Comparative Study of Oral Isotretinoin versus Oral Isotretinoin + 20% Salicylic Acid Peel in the Treatment of Active Acne

Background: Acne is a self limiting condition that often results in scarring and disfigurement disproportionate to its clinical severity. Isotretinoin is considered the gold standard in the medical management of severe form of acne vulgaris. Salicyclic acid (SA) peels, a β- hydroxy acid peel has got sebosuppressive effect and helps in faster resolution of acne with minimal scarring. It also decreases the post inflammatory hyperpigmentation. Combining both the modalities is usually not advocated because of expected excessive dryness and irritation **Aims:** To compare the efficacy of oral isotretinoin and oral isotretinoin with 20% SA peels in patients with moderate to severe acne. **Materials and Methods:** 60 consecutive patients with moderate to severe facial acne attending the skin department were randomized in to 2 groups. 1st group received 20mg oral isotretinoin once daily for 16 weeks and 2nd group received 20mg oral isotretinoin once daily along with 20% SA peels every two weeks for 16 weeks. Baseline grading of acne was done with Michelsons Acne severity index (MASI).Right and left sides of the face were scored separately and total score was taken. Severity score was assessed monthly .Clinical photographs were obtained for evaluation every month. Patients were asked to follow up once every 2 weeks or earlier in case of any adverse events. **Results:** Patients in both the groups revealed a reduction in the number of lesions. The 1st group showed a reduction of approximately 73.4% after receiving 20mg oral isotretinoin for 16 weeks. The 2nd group showed a reduction of approximately 92.5 % after receiving 20mg oral isotretinoin along with 20% SA peel once every 2 weeks for 16 weeks. **Conclusion:** Both oral isotretinoin and combination of oral isotretinoin with 20% SA peels once every 2 weeks are effective in treating moderate to severe acne but the combination showed significantly better clearance of acne than monotherapy with isotretinoin.

KEYWORDS: Acne, isotretinoin, salicylic acid peel

INTRODUCTION

Acne is the most common skin disease requiring attention of health practitioners. It is a self-limiting disease of the pilosebaceous unit, which can lead to devastating and frustrating scars and pigmentary alterations.

Isotretinoin until today is considered to be the gold standard[1] in the medical management of moderate to severe forms of acne vulgaris. Given at a dose of 0.5-2 mg/kg body weight the molecule has got a significant sebosuppressive effect. At times isotretinoin has proven curative for the severe forms of acne also though the disease can relapse later.

Salicylic acid (SA) has got potent sebostatic effect, which makes it useful in the treatment of acne.

Therapies combining isotretinoin and SA are usually not advocated in acne patients fearing excessive dryness and unpredictable penetration of the peeling agent. We conducted this study to compare the efficiency of oral isotretinoin and oral isotretinoin with 20% SA peel once every 2 weeks in acne vulgaris.

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MATERIALS AND METHODS

The study was carried out in the Department of Skin and VD of a Tertiary Care Hospital of Eastern India between April 2012 and March 2013.

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60 consecutive patients of either sex with moderate to severe acne were recruited for the study. Michaelson acne severity index (MASI) was used as a tool to calculate the severity of acne. Patients were randomised using a random number table. 30 patients were allocated into in each group. Patients below 18 years and above 25 years of age, patients with contraindications for isotretinoin use, pregnant patients and patients with keloidal tendency, patients with endocrine abnormalities and those with a very mild form of acne were excluded from the study. The ethical committee of IMS and SUM Hospital, Bhubaneswar approved the study and written consent was obtained from every patient. Investigator 1 (1st author) did the group allocation of the patients using a random number table. Investigator 2 (2nd author) performed the chemical peeling on patients in the second group using 20% SA. The 3rd investigator (3rd author) was blinded from the group allocation and treatment modalities. She did the MASI scoring and evaluation of all patients at all the visits. Patients were assigned into two groups. 1st groups included patients receiving 20 mg isotretinoin as a monotherapy and 2nd groups included patients receiving 20 mg isotretinoin once daily in combination with 20% SA peels (Vedasol - 20 gel, vedaderm Inc., Chicago, supplied by Percos) at a 2 weekly interval. The 20 mg dose of isotretinoin for both groups was arrived taking into consideration the probable adverse effects of combined modalities of isotretinoin and SA. Isotretinoin (Capsule Tretiva 20 mg) was supplied by Intas pharmaceuticals Ltd., with lot number S12B018 and expiry date 1/2014. SA peeling was started on day 1 of starting oral isotretinoin keeping in view the slow onset of action of isotretinoin. All necessary lab investigations (complete blood count, liver function test (LFT), renal function test, lipid profile, urine routine and microscopy) were carried out at baseline and at the final follow-up time to look for any drug induced adverse effects. However lipid profile and LFT were carried out at monthly intervals. Patients were reviewed every 2 weeks and were instructed about the possible side-effects and asked to report immediately if any occurred.

