DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20195199

Original Research Article

Effectiveness of a combination of anti-pigmentary products in facial post-inflammatory hyperpigmentation

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Received: 02 September 2019
Revised: 29 October 2019
Accepted: 05 November 2019

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ABSTRACT

Background: Post-inflammatory hyperpigmentation (PIH), also has psychosocial implications. Hydroquinone containing preparations though effective, have unacceptable side effects. Molecules like kojic acid, arbutin, vitamins C and E, niacinamide and many others have depigmenting effect, singly or in combination. The objective of this study was to assess the effectiveness and tolerability of a cream containing a combination of niacinamide-4.0%, glycolic acid-2.0%, vitamin E acetate-0.1%, kojic acid dipalmitate-2.0%, soy isoflavones-0.5%, arbutin-2.0%, pterowhite-0.12%, licorice-40% CA-0.12%, ascorbyl glucoside-0.1% (Melaglow-Rich, Abbott Healthcare Pvt. Ltd.) in treatment of PIH. The specific objectives were to evaluate the changes in pigmentation, safety of the cream and patient opinion regarding the cream after 90 days of use.

Methods: After IEC approval, adult males and non-pregnant, non-lactating females aged upto 50 years with PIH were included. Those with endocrinopathies who received systemic steroid therapy in the preceding month were excluded. 114 participants who were enrolled in this open-label, non-comparative study, applied study medication (b.i.d) and sunscreen (SPF-30; q.d). Effectiveness was assessed by PIH severity scale, Mexameter assessment, Patients' and Physicians' Global Assessment Scale and clinical photographs. Adverse events were documented.

Results: Mean PIH score and mean mexameter reading for melanin and erythema in the hyperpigmented and non-hyperpigmented skin reduced by day 90 ($p=0.0009$, $p<0.0001$, $p<0.001$). Significant reduction in physicians' ($p=0.004$) and patients' ($p=0.006$) global assessment score was evident by day 90. Itching (n=1), burning (n=3) and stinging (n=3) were noted.

Conclusions: Melaglow rich cream was found to be effective and well-tolerated in the treatment of PIH.

Keywords: PIH, Mexameter, Anti-pigmentary

INTRODUCTION

Post-inflammatory hyperpigmentation (PIH) defined as an "acquired hypermelanosis occurring after cutaneous inflammation or injury" is of particular concern in darker skinned individuals and has psychosocial impact.[1-3] The prevalence of PIH in multiple studies has varied from 0.7% to 19.9%.[3-9] The prevalence ranged from 0.3% to 2.3% in the Indian population.[2,3]

Common causes of PIH are acne, infections (fungal and viral), insect bites, psoriasis, lichen planus, drug reactions and contact dermatitis.[3] PIH can be epidermal or dermal.[10] One mechanism suggested is increased production and transfer of melanocytes to other epidermal cells induced by inflammatory cytokines.[3] Inflammatory damage to basal keratinocytes and melanophage formation lead to dermal pigmentation.[10]

Various treatment modalities available for PIH include 2-4% hydroquinone (tyrosinase inhibitor) used alone or in combination with a steroid and tretinoin (Kligman's formula). Though this has remained the mainstay of management of hyperpigmentation, particularly PIH for a long time, a number of side effects have been reported following the use of this regimen. Some of the side effects are ochronosis, cataract, milia, nail pigmentation, loss of skin elasticity. Some animal studies have documented DNA damage by hydroquinone, leading to concern about the regular use of hydroquinone.[2,11]

Kojic acid inhibits the production of free tyrosinase and may be useful in patients not responding to hydroquinone therapy.[2,12] Other products for hyperpigmentation include: arbutin (tyrosinase inhibitor); vitamin C (antioxidant activity); vitamin E (intervenes in lipid peroxidation); and niacinamide (melanogenesis inhibitor). Plant extracts from grape seed, orchids, aloevera, marine algae, flavanoids, green tea, licorice, soy, umbelliferone and boswellia are also useful. These products act through mechanisms such as inhibition of tyrosinase activity, mediation in transfer of melanosomes to keratinocytes, or anti-inflammatory and anti-oxidant activity.[2,3] A lot of products available for treating PIH are a combination of the above mentioned products.[2]

Chemical peels and lasers are often used to treat PIH. Chemical peels used to treat PIH include glycolic acid and salicylic acid. Glycolic acid is an alpha hydroxy acid which at low concentrations results in weakening intercellular cohesion and dispersion of basal cell melanin.[3,13,14] Though lasers have been used to manage PIH in all skin types, larger clinical trials are required for understanding their role in management of PIH.[3,15] UV radiation may result in hyperpigmentation, particularly in patients with skin types IV to VI, therefore sunscreen use is a must for PIH.

