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RESEARCH ARTICLE

TO COMPARE EFFICACY OF ORAL ISOTRETINOIN AND ITRACONAZOLE COMBINATION WITH SALICYLIC ACID 30% CHEMICAL PEEL FOR TINEA CORPORIS AND TINEA CRURIS

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ABSTRACT

Background: Indiscriminate use of corticosteroids, widespread use of broad-spectrum antibiotics, increase in the pool of immunocompromised patients and development of drug resistance has made treatment of superficial fungal infections challenging with increased rates of recurrence. There is an utmost need for novel drug combinations and improved treatment strategies to tackle this complex situation. **Objective**: To compare the efficacy of oral isotretinoin (20mg/day) and itraconazole (200mg/day)combination with salicylic acid 30% chemical peel for Tinea corporis and Tinea cruris. **Methods**: A non-randomized comparative trial was done. Adult patients between the age of 20-40 years. The diagnosis of Tinea corporis and Tinea cruris was confirmed by performing a KOH preparation. Patients with history of liver or kidney disease, diabetes, hypertension, those on corticosteroids or immunosuppressive therapy, pregnant and lactating women were excluded from the study. Outcome measure was change from baseline inerythema, scaling, pruritus and vesicles at one month. Skin scrapings for potassium hydroxide preparation (KOH) were obtained at baseline and at end of intervention (1 month). Clinical cure was defined as an absence of classical signs and a negative KOH preparation at one month. Difference in means between the two groups were compared with paired t-tests. Chi-square tests were used for proportions. Comparisons of the mean change in continuous measures between trial groups and associated 95% confidence intervals were based on linear regression with a robust variance estimator. **Results**: Within each group, there was a significant improvement (P<0.001) in erythema, scaling, pruritus and vesicles within after one month of intervention. Between the groups, there was a significantly greater improvement in erythema in Group 2 by a factor of 0.457(95% CI, 0.088-0.825, P=0.017). Improvement in scaling was more in Group 2 by a factor of 0.17, but the difference between the groups was not statistically significant (Paired t-test, P=0.381). The improvement in vesicles was not statistically significant between the two groups (Paired t-test, P=0.571). At study endpoint, 32(91%) patients in Group 1 and 26(74%) patients in Group 2 had a negative KOH preparation. Liver functions were not deranged in any patient on itraconazole therapy at 2weeks. **Conclusion**: Oral combination of itraconazole and isotretinoin was more effective in achieving microbiological eradication than salicylic acid 30% chemical peel for Tinea corporis and cruris.

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INTRODUCTION

Superficial fungal infections are usually caused by dermatophytes, moulds and commensal yeasts. Amongst these, dermatophytes are the most common cause of superficial fungal infections throughout the world. Recently, there has been a rising trend in the prevalence dermatophyte infections in developing countries like India; the prevalence ranges from 36.6–78.4%. High temperature and humidity offer a favourable environment for dermatophytes in the Indian subcontinent. These organisms cause a wide range of clinical presentations, including tinea pedis, tinea corporis, and tinea cruris (Gupta, 2014; Sahoo, 2016). Trichophyton rubrum is the most common isolate with tinea corporis and cruris the most common clinical presentation in relatively large studies from north and south India. In the current scenario, the treatment of dermatophyte infections has become complex and challenging due to indiscriminate use of corticosteroids, widespread use of broad-spectrum antibiotics, increase in immunocompromised patients and development of drug resistance (Verma, 2017; Dogra, 2016). Topical antifungal agents, whether alone or in combination have been used to treat localized tinea corporis and tineacruris.

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Systemic antifungal agents are indicated in case of extensive involvement and patients who fail to respond to topical therapy. Itraconazole is an antifungal drug which acts by inhibiting cytochrome P450-dependent enzyme, hence interfering with demethylation of lanosterol to ergosterol. It raconazole 200mg/ day is the preferred drug for recalcitrant cases (Donckar, 2017). A double-blind trial comparing itraconazole with griseofulvin for tinea corporis or tinea cruris has shown significantly better clinical and mycological outcome in favour of itraconazole (Bourlond, 1989). Studies have found that combination of keratolytic agents along with systemic antifungals are more effective in achieving clinical and mycological cure as well as in decreasing the duration of oral therapy (Shi, 2014). There is paucity of literature comparing isotretinoin itraconazole combination and salicylic acid 30% chemical peel. A MEDLINE and PubMed search using the keywords 'isotretinoin,' 'itraconazole,' and 'salicylic acid,' did not reveal study comparing the two treatment modalities. The present comparative study aimed to evaluate whether combination of oral itraconazole and isotretinoin was more effective than salicylic acid 30% chemical peel for Tinea corporis and Tinea cruris.