Response to therapy and side-effects were noted at each visit and patients were instructed to avoid sun exposure by using the adequate photo protective measures. They were also instructed to use emollients in case of excessive dryness. The Consort-2010 flow chart showing the enrollment and group allocation of the patients is given in Figure 1.

Epidemiologic profile of both groups is given in Table 1.

Baseline grading of acne was done using MASI [Table 2].[2]

Number of comedones, papules, pustules, infiltrated lesions and cystic lesions were counted and multiplied with its severity index and added together to give the final score. However in our study, right side and left side of the face were scored separately and summed up for a total score for better correlation with photographic

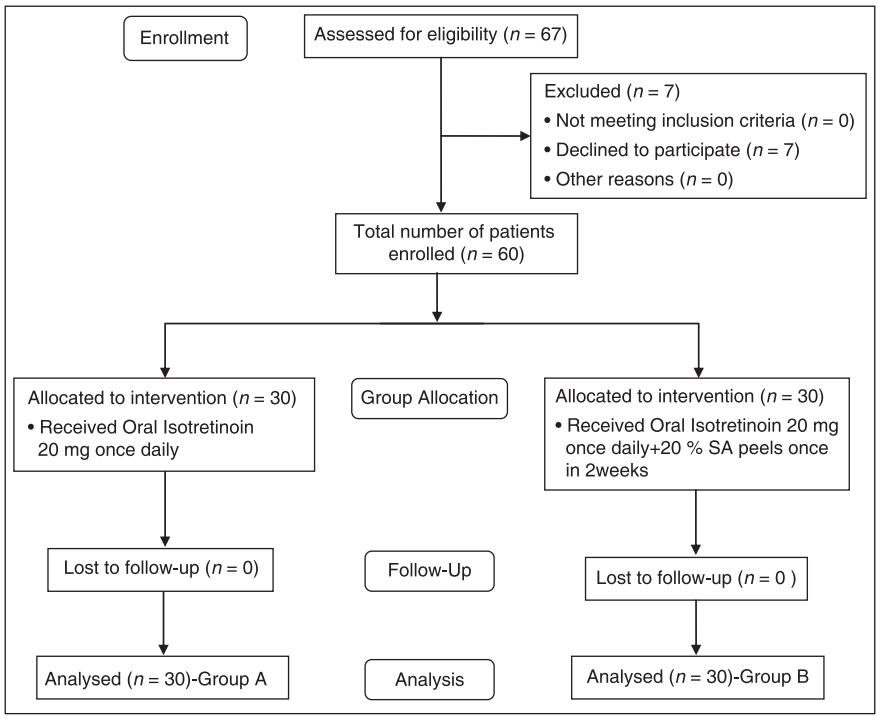

Figure 1: Flowchart showing allocation of patients

evaluation. Acne scoring was done by a blinded observer (3rd author).

A baseline 20% SA test patch in the retro auricular region was carried out for all the patients in Group B, 2 weeks following which the patients were subjected to the 1st sitting of SA peel.

Each patient's face was cleaned and degreased with spirit and acetone and the sensitive areas (around nostrils and mouth) were protected with petrolatum jelly. The peel was applied quickly with a brush, exerting moderate pressure during the application, beginning with the forehead working from the centre out followed by each side of the face, working from the cheek down.