Though studies have been conducted to assess the role of many depigmenting products, these have evaluated the effectiveness of individual compounds while combinations are available for use.[2,16-21] These studies have mostly used subjective parameters and scales; few have used objective measures such as Mexameter readings. Hence, it is important to document the subjective and objective reduction in pigmentation in patients who present with PIH, particularly with products that are a mixture of compounds. With this background, we designed the present study to assess the effectiveness and tolerability of a cream containing a combination of niacinamide 4.0%, glycolic acid 2.0%, vitamin E acetate 0.1%, kojic acid dipalmitate 2.0%, soy isoflavones 0.5%, arbutin 2.0%, pterowhite 0.12%, licorice 40% ca 0.12%, ascorbyl glucoside 0.1% (Melaglow Rich, Abbott Healthcare Pvt. Ltd.) in treatment of PIH.

The objective of this study was to assess the effectiveness and tolerability of a Melaglow rich cream (Abbott Healthcare Pvt. Ltd.) in treatment of PIH.

The specific objectives were to evaluate the changes in pigmentation, safety of the cream and patient opinion regarding the cream after three months of use in patients with PIH.

METHODS

A prospective open label non-comparative study conducted at the Department of Dermatology, TN Medical College and BYL Nair Hospital for one year after approval from the Ethics committee. This study was done over a period of 8 months from 16th June 2017 to 16th February 2018.

All consecutive consenting individuals aged 18 to 50 years, who presented with PIH on face, neck or both face and neck, who were willing to provide written informed consent including consent for being photographed and were willing to follow all study procedures, were enrolled for this study. Diagnosis of lichen planus pigmentosus and melasma, use of corticosteroids orally or by inhalation in the past one month, known allergy to any of the ingredients of the cream, known history of endocrinopathies, participation in other clinical trials in the past one month and pregnant, lactating or planning pregnancy in the next three months, were criteria for exclusion.

All eligible participants who had not applied any medication on the lesions were enrolled directly. Those who had applied some medications on the lesions were enrolled after a washout period of two weeks.

History taken included demographic information such as age, sex, socio-economic status (using the modified Kuppuswamy scale). Anthropometric parameters such as height and weight were recorded. Details like duration of PIH, prior lesions at the site and their duration and treatment taken were recorded. History of diabetes mellitus, hypertension, any other chronic illness were noted. Use of any topical or oral medications, sunscreens etc. was noted. The number of lesions, their size, epidermal/dermal nature of pigment were noted.

PIH was evaluated using the PIH severity scale with parameters of overall disease severity (scale of 0-8 [normal to severe]; pigmentary intensity (scale of 0-5 [none to severe]); area of hyperpigmented lesions (percentage of facial area – scale of 0-5 [none to severe]); degree of hyperpigmentation (scale of 0.-5 [none to severe]); and erythema, burning, peeling, and dryness (scale of 0-5 [none to severe]).[22]

We used the Mexameter (® Courage+Khazaka Electronic GmbH, Mobile data collector DC 3000, Germany) to assess the hyperpigmented lesions.[20,23-27] The two main pigments (melanin and haemoglobin) absorb light at different spectrums. Haemoglobin absorbs light in the green area of the spectrum while melanin is known to absorb light of all wavelengths. It has been argued that

reflectance of narrow band light in the red spectrum is a good estimate of melanin pigment.[28,29] We measured the melanin and erythema intensity both in the PIH lesions and normal skin. Three measurements each in the PIH lesions and normal skin were taken; a mean of these three values was recorded.[18]

We took standardised, reproducible clinical photographs of the participants on day 0, 60, 90 for comparison of change in number, size, and intensity of the PIH lesions and for Physician's Global Assessment.

