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COMPARATIVE STUDY OF EFFICACY AND TOLERABILITY OF SINGLE DOSE ITRACONAZOLE VERSUS FLUCONAZOLE IN TINEA VERSICOLOR

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ABSTRACT

Background: Tinea versicolor is one of the most common superficial fungal infections of the skin, caused by Malassezia furfur. It is characterized by a macule covered with brany scales, predominantly on trunk and upper arms. Topical therapy as first line treatment ranging from selenium sulfide to imidazole's can be curative. Itraconazole and fluconazole have revolutionized the treatment in tinea versicolor both in single and divided doses. **Objectives:** To study and compare the efficacy and tolerability of Itraconazole versus Fluconazole. **Methods:** The study was conducted on 100 newly diagnosed patients of tinea versicolor of either sex attending Dermatology outpatient department at Basaveshwara Teaching and General Hospital, Kalaburagi. They were alternatively allocated in to either group A or group B with 50 patients in each group. Group A patients received oral Itraconazole (1000 mg stat) and group B patients received oral Fluconazole (400 mg stat). They were evaluated both clinically as well as mycologically. **Results:** Clinical cure in group A was 60% and in group B it was 80%, the difference is considered statistically significant ($p=0.029$, $p<0.05$). Mycological cure in group A was 56% and in group B it was 82% the difference is statistically highly significant with a p value of 0.005 ($p<0.01$). Complete cure in group A was 56% and in group B it was 80%, this

difference between the two groups is also statistically significant (p=0.01, p<0.05). Both the drugs were well tolerated without any serious adverse reactions. **Interpretation and Conclusion:** Single dose fluconazole is more efficacious compared to itraconazole in the treatment of tinea versicolor. Both itraconazole and fluconazole were well tolerated without any serious adverse effects.

KEYWORDS: 'Fluconazole', 'Itraconazole', 'Tinea versicolor (TV)'.

INTRODUCTION

Tinea versicolor (TV), also called as pityriasis versicolor, is one of the most common superficial fungal infections of the skin affecting stratum corneum.[1] It is caused by Malassezia furfur, which is an anthropophilic fungus belonging to the commensal skin flora, growing in yeast form on non-affected skin and in mycelial form causing clinical disease. Tinea versicolor is characterized by a macule that may be hypo-pigmented or hyper-pigmented and covered with brany scales,[2] predominantly on trunk and upper arms although other parts may be involved. Although tinea versicolor is prevalent throughout the world, but it is more common in tropical countries and incidence is as high as 30-40%.[3]

The expression of infection is promoted by heat, humidity. [4] The disease affects all races and both sexes usually between the age group of 16 to 40 years and is rare in children, elderly people.[5] Although the infection does not pose significant health risk but the psychological and social implications can be profound.

There is a little evidence that the disease is contagious. Other factors which lead to increased susceptibility are genetic predisposition, poor general health, cancer, use of oral contraceptives, hyperhidrosis, pregnancy and other immunocompromised states.[6]

The diagnosis is essentially based on clinical examination of skin lesions and mycological examination such as KOH mount and wood's lamp test.[7]

Spontaneous improvement is rare, the majority of patients require treatment. Most of the time, treatment is sought only for cosmetic reasons. Topical therapy as first line treatment ranging from selenium sulfide to imidazole's can be curative. However it is inconvenient, inadequate for large lesions, some patients may not respond well and experience relapses. In these cases "azole" antifungal drugs are considered as treatment of choice which includes Ketoconazole, Itraconazole and Fluconazole. An oral drug able to eradicate the fungus with

good safety profile and tolerability should be selected. Use of ketoconazole is limited by the risk of its hepatotoxicity and effect on androgen metabolism.[8]

Itraconazole and fluconazole have revolutionized the treatment in tinea versicolor both in single and divided doses. Itraconazole is an oral synthetic triazole compound which acts by inhibiting the cytochrome-P450 dependent 14-alpha-demethylation step in the formation of ergosterol and lead to accumulation of 14-alpha-methylsterols, these methylsterols may disrupt the close packing acyl chains of phospholipids, impairing the functions of certain membrane bound enzyme systems, thus inhibiting the growth of fungi.[9] Fluconazole is an oral synthetic bis-triazole compound that functions in the same way as Itraconazole.

