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Original Article

A randomized comparison of terbinafine vs. itraconazole for the treatment of tinea capitis- A prospective comparative study in health care centers of Southern Punjab

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Abstract

Objective To evaluate the therapeutic efficacy of terbinafine in comparison with itraconazole in treatment of tinea capitis. It is pertinent to mention that tinea capitis is a pronounced disease of Southern Punjab with specific prevalence in children of Bahawalpur and surroundings in prepubertal stage, which merits a definite consideration owing to inherent implications and limitations of the disease.

Methods The Prospective comparative study conducted at health care centers of southern Punjab. It comprised 100 children aged 5-16 years, with clinically and mycologically confirmed tinea capitis by 10-30% KOH microscopy and by Sabouraud agar. The children randomized to 8 weeks' treatment with terbinafine or 8 weeks with itraconazole. Evaluation criteria resorted to constitute inspection of random sample of patient at 0, 2, 4 and 8-week interval. Efficacy analysis based upon pooled data and photographic documentation. Outcome determined by absence of clinical signs. Safety assessment included monitoring of the frequency and severity of adverse events (AEs). Hepatic safety of itraconazole (Azole group) determined by LFTs after 4-week treatment. Data analysis conducted with SPSS and graph pads. Result presented in tabular and pictorial form.

Results There were 80 cases in both group A (Terbinafine) and group B (Itraconazole), with no tremendous contrast as far as average age, weight, pre-treatment, total sign and symptom score and number of sores. Fix was seen remarkably superior in bunch B where 70 (87.5%) cases were relieved when contrasted with bunch A where 56 (70%) cases were restored. The tolerability was likewise essentially better in bunch B, where 62 (77.5%) sufferers have either excellent or great reaction to medicate resilience as compare to bunch A where it is noticed in 42 (52.5%) sufferers.

Conclusion Itraconazole manifest noteworthy benefits with regards to cure rate, time requires for rehabilitation and acceptability which appears differently in relation to terbinafine.

Key words
Tinea Capitis; Terbinafine; Itraconazole.

Introduction

Ringworm infection of scalp and hair is known as tinea capitis, predominantly discern among children especially prepubescent are mostly infected, peaking between 3 to 7 years of age.[1] Scalp ring worm is exceedingly contagious and commonly affected the male than female often with the frequency of about two to five times higher.[2] The scalp can be contaminated if fungi or bacteria enter the skin through hair follicles or damaged skin. Common scalp infection includes

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folliculitis, impetigo, ringworm infection (tinea capitis) and lichen planus. Low socio-economic status, close contact with animals, warm humid climate and use of fomites are considered to be the principal risk factors of tinea capitis.[3] The scalp comprises of five layers including skin, connective tissue, epicraniel aponeurosis, loose areolar tissue, and periosteum. Skin is the thick layer of scalp contains sebaceous gland, hair follicles. Sebaceous glands are exocrine gland, secrete oily substance called sebum, these glands are situated in dermis.[4] The causative species for tinea capitis differ from one geographic region to another, though mostly attributable to Microsporum and trichophyton species. The principal dermatophyte causing tinea capitis in a topographic region is swap over time; in consequence the constant surveillance is required to determine the epidemiological trending of tinea capitis infection.[5] Regardless of advancement in prevention and treatment of tinea capitis it continues to exist as global public health problem, chiefly aiming school children in economically underdeveloped states.[6] The diagnosis of tinea capitis is established on account of clinical examination and laboratory investigations. The clinical diagnostic aid for the diagnosis of tinea capitis comprises of wood's light (ultraviolet light with peak of 365nm) and dermoscopy.[7] The clinical diagnosis of tinea capitis is often relatively accurate, when contemplate, however identification of causative agent is crucial for the choice of antifungal therapy and for unveiling the infection chain. Treatment of tinea capitis should be guided by the treatment goals including, elimination of causative species, both clinical and mycological cure, symptom relief and avoidance of permanent hair loss. The term antifungal encloses all chemical compounds, pharmacological agents and native products used to treat mycoses.[8] Antifungal drugs represent a pharmacologically varying group of drugs that are essential integrant in the present-day management of mycoses. Antifungal agents are available both as topical and as systemic antifungal agents, however topical antifungal are less effective for the treatment of tinea capitis Topical antifungals and other topical agent such as corticosteroids and selenium sulphide are utilized as adjunct to stave off expansion and recurrence of infection and to ameliorate itching and clinical appearance in treatment of tinea capitis.[9] Treatment of fungus capitis depends on the utilization of systemic antifungal such as terbinafine, itraconazole, griseofulvin and fluconazole.[10] It is logical to start treatment on the basis of one or more than one vital sign.[11] Griseofulvin an antifungal agent introduced in 1958, contemplated as gold standard therapy for the treatment of tinea capitis.[12] It is an FDA approve drug for the treatment of tinea capitis and also listed on the world health organization (WHO) essential medicine list.[13] Griseofulvin maintain a high cure rate, however due to unavailability of pediatric preparations, long duration of treatment and decrease patient compliance the drug is replaced by other modern antifungals such as itraconazole and terbinafine because of their effectiveness, safety and short duration of treatment.[14]