All the participants were advised to use Melaglow rich cream twice daily on their face and neck including PIH lesions and a sun-screen (SPF-30) thrice daily.

All the participants were followed five times after the baseline visit. These visits were on day seven (2nd visit), day 15 (3rd visit), day 30 (4th visit), day 60 (5th visit), and day 90 (6th visit).

In addition, at every visit, we measured the following:

Physician's global assessment scale

This was a subjective assessment of changes in the PIH lesions by a Likert-type scale measuring the changes from a scale of 0 (clear, except for possible residual discolouration) to 6 (worse than baseline).[29]

Patient's global assessment scale

This was a subjective assessment of the PIH lesions by the participants by a Likert-type scale measuring changes from a scale of 0 to 6 (as above).

Safety assessment scale

This assessed five aspects of safety viz. scaling, erythema, itching, burning, stinging each on a scale of 0 [none] to 3 [severe]).[22,30] We also recorded any other side effects mentioned by the patients such as occurrence of acne etc. We also measured the adherence of all the participants.

Statistical analysis

We estimated the means and standard deviations (SD) for continuous variables (such as Mexameter scores) and proportions for categorical outcomes (such as the category of adherence). The means were compared using the t-test for two groups and Analysis of Variance (ANOVA) for more than two groups for parametric data. We used the Tukey's correction for multiple pair-wise comparisons. We used the Kruskal Wallis test with Dunn's test for multiple pair-wise comparisons for non-parametric data. We assessed the proportion of adherence across various visits; and compared using the chi square test or Fisher's exact test for low expected cell counts.

Data were analysed using Stata 13.1 (© StataCorp, College Station, Texas, US)..

RESULTS

114 subjects were included in the study. The mean age (SD) was 27.3 (9.9) years, 91 were female (80%), 23 (20%) were male. 77 (68%) were currently unmarried while 37 (32%) were married. 43 (38%) were from the upper and upper-middle class each. The mean body mass index (SD) was 22.2 (3.6).

The mean age (SD) of these individuals was 27.3 (9.9) years. Majority of these were females, currently not married, and from the upper and upper-middle class. Additional details of all the baseline demographic characteristics are presented in Table 1.

Table 1: Baseline characteristics of individuals included in the study (n=114).

Variable	N (%)
Age (years)	
Mean (SD)	27.3 (9.9)
Gender	
Male	23 (20)
Female	91 (80)
Marital status	
Currently married	37 (32)
Currently not married	77 (68)
Socio-economic status	
Upper class	43 (38)
Upper middle class	43 (38)
Lower middle class	9 (8)
Upper lower class	19 (17)
Lower class	0 (0)
Body mass index	
Mean (SD)	22.2 (3.6)

The median duration (IQR) of hyperpigmentation was 9.6 months (least 3 months, longest 24.3 months). Acne was the commonest lesion prior to the appearance of hyperpigmentation in these individuals. 19% had used some form of treatment for the hyperpigmentation; mostly (59%) topical medications. 33% of the individuals reported use of sunscreens (Table 2).

None of the patients had diabetes, one had hypertension, and seven reported other clinical conditions, with 11% being currently on oral medications.

The mean (SD) baseline PIH score was 10.7 (3.7). It had reduced significantly to 9.1 (3.0) by the end of three months (p=0.0009) (Table 3).

The mean (SD) mexameter reading for melanin in the hyperpigmented region at baseline was 473.4 (123.7) which gradually declined to 358.2 (112.2) on day 90. The

difference across these six readings was statistically significant (p<0.0001). In the pair wise comparison, there was a significant reduction in the mexameter readings between the baseline visit and each visit from day 15 onwards. This reduction in the Mexameter readings was also observed in the non-hyperpigmented area (Table 4).

The mean (SD) mexameter reading for erythema in the hyperpigmented region at baseline was 481.1 (84.1) which declined to 360.9 (65.9) on day 90. The difference across these six reading was statistically significant (p<0.0001). In the pair wise comparison, there was a significant reduction in the mexameter readings between the baseline visit and each visit from day 7 onwards. There was significant reduction in the mexameter readings in the non-hyperpigmented area also (Table 5).