So an attempt is made in this study to evaluate the efficacy and tolerability of single dose Itraconazole versus Fluconazole.

MATERIALS AND METHODS

Study design: It is a prospective, open label, parallel group, comparative study done to compare the efficacy and tolerability of Itraconazole versus Fluconazole.

Sample size: 100 newly diagnosed patients of tinea versicolor of either sex.

Duration of study: 15 months (from Jan 2015 to March 2016).

Study Population: After approval by the Institutional Ethics Committee (IEC), M.R.Medical College, Kalaburagi, 100 newly diagnosed patients of tinea versicolor of either sex attending Dermatology outpatient department at Basaveshwara Teaching and General Hospital, attached to M.R. Medical college, Kalaburagi were included in the study.

Inclusion criteria

1. Above 16 years of age.
2. Moderate to severe cases
3. Those who have not received any systemic or topical antifungal therapy for at least four weeks prior to the study.

Exclusion criteria

1. Very sick patients (those on multiple therapies).
2. Known hypersensitivity with drugs used in the treatment.

3. Pregnant and lactating women.
4. Those with systemic mycoses.
5. Patients on Corticosteroids, Antibiotics or Immune-suppressive drugs.

Procedure: 100 Patients were randomly allocated in to either of the groups after applying inclusion and exclusion criteria. Written informed consent was taken from the patients before enrolling them into the study.

1. Group A –50 patients were given Itraconazole (Capsule 1000 mg) stat.
2. Group B –50 patients were given Fluconazole (Tablet 400 mg) stat.

Patients were evaluated clinically and mycologically before treatment and then at 2^{nd} and 4^{th} week after starting the treatment.

Investigations: The following investigations were done before enrolling patients into the study and during follow up.

1. Skin scrapings for KOH Mount.
2. Wood's lamp test.
3. Routine blood and urine tests.
4. Random blood sugar.

Statistical Analysis

The data collected was analysed statistically using descriptive statistics namely mean and standard deviation of quantitative variables and causal relationship was examined using Chi square test on SPSS 20.0 version. Wherever necessary the results are depicted in the form of percentage and graphs. Microsoft word and Microsoft Excel have been used to generate graphs, tables etc.

RESULTS

Study Population

In our study 50 patients received Itraconazole and 50 patients received fluconazole. All the patients in both the groups were followed up at 2 weeks. After 4 weeks, 6 patients in group A and 4 patients in group B were dropped out from the study. So 44 in Group A (Itraconazole group) and 46 in the Group B (fluconazole group) completed the study with a completion rate of 88% and 92% respectively. Overall number of patients dropped out of the study was 10 with a rate of 10%, the major reason for drop out was fail to follow up after 4 weeks. Last

observation carried forward method (LOCF) was employed, so all the patients in both the groups were included for the final analysis.

