3 dropouts (2 – inability to contact, 1 – started alternate treatment) in group A and 2 dropouts (1- inability to contact & 1 – felt no improvement at 30 days) in group B. Total 60 patients were analysed in this study after excluding dropouts. Baseline population and their demographic parameters were comparable in both groups (*Table 1a and 1b*).

mMASI Score: The mean mMASI was reduced at 30 days, compared to baseline, with group A and group B, but significant reduction was seen from 60 days and 90 days in both groups (1.34 ± 0.87 in group A and 3.12 ± 2.08 in group B) ($p < 0.001$) (*Fig 1*). Percentage change in mean mMASI over 90 days was significant in group A (67.40 ± 33.69) over group B (44.13 ± 32.92) ($p=0.009$). Photographs were taken at 0 days and 90 days (*Fig 2a and 2b*).

PGA Score: In both groups, significant improvement in PGA score was observed from 60 days, compared to 30 days, till 90 days($p < 0.001$). There was significant improvement in PGA score in group A (median PGA score – 2) than group B (median PGA score – 3) at 90 days($p < 0.001$) (*Table 2 & 3*).At 90 days, 93.34% subjects showed improvement with group A, compared to 69.99% subjects with group B. No subject had totally clear (PGA score 0) or worsened melasma (PGA score 6) in either group (*Table 4*).

MELASQOL Score: The reduction in MELASQOL score was significant ($p<0.001$) at 90 days with both group A (18.67 ± 10.62) and group B (12.70 ± 10.44) compared to baseline. There was significant improvement in MELASQOL score in group A (42.06 ± 20.06% change) than group B (28.40 ± 21.80% change) over 90 days ($p=0.012$).

Safety Profile: The only adverse effect observed in group A was redness (mild, n = 2 [6.67%]).Total five

Table:1a Intergroup Comparison of Various Parameters at Day '0'

Parameter	Group A n (%)	Group B n (%)	p value
Mean Age (years)	29.83 ± 8.17	33.60 ± 8.73	0.09[a]
Females	21 (70.00)	25 (83.33)	0.360[b]
Males	9 (30.00)	5 (16.67)	
OCCUPATION			
Housewife	9 (30.00)	15 (50.00)	
Salaried class	6 (20.00)	4 (13.33)	
Student	6 (20.00)	2 (6.67)	0.172[c]
Self-business	1 (3.33)	4 (13.33)	
Others	8 (26.67)	5 (16.67)	
MELASMA TYPE			
Malar	11 (36.67)	12 (40.00)	
Centrofacial and Malar	6 (20.00)	11 (36.66)	
Malar and Mandibular	5 (16.67)	4 (13.33)	0.567[c]
Centrofacial	6 (20.00)	2 (6.67)	
Mandibular	1 (3.33)	1 (3.33)	
Centrofacial, Malar and Mandibular	1 (3.33)	0 (0.00)	
SUN EXPOSURE			
< 30 mins	7 (23.33)	11 (36.67)	
30 mins to 1 hour	3 (10.00)	5 (16.67)	
1 to 2 hours	8 (26.67)	7 (23.33)	0.549[c]
2 to 3 hours	9 (30.00)	6 (20.00)	
> 3 hours	3 (10.00)	1 (3.33)	
ANEMIA			
No	22 (73.33)	19 (63.33)	
Mild	5 (16.67)	6 (20.00)	0.458[c]
Moderate	2 (6.67)	5 (16.67)	
Severe	1 (3.33)	0 (0.00)	
FITZPATRICK SKIN TYPE			
Type-IV	14 (46.67)	9 (30.00)	0.288[c]
Type-V	16 (53.33)	21 (70.00)	

Others - electricians, domestic help, salesman, computer analyst and driver [prevalence < 5%]

*p>0.05: Not significant, *p<0.05: Significant; **p<0.001: Highly significant*

[p value: a - Unpaired t test, b - Two proportion Z-test, c - Chi Square test]

patients had adverse effects in group B – 1 patient [3.33%] had scaling (mild), 2 [6.67%] patients- redness (moderate) and scaling (moderate) and 2 [6.67%]patients - redness (mild) and irritation (mild). Both groups had comparable adverse effects (p = 0.140).There were no serious ADRs and no subject had to discontinue the study due to any ADR.