Terbinafine is a fungicidal and belongs to allylamine group of antifungals. The terbinafine is effective against every single dermatophyte but manifest high efficacy against trichophyton species.[15] Terbinafine was approved by FDA for the treatment of dermatophyte infection in 2007. It is considered to be a first line antifungal agent for the therapy of tinea capitis due to its potency, efficacy, few adverse effects and short duration of treatment. A meta-analysis of randomized clinical trial did not illustrate noteworthy dissimilarity in effectiveness of terbinafine compared to griseofulvin.[16] Itraconazole, a triazole is another effective antimycotic agent for the treatment purpose of superficial mycosis, act by inhibiting cytochrome P-450 enzyme,

consequently impedes the demethylation of lanosterol to ergosterol. It has a remarkable result in treatment of tinea capitis at a dose of 100mg once daily for 2-4 weeks.[17] It manifest equivalent efficacy to griseofulvin and terbinafine.[18] The causative agent for tinea capitis varies geographically and it has been endorsed recently that there has been extensive resistance to various antifungal agents used in standard dose with an increased in relapse rate and decrease patient compliance prompting a need to find an effective first-line antifungal agent, to achieve maximum results with few relapses and with limited adverse effects. Hence, the present study was conducted to compare the efficacy of oral terbinafine versus itraconazole in treatment of tinea capitis.

Methods

This is a randomized perspective comparative study where the impact of terbinafine vs. itraconazole on tinea capitis measured on such basis as self-reported perception involving respondents with regards to these variables. The unit of analysis for this research thesis is individual (affected patients of tinea capitis) of all fields of life of Southern Punjab specifically Bahawalpur. The population of the current research study comprised of the patients affected with tinea capitis and spread over in entire Southern Punjab. The sampling population consists of children between 5-14 years of age, as fungus capitis is a prevalent scalp ringworm disease in minors. The patients were diagnosed by registered medical practitioners and dermatologists by trichoscopy and KOH microscopy. The study population was randomly separated into two gatherings, itraconazole group and terbinafine group. A total of 200 patients with tinea capitis were divided in terbinafine group and itraconazole group, 100 in each intervention group. Consequently, a total of 80 patients were included in both groups as they met the inclusion criteria. Both groups were intervention groups. Group A received terbinafine at a portion of 62.5mg/day for kids under 20kg, 125mg/day for 20-40 and 250mg/day for above 40kg. Group B was remedied with itraconazole, 200mg/day for patient above 40kg, 100mg/day for patients between 20-40kg and 50mg/day for patients between 10-19kg. These cases were surveyed and circled back to OPD premise at 2,4,6 weeks and two months, the patients were evaluated based on potassium hydroxide (KOH) microscopy and all out sign and symptom score (TSSS).The minors with absence of clinical signs according to total sign and symptom score and normal potassium hydroxide (KOH) microscopy were ordered as restored. Patients likewise asked about incidental effects and abstract sentiments in regards to adequacy (Very good/ good/ moderate/ poor and very poor). The quantitative research method was applied by conducting a relational survey design through self-administered questionnaire to explore the degree of association among variables.[19,20] Keeping in view the true reflection of population, the non-probability sampling method resorted to in the study to collect data. Convenience sampling technique incurs relatively less time and financial costs as compared to other sampling techniques; therefore, it was instrumental in selecting the sample size quickly and efficiently. In line with appropriate sample size for the population suggested,[21] requisite patients were selected from four selected treatment centers in the major city of Pakistan i.e., Bahawalpur to form a reasonable sample size. All out efforts made to devise a methodology to get good feedback on the treatment compliance with a sole concern to earn a sufficient response %. Patients' inclusion criteria were KOH positive cases of tinea capitis test. Exclusion criteria were: a) children less than 3 year of age, b) consumption of antifungal agents and systemic steroids in recent 4 weeks,

c) immunodeficiency, d) any history of photosensitivity, e) notable abnormality in complete blood count (CBC), liver function test (LFT), Renal function test (RFT) and electrocardiograph (ECG), f) patients with any other disease requiring systemic therapy. In this study data was gathered through adopted and adapted structured interaction. The outcome variable includes drug efficacy, patient compliance/tolerability and medicine associated side effects. The drug efficacy was the primary clinical outcome measure. One way ANOVA was performed to control for variations in dependent variable(s). Data entered and analyzed by using SPSS version 16.