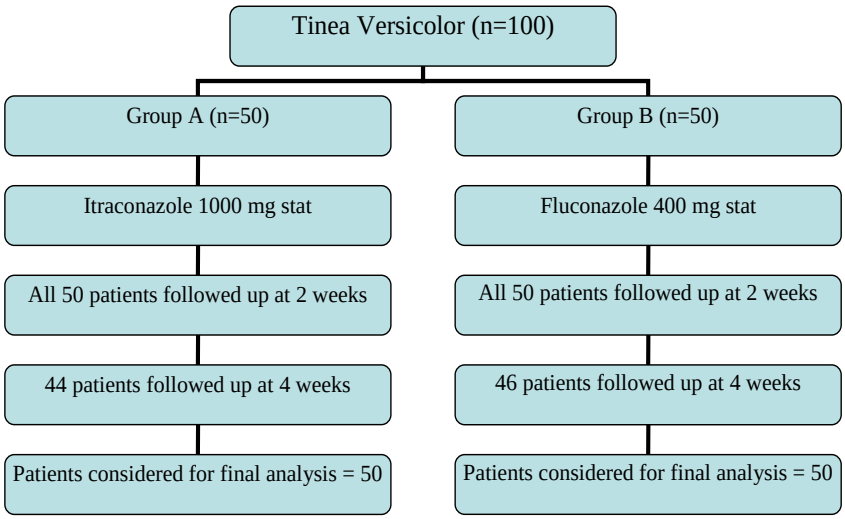
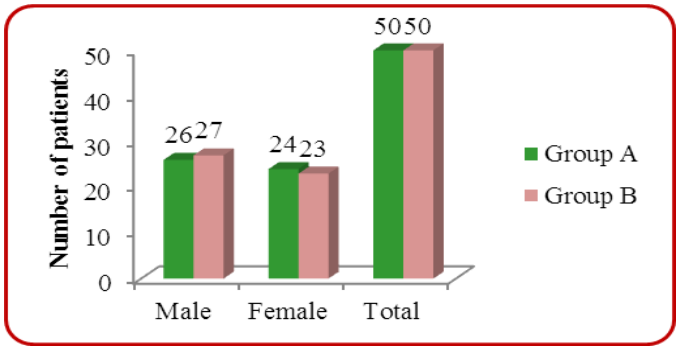


Figure 1: Patients Enrolled in the study.

Demographic Data



In group A, male: female ratio is 26:24

In group B, male: female ratio is 27:23

Figure 2: Gender wise distribution of patients.

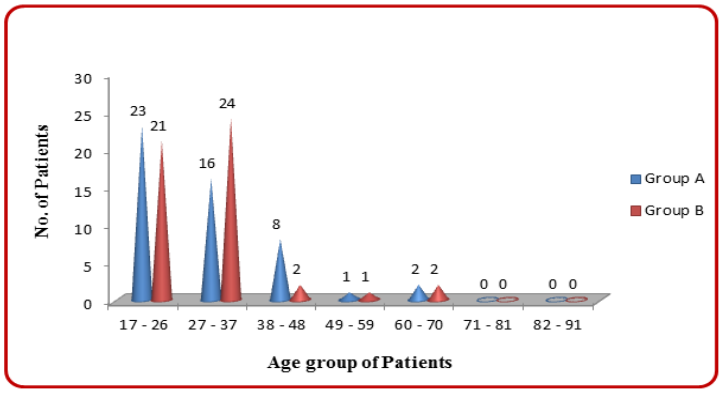


Figure 3: Age wise distribution of patients in both groups.

Mean age of patients of Group A is 30.84 ± 10.57 years. Mean age of patients of Group B is 30.38 ± 9.98 years. By applying *'t test'* to compare the mean age of two groups, we got a p value of 0.487 (p>0.05). By conventional criteria, this difference is considered to be statistically not significant.

Table 1: Mean duration of Tinea versicolor in each group

Group	Group A	Group B
Mean duration (In months)	2.85 ± 0.98	2.77 ± 1.1

Evaluation of clinical parameters

The following clinical parameters evaluated at the time of diagnosis, at 2nd week and 4th week.

1. Scaling
2. Pigmentation

Evaluation of Scaling: Scaling was present in all the patients in both the groups at the time of diagnosis.

Table 2: Disappearance of scaling after treatment in both the groups.

