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Clinical trial

Comparative evaluation of griseofulvin, terbinafine and fluconazole in the treatment of tinea capitis

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Abstract

Tinea capitis (TC) is a common childhood fungal infection which, if untreated, can cause long-term scarring. A number of antifungal drugs with proven efficacy are available for the treatment of TC. However, varying dosage schedules, changes in epidemiology, and rising drug resistance are factors that hamper treatment in some cases. A prospective, non-blinded, cross-sectional study of three commonly used drugs (terbinafine, griseofulvin, and fluconazole) was undertaken in children aged ≤12 years, presenting to a pediatric super-specialty hospital. The comparative efficacies of these three drugs were evaluated. A total of 75 patients (25 in each treatment group) who completed the designated treatment protocol were included in the final analysis. Of these, 60% had non-inflammatory TC and 56% had an ectothrix pattern on hair microscopy. *Trichophyton violaceum* was the most commonly isolated fungus. Cure rates of 96%, 88%, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of TC. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications.

Introduction

Tinea capitis (TC) is a fungal infection of the scalp common in children.[1] Early diagnosis and appropriate treatment are important to prevent transmission, scarring, and permanent hair loss. Various systemic antifungal drugs, such as griseofulvin, terbinafine, fluconazole, ketoconazole, and itraconazole, have been used in the treatment of TC.[2] Griseofulvin represents the mainstay of therapy,[2] but rising levels of resistance to this drug have been reported.[1]

The present study was carried out to assess the comparative efficacy of three antifungal drugs: griseofulvin, fluconazole, and terbinafine.

Materials and methods

A prospective, cross-sectional study was carried out in children with TC (confirmed on microscopic examination) aged ≤12 years. Subjects included children presenting with patchy hair loss and hair that was easily plucked out, with or without any associated inflammatory changes. Patients who had used any oral or topical antifungal therapy during the six weeks prior to the study and those who did not consent to participate were excluded.

Demographic and socioeconomic data and factors predisposing towards the spread of TC were analyzed. The initial morphologic type of TC and any changes during treatment were recorded. Any evidence of tinea elsewhere or in individuals with whom the study subject had close contact was also assessed.

On the basis of hair microscopy under 10% potassium hydroxide (KOH), infections were classified as endothrix, ectothrix, or of a mixed pattern. Culture on Sabouraud's Dextrose Agar® (Oxoid, Basingstoke, UK) was performed in all cases to isolate the fungus.

The patients were assigned to three treatment groups.

Group 1 included seven patients with inflammatory TC, 15 patients with non-inflammatory TC, and three patients with a mixed pattern of TC. All patients received griseofulvin 15–20 mg/kg/d administered in two doses per day for six weeks and taken with fatty food.

Group 2 was comprised of nine patients with inflammatory TC, 14 with non-inflammatory TC, and two with a mixed pattern. The patients in this group received fluconazole 6–8 mg/kg administered weekly for six weeks.

Group 3 consisted of seven patients with inflammatory TC, 16 patients with non-inflammatory TC, and two with a mixed pattern. These patients received terbinafine 3–5 mg/kg/d for two weeks.

Because of the variations in dosage schedules, blinding was not possible. Treatment in each group could be prolonged for a

further 2–4 weeks if the patient showed improvement but not complete cure. *Clinical cure* was declared when clinical signs of scaling had completely subsided and the hair was no longer easily plucked. *Mycologic cure* was defined as the complete absence of fungal spores on KOH examination of samples from representative areas. A *complete cure* (both clinical and mycologic) was required before a patient could be declared cured and released from therapy. Outcomes of treatment with each of the three drugs were compared statistically using Fisher's exact test of significance.

General measures, such as the non-sharing of combs, towels, and hair accessories, were advised. None of the patients were advised to shave their heads or to remain absent from school. All patients were advised to use ketoconazole 2% shampoo. No topical therapy was prescribed. A few patients with extensive inflammation were prescribed oral prednisolone 1 mg/kg/d for 1–2 weeks.

Routine hematologic and biochemical tests were performed at baseline and repeated at two weeks in Group 3 and at 3-weekly intervals in Groups 1 and 2. Any side effects of the therapy in the form of diarrhea, dysgeusia, etc., were also recorded.

Results

A total of 75 patients (25 in each group), who completed the treatment protocol, were included for final analysis. The mean age of the affected children was 6.46 years (the youngest was one year old). The majority of the children (25.3%) belonged to the 8–10 year age group. Both sexes were almost equally affected; the male : female ratio was 1 : 1.14.

