Seborrheic Dermatitis (SD) is common chronic relapsing inflammatory dermatoses characterized by erythematous plaques with yellowish greasy or dry whitish scales [1]. It commonly involves areas of body having high concentration of sebaceous glands such as scalp, anterior hair line, flexures; face (eyebrows, eyelashes, nasolabial fold, maleolabial fold, glabella), ear (external auditory canal, retro auricular area), central chest and genital area [1]. The reported prevalence of SD is 1.5-2% in immune-competent adults.

The disease is commonly seen more in males [2] as compared to females. It has two peaks of onset [2], first during infancy first three months of life and the latter in the 4th to 7th decades of life.

Review of Literature

The exact causes of SD are yet not completely understood, multiple factors appear to be involved in the pathophysiology of the disease. The principle three factors involved are: sebum secreted from sebaceous gland, presence of Malassezia yeast [3], and the immune response [4] of the host. SD is often resistant to the treatment with chronic relapsing course at variable interval. The frequent relapses of disease have got substantial negative impact on quality of life of affected individuals. The primary goals of any therapy for SD are to clear the visible signs, acute flares of disease and reduce bothersome symptoms, especially pruritus. Usually long-term therapy in some form is required to maintain remission.

Although SD has no permanent cure, a variety of treatment options are available that can effectively treat this condition. Antifungal agents [5–9], anti-inflammatory agents (including topical corticosteroids [10] and topical calcineurin [11] inhibitors), topical metronidazole [11], azelaic acid and keratolytic [12] agents are available in a variety of formulations (shampoo, lotion, cream, foam, gel) for treatment of SD. Other topical therapies such as non steroid anti-inflammatory antifungal protein cream [13], synthetic antimicrobial peptides and photodynamic therapy [14] are emerging as newer treatment option for SD. Mild to moderate form of SD often responds well to topical therapies without the need to add oral antifungal [15] therapy; which is often reserved only for recalcitrant, treatment resistant and severe form of disease.

Different issues such as age of patient, compliance, cost-effectiveness, adverse effect of drugs, acceptability of formulations are need to be considered when selecting a treatment to provide the best clinical outcome. It has been widely observed in clinical practice that most dermatologists co-prescribe combinations of topical antifungal and steroid preparations initially and then gradually taper its usage and concomitantly introduce calcineurin inhibitors like tacrolimus, pimecrolimus for maintenance phase of management. Although there are many studies which suggests use of different topical drugs and their multiple formulations but comparative studies using different classes of drugs are very few.

Thus it prompted us to conduct such a study including four different drugs for the treatment of seborrheic dermatitis. The combination therapy of topical agents was deliberately not considered as this would cause bias and acts as hindrance to assess the individual drug’s efficacy.

Aims and Objectives

The study was conducted with the primary objective of comparing the efficacy of different topical modalities such as antifungal (ketoconazole 2% cream), corticosteroid (desonide 0.5% cream), calcineurin modulator topical tacrolimus and metronidazole 1% gel for 12 weeks. Assessment of response was done with reduction in Seborrheic Area Severity Index (SASI) score as well as visual analogue scale (VAS) at 4, 8, 12 and 16 weeks and outcome of the treatment was statistically analyzed.

Keywords: Seborrheic dermatitis; Ketoconazole; Desonide; Tacrolimus; Metronidazole
calcineurin inhibitor (tacrolimus 0.1% cream) and metronidazole 1% gel in patients suffering with seborrheic dermatitis. The study also gave an opportunity to assess the response to the treatment by reduction in mean SASI scoring as well as patient and physician VAS scoring. In this study medicinal frequency, usage, compliance, adverse events and cost-effectiveness of topical agents were also studied.

Materials and Method

Single blinded randomized interventional controlled analysis was conducted at ESI PGIMER Model Hospital Basaidarapur, New Delhi; during November 2016 to April 2017 (total duration-six months) after obtaining approval from institutional ethics committee. One hundred consecutive patients of both sexes of age more than two years which were clinically diagnosed as mild to moderate seborrheic dermatitis; who were not using any kind of topical or systemic medications in the form of antifungal, keratolytic or immune-suppressant since last three months were included in the study. Pregnant, lactating females, children less than two years of age, patients those on immunosuppressants and non-consenting patients were excluded from the study. Informed and written consent was taken from all the patients.

