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Original Research Article

Role of different topical modalities in improvement of facial hyperpigmentation and skin rejuvenation

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ABSTRACT

Background: Facial hypermelanosis is a psychologically stressful condition for modern men and women who are cosmetically more conscious than their ancestors. There are various lightening agent used for several months before effect becomes apparent and are much more effective when pigment is epidermal. these topical agents include hydroquinone, liquorice derivatives niacinamide, glycolic acid, arbutin and deoxyarbutin, ascorbic acid, 4-n-butyl resorcinol, retinoids topical steroids mequinol, kojic acid, azelaic acid, 5% tranexmic acid, glutathione cream etc.
Methods: A randomized, controlled study was done. 220 patients were given either treatment will be given depending upon the physician choice after taking well informed consent from the patient. Patients' assessment regarding the degree of improvement of complexion since the beginning of therapy was evaluated.
Results: The percentage satisfactory response for different modalities was as follow kojic acid 2% cream- 55.55%, 20% azelaic acid cream- 53.12%, 4-n-butyl resorcinol 0.3% cream- 57.89%, 5% tranexmic acid lotion- 48.83% and glutathione cream- 55.76%.
Conclusions: Out 220 patients post inflammatory hyperpigmentation was the most common facial condition. Total 61 patients of PIH were there in the present study including 26 males and 35 females followed by melasma. All The modalities were effective in the treatment of different types- pigmentary conditions.

Keywords: Kojic acid, Azelaic acid, 4-n-butyl resorcinol, Tranexamic acid, Glutathione

INTRODUCTION

Facial hypermelanosis are a common presentation in most of patients, causing cosmetic disfigurement with considerable psychological impact. With age skin starts to show sign of ageing, especially on face and exposed parts of body. Apart from this, facial skin can lose its complexion and texture due to many other dermatological conditions. Long duration outdoor activities result in tanning, and photo aging. Melasma in another very common hyperpigmentary disorder and its prevalence is high in females due to intrinsic factors.

Normal skin color is determined by number of chromophores, the most important of which is melanin. Racial and ethnic differences is in skin color are related to number, size, shape, distribution and degradation of melanin-laden organelles called melanosomes. These are produced by melanocytes and are transferred to keratinocytes.[1]

Lightening agents need to, be used for several months before effect becomes apparent and are much more effective when pigment is epidermal. Our aim was to study these topical agents and to compare the effect of topical agents in facial dyschromias, melasma and other pigmentary conditions

The aim of the study was to evaluate the effects of these topical agents and to compare the effect of topical agents in facial dyschromias, melasma and other pigmentary conditions.

METHODS

A prospective observational study was carried out on 220 patients of facial hypermelanosis attending the skin OPD of BRD Medical College, Gorakhpur. The study was conducted from July 2018 to June 2019. Either treatment will be given depending upon the physician choice after taking well informed consent from the patient.

Inclusion criteria

Male and females patients of age group 15-45 years. Healthy adults of either sex clinically diagnosed as hyperpigmentary disorders attending the dermatology outpatient department

Exclusion criteria

Exclusion criteria were pregnant and lactating mother; patients with severe actinic damage; on drugs causing or aggravating pigmentation; known allergy to any of the ingredients.

All the patients were subjected to complete examination and detailed history of onset, duration, relationship to pregnancy, hormonal therapy, sun exposure, cosmetic use, and previous complexion of skin and response to various therapies.

Written informed consent was taken from each patient. Patients were explained in detail about the possible side effects of topical agents.

Patients were registered into five different groups and allocated to five different modalities-

Modality	I	Kojic acid cream 2%
Modality	II	Azelaic acid gel 20%
Modality	III	4-n-butyl resorcinol 0.3% cream
Modality	IV	Tranexamic acid 5% solution
Modality	V	Glutathione 2% gel.

All the patients were advised to apply a broad spectrum sunscreen of SPF above 30 during day time with oral vitamin C 1000 mg and to protect their facial skin from sunlight as much as possible. The topical solutions of 5% tranexamic acid was 5 g tranexamic acid dissolved in 10 cc ethanol, 10 cc 1, 3- butanediol and distillated water up to 100 cc

Patients' assessment regarding the degree of improvement of complexion since the beginning of therapy as follows:

- No improvement
- Mild, unsatisfactory improvement
- Moderate, satisfactory improvement
- Good, very satisfactory improvement

Criteria for successful modalities

- Tolerance to the treatment
- No side effects produced by the particular treatment.
- Regression of lesion
- Absence of recurrence at same site
- No significant side effects, disfigurement or other complications

Criteria for failure of modalities

- Intolerance to a particular treatment
- Side effects produced by the particular treatment
- Recurrence of treated lesions

RESULT

The type of hyperpigmentary condition at the start of therapy and the number of cases of particular hyperpigmentary conditions are given below:

Clinical profile of patients with facial hyper-pigmentation and facial rejuvenation

Out of total of 220 patients, 34 patients (20 males, 14 females) had tanning as hyperpigmented disorder, 46 patients (10 males, 36 females) had melasma, 28 patients (07 males, 21 females) had periorbital hyperpigmentation, 61 patients (26 males, 35 females) had post-inflammatory hyperpigmentation, 18 patients (4 males, 14 females) had freckles, 19 patients (5 males, 15 females) with facial complexion problems, and 14 patients (5 males, 9 females) who asked for facial rejuvenation. In total of 220 patients, 77 males and 143 females were selected.