Results

There were 100 cases in each group, however, only the cases which undergo complete treatment accounted for compilation of results. Consequently 80 cases in each group after discarding 20 cases which did not undertake complete treatment. The 39 (48.75%) masculine and 41 (51.25%) feminine were allocated in group A, whereas in group B 45 (56.25%) masculine and 35 (44%) feminine were assigned (P esteem=0.37). There was no importance contrast regarding average age, status, financial status, dietary status and openness to homegrown creatures/ plants **(Table 1)**.

Rehabilitation rate was seen fundamentally significant in group B where 70 (87.5%) cases were restored when contrasted with group A with fix pace of 56 out of 80 (70%) (p worth of 0.01) **(Table 2)**. There was again massive contrast was identified with regards to curative time where 70 (87.5%) affected patients in group B were relieved by about two months when contrasted with group A having outcome in 56 (70%) patients in comparable time (p esteem 0.03) **(Table 3)**. Among secondary effects stomach torment was the most revealed and found in 15 (18.75%) cases in group A and 12 (15%) cases in Group B and anorexia and regurgitating were other less detailed secondary effects with no massive contrast in the two gatherings (p=0.45) **(Table 4)**. The acceptability

Table 1 Comparison between variables of two groups.

Variable	*Group A*	*Group B*	*Total*
1. Gender			
a. Male	39	45	84
b. Female	41	35	76
2. Age (Years)			
a. 5 – 9	40	40	80
b. 10 – 14	40	40	80
3. Status			
a. Urban	26	25	51
b. Rural	54	55	109
4. Socio economic status			
a. Low	50	50	100
b. Medium	15	20	35
c. High	15	10	25
5. Nutritional status			
a. Under nourished	50	55	105
b. Well nourished	30	25	55
6. Exposed to domestic animals/ plants			
a. Yes	50	55	105
b. No	30	25	55

Table 2 Cure status in dual groups.

	Treatment groups		
Cure	*Group A No (%)*	*Group B No (%)*	*Total*
Yes	56 (70 %)	70 (87.5 %)	126 (78.75 %)
No	24 (30 %)	10 (12.5 %)	34 (21.25 %)
Total	80 (100%)	80 (100 %)	160 (100 %)

Table 3 Time taken to cure in dual groups.

	Treatment groups		
Cure time	*Group A No (%)*	*Group B No (%)*	*Total*
1 Week	0 (0 %)	0 (0 %)	0 (0 %)
2 Week	6 (7.5 %)	9 (11.25 %)	15 (9.375 %)
4 Week	22 (27.5 %)	25 (31.25 %)	47 (29.375 %)
8 Week	28 (35 %)	36 (45 %)	64 (40.0 %)
Not cured	24 (30 %)	10 (12.5 %)	34 (21.25 %)
Total	80 (100 %)	80 (100 %)	160 (100 %)

Table 4 Side effect profile in dual groups.

Side effects	*Treatment groups*		
	Group A No (%)	*Group B No (%)*	*Total*
None	52 (65 %)	60 (75 %)	112 (70 %)
Abdominal pain	15 (18.75 %)	12 (15 %)	27 (16.875 %)
Vomiting	8 (10 %)	3 (3.75 %)	11 (6.875 %)
Anorexia	5 (6.25 %)	5 (6.25 %)	10 (6.25 %)
Total	80 (100 %)	80 (100 %)	160 (100 %)

Table 5 Tolerability of the drugs in dual groups.

Tolerability	*Treatment Groups*		
	Group A No (%)	*Group B No (%)*	*Total*
Very good	9 (11.25%)	17 (21.25%)	26 (16.25%)
Good	33 (41.25%)	45 (56.25%)	78 (48.75%)
Moderate	35 (43.75%)	15 (18.75%)	50 (31.25%)
Poor	3 (3.75%)	3 (3.75%)	6 (3.75%)
Very poor	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	80 (100%)	80 (100%)	160 (100%)

for medication was essentially superior in Group B where 62 (77.5%) has either generally excellent or great reaction to tranquilize resilience when contrasted with bunch A where it was noticed in 42 (52%) of sufferer (P=0.02) **(Table 5)**. By and large itraconazole established as an effective and better medication decision in contrast with terbinafine.