Non-inflammatory TC was more common (60.0%) than inflammatory TC (30.7%). A mixed morphologic pattern was seen in 9.3% of cases. Three cases showed a change in morphology (a gray patch became pustular) on treatment. Among the non-inflammatory cases, black dot TC was the more common pattern (34.6% of cases).

Microscopically, an ectothrix pattern was more common (56%) than an endothrix pattern (42%). Both patterns simultaneously were seen in one patient on initial examination and in four cases on treatment (initially considered as endothrix).

Trichophyton violaceum was the most common isolate and was found in 68% of patients (n = 51). One isolate each of *Trichophyton rubrum* and *Trichophyton tonsurans* were recorded. Two specimens grew contaminants. Culture revealed no growth at the end of six weeks in 20 cases. The species encountered in different treatment groups are shown in Table 1.

The treatment results are detailed in Table 2. In Group 1, 24 patients were cured (96%). Four patients in this group required prolonged treatment of 7–8 weeks. Of these, three patients had non-inflammatory TC (black dot) with *T. violaceum* and one patient had inflammatory TC (kerion) with no growth on culture. Only one patient with non-inflammatory TC with *T. violaceum* remained untreated in this group.

In Group 2, 21 patients were cured (84%), one of whom required prolonged therapy. This patient had inflammatory TC (kerion) with negative fungal culture and required 10 weeks of fluconazole therapy. Four patients (one with inflammatory and three with non-inflammatory TC) infected with *T. violaceum* failed to respond to this therapy.

In Group 3, 22 patients (88%) were declared cured, although two of them required prolonged therapy. Both of these latter two children had non-inflammatory TC; one was infected with *T. violaceum* and another with an unidentifiable fungus and required prolonged therapy of

Table 1 Clinico-etiologic profile of tinea capitis (TC) in the three treatment groups

Treatment group	Clinical types	*Trichophyton violaceum*	*Trichophyton tonsurans*	*Trichophyton rubrum*	No growth	Contaminants	Total
Group 1 (griseofulvin)	All	16	–	–	8	1	25
	Inflammatory TC	6	–	–	1	–	7
	Non-inflammatory TC	8	–	–	6	1	15
	Mixed pattern	2	–	–	1	–	3
Group 2 (fluconazole)	All	16	–	1	7	1	25
	Inflammatory TC	5	–	–	4	–	9
	Non-inflammatory TC	9	–	1	3	1	14
	Mixed pattern	2	–	–	–	–	2
Group 3 (terbinafine)	All	19	1	–	5	–	25
	Inflammatory TC	5	–	–	2	–	7
	Non-inflammatory TC	12	1	–	3	–	16
	Mixed pattern	2	–	–	–	–	2
Total		51	1	1	20	2	75

Table 2 Comparative evaluation of various treatment modalities in tinea capitis

	Total cases		Cured		Cured on prolonged therapy		Not cured	
Group	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
1 (Griseofulvin)	25	100	24	96	4	16	1	4
2 (Fluconazole)	25	100	21	84	1	4	4	16
3 (Terbinafine)	25	100	22	88	2	8	3	12

four weeks to achieve cure. Three patients infected with *T. violaceum* could not be cured with terbinafine (Table 2).

A comparison of outcomes in Groups 1 and 2 produced an odds ratio (OR) of 1.14 (95% confidence interval [CI] 0.94–1.38; Fisher's exact text, $P = 0.349$). The same comparison of Groups 1 and 3 revealed an OR of 1.09 (95% CI 0.92–1.28; $P = 0.609$). Similarly, comparing Groups 2 and 3 produced an OR of 0.95 (95% CI 0.76–1.19; $P = 1.000$). The differences in treatment outcomes among the groups were not statistically significant.

Six patients needed oral prednisolone (1 mg/kg) for 1–2 weeks. These included two cases of kerion, three cases of pustular TC, and one case of gray patch TC which converted to pustular TC upon initiation of treatment. No side effects to therapy were recorded in any of the treatment groups.

Discussion

Tinea capitis is a common fungal infection, particularly among children in urban areas.[2] It is contagious and should be recognized and treated early. The 75 children included in our study were mostly school going, urban children in the age group of 8–10 years.

As in earlier reports,[3,4] non-inflammatory TC was found to be more common than inflammatory variants in our series. The fungal species found most predominantly in our series was *T. violaceum*; this is the most common fungus found in India,[4] Pakistan,[5] and Nepal.[3] An ectothrix pattern of invasion was found to predominate in our study.