The mean (SD) PIH as assessed by the physician was 3.95 (0.32) on day seven and reduced to 3.75 (0.59) at the end of three months (p=0.004). Similarly the mean (SD) PIH assessed by patients themselves was 3.95 (0.32) on day seven and had significantly reduced to 3.75 (0.60) at day 90 (Figure 1 (A-C) and Figure 2 (A-C)).

The adherence to sunscreen and cream application was not less than 98% in the subjects in any week during the study period. We also examined the proportion of medication applied from subjects using a VAS scale. The mean proportion was consistently higher than 99% at each visit.

We assessed the safety based on safety assessment scale (scaling, erythema, itching, burning, and stinging). The mean and medians were close to zero (on a scale of 0 to 15) in all the five follow up visits.

Table 2: Baseline clinical characteristics of individuals included in the study (n=114).

Variable	N (%)
Duration of hyperpigmentation (months)	
Median (IQR)	9.6 (3–4.3)
Lesions prior to appearance of hyperpigmentation*	
Acne	97 (85)
Injury	3 (3)
Other skin lesions	8 (7)
None	7 (6)
Used treatment for hyperpigmentation	
Yes	22 (19)
No	92 (81)
Use sunscreens	
Yes	38 (33)
No	76 (67)
Co-morbidities	
Diabetes mellitus	
Yes	0 (0)
No	114 (100)
Hypertension	
Yes	1 (1)
No	113 (99)
Other conditions	
Yes	7 (6)
No	107 (94)
Currently on any oral medications	
Yes	13 (11)
No	101 (89)

*The % may be more than 100 due to multiple lesions in individuals.

Table 3: Changes in PIH scores over a three month period (n=114).

	Baseline	Day 7	Day 15	Day 30	Day 60	Day 90
Mean (SD)	10.7 (3.7)	10.6 (3.6)	10.2 (3.6)	9.8 (3.3)	9.4 (3.2)	9.1 (3.0)

*Overall p=0.0009; Baseline vs. Day 90: p=0.004; Day 7 vs. Day 90: p=0.009.

Table 4: Changes in mexameters readings for melanin in the hyperpigmented and non-hyperpigmented skin over a three month period (n=114).

	Baseline	Day 7	Day 15	Day 30	Day 60	Day 90
Hyperpigmented site	473.4 (123.7)	445.3 (119.7)	421.2 (117.2)	400.3 (114.5)	380.9 (115.4)	358.2 (112.2)
Non-hyperpigmented area	300.3 (90.5)	282.7 (89.1)	265.2 (90.5)	248.3 (81.7)	231.1 (80.7)	212.4 (78.7)

Hyperpigmented site: Overall p<0.0001; Pairwise comparison: Baseline vs. Day 15 p=0.01, Baseline vs. Day 30 p<0.001, Baseline vs. Day 60 p<0.001, Baseline vs. Day 90 p<0.001; Non-hyperpigmented site: Overall p <0.0001; Pairwise comparison: Baseline vs. Day 15 p=0.02, Baseline vs. Day 30 p<0.001, Baseline vs. Day 60 p<0.001, Baseline vs. Day 90 p<0.001.

Table 5: Changes in mexameters readings for erythema in the hyperpigmented and non-hyperpigmented skin over a three month period (n=114).

	Baseline	Day 7	Day 15	Day 30	Day 60	Day 90
Hyperpigmented Site	481.1 (84.1)	448.6 (75.1)	426.5 (70.1)	403.9 (69.0)	382.9 (66.7)	360.9 (65.9)
Non-hyperpigmented area	358.4 (81.1)	332. 9 (78.4)	311.1 (78.0)	288.4 (71.9)	269.8 (71.6)	248.3 (72.3)

Hyperpigmented site: Overall p <0.0001; Pairwise comparison: Baseline vs. Day 7 p=0.009, Baseline vs. Day 15 p<0.001, Baseline vs. Day 30 p<0.001, Baseline vs. Day 60 p<0.001, Baseline vs. Day 90 p<0.001; Non-hyperpigmented site: Overall p <0.0001; Pairwise Comparison: Baseline vs. Day 15 p<0.001, Baseline vs. Day 30 p<0.001, Baseline vs. Day 60 p<0.001, Baseline vs. Day 90 p<0.001.

