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Original Article

Comparative evaluation of efficacy and safety of topical fluconazole and clotrimazole in the treatment of tinea corporis

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Abstract

Objective To assess the clinical efficacy and safety of fluconazole 0.5% gel in patients with mild to moderate grades of tinea corporis in comparison to clotrimazole 1% cream.

Patients and methods Patients presenting with symptoms of tinea corporis were mycologically confirmed for presence of fungal hyphae and were randomly divided into two groups, one group received fluconazole and the other received clotrimazole. Treatment duration was for 4 weeks and study duration was for 8 weeks. Clinical evaluation was carried out on day 1, day 14, day 28 and a follow-up on day 56. Adverse effects were also recorded. Data entry was done in Excel data sheet and analyzed with Epiinfo 2002. Chi-square test and *t test* were carried out according to the type of data.

Results Both the groups were matched at baseline in respect to their demographic profile. Significant improvement in efficacy parameters was seen in both the groups suggesting that both the drugs are effective against tinea corporis infection. Between groups comparison of mycological cure rate and clinical improvement showed no significant difference. The safety and tolerability profile of both regimens were good and statistically comparable.

Conclusion Fluconazole 0.5% gel is found to be safe, effective and tolerable for mild to moderate tinea corporis. Its clinical effectiveness is comparable to that of clotrimazole, when used topically in tinea corporis.

Keywords
Fluconazole, clotrimazole, tinea corporis, topical antifungal agents.

Introduction

Tinea corporis is a very common form of superficial dermatophytosis infection of the skin in patients seeking treatment at our hospital, a tertiary care center. Dermatophytes are fungi capable of causing skin changes of the type known as ringworm or dermatophytosis. The ringworm species are all moulds belonging to three asexual genera: *Microsporum*, *Trichophyton* and *Epidermophyton*.

With increasing number of people travelling worldwide, mycoses that were previously restricted to certain geographic areas can now be seen in other areas as well. In recent years, the number of fungi recognized as human pathogens

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has risen, partly in debilitated and immunocompromised patients.[1] A survey conducted by World Health Organization on the prevalence of dermatophytic infection has shown that 20% of people presenting for clinical advice are suffering from cutaneous fungal infections worldwide.[2]

Tinea corporis refers to tinea infection anywhere on the body except the scalp, beard, feet, or hands. This lesion presents as an annular plaque with a slightly raised and often scaly, advancing border and is commonly known as ringworm. Each lesion may have one or several concentric rings with red papules or plaques in the center. As the lesion progresses, the center may clear, leaving post-inflammatory hypopigmentation or hyperpigmentation.

Both topical and systemic therapies may be used to treat dermatophyte infections. Topical therapy is generally effective for uncomplicated tinea corporis of small areas and of short duration.[3] An ideal topical agent for superficial fungal infections should have broad-spectrum activity, high mycological cure rate, convenient dosing, low incidence of side effects and low cost. The imidazole antifungal agent clotrimazole has been widely used topically for the treatment of superficial dermatophytosis for a long time.[4,5] Although there is no report of resistance to this drug in dermatophytosis, alternatives are in search in anticipation.

Fluconazole, a fluorinated bis triazole compound is in use as an oral antifungal agent for a long time. It is used in candidiasis, cryptococcosis, dermatophytoses and other mycoses.[6] So far very little data are available on the efficacy of topical fluconazole on mycoses of keratinized tissue, and experience with this therapy is limited. A microemulsion based lecithin organogel formulation of fluconazole studied for topical delivery of fluconazole, has shown beneficial results in terms of easy preparation, safety, stability and low cost.[7] Results of another in-vitro study using different formulations of fluconazole in microemulsion base has indicated that the microemulsion system would be a promising tool for enhancing the percutaneous delivery of fluconazole.[8] A topical formulation of fluconazole as 0.5% gel is available in the Indian market for use in tinea corporis. This study aims to assess the efficacy and safety of fluconazole 0.5% gel as compared to clotrimazole 1% cream as antifungal agent in dermatophytic infection.

