Original Research Article

Effectiveness and safety of a novel topical depigmenting agent in epidermal pigmentation: an open-label, non-comparative study

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ABSTRACT

Background: Active compounds isolated from plants are known to inhibit melanogenesis without melanocytotoxicity. The aim of this study was to assess the effectiveness and safety of a cream containing a combination of niacinamide, glycolic acid, vitamin E acetate, kojic acid, soy isoflavones, arbutin, pterowhite, licorice and ascorbyl glucoside for the treatment of epidermal pigmentation.

Methods: Sixty subjects (between 18-45 years) with epidermal pigmentation were enrolled in this 12-week, open-label, non-comparative study. Clinical/dermoscopic aspects (grade-1: <25%; grade-2: 25-50%; grade-3: 50-75%; grade-4: >75% reduction in the amount of epidermal pigment); melanin index/erythema measure (Dermacatch); extent, depth and density of pigmentation (FotoFinder) and safety were assessed.

Results: Out of 60 enrolled subjects, 53 completed the study. Overall percentage of melanin and erythema improvement (Dermacatch) was 24.2% and 7.4% respectively ($p < 0.05$). Based on FotoFinder images, 13% had grade 4 improvement, 47% had grade 3 improvement, 30% had grade 2 improvement while 9% subjects had grade 1 improvement. On the basis of clinical photographic images, 15% had grade 4 improvements in the skin colour, 41% had grade 3, 34% had grade 2 and 9% subjects had grade 1 improvement. Adverse effect of skin irritation was reported in one subject, which resolved after discontinuing the treatment.

Conclusions: 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% was found to be safe and effective in the treatment of epidermal pigmentation.

Keywords: Arbutin, Dermacatch, Epidermal pigmentation, FotoFinder, Glycolic acid, Kojic acid, Licorice, Niacinamide, Melasma, Soy isoflavones

INTRODUCTION

Pigmentary disorders are considered to be one of the most common dermatologic disorders, worldwide. These disorders result in significant psychological distress, negatively impacting the overall quality of life of the individual.¹ Facial melanoses is a form of hyperpigmentation of face, associated with increased melanin synthesis. This is a common presentation

reported in Indian subjects.² Some of the well-defined causes of facial melanoses include melasma, Riehl's melanosis, lichen planus pigmentosus, post inflammatory hyperpigmentation, erythema dyschromicum perstans, erythrosis, and poikiloderma of Civatte. These pigmentary abnormalities are often perceived as aesthetically uncomplimentary, and have paved way for the development of cosmetic and therapeutic treatment modalities, though with variable success. The

pharmacological agents commonly used selectively target hyperplastic melanocytes and inhibit key regulatory steps in melanin synthesis.²

Since the past decade, there has been an enormous surge in the prominence of skin brightening products to treat hyperpigmentation, especially facial melanoses. However, in spite of the availability of multiple treatments for the condition, hyperpigmentation continues to present clinical management challenges for dermatologists. Hydroquinone, though often considered as the gold standard among traditional topical treatments for hyperpigmentation, its use has been associated with a number of adverse effects, including skin irritation, contact dermatitis, and exogenous ochronosis in dark-skinned people.² Infact, hydroquinone use in cosmetics is banned in Europe and some parts of Asia.² Other commonly available topical agents such as corticosteroids though effective are more likely to cause local or systemic side effects after long-term use.³

These safety and efficacy concerns of the currently available topical agents have prompted research to develop an alternative skin lightening agent, with efficacy comparable to hydroquinone, but with better safety profile. Evidence shows that the active compounds isolated from plants such as arbutin, aloesin, gentisic acid, flavonoids, hesperidin, licorice, niacinamide, yeast derivatives and polyphenols are potent inhibitors of melanin formation and are not usually associated with cytotoxicity or mutagenicity of melanocytes.^{4,5} Hence the objective of this study was to assess the effectiveness and safety 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% and ascorbyl glucoside 0.1% (Melaglow Rich™, Abbott Healthcare Pvt Ltd, Mumbai, India; study medication) for the treatment of epidermal pigmentation.