The peel was allowed to dry. Duration of contact was decreased with each sitting, starting with 20 min in the first sitting and 4 min in the last. The peel was removed from the face with a cotton swab dipped in water following which a lotion containing calamine and elovera was applied to the treated area to provide soothing, moisturising as well as the photo-protective effect. Patients were advised to avoid direct sun exposure for 5 days following the procedure.

Severity index was calculated every 2 weeks and photographs were taken at baseline and at the end of 16 weeks for comparison. Results were statistically analysed using SPSS 17 software IBM, Chicago.

RESULTS

60 patients of either sex between 18 and 25 years of age were included in this study. Group A had 16 males and 14 females. All the patients were started on 20 mg of isotretinoin once daily. The mean age was 20 ± 1.9 years. The average baseline MASI score was 64.1 ± 4.4. MASI score at the end of 1st month showed a slight increase at 66.4 ± 3.7. At the end of 2nd month, the average MASI was 63 ± 4.3. MASI score at the end of 4th month was 17 ± 2.9. Photographs taken at baseline and at 16 weeks demonstrate the reduction in MASI score [Figure 2]. Intragroup analysis showed that the baseline profiles were comparable and the difference in MASI scores at the end of treatment compared with the baseline is statistically significant.

Group B had 13 males and 17 females. All patients were started on 20 mg of oral isotretinoin along with a 2 weekly peel with 20% SA in gel form. The mean age was 20.6 ± 1.9. The mean MASI at baseline was 63 ± 5.1. MASI at the end of 1st month was 52.8 ± 4.8. MASI at the end of 4th month was 4.7 ± 2.1. Photographs taken at baseline and at 16 weeks demonstrate the significant change in MASI [Figure 3]. The atrophic scars with erythematosus base are usually less conspicuous in this group compared with Group A. Intragroup analysis showed statistically significant difference between baseline and 16 week MASI scores.

The monthly change in MASI scores in both groups are given in Table 3 and Figure 4. Error bars depicting 2 standard deviation or 95% of confidence interval are given in Figure 5. The graphs clearly depict that there is a significant change in MASI in both groups of patients and unpaired *t*-test between the two groups shows that the reduction in MASI in Group B is significantly higher compared with Group A ($P < 0.05$).

No adverse side-effects other than drying of lips were observed during the study period.

DISCUSSION

Isotretinoin is considered as the gold standard[1] in the medical management of acne vulgaris. Oral isotretinoin at a dose of 0.5-2.0 mg/kg/day[3] reduces sebaceous gland activity within 6 weeks[4] of starting therapy. Isotretinoin induces a dose-dependent decrease in size and cross-sectional area of sebaceous glands; dose-dependent reduction in sebum production; sebocyte apoptosis[5,6] and histological changes, such as lobular collapse, follicular atrophy and greater preponderance of undifferentiated acinar cells. Augmented production of neutrophil gelatinase associated lipocalin[7] in the skin by isotretinoin has been correlated with human

Table 1: Epidemiological profile of patients in Group A and Group B with tests of significance showing no statistically significant baseline values between both the groups

	Group A	Group B	*P* value
Number of patients	30	30	–
Age range	19-25	18-23	–
Age	20.4±1.9	20.6±1.9	0.62
Sex	16:14	13:17	–
MASI (baseline)	64.1±4.4	63.0±5.1	0.3879

MASI: Michaelson acne severity index

Table 2: Michelson acne severity index

Lesion	Severity index
Comedones	0.5
Papules	1.0
Pustules	2.0
Infiltrates	3.0
Cysts	4.0

Table 3: MASI scoring (mean±SD) at baseline and at each follow-up visit

	MASI (BL)	MASI (1)	MASI (2)	MASI (3)	MASI (4)
Group A	64.1±4.4	66.4±3.7	63.0±4.3	31.6±1.3	17.0±2.9
Group B	63.0±5.1	52.8±4.8	22.9±4.1	12.1±1.8	4.7±2.1
P value	0.3879	0.0001	0.0001	0.0001	0.0001