Patients and methods

Patient screening and recruitment were carried out at the Dermatology outdoor clinic of School of Tropical Medicine, Kolkata which is a tertiary care hospital. One hundred and fifty patients of either sex in the age group 18-65 years with a clinical diagnosis of mild to moderate grades of tinea corporis were selected for the study. Patients were evaluated following the pre-determined inclusion and exclusion criteria. Written informed consent was mandatory for participation in the study. Necessary ethical clearance was obtained from the institutional ethical committee.

Patients with uncontrolled diabetes, HIV infection or suffering from concomitant bacterial infection were excluded from the study. Pregnant or lactating mothers and female patients of the reproductive age group practicing unreliable methods of contraception were excluded from the study. Those who received systemic and/or topical antifungal agents during the last one month were also excluded. Patients with negative skin scraping for fungus from a clinically suspected lesion on baseline visit were also excluded from the study.

Study design This is a randomized, controlled trial with three parallel treatment arms. The 150 patients selected for the study were divided into three groups randomly. Each group was allocated one topical antifungal, namely, clotrimazole, fluconazole or amorolfine. The results of the comparative study regarding efficacy and safety of topical clotrimazole and amorolfine have already been published.[9] In the present study, we report the results of the efficacy and safety of topical fluconazole in comparison to that of topical clotrimazole.

Each patient visited the investigator four times during the trial. After the baseline visit, they were asked to report again on day 14, day 28 and on day 56 for follow-up to look for any relapse. The study was designed as single-blind, as the dermatologist who recruited and evaluated the patients was kept blinded regarding the treatment allocation.

Study drugs Fluconazole 0.5% gel and clotrimazole 1% were dispensed to the patients according to randomization. The patients were instructed to apply the medications twice daily for four weeks. The first application was supervised. Thereafter, the patient was advised to use the medication as per the study schedule. Accountability was assessed by evaluating the trial diary asked to be maintained by the patient.

Patients enrolled for the study were not permitted to concomitantly use any antifungal other than the trial drug. Any other medication known to interact with or potentially alter the response to the study drugs was not permitted. Systemic antifungal and corticosteroids were not allowed. No systemic antihistaminic was given. They were asked to discontinue the drug and report at the earliest if any discomfort was felt.

Assessment of efficacy and safety During the first visit, the patient was screened which also served as the baseline visit if he/she was not receiving any interacting drug. A separate baseline visit was advised for those taking any interacting drug, after appropriate wash-out period on withdrawal of the drug. At screening a thorough medical history was taken and clinical examination of the potential subjects was done to assess their suitability for participation in the study. Informed consent was obtained. Skin scrapings were collected, treated with 10% KOH and examined under microscope for determination of fungal elements. In patients with history indicating diabetes or co-existing disease, routine blood examinations were taken up. The study medication was dispensed to the subject following randomization, provided all inclusion and exclusion criteria were satisfied. The patients were instructed to apply the cream thinly to the affected area twice daily. All patients were asked to maintain a trial diary.

On the second visit at day 14, the patient was clinically examined and compliance determined from the trial diary. Adverse events if any were recorded. Mycological examination was repeated. A second dose of study medication was dispensed if necessary.

During the third visit on day 28, clinical assessment was repeated, compliance determined, adverse events if any recorded and mycological examination was also done. The patients were instructed to discontinue application of the medicine.

The end-of-trial visit was 4 weeks thereafter, i.e. on day 56 from inclusion of the subject, to record relapse, if any. A repeat clinical evaluation was carried out and mycological examination was taken up from the treated area.

The clinical parameters for evaluation were signs and symptoms, which included itching, erythema and scaling. These parameters were assessed on a pre-determined four point scale as: absent, mild, moderate and severe.

The mycological cure rate was studied in patients of both the groups. Absence of fungal elements in the skin scraping material constituted mycological cure.