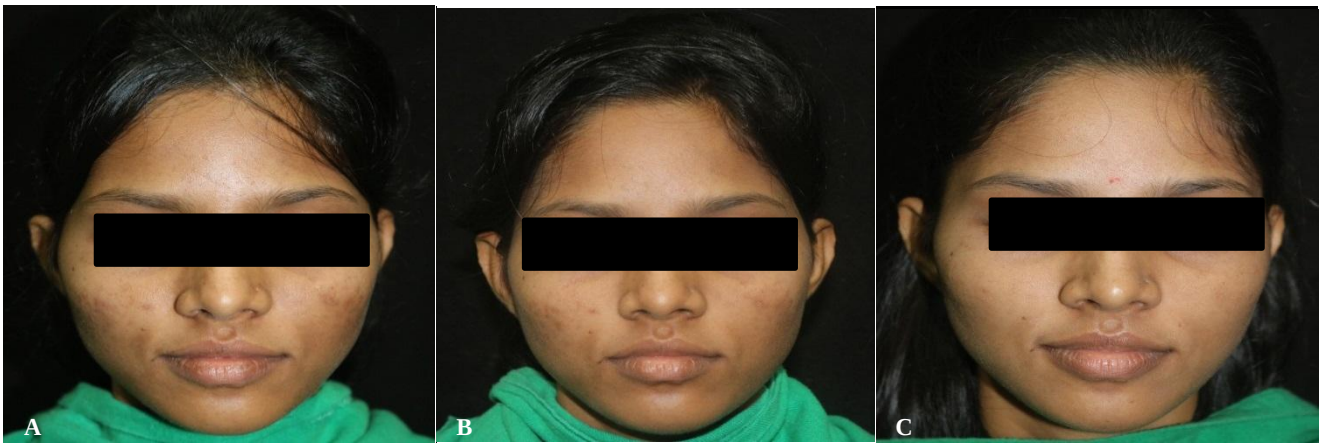

Figure 1: Case 1 presentation. A) Pigmentation on day 0, B) improvement in pigmentation on day 60, C) almost complete resolution of pigmentation on day 90.

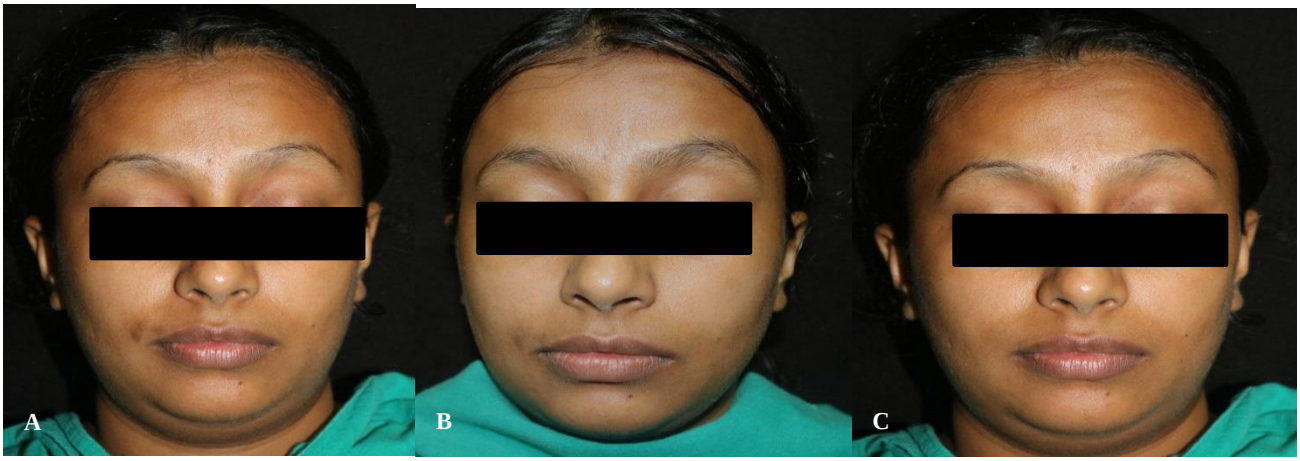

Figure 2: Case 2 presentation. A) Pigmentation on day 0, B) improvement in pigmentation on day 60, C) almost complete resolution of pigmentation on day 90.