Discussion

Tinea capitis is extremely contagious apparent infection of scalp, observed all around the word and infected children mostly between the age of 5 to 10 years. Regardless of advancement in prevention, treatment of tinea capitis, it continues to exist as global health problem as the causative dermatophyte for tinea capitis differs geographically. Antifungal drugs constitute a pharmacologically multiple groups of drugs that are pivotal for the management of dermatophyte and other fungal infections. The prescribing of specific antifungal for the treatment of superficial fungal infection begins with the healthcare professional designating the proper regimen in accordance with culture,

Figure 5 Pictorial representation for application effects of medicine in Group A and B.

sensitivity data, patient history and sociodemographic factors. Treatment of tinea capitis has shown substantial progression in last decades. The common antifungal agents for the treatment of tinea capitis are griseofulvin, terbinafine, itraconazole and fluconazole. Any new therapy for tinea capitis should carry swift clinical and mycological cure, unaccompanied by relapse and possess fewer adverse effects. Both terbinafine and itraconazole are highly lipophilic and keratophilic, hence persist in stratum corneum and hair in excessive concentration for three weeks after therapy is terminated. These levels are far over the minimum inhibitory concentration for most of dermatophyte that's why adequate to impede the fungul growth. According to previous studies terbinafine and itraconazole are suitable, well tolerated and efficacious antifungal agents for the treatment of tinea capitis. Result of our study demonstrates that itraconazole showed statistically and significantly better result with regards to efficacy, cure rate and tolerability than terbinafine. Many studies have demonstrated and compare the efficacy of terbinafine and itraconazole in shorter treatment period. In our study there were 160 cases randomly allocated in two groups, 84 were male and 76 were female. The proportion of masculine to feminine was seen somewhat elevated with male predominance, albeit this difference isn't genuinely huge. This was indistinguishable to past investigations done by Adesiji *et al.* and Bhatia *et al.* who also found higher percentage in male.[17,22] The two groups, group A (terbinafine) and group B (itraconazole) were assessed for 8 weeks to determine the efficacy of two drugs. The variables to determine the efficacy were cure percentage, cure time, side effect profile and tolerability.

There are three explanations of cure. The first one and chief end point is mycological cure, where there should be negative culture and no dermatophyte should be noticed on microscopic examination. The next is clinical cure and ultimately absolute cure a blend of both clinical and mycological cure. In our study cure percentage (both clinical and mycological cure) is significantly superior in bunch B where 52 (86.6%) sufferers were rehabilitating in contrast to group A where 61 out of 80 (68.67%) were rehabilitated with p value of 0.01. This was inverse to Gupta *et al.* who tracked down fix level of 94% in Terbinafine when contrasted with 82% of Itraconazole.[23] Our study results are in contrast to Sami Ullah Khan *et al.* whose study manifested the mycological cure rate with terbinafine was 60% while with Griseofulvin the mycological cure rate was 50%.[24] In other study by A Bhatia *et al.* the clinical and mycological cure rate after 4-week treatment showed 91.8% cure rate with itraconazole vs. 74.3% with terbinafine.[17] The study by Zainab *et al.* manifested shows higher cure rate with itraconazole around 86% while 68% with terbinafine.[25] In an additional study by Friedlander FS, they found 65% cure rate with terbinafine.[26] Jin Yu study outlined itraconazole, a better antifungal agent against other fungal species causes cutaneous mycosis in combination with terbinafine and amphotericin B.[27] Probably the efficacy of terbinafine is declining due to development of resistance The studies showed that cure rate with Itraconazole persisted over 80% while with terbinafine remained on declining side The examinations showed that fix rate with itraconazole persevered more than 80% while with terbinafine stayed on declining side from 94% in a review did in 2001 to introduce study showing efficacies in 60 percent and 70 percent. Probably the efficacy of terbinafine is declining due to development of resistance by causative fungi against drug. In our review unfortunate resilience and consistence to terbinafine might be another issue prompting intruded on admission of this medications, thus lesser