A four-point scale as poor, satisfactory, good and excellent was used for overall clinical evaluation based on efficacy and tolerability of the treatment by the investigator.

The patient's assessment regarding efficacy and acceptability of treatment was recorded on a four-point scale as poor, satisfactory, good and excellent.

Statistical analysis Efficacy data were evaluated for subjects who reported for the follow-up visit at the end of 4 weeks. Data entry was done in Microsoft Excel Sheet and analysis was carried out in Epiinfo 2002. Chi-square test and *t test* were carried out according to the type of data.

Results

After randomization, 51 of the selected patients were given clotrimazole cream and another 51 patients received fluconazole gel.

Comparison of mean age between the two groups were not significant (p=0.85). Comparison of male to female ratio in the study population were also not significant (p=0.36). The groups were thus matched in respect to their baseline demographic profile (**Table 1)**.

Table 1 Baseline demographic profile in the two groups.

	Group A (Clotrimazole) (n=51)	*Group B (Fluconazole) (n=51)*
Age (years)	29.88+/-10.86	30.33+/-12.80
Male:female	31:20	28:23

Of the 51 patients in the clotrimazole group, 6 patients did not turn up for follow up on day 14 or their compliance was not satisfactory; 3 patients in this group were not considered suitable for evaluation on day 28 for similar reasons. In the fluconazole group, 4 patients did not attend visit on day 14 and another 6 were not considered for evaluation on day 28 for non-compliance.

There was clinical improvement in all the efficacy parameters on day 14, with further improvement continuing till day 28 in either group. In the clotrimazole group, itching subsided in 71.1 and 95.4% of patients, erythema was absent in 73.3 and 92.9% and scaling subsided in 77.8 and 92.9% of patients on days 14 and 28 respectively. In those receiving fluconazole, itching subsided in 76.6 and 97.56 % of patients, erythema was absent in 68.08 and 97.56 % on days 14 and 28 respectively. Scaling improved in 6.38% and was absent in 55.31% on day 14, absent in 90.24 % of patients on day 28. (**Table 2**). The results indicate efficacy of both drugs as anti-fungal agents and there is continuous reduction in patient's suffering with both the drugs.

Between group comparisons of the primary efficacy parameters showed no significant difference in any of the parameters between the two groups at any point of time (p>0.05) **[Table 2]**. Thus it is seen that both the drugs provided effective relief to the signs and symptoms of tinea corporis and there was no difference in efficacy between them.

Table 2 Serial change in the distribution of efficacy parameters in the two treatment groups at different points of time.

Parameter	*Clotrimazole*			*Fluconazole*			*p value*
	Day 0 (n=51)	*Day 14 (n=45) {%}*	*Day 28 (n=42) {%}*	*Day 0 (n=51)*	*Day 14 (n=47) {%}*	*Day 28 (n=41) {%}*	
Itching	Mild-10 Mod-22 Severe-19	No imp-4 {8.9} Improved-9 {20} Subsided-32 {71.1}	No imp-1 {2.4} Improved-1 {2.4} Subsided-40 {95.4}	Mild-14 Mod-27 Severe-10	No imp-5 {10.63} Improved-6 {12.76} Subsided-36 {76.6}	No imp-0 {0} Improved-1 {2.43} Subsided-40 {97.56}	0.14 (Day 0) 0.64 (Day 14) 0.98 (Day 28)
Erythema	Mild-23 Mod-27 Severe-1	No imp-4 {8.9} Improved-8 {17.8} Subsided-33 {73.3}	No imp-3 {7.1} Subsided-39 {92.9}	Mild-28 Mod-20 Severe-3	No imp-6 {12.76} Improved-9 {19.14} Subsided-32 {68.08}	No imp-1 {2.43} Subsided-40 {97.56}	0.28 (Day 0) 0.81 (Day 14) 0.63 (Day28)
Scaling	Mild=38 Mod-11 Severe-2	No imp-10 {22.2} Subsided-35 {77.8}	No imp-1 {2.4} Improved-2 {4.7} Subsided-39 {92.9}	Mild-39 Mod-7 Severe-5	No imp-18 {38.29} Improved-3 {6.38} Subsided-26 {55.31}	No imp-3 {7.31} Improved-1 {2.43} Subsided-37 {90.24}	0.33 (Day 0) 0.09 (Day 14) 0.50 (Day 28)
Skin scraping for fungus Positive	All	14 (31.1%)	10 (23.8%)	All	12 (25.53%)	8 (17.02%)	0.55 (Day 14) 0.63 (Day 28)