Out of 220 patients only 201 patients completed the study and remained in follow up for more than 3 months. Post inflammatory hyperpigmentation was the most common hyper pigmentary condition followed by melasma as given in Table 1.

Distribution of patients according to age and sex

The selected patients were grouped as 0-10 years, 11-20 years with 16 patients (5 males, 11 females), 21-30 years with maximum number of patients i.e. 82 (30 males, 52 females), 31-40 years with 64 patients (22 males, 42

females), 41-50 years with 58 patients (20 males, 38 females) and 51- 60 years. Out of total 220 patients maximum numbers of patients with hyper-pigmentary disorders belongs to age group 21-30 years (37.27) thus illustrating that hyperpigmentary disorders are seen in adolescent and young adults, in the age group 21-30 years. Females more commonly affected than males.

Table 1: Clinical profile of patient with hyperpigmentary disorders who underwent therapeutic trial.

Hyperpigmentary disorders	Male		Female		Total number undertaken therapy
	Selected patient	Under-taken therapy	Selected patient	Under-taken therapy	
Tanning	20	18	14	12	30
Melasma	10	9	38	34	43
Periorbital hyperpigmentation	07	06	21	20	26
Post inflammatory hyperpigmentation	26	24	35	32	56
Freckles	04	3	14	14	17
Facial complexion	05	04	14	13	17
Facial rejuvenation	05	04	09	08	12
Total	77	68	143	133	201

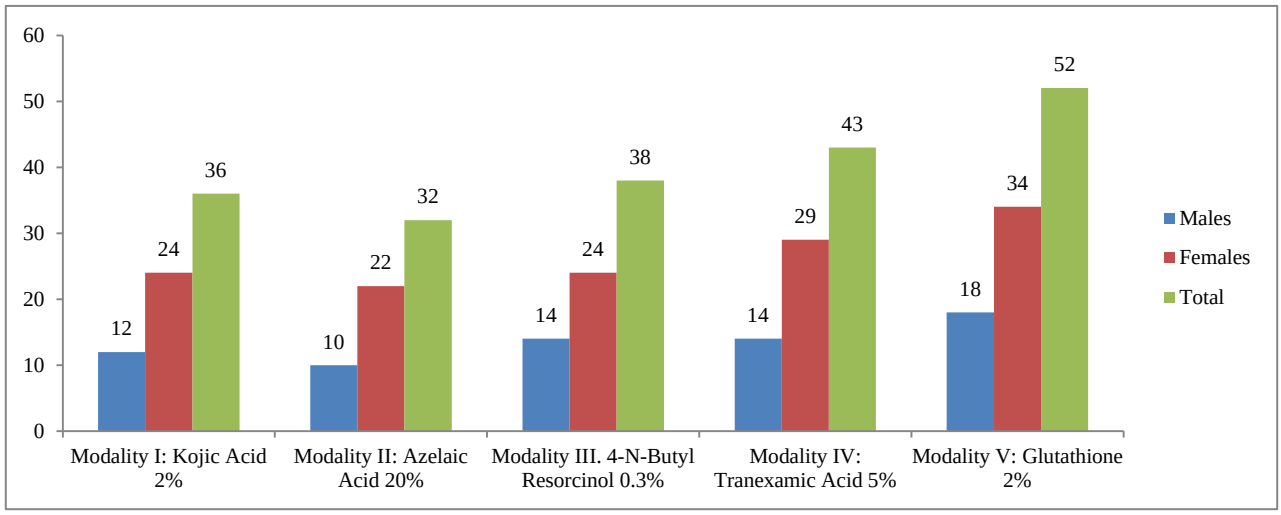

Figure 1: Treatment of modalities wise distribution of patients.

Table 2: Patient's selection in different modalities (I, II, III, IV and V) of treatment.