Detailed clinical history about the onset, duration, progress, associated and aggravating factors, treatment received in past, relapses, history of atopic dermatitis was taken in all patients. A through clinical examination and grading of disease by seborrheic dermatitis area and severity index score (SASI) was performed by same treating physician. For determining the severity of seborrheic dermatitis, we used the SASI scoring system suggested by Koc et al. [16] and used in previous studies. In this scoring system, four different parts of the face including eye brows, retro auricular areas, perioral areas/chin and the nasolabial folds were evaluated.

The SASI score is calculated as follows:

A) Area of involvement of face and scalp are scored independently from 0-6 as follows: Degree of involvement in %-score 1) % <1% = 1, 2) 1-10 % = 2, 3) 11-20 % = 3, 4) 21-35 % = 4, 5) 36-50 % = 5, 6) 51-75 % = 6, 7) 76-100 % = 7.

B) The erythema and scaling of the face and scalp are scored independently as none-0, very mild-1, mild-2, moderate-3 and severe-4.

Face = erythema -(ef), scaling - (sf)
Scalp = erythema – (es), scaling – (ss)
SASI = 0.5 (af) (ef+sf) + 0.5 (as) (es+ss)
SASI = __________ (maximum score = 48)

Face = area -(af), erythema - (ef), scaling – (sf)
Scalp = area-(as), erythema –(es), scaling -(ss)
SASI = 0.5 (af) (ef+sf) + 0.5 (as) (es+ss)
SASI = __________ (maximum score = 48)

The severity of pruritus was evaluated by visual analogue scale (VAS). VAS is graded on 0 to 10 scales, in which point 0 refers to existence of no pruritus and point 10 refers to the most severe pruritus. According to this scale, we scored the pruritus of the patients from point 1 to 3 as mild pruritus, from point 4 to 6 as moderate pruritus and from point 7 to point 10 as severe pruritus.

Patients were randomized into four groups A, B, C, and D, each containing 25 patients. Group A received topical antifungal (ketoconazole 2% cream), group B received topical corticosteroid (desonide 0.5% cream), group C received topical calcineurin inhibitor (tacrolimus 0.1% cream) and group D topical metronidazole 1% gel respectively; for twice daily application.

Subjective and objective assessment of response was done by patient and treating physician respectively at every 4 weeks and was noted separately. Evaluation of response was done on 5 point visual analogue scale and graded as 1-worse, 2-no change, 3 <-30%, 4 = 30-60%, 5 = >60% improvement. After 12 weeks of treatment patients were followed for 4 more weeks to note for any adverse effects or recurrence of symptoms.

The statistical evaluation was carried out using statistical package for social sciences (version 15.0 for windows, SPSS Inc., Chicago II, USA). p < 0.05 was taken as significant.

Results

Out of 100 patients who were enrolled in the study, four patients opted out (didn't turn up for follow up) so total of 96 patients were divided into four equal groups each containing 24 subjects. Majority of the cases, i.e. 46%, were in the age group of 20–40 years. Mean age of participant’s was 30.75. The youngest and the oldest patients being 11 and 59 years, respectively. The male to female ratio was 1.53; suggesting males predominated the study population, comprising 60.4% of the total. History of atopy was present in 11.46% of patients. Average duration of SD was 4.39 months in all the patients, 76.81% of cases gave history of disease severity in winter months but for rest others it was equally bothersome in summer also. Pruritus was the most annoying symptom in 66.67% for all cases followed by, visible scaling and redness (Table 1).