Table 3 Global assessment of physician and patients at the end of study.

Parameter	*Clotrimazole (n=51) 2nd Follow-up (Day 28) (n=42)*	*Fluconazole (n=51) 2nd Follow-up (Day 28) (n=41)*	*p value*
Physician's assessment of efficacy (good and excellent)	40 (95.23%)	37 (90.24%)	0.65 (Yates corrected)
Patient's assessment of efficacy (good and excellent)	38 (90.47%)	36 (87.8%)	0.97 (Yates corrected)

As per inclusion criteria all patients selected for the study were skin smear positive for fungus at baseline in both the groups. After 14 days of treatment with clotrimazole, skin smear was positive in 14 (31.1%) patients; thus a mycological cure of 68.9% was achieved. On day 28 the cure rate reached was 76.2%. In fluconazole group, the mycological cure rate was 74.47% on day 14 and 82.98% on day 28. These differences between two groups were not statistically significant (**Table 2**).

Between groups comparison of physician's assessment of efficacy at the end of the study showed no significant difference (p=0.65). Also no significant difference could be detected

between the groups in patient's assessment of efficacy and tolerability (p=0.97) [**Table 3**].

Only 3 patients in clotrimazole group and 4 in fluconazole group attended for follow up on day 56, i.e. 4 weeks after discontinuation of treatment. None of these patients had any sign of activity of the disease nor were the skin scrapings from old sites positive for fungus at that point.

One patient in clotrimazole group showed increased erythema on day 14. The patient continued application without improvement up to day 28. In the fluconazole group, 1 patient showed signs of increased erythema which continued even at the visit on day 28. In either patient, the severity of erythema was not that severe so as to discontinue treatment. Thus both the topical medications were seen to be tolerated well.

Discussion

Tinea corporis is a superficial fungal infection presenting in tropical countries, commonly known as 'ringworm'. Dermatophytes are fungi that infect epidermis of the skin, hair and nail due to colonization in the keratinized layers.[10] Dermatophytes of the anthropophilic species usually produce mild but chronic lesions. The degree of inflammatory response depends in part on the site of infection and the immune status of the host. The dermatophytes are restricted to the keratinized tissues although inflammation involves the dermis and malpighian stratum of epidermis. The most common dermatophytes that cause tinea corporis are *T. rubrum, T. mentagrophytes, M. canis, T. tonsurans.*

Proper treatment of dermatophytosis is of utmost importance as persistent infections can compromise the quality of life to a remarkable extent. Both topical and systemic therapies are used to treat dermatophyte infections depending upon the site involved and type and extent of infection. Topical therapy is effective for uncomplicated tinea corporis of mild to moderate grades. Topical agents used in these infections are the imidazoles, allylamines, tolnaftate and ciclopirox. Clotrimazole, an imidazole antifungal has been widely used topically for treatment of superficial dermatophytosis for a considerable period of time.[4,5] There is as yet no report of resistance to this drug. So we have selected this drug to compare the efficacy and safety of topical fluconazole 0.5% gel, which is a comparatively new drug for topical use in uncomplicated cases of tinea corporis infection.

