ORIGINAL RESEARCH PAPER

Dermatology

KEY WORDS: Superficial Dermatophyte Infection, Recalcitrant, Isotretinoin, Itraconazole, Tinea Cruris , Tinea Corporis

COMPARATIVE EFFICACY OF MONO THERAPY OF ORAL ITRACONAZOLE AND ORAL ITRACONAZOLE WITH ISOTRETINOIN IN CHRONIC AND/OR RESISTANT SUPERFICIAL DERMATOPHYTOSIS

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ABSTRACT

Introduction- Superficial dermatophytosis such as Tinea corporis and tinea cruris are common in developing countries like India. Mono therapy with oral antifungals leads to partial clearance or relapse of lesions. Isotretinoin due to its keratolytic effect used as a an adjuvant to oral antifungals for recalcitrant dermatophytosis

Objectives- to compare the efficacy of mono therapy of oral antifungals and oral antifungals with isotretinoin in the treatment of recalcitrant superficial dermatophytosis

Methods- a pilot study of 76eleigible patients of KOH positive superficial dermatophytosis were allocated to two groups. Both groups were taking oral itraconazole 100mg BD with topical antifungals (Clotrimazole) for 15 days. After 2 weeksone group was continued with same line oftreatment and second group were received oral isotretinoin 0.3 – 0.4 mg/kg/day, In Adition after Normal, baseline investigation.

After 2 weeks both groups were switched to only topical antifungal clotrimazole for additional 15 days to sustain the response. patients were followed up at 2, 4 and 6 months from baseline for signs of relapse.

Results- Clinical cure and mycological cure from baseline were more significant in the group receiving both the drugs.

Conclusion- a 2 weekly course of isotretinoin can be an effective adjuvant to oral antifungals in treating recalcitrant superficial dermatophytosis.

Introduction :-

The term superficial dermatophytosis refer to the fungal infection of keratinised tissues including the stratum corneum of the epidermis, hair ,nails and horny tissue of animals[1]. The dermatophytes belongs to 3 asexual genera:- microsporum, trichophyton and epidermophyton. It affects millions of people worldwide especially in the developing country like India. It needs to be treated because of long term morbidity but in present era the treatment is challenging because of recurrences and/or relapses. Topical treatment with different topical antifungals have a limited role especially in adult population. Older systemic medications like gresiofulvin, ketoconazole and terbinafine are associated with low cure rates and a potential of side effects adverse drug interactions[2]. On the other hand,newer antifungals like itraconazole have higher cure rates and fewer adverse reactions but still there are relapses that we are facing in our daily practise. So there emerges a need to have some effective adjuvant which reduces the time duration of oral antifungals and also take care of recurrences and relapses. In this study we add oral isotretinoin due to its keratolytic effectas an adjuvant to oral antifungals for recalcitrant dermatophytosis.

Methods-

The study was conducted at the department of dermatology venerology and leprosy of G.K GENERAL HOSPITAL, GAIMS, Bhuj , Kachchch , Gujarat after approval from the ethics committee

Inclusion criteria-

In this study 38 patients were included in each arm. Patients of T.Cruris and T.corporis with >30%BSA and duration of infection >= 3 months with positive KOH preparation were recruited between August 2015 to August 2016.

Exclusion criteria-

1) BSA<=30%
2) Infection within 3 months
3) Severe systemic disease
4) Pregnancy and lactation
5) Immunosuppressive state of patients
6) Age >= 70years

Informed consent was obtained from all patients prior to their enrolment. Details of duration and progression of the disease, treatment taken , occupation and other co morbidities were obtained in all patients and general physical and systemic examination were carried out. The fingernails with skin were also examined for evidence of fungal infection. The percentage of body surface area involved and duration of infection were recorded. The worst affected area was selected as a target area. Severity of infection was assessed on the basis of erythema,pruritis and scaling on 4point scale (0,1,2,3) .on each of the three parameters: no, mild , moderate and severe. Then the three scores of target area were added to get a three scores of the target area were added to get a clinical assessment score (CAS). (Maximum score 9 per area involved) .Baseline investigation including CBC LFT RFT and pregnancy test in eligible formats were done in all patients. Photographic documentation was done at baseline and at every follow up visit.