Groups	Disappearance of scaling	
	At 2 weeks	At 4 weeks
Group A	25 (50%)	32 (64%)
Group B	35 (70%)	43 (86%)

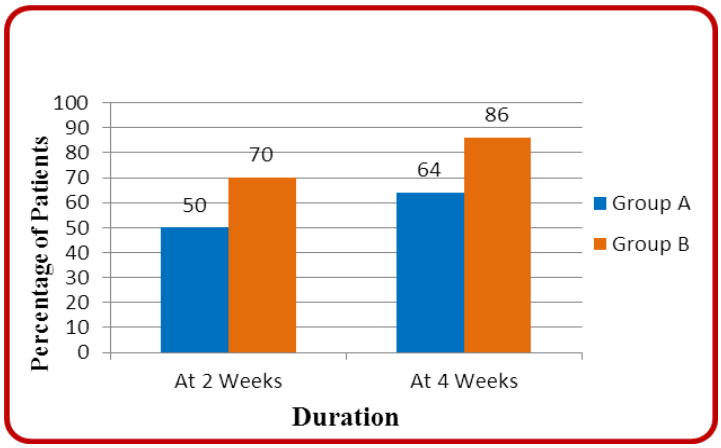


Figure 4: Disappearance of scaling after treatment in both the groups.

Evaluation of Pigmentation: Pigmentation was present in all the patients in both the groups.

Table 3: Disappearance of pigmentation after treatment in both the groups.

Groups	Disappearance of pigmentation	
	At 2 weeks	At 4 weeks
Group A	27 (54%)	30 (60%)
Group B	29 (58%)	40 (80%)

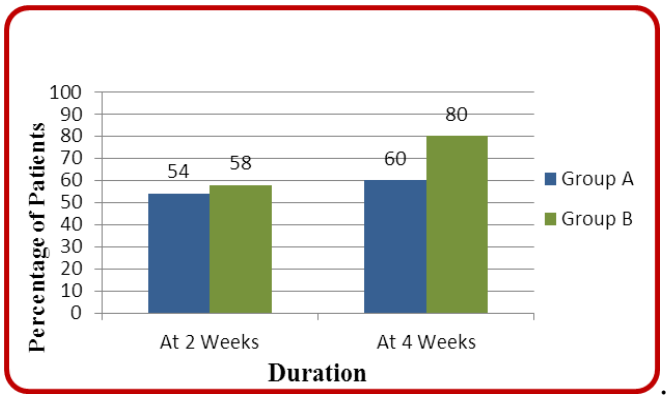


Figure 5: Disappearance of pigmentation after treatment in both the groups.

Evaluation of mycological parameters

The following clinical parameters evaluated at the time of diagnosis, at 2nd week and 4th week.

1. KOH mounts
2. Wood's lamp test

Evaluation of KOH mounts: All the patients in the both groups were KOH mount positive at the time diagnosis.

Table 4: Evaluation of KOH mounts after treatment in both the groups.

Groups	KOH mount negativity	
	At 2 weeks	At 4 weeks
Group A	25 (50%)	30 (60%)
Group B	31 (62%)	42 (84%)

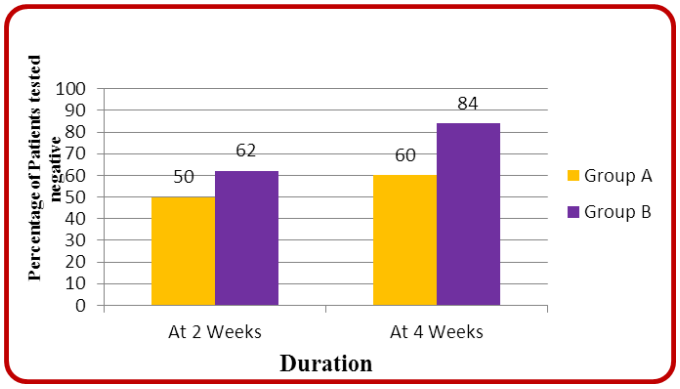


Figure 6: Evaluation of KOH mounts after treatment in both the groups.

Evaluation of Wood's lamp test: All the patients in the both groups were Wood's lamp test positive at the time diagnosis.

Table 5: Evaluation of Wood's lamp test after treatment in both the groups.