Fluconazole is a triazole antifungal with similar mechanism of action as clotrimazole, an imidazole. Both inhibit sterol 14α-demethylase, a microsomal cytochrome P450 enzyme in fungi. Thus there is impairment of ergosterol biosynthesis for the cytoplasmic membrane and accumulation of 14α-methyl sterols. This leads to disruption of enzyme systems and electron transport system within the fungus.[6]

Fluconazole is widely used orally in onychomycosis and other dermatomycosis.[11,12] It is also effective in oral candidiasis and candida Vaginitis.[13,14] An in vitro study to determine activity of ten antifungals against dermatophytes has shown that, was more *T. rubrum*, one of the most frequent species causing chronic diseases with frequent remissions and relapses susceptible to fluconazole than other species.[15] Topical fluconazole has shown to be effective and safe in superficial dermatomycosis.[16] The effectiveness and tolerability of the topical formulation of fluconazole 0.5% gel in the treatment of the dermatomycoses with localized lesions was carried out in Italian patients.[17]

This present study compared the efficacy and safety of topical fluconazole in cases of mild to moderate grades of tinea corporis to the conventional topical preparation of clotrimazole. The results show that both the drugs are equally effective in bringing about clinical cure and relief of symptoms. There was no significant difference at any point of time within the two groups.

With clotrimazole, itching subsided in 71.1% of patients on day 14 and in 95.4% on day 28. Clinical improvement was seen also in erythema and scaling on day 14, with further improvement on day 28. Scaling persisted in 7.10% of patients in this group even on day 28. Scaling is a sign of healing and indicates good efficacy of the drug. Thus with clotrimazole, gradual clinical improvement is seen continuing up to 4 weeks.

With fluconazole, itching subsided in 76.6 % of patients on day 14 and in 97.56 % on day 28. Erythema subsided in 68.8 % of patients on day 14 and still further in 97.56 % on day 28. Scaling persisted in 9.74% of patients on day 28. Thus fluconazole is also seen to be effective as a topical antifungal in tinea corporis. Clinical improvement also continued with fluconazole till day 28.

Between groups comparisons of the efficacy parameters for clinical improvement showed no significant difference in any of the parameters at baseline. **[Table 2]**. Similar comparisons on day 14 and day 28 did not show any significant difference between the groups.

It can thus be concluded that both the drugs provided effective relief to the signs and symptoms of tinea corporis though there was no statistically detectable difference in the efficacy between them.

The mycological cure rate does not show any significant difference between the two groups either on day 14 or on day 28. With clotrimazole, mycological cure rate achieved on day 28 was 76.2%. This finding is similar to the result of a previous study done with clotrimazole 1% cream in interdigital tinea pedis[5]. The fluconazole group showed 82.98% of mycological cure rate on day 28. A study done with oral fluconazole in candida balanitis showed mycological eradication in 72.22% of patients.[18]

One patient in clotrimazole group had increased erythema on day 14 which persisted on day 28. This may be considered as an adverse event with use of clotrimazole. With fluconazole, one patient had increased erythema that persisted without improvement till day 28. No systemic adverse event was reported in any patient in either group. Hence both the drugs were seen to be safe for topical use. The physician as well as the patients was satisfied with the application of either drug.

The number of patients who returned for follow up 4 weeks after stoppage of treatment was very low and none of them showed any sign of the disease. Any conclusion regarding the chance of relapse with either drug was not possible with such a limited number of patients.

Thus both the drugs showed good results against dermatophytosis, in respect of providing clinical and mycological cure. There was no significant difference in the outcome of the two study groups. A limitation of this study was that it was a single-center study with a small number of patients. Also we had a limitation that our study was not double-blinded as the formulations were dissimilar.

In conclusion, the study shows that fluconazole on topical use is comparable to clotrimazole regarding efficacy and safety in treatment of mild to moderate grades of dermatophytosis. Fluconazole 0.5% gel may present as a preferable alternative for topical treatment of dermatophytosis.