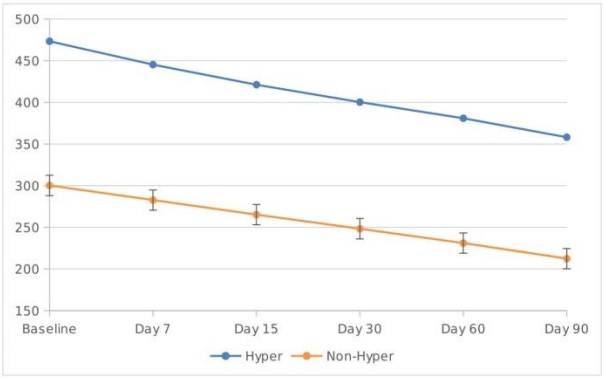

Figure 3: Mean mexameter readings and 95% confidence intervals for melamin in the hyperpigmented and non hyperpaigmented skin over a three month period (n=114).

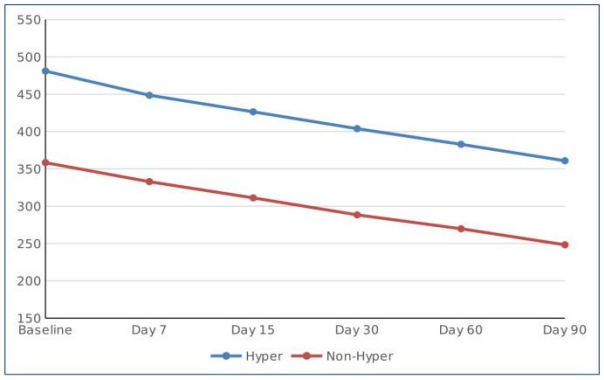

Figure 4: Mean mexameter readings and 95% confidence intervals for erythema in the hyperpigmented and non hyperpaigmented skin over a three month period (n=114).

DISCUSSION

114 patients were screened and enrolled as per the inclusion and exclusion criteria. Among these, 91 (80%) were female while 23 (20%) were male with a mean age of 27.3 years. Though there is literature on pigmentary disorders in various populations around the world, this is the only Indian study that has included exclusively subjects with PIH.3

More than three quarters of the subjects belonged to the upper and upper middle class while the remainder belonged to the upper lower class (Kuppuswamy scale). This probably reflects the greater concern about appearance in the higher socio-economic classes. The lower class probably may be less concerned about appearance or less able to spare time and other resources to address the problem of hyperpigmentation.

The mean BMI (SD) was 22.2 (3.6). None of the subjects were obese or malnourished. As there were no obese patients it was less likely that the PIH was confounded by acanthosis nigricans which may present as facial pigmentation.

Duration of hyperpigmentation ranged from three months to as long as two years with a median duration of 9.6 months and did not make a difference to its rate of improvement with treatment. No literature was found showing that duration of hyperpigmentation had any bearing on the response of PIH to treatment.

Acne was the cause of hyperpigmentation in 85% of the subjects, 3% had preceding injury while 6% had no prior lesions. Acne as a common cause of PIH was seen in other studies also.[3,4]

Only 19% of the subjects had taken treatment for the hyperpigmentation prior to inclusion in this study, 59% of these had used topical medications. 33% of the subjects, with not much difference between sexes, had used sunscreen. Socio-economic status of the subjects did not have a significant bearing on the use of sunscreen. A survey of African Americans revealed that only 9% of the 1583 surveyed declared themselves likely to use sunscreen.[3]

One patient had hypertension and was on medication, none had diabetes mellitus. Only 11% were on some oral medication.

The adherence of the subjects to the topical regimen was more than 98% at all visits. Only seven episodes of side effects (such as itching, burning, and stinging) were reported during the entire follow-up period; they were reported day 15 onwards.

The mean (SD) PIH score at baseline was 10.7 (3.7) and had reduced significantly to 9.1 (3.0) by the end of three months (p=0.0009) which has been depicted in.