METHODS

Study design

This open-label, non-comparative, single-centre study enrolled subjects between July 2016 to March 2017. The assessments were done at the following visits: visit 1 (baseline/day 0), visit 2, (6th week) and visit 3 (12th week). At baseline, all participants were advised to use study medication on the face, once daily. Each subject was given instructions on the quantity of application of cream as per the FTU (Finger Tip Unit)¹. Further, the subjects were instructed to use a sunscreen (SPF-30) thrice daily and face wash, twice daily, for 12 weeks.

Study population

Adults (between 18-45 years; inclusive) with epidermal pigmentation, agreeable to follow all the study procedures including abstinence from usage of any over-

the-counter product related to face applications, and willing to provide written informed consent form (along with consent for being photographed) were enrolled in this study. Subjects using other pigment reduction creams (except sunscreen and moisturizer); with other dermatological disorder of the face that may interfere with the study evaluation (acne, dermatosis papulosa nigra (DPN), melasma, seborrheic melanosis); with known hypersensitivity to any of the study drugs/constituents; expected to be exposed to the triggering factors (excessive sun exposure, UVB photo therapy etc.); who have received facial procedures like dermabrasion, chemical peels or laser procedures within the last one month; or who were deemed unfit for participation by the investigator were excluded from the study. Pregnant or lactating women were also not included in this study.

Subjects attending the out-patient service requesting complexion improvement, and who had no other underlying facial melanosis were examined to confirm epidermal hyperpigmentation. Epidermal hyperpigmentation was confirmed using clinical photographs, Dermacatch and FotoFinder.

The study protocol was approved by local independent ethics committees. The study was conducted in accordance with the principles of Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All subjects provided written consent to participate in the study.

Study assessments

The melanin index and erythema index was measured using Dermacatch (Dermacatch™, Colorix, Neuchatel, Switzerland). The extent, depth and density of pigmentation was assessed using FotoFinder (FotoFinder™ Systems, GmbH, Deutschland). Reduction in the amount of epidermal pigment was assessed at each visit by comparing clinical photographs. Grading was done as following: Grade 1: <25% reduction; Grade 2: 25-50% reduction; Grade 3: 50-75% reduction; Grade 4: > 75% reduction. At end of week 12, subject satisfaction was measured as excellent, very good, good and not satisfied. Tolerability was also assessed at each visit.

Statistical methods

Data was summarized descriptively. Dermacatch values were analyzed using repeated measures of ANOVA, with p value less than 0.05 being considered statistically significant. Clinical and Fotofinder photographs were assessed subjectively and a grade was given based on percentage improvement.

RESULTS

A total of 53 out of 60 enrolled subjects completed the study. Seven subjects were lost to follow-up. The mean age of the subjects was 26.6 years. Out of 60 enrolled subjects, 20 were men and 40 were women. All the subjects were confirmed cases of epidermal hyperpigmentation.

Melanin and erythema measure: Dermacatch

There was a significant reduction in melanin and erythema values at week 12, compared to baseline, for all

subjects ($p < 0.05$; Table 1). The overall percentage of melanin improvement was 24.2% and erythema improvement was 7.4% ($p < 0.05$). The percentage of Dermacatch improvement is depicted in Figure 1A and B.

Figure 1A: Percentage of melanin reduction after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Dermacatch (N=53)

Figure 1B: Percentage of erythema reduction after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Dermacatch (N=53)

Table 1: Melanin and erythema measure at baseline, week 6 and week 12, post treatment with melaglow rich, in subjects of epidermal hyperpigmentation: Dermacatch (N=53).

	Baseline	Week 6	Week 12	P value
Melanin mean values				
Forehead	741	654	555	0.004
Right face	703	622	528	0.001
Left face	694	617	531	0.016
Chin	710	644	544	0.028
Erythema mean values				
Forehead	454	441	419	0.037
Right face	453	439	421	0.043
Left face	453	436	420	0.0002
Chin	453	438	419	0.015

P value measured by ANOVA.

Figure 1: (A) Percentage of melanin reduction after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Dermacatch (N=53); (B) Percentage of erythema reduction after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Dermacatch (N=53).

Extent, depth and density of pigmentation: Fotofinder

A reduction in pigmentation of about 51-75% was reported by nearly 47% subjects. Overall, 7 subjects (13.2%) demonstrated grade 4 improvement, 25 subjects (47.2%) demonstrated grade 3 improvement, 16 subjects (30.2%) demonstrated grade 2 improvement and 5 subjects (9.4%) demonstrated grade 1 improvement (Figure 2 and Figure 3).