References

1. Hay RJ, Ashbee HR. Mycology. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. *Rook's Textbook of Dermatology. Vol 2. 8th ed.* London: Wiley-Blackwell; 2010. p. 36.1.
2. Marques SA, Robles AM, Tortorano AM *et al*. Mycoses associated with AIDS in the third world. *Med Mycol*. 2000;**38**:269-79.
3. Calvin O M, Thomas JL. Eczema, psoriasis, cutaneous infections, acne and other common skin disorders. In: Fauci, Braunwald, Kasper, *et al* editors. Harrison's Principles of Internal Medicine. Vol 1. 17th ed. New York: McGraw-Hill; 2008. P. 318.
4. Sharma RP, Sharma NK, Gupta S, Agarwal AK. Comparative study of topical imidazoles in dermatophytosis. *Indian J Dermatol Venereol Leprol.* 1993;**59**:57-9.
5. Barnetson RS, Marley J, Bullen M *et al*. Comparison of one week of oral terbinafine (250 mg/day) with four weeks of treatment with clotrimazole 1% cream in interdigital tinea pedis. *Br J Dermatol.* 1998;**139**:675-8.
6. Bennett JE. Antifungal agents. In: Brunton LL, Lazo JS, Parker KL editors. *Goodman & Gillman's The Pharmacological Basis of Therapeutics. 11th ed*. Philadelphia: McGraw-Hill; 2006. P. 1233-37.
7. Kisan J, Kadam V, Sambhaji P. Formulation and evaluation of lecithin organogel for topical delivery of fluconazole. *Curr Drug Delivery*. 2009;**6**:174-83.
8. Shah RR, Magdum CS, Wadkar KA, Naikwade NS. Fluconazole topical microemulsion: preparation and evaluation. *Res J Pharm Tech*. 2009;**2**:353-7.
9. Banerjee M, Ghosh, Gangopadhyay DN *et al*. Comparative evaluation of effectivity and safety of topical amorolfine and clotrimazole in the treatment of tinea corporis. *Indian J Dermatol*. 2011;**56**:657-62.
10. ***Fungal diseases. In: Wolff K, Goldsmith LA, Katz SI, et al., editors. *Fitzpatrick's Dermatology in General Medicine. 17th edn, Vol 2*. McGraw Hill; 2008. P. 1807-10.
11. Gupta AK, Albreski D, Del Rosso JQ, Konnikov N. The use of the new oral antifungal agents, itraconazole, terbinafine, and fluconazole to treat onychomycosis and other dermatomycoses. *Curr Problems Dermatol.* 2001;**13**:220-46.
12. Suchil P, Gei FM, Robles M *et al*. Once-weekly oral dose of fluconazole 150 mg in the treatment of tinea corporis/cruris and cutaneous candidiasis. *Clin Exp Dermatol.* 1992;**17**:397-401.
13. Koletar SL, Russell JA, Fass RJ, Plouffe JF. Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother*. 1990;**34**:2267-8.
14. Sobel JD, Brooker D, Stein GE *et al*. Single oral dose fluconazole compared with conventional clotrimazole topical therapy of Candida vaginitis. *Am J Obstet Gynecol.* 1995;**172**:1263-8.
15. Fernández-Torres B, Carrillo AJ, Martín E *et al*. In vitro activities of 10 antifungal drugs against 508 dermatophyte strains. *Antimicrob Agents Chemother*. 2001;**45**:2524-8.
16. Yim SM, Ko JH, Lee YW *et al*. To compare the efficacy and safety of fluconazole cream with flutrimazole cream in the treatment of superficial mycosis: a multicentre, randomised, double-blind, phase III trial. *Mycoses.* 2010;**53**:522-9.
17. Aste N, Baldari U, Bellini M *et al*. Efficacy and Tolerability of the topical formulation of fluconazole 0.5% (gel containing an emulsion oil/water) for the treatment of dermatomycoses with localized lesions. *Italian J Dermatol Venereol.* 1999;**134**:61-5.
18. Stary A, Soeltz-Szoets J, Ziegler C, et al. Comparison of the efficacy and safety of oral fluconazole and topical clotrimazole in patients with candida balanitis. *Genitourin Med.* 1996;**72**:98-102.