Patient with	No. of patients in modality I (kojic acid 2%)	No. of patients in modality II (azelaic acid 20%)	No. of patients in modality III (4-n-butyl resorcinol 0.3%)	No. of patients in modality IV (tranexamic acid 5%)	No. of patients in modality V (glutathione 2%)
Tanning	6	3	8	5	8
Melasma	5	4	6	19	9
Periorbital hyperpigmentation	5	3	5	5	8
Post inflammatory hyperpigmentation	11	18	11	7	9
Freckles	4	2	5	1	5
Facial complexion	3	1	2	4	7
Facial rejuvenation	2	1	1	2	6
Total	36	32	38	43	52

A of 36 patients underwent through modality I- kojic acid 2% in which 12 males (33.33%) and 24 females (66.66%). 32 patients were kept in treatment modality II- azelaic acid 20%. There were 10 males (31.25%) and 22 females (68.75%). A total of 38 patients including 14 males (36.84%) and 24 females (63.15%) underwent treatment modalities III- 4-n-butylresorcinol 0.3%. Forty three patients were included in this treatment modality IV - tranexamic acid 5% and there were 14 males (32.55%) and 29 females (67.44%). Fifty two patients including 18 males (34.61%) and 34 females (65.38%) were undergoing the treatment modality V- glutathione 2%, (Table 2).

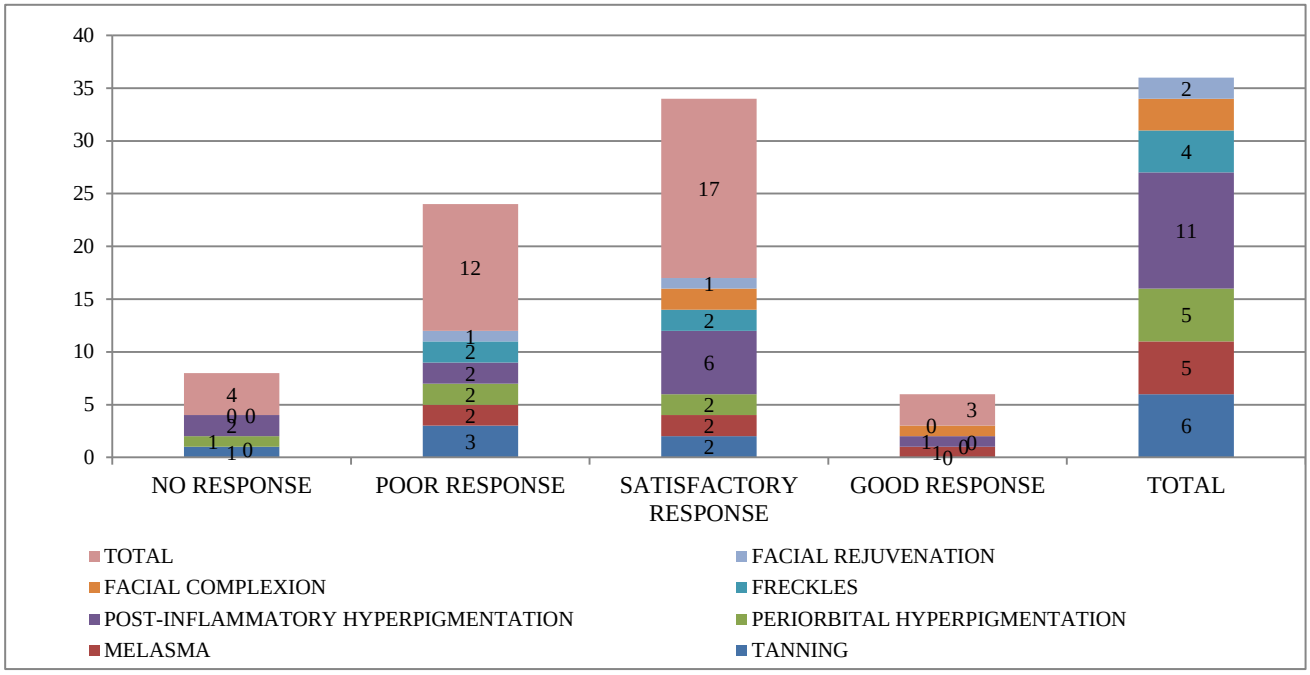

Figure 2: Response to treatment (subjective assessment) to modality–I (kojic acid 2%).