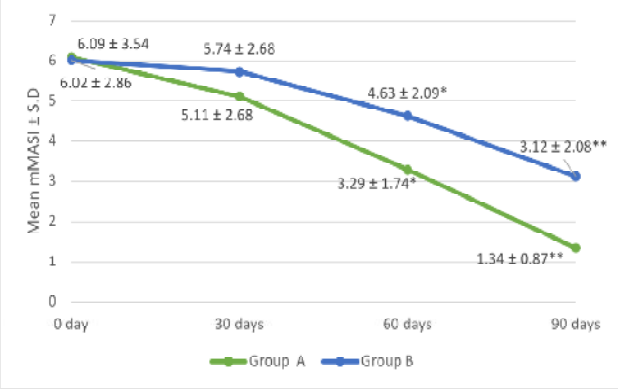
Discussion

mMASI score: Our results are in concordance with Farahat *et al.*, an interventional study (n=30) comparing topical glutathione (2%) (oxidized/reduced form not mentioned) on right side and placebo cream to left side

Table:1b: Intergroup Comparison of Woods Lamp Examination at Day '0'

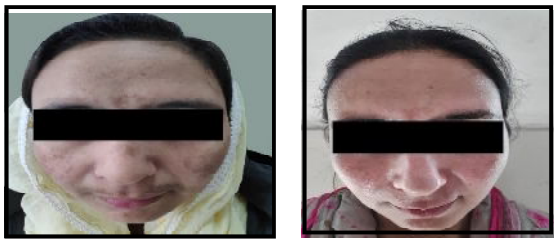
Parameter	Group A n (%)	Group B n (%)	p value
Woods Lamp Melasma Type:			
Epidermal	21(70.00)	18 (60)	
Dermal	6 (20.00)	8 (26.67)	0.838
Indeterminate	2 (6.67)	2 (6.67)	
Mixed	1 (3.33)	2 (6.67)	

p>0.05: Not significant, *p<0.05: Significant; **p<0.001: Highly significant [p value: Chi square test]



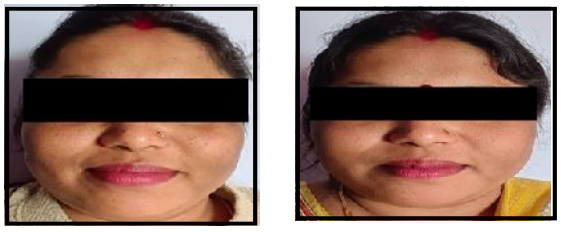
*p>0.05:Not significant*p<0.05:Significant;**p<0.001:Highly significant [p-value:Paired t-test]*

Fig: 1 Inter group comparisonof mMASI Scor eover 90 Days



a. 0 days a. 90 days

Fig 2a: Group A – 2 % Topical Glutathione



b. 0 days *b. 90 days*

Fig 2b: Group B – 3 % Topical TA

BD for 10 weeks. Significant mean mMASI reduction of 0.61 was observed with topical glutathione at 10 weeks (p=0.011). Watanabe *et al*., a placebo-controlled trial (n=30)of 10 weeks with 2% topical oxidized glutathione BD, showed significant mean melanin index reduction at 10 weeks with topical glutathione (p <0.001). [12] The present study used reduced glutathione (active form).

The results on topical TA are supported by Kim *et al*., an interventional study (n=23) for 12 weeks with 2 % topical TA (2 % TA BD and face mask of 2 % TA thrice a week) and observed significant reduction in mean mMASI of 1.46 after 12 weeks (p<0.05).[13]

No study evaluating mMASI that compared topical glutathione and TA could be found in available literature. In present study, both agents produced improvement in mMASI by 4 weeks with significant improvement by 8 weeks. Onset for significant reduction in mean mMASI varies in different studies with topical TA (4 weeks [13], 6 weeks [14]). The variation may result from different formulations (varying strength & adjuvants) of topical TA with different skin penetration.

Late onset for significant improvement in present study (8 weeks) with TA may be due to higher no. of darker skin types compared to other studies and higher baseline mMASI. For topical glutathione, onset for significant reduction in mean mMASI was not mentioned in available studies so no comparison could be made.