MATERIALS AND METHODS

A non-randomized comparative trial was done at a tertiary care teaching hospital. The institutional review boards and the local ethics committee approved the trial. Written informed consent was obtained from all patients willing to participate in the study based on the tenets of the declaration of Helsinki.

Eligibility criteria: The study was carried out in adult patients between the age of 20-40 years. The diagnosis of Tinea corporis and Tinea cruris was confirmed by performing a KOH mount preparation.

Exclusion criteria: Patients with history of liver or kidney disease, diabetes, hypertension, those on corticosteroids or immunosuppressive therapy, pregnant and lactating women were excluded from the study.

Allocation and Sample Size Calculation: To calculate the sample size and to compare the mean difference in erythema scores between the 2 groups, a pilot study was first done on 10 subjects. The mean decrease in erythema score in Group 1 was 1.7 and in Group was 1.0, respectively. The common standard deviation was 1.05. Assuming 1:1 allocation, 80% power (a = 0.05), and a precision error of 5% to detect difference of 20% or more in erythema score between 2 groups, the estimated sample size in each group was calculated to be 38 (http://www.stat.ubc. ca/~rollin/stats/ssize/n2.html).

Trial Groups: Consecutive patients with Tinea corporis or cruris were allocated to 1 of the 2 groups by a parallel assignment (1:1). The allocation codes were generated by a web-based module and was stratified with a permuted block method with randomly chosen block sizes. The generated codes were sealed in green envelopes and were opened by health care personnel not involved in patient care. Group 1 received oral isotretinoin 20mg plus oral itraconazole 200mg daily for one month and Group 2 received salicylic 30% chemical peeling once per week for one month (every Monday). The regimen was reduced in frequency or suspended when the patient reported any symptoms or when a contraindication to treatment to any of active ingredients developed. With resolution of symptoms or contraindications, the patient could restart or resume the regimen.

Outcome measures: Patients were evaluated both clinically and microbiologically. The primary outcome measure was change from baseline in the classical signs of Tinea infection like erythema, scaling, pruritus and vesicles at one month. For comparisons, a score (0-3) was assigned to each clinically observed sign. Skin scrapings for potassium hydroxide preparation (KOH) were obtained at baseline and at end of intervention (1 month). Clinical cure was defined as an absence of classical signs and a negative KOH preparation at one month. Liver function tests were monitored at baseline and repeated at 2 weeks interval. The regimen was reduced in frequency or suspended when the patient reported any symptoms, liver function tests were deranged or when a contraindication to treatment to any of active ingredient developed. With resolution of symptoms or contraindications, the patient could restart or resume the regimen.

Statistics: Statistical analysis was performed on an intent-to-treat basis using IBM, SPSS Statistics version 25 (IBM Inc.). Independent t tests were performed to ensure group similarities at baseline; the assumptions of performing t tests were met. The values used for assessing change were the means of values obtained during the 15 day and 1-month visits; if a value from only one of these visits was available, that value was used. Difference in means between the two groups were compared with paired t-tests. Chi-square tests were used for proportions. Comparisons of the mean change in continuous measures between trial groups and associated 95% confidence intervals were based on linear regression with a robust variance estimator. Differences between trial groups in the cumulative proportion of patients with an adverse event were evaluated with the log-rank test.