viability and development of opposition. There was impressive distinction seen when both the medications contrasted with regarding healing time. Curative time determines that duration requires to cure a disease. The terbinafine was given to group A at the dose of 62.5mg/day, 125 mg/day and 250mg/day according to patient's body weight <20kg, 20-40kg, and >40kg respectively. Itraconazole was given to the patients of group B at the dose of 100mg/day. Patients were assessed at 1, 2, 4 and 8 weeks based on potassium hydroxide microscopy and clinical manifestation score. In this study the 25 (31.25%) patients in group B were rehabilitated in 4 weeks interval as looked at of gathering A where 22 (27.5%) cases were cured (mycologically and clinically) in comparable time with p worth of 0.03. The patients were assessed at 1, 2, 4 and 8 weeks on the basis of KOH microscopy and TSSS. The patients were assessed after 8 week manifested higher cure rate in group B 36 (45%) patient, while 28(35%) patients were cured (both clinically and mycologically) in group A. Similar study conducted in China by S Deng *et al.* manifested highest rate of cure with terbinafine at week 8 about 85.2% which is opposite to this study might be due to the difference of specific strain prevalent here as compare to China.[28] The study by Kumar *et al.* represented better improvement in symptoms such as scaling 76.6%, and erythema 95.6% with itraconazole while only 65.5% improvement with terbinafine after 4 weeks. These results shows that Itraconazole manifested swift improvement in symptoms as compared to terbinafine. The common side effects with terbinafine are nausea, vomiting, taste disturbance and abdominal cramping, the continuation of medicine rest on severity of side effects. The FDA advocate serum transaminase estimation before initiation of treatment, however the drug induced liver injury results usually within three months.[29] The itraconazole adverse effect included nausea, vomiting, headaches and stomach upset, the drug rarely caused serious liver disease. In this study laboratory testing was not required in any of patients. In present study adverse effects were observed only in few (28.5%) of patient. All of adverse effects were mild to moderate in severity and only few of patients discontinued the treatment. Most of the adverse effect were noticed with terbinafine where 15 (18%) patients manifested abdominal pain while 8 (10%) patients presented with vomiting, followed by group B (itraconazole) where 12 (15%) patients presented with complain of abdominal pain while only 3 (3.75%) patient manifested vomiting as a side effect, that is opposite to study done by Sharma *et al.* where adverse effect were higher with itraconazole (40%) as compared to terbinafine.[30] In our study the adherence to the treatment in both group was comparable and patients did not decline the treatment due to adverse effects. The tolerability was notably higher in itraconazole group where 17 (21.25%) patients had very good feedback to drug tolerance and 45 (56.25%) patients respond good drug tolerance. Only 3 (3.75%) in group B (itraconazole) respond very poor drug tolerance but none of the patient manifested very poor response or declined treatment. In patients with dermatophytosis and on Itraconazole therapy recurrence rate is found to be low in previous studies.[31,32] In present study the results are same the lowest recurrence rate is noted with itraconazole which can be attributable to its compliance and ability to persist in stratum corneum for several month after ceasing the treatment.[33] Fungal infections are extensively metastasized among global population. It has been estimated approximated that there are 5 million fungal species and more or less 300 species caused disease in human. The antifungal agents are group of drugs prescribed for the treatment of fungal infection. The pharmacokinetic and pharmacodynamic properties such as route of administration,

absorption, distribution, route of elimination and plasma protein binding influence the efficacy and therapeutic success in particular fungal infection. The systemic route of administration of both itraconazole and terbinafine, high plasma protein binding, and elevated lipophilicity make these two drugs the most effective and prescribed drugs in treatment of tinea capitis. Most fungi develop resistance against traditional antifungal agents either due to judicious use of antifungal agents or due to change in prevalence of causative agent in particular area. The above discussion and comparisons of our study with other studies demonstrated itraconazole the more efficacious in terms of cure time, cure rate, side effect profile and tolerability. The drug is effective against the fungal agents prevalent in southern Punjab. Terbinafine considered as gold standard for the treatment of tinea capitis but in our study the itraconazole showed better results in terms of cure rate and tolerability probably due to resistance developed by fungal agents against terbinafine and subjective acceptability by patients for itraconazole.

Conclusion

Itraconazole has superior clinical and mycological cure rates as compared to terbinafine. Although the cost of terbinafine is lower than that of itraconazole that is why terbinafine is the commonly prescribed drug. Due to prolonged period of treatment, and extensive use of terbinafine there is emergence of resistance in causative fungi against this drug so the failure rate is higher. Itraconazole showed outstanding benefits with reference to restore rate in patients as well as in term of curative time and it has better acceptability when contrasted with terbinafine.

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