PGA Score: No study using topical glutathione or comparing topical glutathione with topical TA that evaluated PGA in melasma subjects could be found in available literature. Handog *et al*., conducted an open-label study (n=30) for 8-weeks using 500 mg OD buccal

Table 2: Intragroup Comparison of Efficacy and Quality of Life Parameters with Group A over '90' Days

Parameter	Baseline	90 days	% Change	p-value
Mean mMASI	6.09 ± 3.54	1.34 ± 0.87	67.40 ± 33.69	<0.001[a**]
Median PGA	5	2	93.34	<0.001[b**]
Mean MELASQOL	43.53 ± 8.31	24.87 ± 9.92	42.06 ± 20.06	<0.001[a**]

*p>0.05: Not significant *p<0.05 : significant **p<0.001 : highly significant [p value: a - Paired t test, b – Kruskal Wallis test]*

Table 3: Intragroup Comparison of Efficacy and Quality of Life Parameters with Group B over '90' Days

Parameter	Baseline	90 days	% Change	p-value
Mean mMASI	6.02±2.86	3.12±2.08	44.13 ± 32.92	<0.001[a**]
Median PGA	5	3	69.99	<0.001[b**]
Mean MELASQOL	42.53 ± 7.30	29.83 ± 9.18	28.40 ± 21.80	<0.001[a**]

*p>0.05: Not significant *p<0.05 : significant **p<0.001 : highly significant [p value: a - Paired t test, b- Kruskal Wallis test]*

Table 4: Intergroup Comparison of Physician Global Assessment Score at'90'Days

PGA SCORE	GROUP A		GROUP B		p-value
	(%)	Improvement (%)	n(%)	Improvement (%)	
0 (Clear)	0 (0.00)	0.00	0 (0.00)	0.00	<0.001**
1 (Almost clear)	8 (26.67)	93.34	1 (3.33)	69.99	
2 (Marked improvement)	17 (56.67)		13 (43.33)		
3 (Moderate improvement)	3 (10.00)		4 (13.33)		
4 (Slight improvement)	0 (0.00)		3 (10.00)		
5 (No improvement)	2 (6.67)	0.00	9 (30.00)	0.00	
6 (Worse)	0 (0.00)	0.00	0 (0.00)	0.00	

p>0.05:Notsignificant*p<0.05:Significant;**p<0.001:Highlysignificant[p-value: Mann-Whitney U test]

glutathione lozenges. Like present study, highest prevalence was found for moderate improvement in global assessment (score 2 in 90% cases), followed by mild improvement (score 1 in 10% cases). [6]

MELASQOL Score: Melasma can severely impact QoL causing psychosocial distress.[15]No study could be found that assessed QoL using MELASQOL in melasma subjects after either topical glutathione or TA.

Safety Profile: The present study results on topical glutathione are supported by Watanabe *et al.*, an RCT of 10 weeks (n=30) using 2 % topical glutathione.It found that one melasma participant had mild erythema.[12]

Results on topical TA are in line with Ebrahimi and Naeini, a split-face study (n=50)of 12 weeks. The side effects with topical TA (3%) were redness, scaling, dryness and skin irritation in 9 subjects (23.1%).[16]

Among other routes, oral TA may cause body ache, difficulty breathing and unusual bleeding while oral glutathione may cause loose stools and pruritus. [17,18]Topical hydroquinone and TCC (gold standard treatment) can have multiple long term adverse effects like ochronosis and skin atrophy respectively[19,20,21].

Present study had followings trengths:

a. It's the first study to compare efficacy and safety of topical glutathione with topical TA as per available literature.
b. It's the first study in Indian melasma subjects (skin type IV and V) and third across other nationalities using topical glutathione therapy and first study to assess mMASI, QoL via MELASQOL in melasma

patients receiving topical glutathione or TA.

Present study had limitations of small sample size (n = 30 - each group), no objective melasma evaluation (e.g. – with mexameter) and no follow-up to assess maintenance of therapeutic effects (3 months duration).

Conclusion

Both topical glutathione and TA have potential as effective and safe melasma therapy, but topical glutathione demonstrates superior efficacy, comparable safety and better improvement of quality of life over topical TA over 3 months. Long term studies with higher sample sizes are needed to further validate role of topical glutathione in melasma.

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