Clinical photographic assessment

Based on clinical photographs, 51-75% improvement was demonstrated by 41% subjects. Overall, 8 subjects (15.1%) demonstrated grade 4 improvement, 22 subjects (41.5%) demonstrated grade 3 improvement, 18 subjects (34%) demonstrated grade 2 improvement and 5 subjects (9.4%) demonstrated grade 1 improvement (Figure 4 and Figure 5).

Figure 2: Percentage of improvement after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Fotofinder (N=53).

Grade 1: <25% reduction; Grade 2: 25-50% reduction; Grade 3: 50-75% reduction; Grade 4: > 75% reduction.

Figure 3: Fotofinder image in patient 1.

FH: forehead, R: right face, L: left face.

Figure 4: Percentage of improvement after 12-week treatment with melaglow rich in subjects of epidermal hyperpigmentation: Photographic assessment (N=53).

Grade 1: <25% reduction; Grade 2: 25-50% reduction; Grade 3: 50-75% reduction; Grade 4: > 75% reduction.

Figure 5: Clinical photographs in patient 2: (A) visit 1; (B) visit 2; (C) visit 3.

Subject satisfaction

Subject satisfaction with respect to the improvement in skin colour was assessed at the third visit. Overall, 17% subjects rated the outcome as excellent, 41.5% subjects rated the outcome as very good, 35.8% subjects rated the outcome as good and 5.7% subjects were not satisfied with the outcome.

Safety

One adverse event of skin irritation in the form of maculo papular rash was reported by a subject, which later resolved on discontinuation.

DISCUSSION

Hyperpigmentation is an increasing concern in Indian population, with successful treatment often proving to be challenging.² The natural pigmentation in subjects with skin of colour though provides many advantages such as sun protection and slowed signs of aging, it also increases the susceptibility to hyperpigmentation, which can have a negative psychological impact.^{2,6} Hence, there is a need for effective treatment of pigmentary disorders based on their prevalence. Although, hydroquinone remains the standard treatment, different botanicals are being increasingly used in various commercial preparations due to the lack of any side-effects.⁴

Arbutin and deoxyarbutin are botanicals that are structurally similar to hydroquinone. Arbutin causes decreased tyrosinase activity without affecting messenger ribonucleic acid expression, while also inhibiting melanosome maturation at non-cytotoxic concentrations, in a dose dependent manner.⁷ Although controlled clinical trials are lacking, in vitro and in vivo experiments have demonstrated its safety and efficacy in hypermelanotic disorders.⁸ Kojic acid is a hydrophilic molecule derived from species of aspergillus and penicillium, acting as a tyrosinase inhibitor that chelates copper at the enzyme's active site. Kojic acid has been found to be effective as a combination therapy in management of facial melanosia, if the subject has difficulty tolerating other first line therapies. A combination of 2% kojic acid and 2% hydroquinone was found to be superior than the combination of 10% glycolic acid and 2% hydroquinone in a study in Chinese women with epidermal melasma.⁹ Further, the

combination of 5% glycolic acid and 4% kojic acid was found to be as effective in the treatment of melasma as a combination of 5% glycolic acid and 4% hydroquinone at 12 weeks.¹⁰ Licorice extracts are skin-lightening agents with the few side effects. Because of its benign profile, licorice extract is one of the most widely used agents in cosmeceuticals for skin brightening. It inhibits tyrosinase, leading to the inhibition of melanogenesis. Licorice extract also has topical anti-inflammatory and anticarcinogenic properties.^{11,12} Ascorbic acid, the reduced form of vitamin C, is an antioxidant that works by interrupting melanogenesis via interactions with copper ions. Because of ascorbic acid's limited stability and rapid oxidation, producing biologically active formulations is difficult. However, some ascorbate esters (magnesium-L-ascorbyl-2-phosphate) avert such outcomes. The magnesium-L-ascorbyl-2-phosphate was found to significantly reduce pigmentation in 19 out of 34 subjects with melasma and senile freckles but only in 3 of 25 subjects with normal skin.¹³ Soy is considered as the most commonly used skin-lightening agent in cosmetic moisturizers. The soybean trypsin inhibitor inhibits the protease-activated receptor-2 pathway that is necessary to regulate keratinocyte phagocytosis of melanosomes and melanosome transfer.^{14,15} The de-pigmenting effect of soymilk is reversible and daily topical treatments for 7 months' resulted in no adverse effects.¹⁶ Vitamin E is the major lipophilic antioxidant in plasma, membranes, and tissues. It has been shown to cause depigmentation by its interference with lipid peroxidation of melanocyte membranes, increase in intracellular glutathione content, and inhibition of tyrosinase.¹⁷ Side-effects such as allergic or irritant reactions are rare with topical vitamin E and hence are used commonly in cosmeceuticals preparations.¹⁶ Niacinamide reduces pigmentation by reversibly preventing the transfer of melanosomes from melanocytes to the keratinocytes. Niacinamide was found to decrease hyperpigmentation compared with placebo alone after 4 weeks of use in a study to assess the melanogenesis in vitro and facial hyperpigmentation and skin colour in vivo in Japanese women.¹⁸ Considering the beneficial effects of these botanicals, the objective of the study was to assess the effectiveness of the study medication 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% in the treatment of epidermal pigmentation.