Eligible patients were randomised using computer generated number into 2 groups. . Patients of both group received oral itraconazole 100mg twice daily for 15 days. After 15 days group A were continued with same line of treatment while group B received oral isotretinoin 0.3-0.4 mg/kg in addition. After 15 days patients of both groups switched to onLy topical clotrimazole for additional 15 days. Patients were followed up after 2,4,6 weeks during treatment and once post treatment at 2month , 4 month and 6 months. Total scores were recorded at each visit.

Overall clinical improvement was also graded at each visit on 4 point scale (global assessment index) both by patient and physician as follows:

- <25% improvement : Poor
- 26-50 % improvement: average
- 50-75% improvement : good
- >75 % improvement: excellent

Efficacy of treatment was assessed on the following parameters at 1 month,2 month and 6 month –

1) Clinical cure : completely normal appearing skin with no residual changes.
2) Mycological cure: negative KOH microscopy
3) Complete cure : Both clinical and mycological cure
4) Clinical effectively: decrease in pruritis, erythema and scaling or >50% improvement in global physician assessment index for the target areas at the end of treatment at 2 month.We used this is an additional parameter to determine early response since the relatively slow follow up period in study could have led to lower cure rate than expected.
5) Treatment failure: persistence of positive KOH ; no clinical improvement (I.e presence of pruritis and / or scaling and/or erythema) or clinical worsening at 2 month and 6 month.
6) Relapse : positive KOH preparation or clinical worsening at

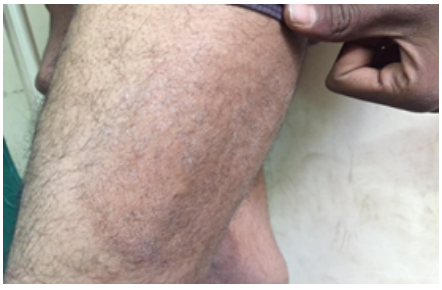
least 4 weeks after a negative KOH or clinical improvement/ cure had been achieved.

Compliance with treatment as well as tolerability and side effects of the drug were also assessed at each visit.

Result

76 eligible patients (67 males and 9 females) Mean age 42.5+/-13.6 were included. The flow of participants in the study was as in Enrolment.

Before



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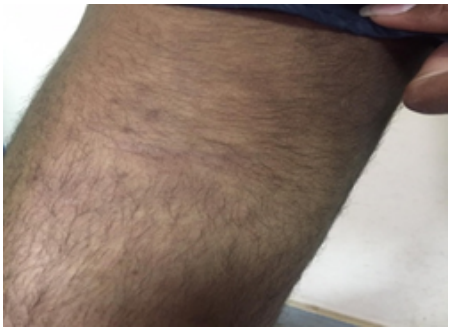

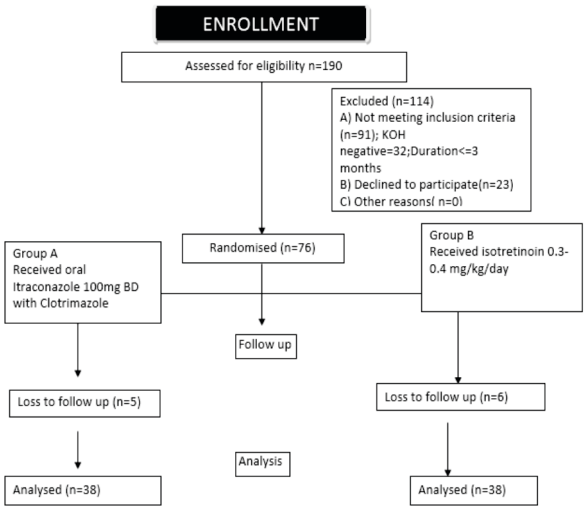

Baseline characteristics of the patient were similar in two groups (table 1)

Demographic profile	Group A N=38 (%)	Group B N=38(%)	Total N=76(%)
Sex Male Female	 34 (89.5) 4(10.5)	 33(86.8) 5(13.2)	 67(88.2) 9(11.2)
Mean age (in years)	43.4+-14.9	41.7+-12.3	42.5+-13.6
History of sharing bath areas	0	1(2.6)	1(1.3)
Past history	1(2.6)	1(2.6)	2(2.6)
Family history	0	1(2.6)	1(1.3)