MSAI: Michaelson acne severity index, SD: Standard deviation

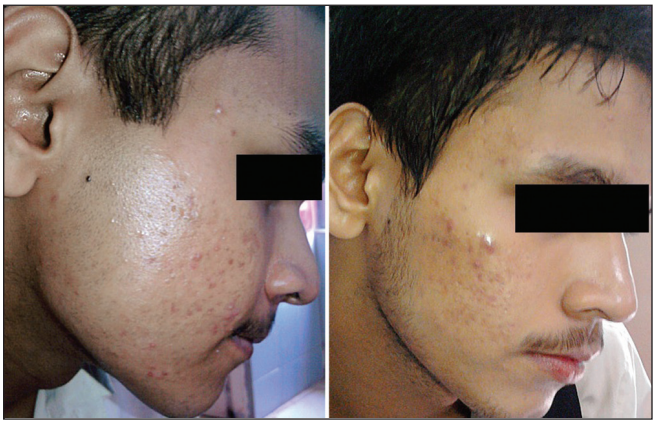

Figure 2: Before and after photographs of patient in isotretinoin monotherapy group

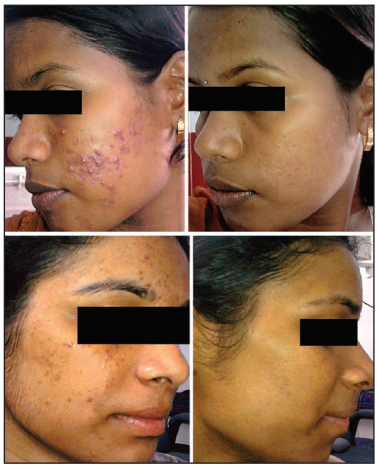

Figure 3: Before and after photographs of patients in isotretinoin + salicylic acid peel group

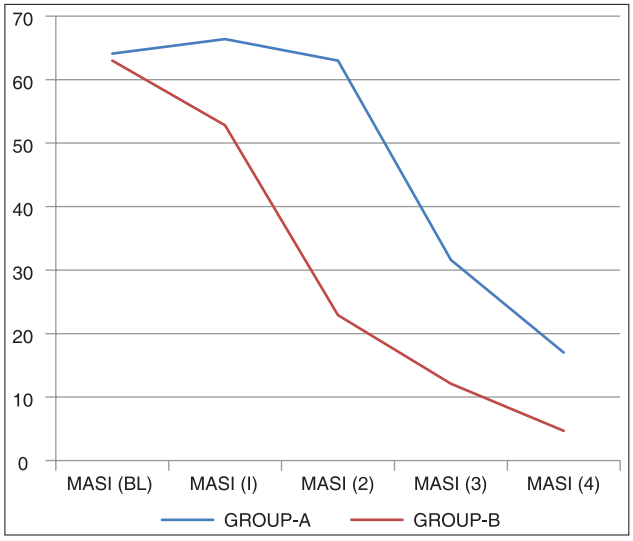

Figure 4: Monthly changes in Michaelson acne severity index in both the groups

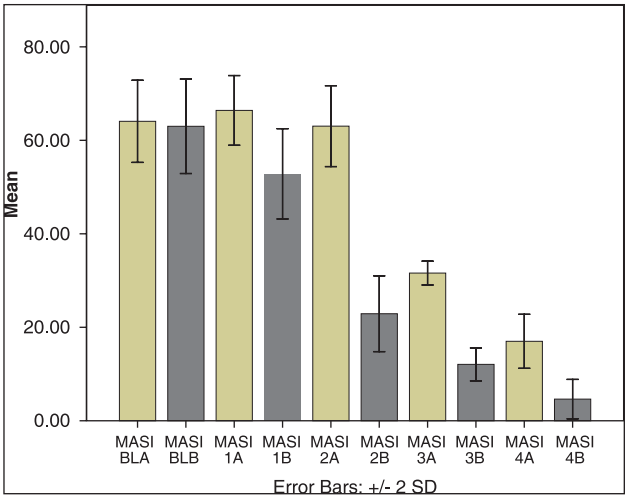

Figure 5: Error bars with 2 standard deviation at baseline and follow-up visits in both the groups

sebocyte apoptosis within sebaceous glands, which leads to decreased production of sebum within the sebaceous glands and lobular collapse. The resultant follicular atrophy leads to marked sebo-suppression.