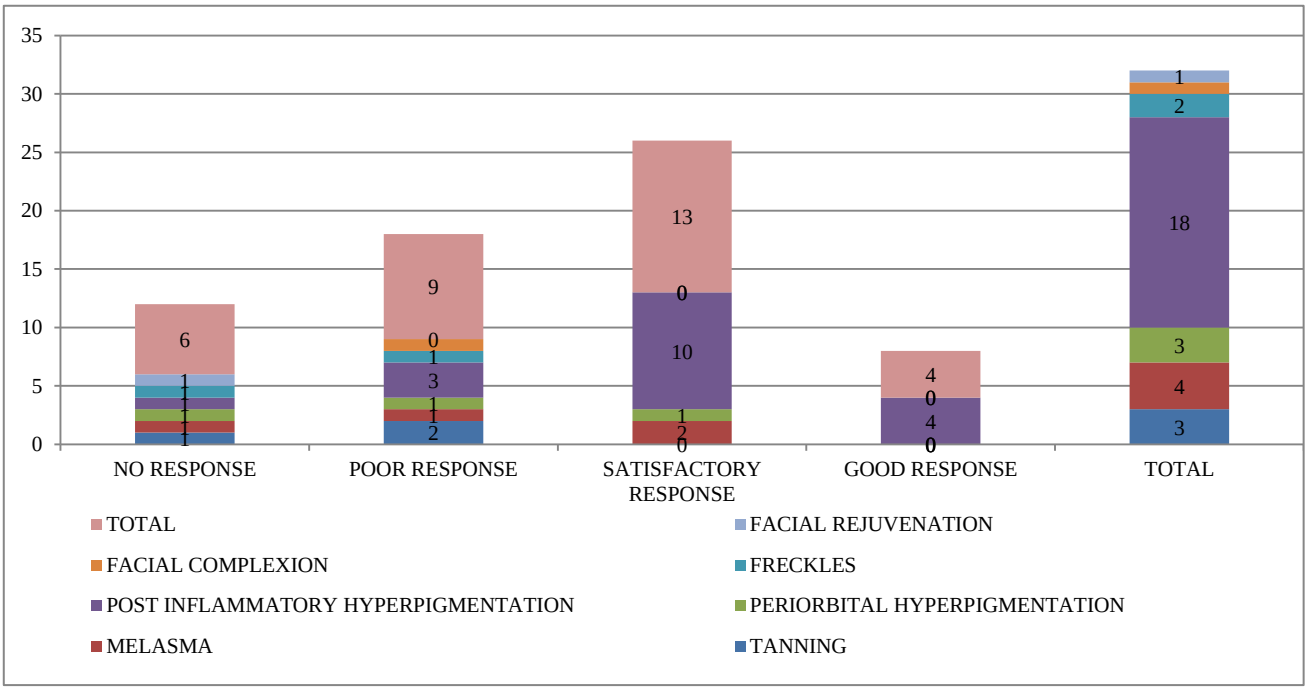

Figure 3: Response to treatment (subjective assessment) to modality–II (azelaic acid 20%).

Among 36 total patient undergoing treatment modality which include kojic acid 2% application at night gave satisfactory respond in 47.22% patients, poor response in 33.33% of patient and good response in 8.33% patient and no response in 11.11%.

Among 32 total patient undergoing treatment modality II which include azelaic acid 20% application twice daily gave satisfactory respond in 40.62% of patients, poor response in 28.12% of patients and good response in 12.5% patient and no response in 18.75%.