Mean severity SASI score was comparable in all four groups at baseline (week 0-p : 0.921). Patients in all the groups showed gradually progressive improvement from 0 to 12 weeks. Mean SASI score of individual group was calculated at every 4 week. At the end of 12 weeks it showed 62.97% reduction in group ketoconazole 2%, 33.08 reductions for group desonide 0.5%, whereas the same was 39.80% and 19.56% for group tacrolimus 0.1% and group metronidazole 1% respectively (Figure 1). On calculating the p value for each group it was further confirmed that this reduction in SASI score was statistically significant in first group with 2% ketoconazole and group tacrolimus 0.1% (Table 2) but not with topical desonide or metronidazole (group B and D). It was seen that

<table>
<thead>
<tr>
<th>Demographic profile</th>
<th>Group Ketoconazole 2% (n = 24)</th>
<th>Group Desonide 0.5% (n = 24)</th>
<th>Group Tacrolimus 0.1% (n = 24)</th>
<th>Group Metronidazole 1% (n = 24)</th>
<th>Mean</th>
<th>P value</th>
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<tr>
<td>mean age (yrs)</td>
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<td>4 (16.67)</td>
<td>4 (16.67)</td>
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</table>

Table 1: Demographic Details.
Mechanism of action in SD is not known but found to be effective

Anaerobic cells. It has also got anti-inflammatory effect through

Calcineurin inhibitors tacrolimus and pimecrolimus belong to

Immunomodulatory steroid sparing agent. Because of its anti-

Ketoconazole not only has antifungal properties against

Malassezia [3] is considered as one of etiological factor. Different antifungal agents in various formulations had been used successfully for treatment and maintenance of remission. Multiple studies [5–7,9] had demonstrated ketoconazole as a primary modality in cream, foam, lotion or shampoo form.

Ketoconazole not only has antifungal properties against malassezia species but also has pronounced anti-inflammatory activities [17]. Other antifungals like allylamines (terbinafine), the benzylamines (butenafine), and the hydroxypyridones (ciclopirox) too have been found to be useful in management of SD. Topical calcineurin inhibitors tacrolimus and pimecrolimus belong to immunomodulatory steroid sparing agent. Because of its anti-inflammatory effects it has been seen as a good therapeutic agent in treatment of SD.

Metronidazole is a nitro imidazole antibiotics, act primarily on anaerobic cells. It has also got anti-inflammatory effect through neutrophil chemotaxis and reduction in oxidative stress. Its exact mechanism of action in SD is not known but found to be effective in topical form [20]. In the present study it was observed that SD was present in all age groups; more commonly being in the 3–4 decade. Males were more commonly affected. Patients gave family history of SD and history of atopy which was in accordance with the previous conducted studies [2]. The disease was present for almost one third of year in most of the patients; winter being the common season. But 23.19% of patients also reported summer episodes, which denotes the chronic relapsing nature of the disease.

When patients were subjected to four different modalities of treatment over three months duration, there was a definite, gradual and sustained reduction in the mean SASI scores and the difference was found to be statistically significant. This effect of treatment was even found to be sustained in one month post treatment, which could be due to the reservoir effect of medication.

In the present study we found topical ketoconazole cream was effective treatment for mild to moderate SD followed by topical tacrolimus, desonide and metronidazole in the descending order could be due to the reservoir effect of medication.

In the present study as well as for relapse prevention and maintenance.

The first three groups i.e. group 2% ketoconazole, desonide 0.5% and tacrolimus 0.1 % (Table 2) but not with topical metronidazole 1% showed change in the both patient’s and physician’s VAS (Table 3) at 4, 8, and 12 weeks. It was statistically highly significant (p < 0.05).

No major adverse events were reported by the patients from any of the groups and the drug formulations used in all four groups were found to be well tolerated by all on evaluation.

Discussion

The etiopathogenesis of SD is multifactorial, Malassezia [3] is considered as one of etiological factor. Different antifungal agents in various formulations had been used successfully for treatment and maintenance of remission. Multiple studies [5–7,9] had demonstrated ketoconazole as a primary modality in cream, foam, lotion or shampoo form.

Earlier Studies conducted by Siadat et al. [20] and Parsad et al.
Lesions of study

The present study was conducted on small sample size with shorter duration of therapy and follow up. As SD is a seasonal disease and may also present over the entire year, it also presents with frequent relapses after discontinuation of therapy which makes it’s particularly difficult to predict effectiveness of a given particular drug unless and until the study also analyzes the trends of treatment response over a longer period. The present study was not a vehicle controlled study and was single blinded.

Acknowledgments

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Conflict of Interest

The authors declare that there is no conflict of interest.

References


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