The mean clinical assessement score of the target area in both the treatment groups declined equally in first follow up but in next 15 days, it was declined rapidly in group B. 24 patients (76.3%) and 34(89.4%) patients in group A and group B respectively has global physician assessement index score of good to excellent (>50%) at 4 weeks (table 2)

TABLE 2

	Mean CAS target area Group A	Group B	95% CI for the difference	P-value	Significance
Baseline	4.7+-1.4	5.0+-1.1	-1.558 to 0.958	0.303	NS
2 weeks	3.9+-1.1	4.1+-0.8	-1.161 to 0.761	0.368	NS
4 weeks	2.0+-1.0	1.4+-0.9	-0.351 to 1.551	0.006	Highly Significant
8 weeks	1.7+-1.1	1.1+-0.8	-0.361 to 1.561	0.006	Highly significant

At 2 weeks clinical cure and complete cure of the target area were achieved in only 1 patient (group A)

Clinical effectivity was achieved in 30 (78.9%) patients of group A as compared to 35 patients of group B at 4 weeks

At 8 weeks more patient in group B achieved mycological cure (35 (92%) VS 30 (84.2%) of group A(table 3)

At 8 weeks, clinical cure of the target area was achieved in 33 patients of group B (86.8%) and 29 patients of group A (76.3%)

At 24 weeks: 10(26.3%) patients were having relapse in group A and 3 patients (7.9%) of group B showed recurrence mycologically(table 3)

Table 3 KOH positivity in the treatment groups at followup

Follow up (weeks)	KOH positive Group A n=38(%)	Group B n=38(%)
0	38(100)	38(100)
4	10(26.3)	6(15.7)
8	8(21.1)	3(7.9)
16	10(26.3)	3(7.9)
24	10(26.3)	3(7.9)

Both treatment regimes were tolerated well. Only complaint of mild discomfort (abdominal) and chelitis of group B patients but it didnot affect compliance. None of the patient developed any hematologic or biochemical abnormalities.

Discussion-

In an attempt to explore adjuvant treatment in recalcitrant dermatophytosis isotretinoin was found to be good to reduce the recurrances and/or relapses. The cure rates at the end of 8 weeks were 79% in group A and 92% cure rate in group B with 3 relapses.

In this study mentione earlier, disease regression with low relapse rate had been the main outcome criteria The drug (itraconazole & topical clotrimazole) included in this regimen have all been shown to have potent anti fungal action and mechanism of action of other drug, isotretinoin , is not fully understood but we can draw clues from the pathogenesis of dermatophyte infection and effect of isotretinoin on human skin.

For successful initiation of infection two factors are important in determining the size and duration of lesion: the growth rate of organism and epidermal turn over rate[3]. The fungal growth rate must either equal or exceed the epidermal turn over rate as otherwise the organism will be shed quickly.

Following adherence, successful installation of dermatophytes requires rapid germination of arthroconidia and penetration of hyphae into the stratum corneum Failure to do so will result in elimination of infection by continuous desquamation[4]. Retinoids act as modulators of epidermal growth and help in differentiation.

Although they help in normalisation of hyper proliferative epithelia in different dermatological disorders.In normal epidermis, they promote cell proliferation[2].

Therefore, increased cell turn over rate in epidermis may halt the spread of ongoing infection.

Retinoids are also known for its keratolytic effect. It reduces the corneoyte cohesiveness and also alter terminal differentiation of epidermis[2].

Dermatophytes works optimally at acidic ph[5] and the skin which being acidic gives an ideal ambient environment for the fungus. High transepidermal water loss and impaired barrier function of the skin are correlated with high skin PH[6] which being increased with retinoid **therapy, raises the skin ph thereby possibly inhibiting the growth of dermatophytes.**

Finally Retinoids stimulate humoral and cellular immunity[2], enhance antibody production and stimulating peripheral blood t helper cells which counteract the immunosuppressive effect of dermatophyte. The present study has shown that positive cure rates in patients who completed treatment in both groups are 74% in group A and 92 % in group B.but the relapse rate at the end of 24 weeks is much lower than group A.

As such we dont recommend oral retinoids for the routine treatment of dermatophytes but it will act as good adjuvant in treating reclacitrant dermatophytosis.

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