The mean (SD) mexameter reading for melanin in the hyperpigmented region at baseline was 473.4 (123.7) which gradually declined to 358.2 (112.2), the difference across these six readings was statistically significant ($p<0.0001$). In the pair wise comparison, there was a significant reduction in the mexameter melanin readings between the baseline visit and each visit from day 15 onwards in the pigmented and non-hyperpigmented area ($p<0.05$) (Figure 3). The improvement in mean Mexameter melanin readings in the PIH site and non-hyperpigmented site reflects the efficacy of the anti-pigmentary cream and sunscreen in reducing pigmentation.

The mean (SD) mexameter erythema reading in the hyperpigmented region at baseline was 481.1 (84.1) which declinedto 360.9 (65.9). The difference across the six readings was statistically significant $p<0.0001$. In the pair wise comparison, there was a significant reduction in the mexameter melanin readings between the baseline visit and each visit from day seven onwards. Significant

reduction in the mexameter erythema readings was observed between the baseline visit and each visit from day 15 onwards in the hyperpigmented area and the non-hyperpigmented site also (p<0.001) (Figure 4). This may be interpreted as follows. The anti-pigmentary cream and sunscreen did not cause any local reaction at site of application. The use of sunscreen may have reduced the local sun exposure induced subclinical vasodilatation in both the pigmented and non-pigmented sites. Melaglow Rich cream reduced PIH and tanning at sites of PIH and tanning of normal skin.

There was a significant reduction in physician's global assessment score (p=0.004) and patient's global assessment score (p=0.006) from baseline to day 90.We observed good adherence both for the medication and sunscreen in all subjects.

Treatment with Melaglow Rich cream and sunscreen resulted in minimal side effects over the three month period.

In a study by Valerie et al on efficacy and safety of clindamycin phosphate 1.2% and Tretinoin 0.025% Gel for the treatment of acne and acne-induced post-inflammatory hyperpigmentation which included 33 patients with acne and PIH, had baseline PIH Severity Scale scores ≥2 and a substantial proportion had scores of 3 or 4 in the clindamycin/tretinoin gel (70%) and placebo groups (69%). The improvement in mean PIH score from baseline to week 12 was greater for clindamycin/tretinoin gel vs. placebo (-1.2 vs. -0.9) which was present consistently through the trial.[31]

In a randomized, double-blind, vehicle-controlled clinical trial by Callender et al over a period of 40 weeks which included 54 black patients, efficacy and safety of of 0.1% tretinoin in the treatment of PIH was determined. They found that efficacy of tretinoin was much more significant in improving PIH than placebo based on clinical (p<0.001) and colorimetric (p=0.05) assessment. However, retinoid dermatitis as a side effect was seen in 50 percent of patients.[32]

In another randomized, double-blind, vehicle-controlled trial, done over a period of 24 weeks, conducted by Lowe et al which included 52 patients with PIH and melasma to assess the efficacy of 20% azelaic acid cream in PIH and melasma, it was found that as compared to vehicle 20% azelaic acid cream was more effective in the treatment of both melasma and PIH based on the investigator's subjective scale (p=0.021) and chromometric analysis (p<0.039) with minimal and transient side effects.[33]

Multiple studies have been done to assess the efficacy of individual compounds in the treatment of PIH but studies to assess the efficacy of combination cream in the treatment of PIH and larger clinical studies for PIH are lacking.

CONCLUSION

This study suggests that the cream containing a combination of niacinamide 4.0%, glycolic acid 2.0%, vitamin E acetate 0.1%, Kojic acid dipalmitate 2.0%, soy isoflavones 0.5%, arbutin 2.0%, pterowhite 0.12%, licorice 40% ca 0.12% and ascorbyl glucoside 0.1% (Melaglow rich cream) used with sunscreen is efficacious and safe in the treatment of PIH. This combination can be a preferred alternative to steroid and hydroquinone based combinations given the efficacy and low incidence of adverse effects with this regimen.

ACKNOWLEDGEMENTS

We would like to thank Dr. Maninder Singh Setia for his contribution in statistical analysis.

Funding: This investigator initiated study was funded by Abbott Healthcare Pvt. Ltd
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Nayak CS, Ansari SMM, Salve V, Patil S. Effectiveness of a combination of anti-pigmentary products in facial post-inflammatory hyperpigmentation. Int J Res Dermatol 2020;6:1-8.