A variety of earlier reports on the clinical spectrum of TC have highlighted the poor correlation between its clinical and microscopic presentations. Zhu *et al.*[6] reported both endothrix and ectothrix patterns in cases clinically presenting as kerion. Neither is the identification of the fungal species a reliable indicator of the clinical or microbiologic pattern in an individual patient. *Trichophyton violaceum* has been reported to produce a very variable clinical picture.[7] *T. rubrum* has been reported to cause both endothrix and ectothrix patterns of invasion of the hair shaft.[6] Hussain *et al.*[7] and Sehgal *et al.*[8] have reported the isolation of *T. violaceum* from both non-inflammatory and inflammatory types of TC, such as black dot, gray patch, kerion, seborrheic and agminate folliculitis. In addition, the coexistence of different clinical morphologies in the same patient was reported by Jahangir *et al.*[5] To account for such wide variations, it has been proposed that the disease may have a very wide clinical spectrum.[5] In addition, inflammatory lesions have been reported to begin developing as the host develops delayed-type hypersensitivity.[5] This may explain why TC evolved to inflammatory (pustular) TC on the initiation of therapy in a few of our patients.

Griseofulvin has been regarded as the reference standard for first-line treatment of TC.[1] It gave the best cure rate (96%) in our study. We encountered no significant side effects. At the dose given, the drug has a good safety profile and is well tolerated.[9] However, 16% of the patients who received griseofulvin required their treatment to be prolonged to 7–8 weeks. This may reflect multiple factors, such as host reaction, type of infection, or drug-related factors. Earlier studies have reported a rising resistance to griseofulvin.[1,9] Step-wise increases in the recommendations of the Infectious Diseases Committee of the American Academy of Pediatrics regarding both the dose and duration of treatment with griseofulvin are clearly indicative of a changing scenario. Doses ranging from 20[1] to 25 mg/kg/d[9] are now being used to achieve optimum results. The reduction in the efficacy of griseofulvin over the years has been attributed to various factors, including changes in patterns of epidemiology, fungal genetic mutations resulting in decreased susceptibility, long-term use of the drug, and poor compliance arising from the long duration of therapy.[1]

With a cure rate of 88%, terbinafine performed second best in our series. It had the added advantage of a shorter course of administration and hence better compliance. The treatment was prolonged to four weeks in 8% of patients in this group. Terbinafine has been reported to be very efficacious against *Trichophyton* species,[1]

although up to eight weeks' administration of terbinafine is reported to be necessary in *Microsporum canis* infections.[10] However, the cost of therapy with terbinafine is higher than that with griseofulvin. In India, terbinafine is only available in tablet form. Better dose formulations are highly desirable.

Fluconazole administered in weekly doses was the least effective treatment option in our series. It had a low cure rate (84%). However, the drug is very safe and easy to administer. Earlier reports have shown that higher doses (≤8mg/kg/week) for longer duration (12–16 weeks) are required if a weekly dosing regime is to be successful.[11] Standard dosing regimens for fluconazole in the treatment of TC have still not been defined. Doses in the range of 6 mg/kg daily[12] or 8 mg/kg once weekly[11] have been reported to have variable efficacy.

Antifungal shampoos, such as ketoconazole 2%, selenium sulfide 2.5%, zinc pyrithione, and povidone iodine 4%, decrease spore load and the shedding of anthroconidia.[9] The non-sharing of headgear and grooming equipment also helps in decreasing fomite-borne transmission. We did not advise the shaving of hair because it can lead to peer group ridicule and ostracism.

Oral prednisolone as an adjunct was required by 8% of our patients. Conflicting reports exist about the usefulness of steroids.[13] However, in our series, prednisolone significantly improved inflammation and prevented subsequent hair loss.

Certain limitations were encountered in the present study. The overwhelming majority of patients in our series were infected with *T. violaceum* and had non-inflammatory TC. The profile in other geographic regions may be different. In addition, results in each treatment group do indicate a definite trend, but because of the limited number of participants, the differences do not achieve statistical significance. Likewise, because of the small number of patients, no further standardization among the groups was possible. In conclusion, griseofulvin proved to be the single most effective treatment in our series. However, its initially clear supremacy over other drugs is being swiftly eroded. Terbinafine offers the advantage of shorter treatment courses in infections with *Trichophyton* species. Fluconazole is easier to administer in small children. Further controlled studies, with larger numbers of patients, comparison among standardized groups, and coverage of different geographic areas are needed to resolve these issues.

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