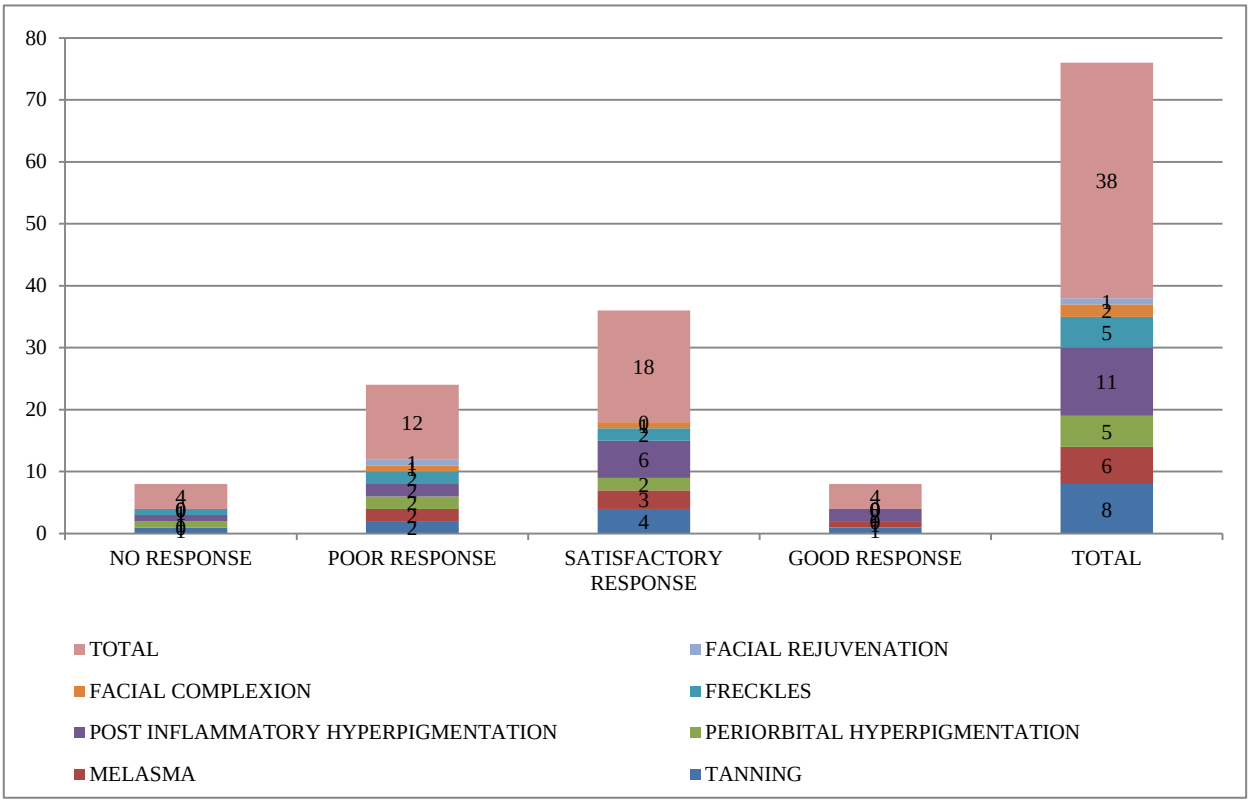

Figure 4: Response to treatment (subjective assessment) to modality–III (4-n-butyl resorcinol 0.3%).

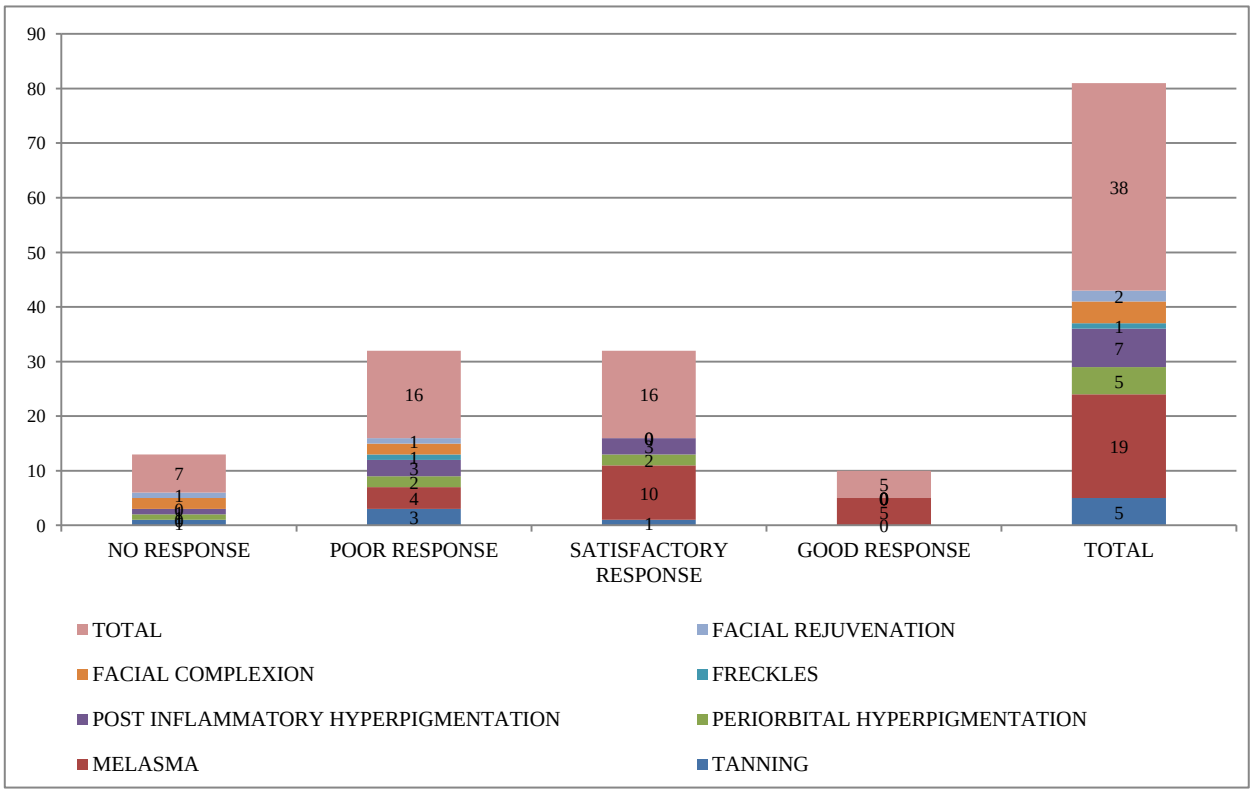

Figure 5: Response to treatment (subjective assessment) to modality–IV (with tranexamic acid 5%).