Groups	Wood's lamp test negativity	
	At 2 weeks	At 4 weeks
Group A	24 (48%)	28 (56%)
Group B	29 (58%)	41 (82%)

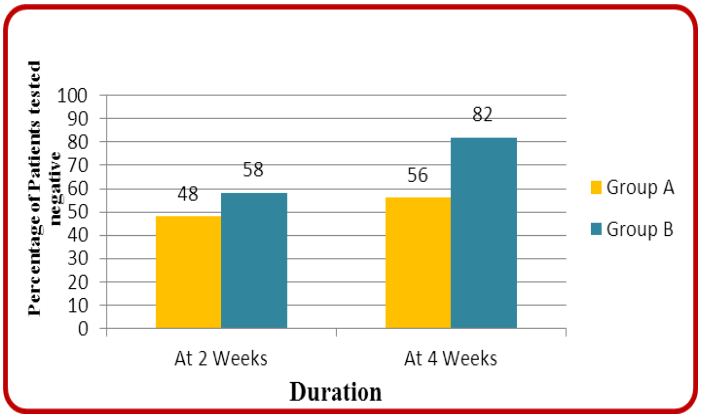


Figure 7: Evaluation of Wood's lamp test after treatment in both the groups.

Comparison between the two groups at the end of therapy

Following comparisons were made between the two groups at the end of therapy

1. Clinical cure: This includes cure from all the symptoms that is scaling and pigmentation
2. Mycological cure: This includes both KOH mount negativity as well as Wood's lamp test negativity
3. Complete cure: This includes both clinical as well as mycological cure.

Table 6: Comparisons between the two groups at the end of therapy (4 weeks).

	Clinical cure	Mycological cure	Clinical and mycological cure
Group A	30 (60%)	28 (56%)	28 (56%)
Group B	40 (80%)	41 (82%)	40 (80%)

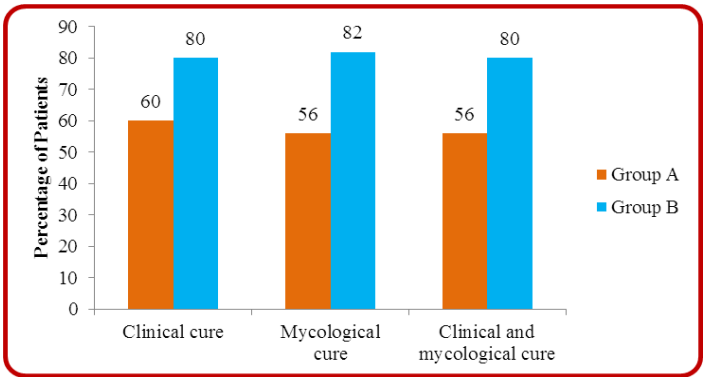


Figure 8: Comparisons between the two groups at the end of therapy (4 weeks).

Both the drugs were well tolerated. Only mild headache and loose stools lasting a day was encountered in one patient in Group A (Itraconazole group).

DISCUSSION

Tinea Versicolor is a superficial fungal infection caused by M. furfur. But 6 species (M. globosa, M. obtusa, M. restricta, M. sympodialis, M. slooffiae and M. pachydermatitis) other than M. furfur have been identified from humans and animals. In some studies, M. globosa and M. sympodialis were the most common isolates from patients with Tinea versicolor. Tinea versicolor is characterized by a macule that may be hypo-pigmented or hyper-pigmented and covered with brany scales, predominantly on trunk and upper arms although other parts may be involved. Although tinea versicolor is prevalent throughout the world, it is more common in tropical countries and incidence is as high as 30-40%.

Itraconazole and fluconazole have been successfully used in the treatment of Tinea versicolor. Both these drugs have been tried in different dosages for varying periods. Itraconazole has been recommended in a dose of 200 mg/day for 7 days [11]. A single dose of fluconazole (400 mg) has been tried in many studies, and it has been found to be effective. Since itraconazole is known to achieve higher concentrations in the stratum corneum which persist for 3–4 weeks even after discontinuation of drug, it is likely to be effective in a single dose.

Mean duration of illness is 2.85 ± 0.98 months in group A and 2.77 ± 1.1 in group B. By applying *'t test'* to compare the mean duration of illness of two groups, we got a p value of 0.499 ($p>0.05$). By conventional criteria, this difference is considered to be statistically not significant. Mean duration of illness was relatively less compared to that in Partap et al[12] study.