RESULTS

The mean age of patients in Group 1 was 29.5±5.4(range, 19-39 years) and the mean age in group 2 was 30±5.2 (range, 19-39 years). The difference in age between the two groups was not statistically significant (Paired t-test, P=0.673). Table 1 shows the demographic profile of study subjects. There were 17 (48.6%) males and 18(51.4%) females in Group 1 respectively. In group 2, there were 16 (45.7%) males and 19(54.3%) females, respectively. The difference in gender between the groups was not statistically significant (Chi-square tests, P=0.311). The was a significant improvement (P<0.001) in erythema, scaling, pruritus and vesicles within each group (Group 1 and Group 2) after one month of intervention. When comparisons were made between the two groups, there was a significantly greater improvement in erythema in Group 2 by a factor of 0.457(95% CI, 0.088-0.825, P=0.017). Improvement in scaling was more in Group 2 by a factor of 0.17, but the difference between the groups was not statistically significant (Paired t-test, P=0.381). The improvement in vesicles was not statistically significant between the two groups (Paired t-test, P=0.571). There was a significantly greater improvement in pruritus in Group 1 (Paired t-test, P=0.09). At the end of therapy, 32(91%) patients in Group 1 had a negative KOH preparation where as 26(74%) patients in Group 2 had a negative KOH preparation despite significantly better improvement in scaling.

Table 1. Demographic Characteristics

Parameter	Group1	Group 2	P value
Age	29.5±5.4	30±5.2	0.673
Gender (n, %)			
Male	17(48.6	16(45.7)	0.311
Female	18(51.4)	19(54.3)	
Type of Lesion (n, %)			
Inflammatory	2(5.7)	1(2.9)	0.05
Non-inflammatory	30(85.7)	29(82.9)	
Mixed	3(8.6)	5(14.3)	

The difference in KOH preparation between the two groups at study end point was statistically significant (Chi-square tests, P=0.013). None of the patients developed any adverse effect serious enough to warrant discontinuation of therapy except mild irritation in Group 2. Liver functions were not deranged in any patient on itraconazole therapy at 2weeks.

DISCUSSION

The results of the present comparative study suggests that oral consumption of the combination of isotretinoin and itraconazole was more effective than salicylic acid 30% chemical peel for Tinea corporis and Tinea cruris infections; ninety one percent patients has a negative KOH preparation at one month as compared to 74% patients on salicylic acid chemical peel at study end point. In dermatophytes causing tinea corporis and cruris infection, oral anti-fungal therapy is recommended for extensive superficial dermatophyte lesions with papules and pustules and those not responding to topical therapy. Experts recommend combination therapy for more extensive lesions and recalcitrant infections (Lesher, 1999; Cole, 1989; Bourlond, 1989). The use of isotretinoin in recurrent dermatophytosis has opened avenues for further research. The rationale behind use of retinoids in dermatophyte infections is that they promote cell proliferation in the epidermis; increase turnover and removal of infected cells from the skin may accelerate removal of dermatophyte infection. Second, retinoids may boost cell mediated immunity in the host (Orfanos, 1997; Bartell, 2006). Dermatophytosis are associated with an increase in epidermal cell proliferation, leading to epidermal thickening with hyperkeratosis and scaling of the skin. Scales retard absorption of topical antifungals, rendering them ineffective. Topical application of salicylic acid causes softening of the horny layer and the shedding of scales (Jensen, 2007; Shi, 2015).

In a 23 old male with recurrent dermatophytosis involving the face, neck, trunk, lower extremities, gluteal and inguinal regions, there was remission following treatment with oral terbinafine and topical eberconazole for 2 weeks. However, there was recurrence after 1 week. Fungal culture revealed growth of T. rubrum. The patient finally put on treatment with oral isotretinoin (20 mg/day) and itraconazole (200 mg/day) along with topical sertaconazole for1 month. According to Ardeshna et al, there was complete resolution of symptoms with no recurrence of lesions at 6-month follow up. In the present study, there was complete microbiological eradication at 1 month in 91 percent patients. At present (2 months follow up) no recurrence has been observed (Ardeshna, 2016). In a randomized clinical trial comparing terbinafine and itraconazole for tinea corporis and tinea cruris, Bhatia et al found that clinical global improvement was significantly better with itraconazole. Adverse effects were comparable between the two groups.

Both were found to be effective and safe for treatment of superficial fungal infections (Bhatia, 2019). In conclusion, oral combination of itraconazole and isotretinoin was more effective in achieving microbiological eradication than salicylic acid 30% chemical peel for Tinea corporis and cruris.

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