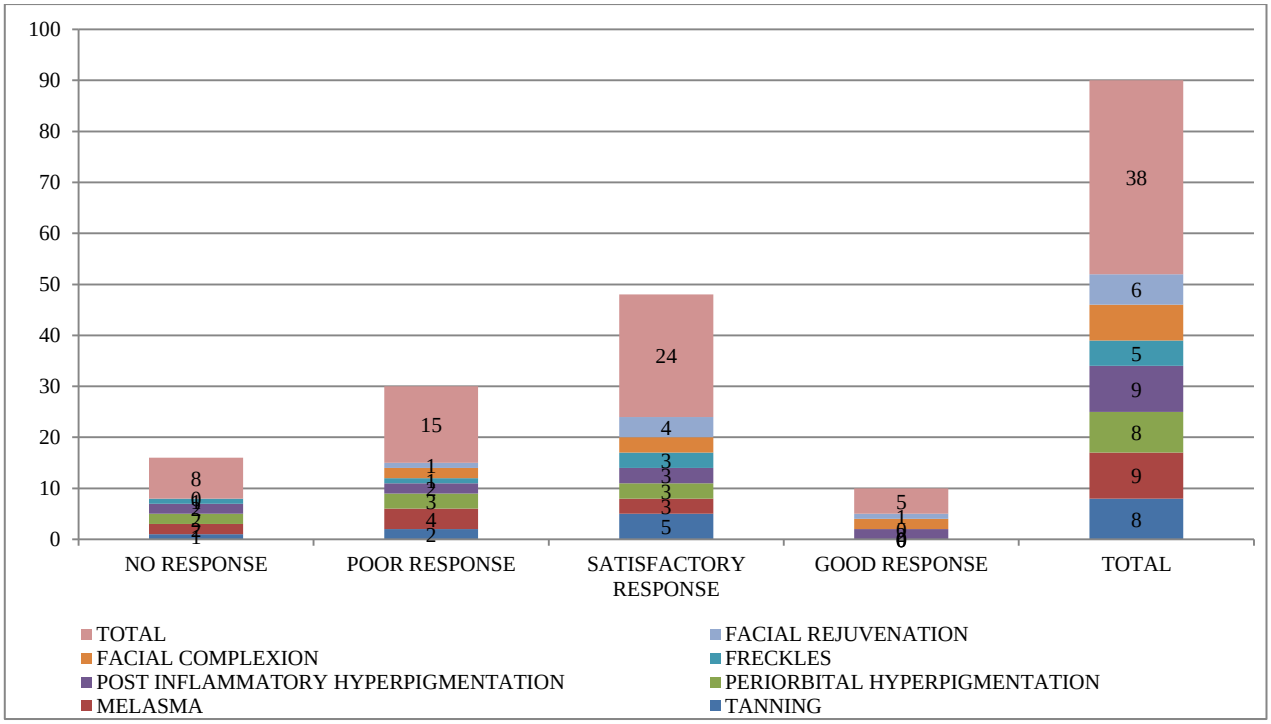

Figure 6: Response to treatment (subjective assessment) to modality–V (glutathione gel 2%).

Table 3: Side effects observed in five different modalities in patients with different hyperpigmentary condition.

Response	Total number of patients in different modality					Total
	I	II	III	IV	V	
Erythematic	7	2	2	4	1	16
Burning	4	4	1	2	-	11
Desquamation	1	1	2	1	-	5
Hypo pigmentation	1	-	-	-	-	1
Hyperpigmentation	-	-	-	-	-	-
Itching	1	3	2	3	1	10
Dryness	-	1	1	2	-	4
Atrophy	-	-	-	-	-	-
Recurrence	2	3	3	3	2	13