Both clinical and mycological parameters were evaluated at the time of diagnosis, at 2nd week and 4th week. The most distressing symptoms in patients with Tinea versicolor are cosmetically unacceptable pigmentation and scaling. Scaling and pigmentation was present in all the patients in both the groups at the time of diagnosis.

At the end of 2 weeks 25 (50%) patients in group A and 35 (70%) in group B were relieved from scaling, this difference between the two groups was statistically significant with a p value of 0.041 ($p<0.05$). At the end of 4 weeks scaling was disappeared in 32 (64%) patients in group A and in 43 (86%) patients in group B, this difference between the two groups was also statistically significant with a p value of 0.011 ($p<0.05$).

Erythematous and hyper-pigmented scaly lesions also disappeared earlier, as has been reported before.[13-15] Residual dyschromia even after successful treatment is a well-known problem.[16] At the end of 2 weeks disappearance of pigmentation was seen in 27 (54%) patients in group A and 29 (58%) patients in group B. The difference between the two groups was statistically not significant as we got a p value of 0.687 ($p>0.05$). At the end of 4 weeks pigmentation was disappeared in 30 (60%) patients in group A and 40 (80%) patients in group B. This difference between the groups was statistically significant as we got a p value of 0.029 ($p<0.05$) after applying Chi-Square test.

At the end of therapy clinical cure rate (includes both disappearance of scaling and pigmentation) in group A was 60% and in group B it was 80%. This difference between the groups was statistically significant ($p = 0.029$). Fluconazole found to be significantly better than itraconazole in clinical cure. Other studies with single-dose fluconazole have reported a very high clinical cure rate of 100% at the end of therapy.[17,18]

Mycological evaluation was done using KOH mounts and wood's lamp test. This was done at the time of diagnosis, at 2 weeks and 4 weeks after treatment. All the patients in both the groups were KOH positive at the time of diagnosis.

At 2 weeks 25 (50%) patients in group A and 31 (62%) in group B were tested negative for KOH mount. This difference between the groups was statistically not significant as we got a p value of 0.227 ($p>0.05$). At the end of 4 weeks 30 (60%) patients in group A and 42 (84%) in group B were tested negative for KOH mount. This difference between the group at the end of 4 weeks was statistically highly significant ($p=0.008$, $p<0.01$).

At 2 weeks 24 (48%) patients in group A and 29 (58%) patients in group B were wood's lamp test negative. This difference between the groups was not statistically significant as we got a p value of 0.316 ($p>0.05$). At 4 weeks 28 (56%) patients in group A and 41 (82%) patients in group B were wood's lamp test negative. This difference between the group at the end of 4 weeks was statistically highly significant ($p=0.005$, $p<0.01$).

So mycological cure (includes both KOH mount negativity and wood's lamp test negativity) was seen in 56% of the patients in group A and 82% of the patients in group B. This difference between the groups regarding mycological cure was statistically highly significant ($p=0.005$, $p<0.01$). Fluconazole was found to be significantly better than itraconazole with regards to mycological cure (82% vs 56%). Rao and Rajashekhar [19] achieved mycological cure in 92% of their patients as observed by KOH mount examination at 6 weeks after fluconazole therapy which is slightly more compared to our study.

Complete cure (includes both clinical cure and mycological cure) was achieved in 28 (56%) patients in group A and 40 (80%) patients in group B. This difference between the group was statistically significant as we got a p value of 0.01 ($p<0.05$). Complete cure was relatively high in both the groups compared to that in Partap et al [12] study.

Limitations

1. Randomization was not done
2. Single center study
3. Relapses after treating with itraconazole and fluconazole was not studied

CONCLUSION

Single dose fluconazole is more efficacious compared to itraconazole in the treatment of tinea versicolor. Both itraconazole and fluconazole were well tolerated without any serious adverse effects.

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