Many studies have shown the effectiveness of botanical combinations in treating hyperpigmentation. In a study in 80 multi-ethnic subjects with mild to moderate facial dyschromia, a preparation containing kojic acid, emblica extract and glycolic acid was compared to 4% hydroquinone. The results showed efficacy parity in skin bleaching between the two groups, indicating that the combination of kojic acid, emblica extract and glycolic acid is an alternative to hydroquinone 4% for participants with mild to moderate facial dyschromia.¹⁹ In another study, clinical and instrumental assessment of a cream containing vitamin C and liquorice extract revealed 35%

improvement of melasma area and severity index score in women having melasma.²⁰ In another study, clinical evaluation of a cream containing kojic acid and licorice extract revealed good improvement in cases of solar lentigo and chloasma. This cream was found to be effective and safe with no side-effects.²¹

The results of our study indicated a significant improvement in the melanin and erythema indices, post treatment with study medication, over a period of 12 weeks. The overall percentage of melanin and erythema improvement was 24.2% and 7.4%, respectively, as assessed using Dermacatch.

Further, the subjects were graded based on the clinical photographs and Fotofinder images. This was performed by blinded assessment, by two independent dermatologists. The Fotofinder images indicated that nearly half of the subjects had grade 3 improvement i.e.: 50-75% reduction in the amount of epidermal hyperpigmentation, post treatment. About 13.2% subjects reported grade 4 improvement, 30.2% had grade 2 and 9.4% subjects had grade 1 improvement. Likewise, based on clinical photographic images, 15.1% reported >75% improvement (grade 4), 41.5% reported 51-75% improvement (grade 3), 34% subjects had 26-50% improvement (grade 2) and 9.4% subjects had less than 25% improvement (grade 1) in the epidermal hyperpigmentation.

Subject satisfaction with respect to the improvement in skin colour was also assessed at the end of 12 weeks' study period. More than half of the subjects (~62%) had rated the treatment as excellent or very good. Only 5.7% subjects were not satisfied with the treatment effect.

An adverse event related to skin irritation was reported by a subject in this study, which later resolved on discontinuation of the treatment. A similar study was done by Guevara IL et al, to assess the safety and efficacy of a cream containing 4% hydroquinone, 10% buffered glycolic acid, vitamins C and E, and sunscreen versus a cream containing sunscreen alone in the depigmentation of epidermal melasma of the face.²² Few of the adverse reactions reported in this study were burning (35%), itching (10%), redness (60%), dryness (60%), peeling (30%), erythema (85%), scaling (65%) and edema (40%). These side-effects could be attributed to the presence of hydroquinone or higher concentration of glycolic acid.²¹ This emphasizes the need for a product which does not contain hydroquinone, or contains lower concentration of glycolic acid.

Few of the limitations of this study are lack of a comparator or control group, and short follow-up period.

CONCLUSION

This study indicated that melaglow rich 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%, was found to be safe and efficacious in the treatment of epidermal pigmentation. This could be attributed to the tyrosinase inhibitors, anti-inflammatory and peeling properties of the botanical components in the cream. This combination hence can be considered as a preferred alternative to steroid and hydroquinone based combinations, given the efficacy and low incidence of adverse effects. However, it should be emphasized that subject follow-up and compliance is indispensable. Long-term studies with a large sample size and a comparator group are warranted to substantiate our findings.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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