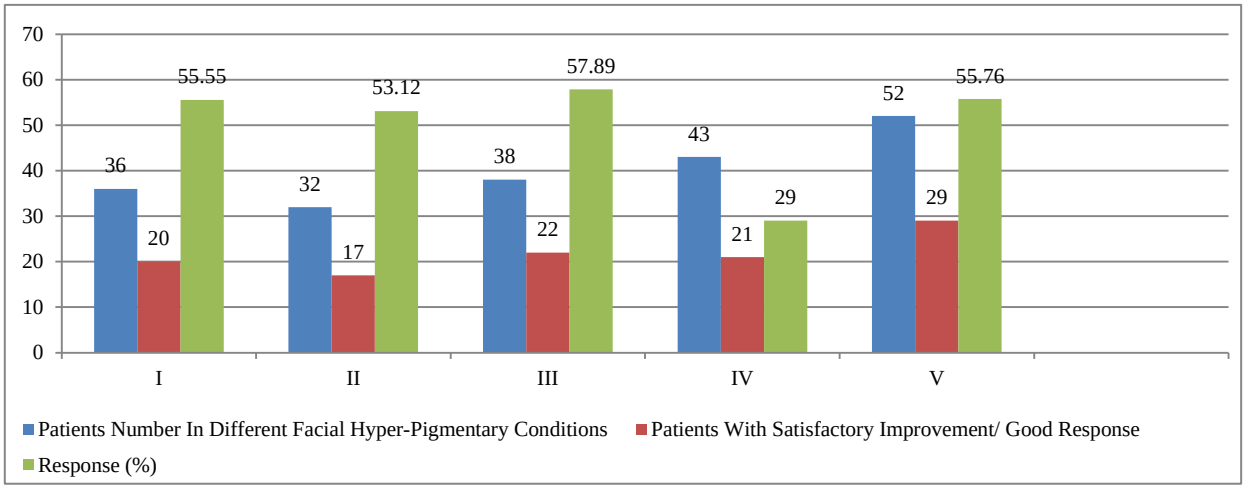

Figure 7: Comparative study of the responses of five different modalities in patients of different hyperpigmentary conditions.

Among 38 total patient undergoing treatment modality III which include 4-n-butyl resorcinol 0.3% twice daily application after 3 month gave satisfactory respond in 47.36% of patient poor response in 31.57% of patient and good response in 10.52% patient and no response in 10.52%.

The IV modality which includes continuing application with tranexamic acid 5% twice daily after 3 month gave very good result in (11.62%) of cases. No response in (16.27%) of case, poor response in (37.2%) of cases and satisfactory response in 37.2% of case.

The V modality which include continuing application of glutathione gel 2% twice daily after 3 month gave good result in 9.61% of cases, satisfactory response in 46.15% of cases, poor response in 28.84% cases, no response in 15.38% of cases

It is obvious from the Table 3, the most common side effects observed in most of the modalities is erythematic followed by burning sensation.

It is evident from the Figure 7 that all the modalities are effective in the treatment of different type- pigmentary confections.

DISCUSSION

Two hundred twenty (220) cases of hyperpigmentary skin disorders between age group 15-45 years were selected in this study.

Out of 220 patients, 201 patients continued the treatment for more than 3 months and only these patients were evaluated in the present thesis. Out of 201 patients, 77 patients were male (38.30%) and 143 patients were female (71.14%).

Maximum cases were selected from post inflammatory hyperpigmentation (27.72%) followed by melasma, tanning, periorbital hyperpigmentation, freckles, facial complexion then facial rejuvenation. Tanning was more common in males (20/34) than females (14/34) due to more outdoor activities and more sun exposure in males. Melasma was more common in females (36/46) as compared to males (10/46) due to intrinsic factors. Post inflammatory hyperpigmentation was seen in females (35/61) than males (26/61) in the study.

Periorbital hyperpigmentation were seen in 21 females and 7 males, 28% of total patients studied in the present study.

Eighteen cases of freckles, 19 cases of facial complexion and last 14 cases of facial rejuvenation were studies in the present study.

Out of total 220 patients maximum patients with hyperpigmentary disorders belong to age group 21-30 years.

Sunscreens are generally more effective in blocking UVB than UVA but effective filtration of UVA is important because these wavelengths contribute to photo aging, coetaneous immunosuppression.[2-4] and carcinogenesis, and can play a central role in photodermatoses such as polymorphic light eruption.

No single compound can achieve all the desired aims, so most commercial formulations contain a mixture of active constituents. These fall into two broad categories-physical sunscreens, which act by reflecting and scattering UV light, and chemical agents, which absorb UV light.[5-7] Physical agents such as titanium dioxide and zinc oxide can block a broad spectrum of UVB, UVA and visible light (the latter can be useful in some photodermatoses.[8,9]

Five different modalities for pigmentary disorders were tried in the present study.

First modality composed of kojic acid 2% with sunscreen in 36 patients (17.91%) of different hyperpigmentary conditions. This group consists of 11 cases of post inflammatory hyperpigmentation, 06 patients of tanning, 5 patients of melasma, 5 patients of periorbital hyper-pigmantation, 3 patients of facial complexion, 2 patients of facial rejuvenation and 4 patients of freckles. In all conditions, 47.22% patients showed satisfactory response and 33.33% showed poor response, 8.33% of the patient had shown an excellent response, 11.11% patients found no improvement even after using the treatment for more than three months. A study conducted with a topical product containing kojic acid, embolic extract and glycolic acid was also as effective as 4% hydroquinone cream in lightening the skin of 80 patients with mild to moderate facial dyschromias in a double blind study.[10]

Second modality in the present study was azelaic acid (20%) application twice daily and day time application of sunscreen. A total of 32 patients (15.92%) underwent treatment with this modality. Out of 32 patients, 4were of melasma, 3 were of periorbital hyperpigmentation, one patient was of facial complexion, 18 were of post-inflammatory hyperpigmentation and 2 were of freckles and one case were skin rejuvenation. With this modality, 12.5% patients showed excellent or good response but 40.62% showed satisfactory response and 18.75% assessed no response even after 3-4 months regular treatment. A similar study was conducted in the Philippines; a study found that 20% azelaic acid was better than 2% hydroquinone.[11]

Third modality was 4-n-butylresorcinol cream0.3% twice application along with sunscreen of SPF above 26.In a study, Okubo et al reported the inhibitory effect of 4-n-butylresorcinol on cultured B melanoma cells and established the role of 4-n-butylresorcinol tyrosinase activity with no cytotoxicity.[12] This paved the way for newer in vivo studies which established more evidences on the activity of both tyrosinase and TRP1.