Oral isotretinoin exhibits antiinflammatory properties[8] by reducing chemotaxis of polymorphonuclear leukocytes and monocytes. The sebum reduction and sebaceous gland atrophy markedly alter the microenvironment that hinders the growth of *Propionibacterium acnes*.[9] Oral isotretinoin also inhibits comedogenesis by decreasing follicular hyperkeratinization.[10]

SA exhibits keratolytic properties[11] as it solubilizes intracellular cement. Its lipid solubility permits the interaction with multi lamellar structures surrounding the keratinocytes in the stratum corneum and hair follicle, thereby exhibiting follicular atrophy and comedolytic action within the sebaceous unit.

SA is effective in comedonal and inflammatory acne.[12] It also facilitates resolution of post inflammatory hyperpigmentation[13,14] of face. SA peel has better efficacy and fewer side effects than glycolic acid peel in acne patients.[15]

Usually, SA peels have a self-neutralising action, they crystalise within a short time on the skin surface once the dissolving spirit/ethanol volatilises exhibiting pseudofrosting,[16] on the contrary the SA peel used our study (Vedasol - 20, gel) has gel as a driver and does not give a pseudofrost when used. The gel base makes penetration and absorption of SA possible for longer duration, hence the duration of contact determines the extent of penetration and observation which has been altered in our study starting from 20 min in the 1st sitting and decreasing by 2 min in each sitting.

Texted literature contraindicates[17] the use of oral isotretinoin with SA peels due to overlapping mechanism of actions and

the expected excessive dryness and irritation. However, being a superficial peel 20% SA may be combined with oral isotretinoin[18] as there is no direct effect on collagen remodelling, which could adversely affect the outcome with keloid formation. The rationality of choosing this combination in our study is to obtain better outcome using a lower dose of both the treatment modalities along with marked reduction in post inflammatory hyperpigmentation.

20% SA is a superficial peeling agent and hence has got little direct effect on collagen remodelling and scar modulation, but the sebotropic and anti-inflammatory effect of the agent lowers the severity of acne and thus makes the scar less conspicuous. The effect on post inflammatory hyperpigmentation due to exfoliation also contributes to a less obvious scar.

The effect on acne scars was not a part of the study and hence was not analysed statistically though scars were less obvious in the group treated with both isotretinoin and SA peel.

The increase in MASI score in Group A at the end of 1st month is because of use of isotretinoin alone in the group, which is known to flare up the disease process during the initial few weeks of therapy. The effect of isotretinoin monotherapy took upto 2 months to set in as a uniform dose of 20 mg was given to all irrespective of their weight. In Group B, however there is a reduction in MASI at the end of 1st month, which could be attributed to the additional sebosuppressive effect of SA. This means that in the initial days of treatment addition of SA could help to gain the confidence of patient because of the improvement in the disease severity.

MASI scores at the end of 2nd month showed a significant difference between both groups. The decline in MASI in Group A at the end of 2nd month is less and this could be due to the slower effect of isotretinoin therapy whereas addition of SA peels has accelerated the decline in MASI score at the end of 2nd month.

Therapy with isotretinoin was not discontinued after 16 weeks in both groups and continued until further clearance of lesions. However, SA peel was discontinued as per the protocol after 16 weeks and statistical analysis was done only upto 16 weeks as per the protocol.

Oral isotreatinoin as a monotherapy leads to significant acne clearance but oral isotreatinoin combined with 20% SA peels at a 2 weekly interval showed better results compared with isotretinoin monotherapy in our study. There were no incidences of any adverse effects apart from chapping of lips in both groups. Since our sample size is small, further studies with a large sample size are required to establish these findings.

WHAT'S NEW?

Isotretinoin along with SA peel has a significantly better outcome in moderate to severe acne than isotretinoin monotherapy. Adverse effects of combination therapies as expected were not seen in our study group.

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