In our study a total number of 38 patients (18.9%) underwent this therapy. Eleven patients were of post-inflammatory hyperpigmentation, 6 patients were of melasma, 8 patients were of tanning, 5 patients were of periorbital hyperpigmentation, 5 patients were of freckles, 2 patients were of facial complexion and 1 patient was facial rejuvenation.

In the present study this modality showed very good to excellent response in 10.52% patients. Poor response was shown in 12 patients (31.57%), satisfactory in 47.36 and no response in 10.52% patients. In all the published studies of 4-n-butylresorcinol have shown the hypo pigmenting efficacy, safety, and tolerability with the 0.1% cream, but there is paucity of clinical studies that used the 0.3% cream. Furthermore, ethnic differences in skin reactivity have been explored through the years, leading to the clinical hypothesis that Asian skin is more reactive than black skin and Caucasian skin. [13]

Tranexamic acid, its positive effect on melasma was first reported in a Japanese study by Nijo.[1] In the study by Wu et al patients with freckles were unresponsive to oral administration of TXA.[14] On the contrary, Kondou et al successfully employed topical TXA emulsion for the treatment of melasma and freckles for 5–18 weeks.[15] Here, the topical TXA also prevented the appearance of new lesions. A combination of oral and topical TXA showed both significant declines in epidermal pigmentation and improvement of dermal melasma.[16] Kanechorn Na Ayuthaya et al conducted a double blind RCT among Asians and used 5% TXA in a liposome gel formulation for epidermal melasma for duration of 12 weeks.[17] This was compared with the vehicle in a split face trial. Even though 78.2% of patients showed a decrease in the melanin index, the results were not significant as compared with the vehicle. in our study tranexamic acid 5% was applied twice daily along with day time sunscreen in which 19 patients with melasma, 5 patient with tanning, 5 patients were of periorbital hyperpigmentation, 7 patients were post inflammatory hyperpigmentation, one patient was of freckles, 4 patients were of facial complexion and two patients were are facial rejuvenation. In present study modality shows very good results in 11.62% of cases, no response is 16.27%, poor response in 37.2% and satisfactory response in 37.2%.

Sixth modality was topical glutathione 2% twice application along with day time sunscreen. In which 8 patients were of tanning, 9 patients were of melasma, 8 patients were of periorbital hyperpigmentation, 9 patients were of post inflammatory hyperpigmentation, 5 patients were of freckles, 7 were of facial complexion and 6 were of facial rejuvenation.

The response of fifth modality was poor in 15 patients (28.84%), satisfactory in 46.15% and good in another 9.61% A randomized, double-blind, placebo controlled clinical trial conducted in 30 healthy Filipino women aged 30–50 years has provided some evidence favoring the efficacy of topical 2% GSSG lotion in temporary skin lightening. Patients were randomized to apply glutathione as 2% GSSG lotion and a placebo lotion in a split face protocol, twice daily for ten weeks. GSSG was preferred over GSH, as GSH is unstable in aqueous solutions. GSSG eventually generates GSH after coetaneous absorption. The changes in the melanin index, moisture content of the stratum corneum, skin smoothness, skin elasticity and wrinkle formation were objectively assessed. The reduction of the melanin index with glutathione was statistically significant when compared to placebo. Glutathione treated areas had significant improvement in other parameters as well. No adverse drug effects were reported. Glutathione has also become available in the form of soaps, face washes and creams.[18] Recently, a glutathione based chemical peel has been launched. Although evidence of efficacy is lacking, the manufacturers claim improvement of melasma, hyperpigmentation and skin ageing.[19]

Regarding the side effect of topical agents in this study, erythema and burning sensation were the commonest and lasted for less than a week, other minor side effect were visible peeling of skin, itching and recurrence of lesions. Rare side effects like hypo pigmentation was also seen.

CONCLUSION

In the present study, two hundred twenty (220) cases of hyperpigmentary skin disorders between age group 15-45 years were included. Out 220 patients, 210 patients underwent the treatment of more than three months in which 77 were males and 143 were females. Post inflammatory hyperpigmentation was the most common facial condition. Total 61 patients of PIH were there in the present study including 26 males and 35 females followed by melasma. The findings of the study conclude that all the modalities are effective in the treatment of different types of pigmentary conditions. Larger studies are required to further confirm the efficacy of different topical agents for improvement of skin complexion and rejuvenation.

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