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Original Article

Clinical Efficacy of Topical Clotrimazole Versus Combination of Isoconazole Nitrate with Diflucortolone Valerate in Tinea Corporis

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Abstract:
Introduction: Tinea corporis also known as 'ringworm' is dermatophytosis of the trunk. It usually presents as an annular plaque with a slightly raised and often scaly, advancing border. Topical azoles in combination with steroids are commonly prescribed. But it is unclear whether they are superior to topical azoles alone or not.
Objective: To compare the clinical efficacy of 1% topical clotrimazole cream vs combination of 1% isoconazolenitrate (ISN)with 0.1%diflucortolone valerate (DFV) cream in patients of tinea corporis.
Methods : A randomized controlled trial was performedon 380 patients of outdoor dermatology unit of Pakistan Institute of Medical Sciences, Islamabad. They were randomly allocated to two groups by lottery method named Group A who were given topical 1% clotrimazole cream (an antifungal) and Group B who were given topical 1% isoconazole nitrate (an antifungal) and 0.1% diflucortolone valerate cream (a corticosteroid). Both groups were asked to apply respective cream twice daily for two weeks.
Results: Among 190 patients of study group A, where 123 (64.70%) patients showed complete clinical cure, 67 (35.3%) still had existent any of the three signs of tinea corporis, hence had negative clinical efficacy. Comparatively in group B, 126 (66.3%) patients showed complete clinical cureand 64 (34.70%) showed persistence of either of the clinical signs of tinea corporis after treatment. Even though the clinical efficacy showed slightly better results with ISN and DFV group, the difference was also not statistically significant. (d.f. 1, χ statistic 0.10, p- value 0.74)
Conclusion: There is no significant difference in clinical efficacy of clotrimazole vs isoconazole nitrate and diflucortolone valerate cream and both are effective treatments for tinea corporis. Azole monotherapy being cheaper should be preferred over combination treatment.
Key Words: Clotrimazole, isoconazole nitrate, difucortolone valerate, tinea corporis

Introduction

Dermatophyte infection of skin of the trunk andextremities excluding hands and feet isknownastineacorporis.[1]The most common dermatophytes that cause tinea corporis are *T. rubrum, T. mentagrophytes, M. canis* and *T. tonsurans*.A survey conducted by the World Health Organization on the prevalence of fungal infections has shown that 20% of people presenting for clinical advice are suffering from cutaneous fungal infections worldwide.[2]Tinea corporis usually presents clinically as pruritic, single or grouped red edematous scaly papules, which progressively enlarge to form annular or nummular erythematousplaques,oftenwithcentralclearingand peripheralscale.Lesscommonly, vesicles,pustulesor large blisters may be clinically evident.[3,4]

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Although tinea corporis does not cause mortality or significant morbidity but produces chronic, difficult-to-treat cutaneous lesions. Furthermore, they lead to a decline in patient quality of life and cause disfigurement.[5] Direct microscopic examination of a KOH (potassium hydroxide) mounted preparation is the most simple and important test for diagnosing tinea corporis.[6.] Most infections can be cured with topical treatments, whereas immunocompromised

hosts or very extensive and severe infections might require additional oral treatment. Different groups of antifungals are available which include azoles, allylamines, benzylamines, hydroxypyridones and thiocarbamates, but it is uncertain which are the most effective.[7] The azoles are the most widely used antifungal drugs.There are two groups of azoles in current clinical use: the imidazoles, and triazoles. Isoconazole and clotrimazole belong to the imidazole group.[8]Clotrimazole has been widely used topically for the treatment of tinea corporis and there is no report of resistance to this drug in dermatophytosis till now.[9]Isoconazole nitrate (ISN)is a broad-spectrum antimicrobial agent with a highly effective antimycotic and gram-positive antibacterial activity, a rapid rate of absorption and low systemic exposure potential. Diflucortolone valerate (DFV) is a potent class III corticosteroid[8]

Controversy exists on the use of antifungals with corticosteroids. One view is that it provides a synergistic benefit in this condition because the steroid rapidly represses the inflammation responsible for the infection-related distress, while the antimycotic effectively targets the pathogen.[10,11] One of the example is the combination of ISN with the DFV. Compared with ISN monotherapy, combination has a faster onset of antimycotic action, faster relief of itch and other inflammatory symptoms, improved overall therapeutic benefits and improved mycological cure rate. The rapid alleviation of itch results in less damage to the skin barrier due to scratching, and therefore, reduces the chance of secondary bacterial infections. It also increases the local bioavailability of ISN and prolongs its activity, leading to more rapid normalization of skin conditions.[8] However, this combination should be used judiciously in the treatment of cutaneous fungal infections and may not be appropriate for use in children.[12]Mark D. Andrews, in his article have not recommended them because of a greater risk of adverse effects, primarily from the higher-potency steroid component. Cure rates are lower and the cost is higher with combination therapy than with antifungal creams alone.[12,13]Similarly, Kelly in his review has not recommended them because these preparations are less effective.[1,12] In a Cochrane review comprising of 129 randomized controlled trials with 18,086 participants evaluated a range of interventions; mostly azoles. Combinations of azoles with corticosteroids were evaluated and found to be slightly more effective than azoles for clinical cure, but there was no statistically significant difference with regard to mycological cure. This treatment approach is still considered controversial and subject to debate, and some clinicians even consider this a form of 'mistreatment', and that it might lead to tinea incognito. The overall duration of the included studies was too short for any assessment and side effects were not reported. So, they could be justified for inflammatory dermatophytosis for short duration but evidence for this is weak.[7]

At present, there is no consensus in literature on the use of combination of topical antifungals with corticosteroids in the treatment of tinea corporis. So the purpose of this study was to compare the efficacy of plain imidazole (clotramizole) alone versus combination of imidazole and steroid (ISN and DFV). Thus, it will help us in managing such a common skin problem much more effectively.[14]

Material And Methods

In this randomized controlled trial, patients with the clinical diagnosis of tinea corporis made by a dermatologist were selected and the presence of one of its clinical signs i.e., pruritus, scaling and erythema noted. Skin scrapings in KOH, done only in selected cases, should show fungal hyphae. Sample size was calculated by WHO sample size calculator and 380 patients were included in study. Consecutive non-probability sampling is done. Patients with tinea corporis who have not received systemic or topical antifungal agents and steroids during the last 1 month were included in study. However, diabetics, immunodeficient, pregnant, lactating or those who are allergic to any of the study drug were excluded from study. After approval from the ethical committee of hospital, informed consent was obtained from the patients fulfilling the criteria and wishing to participate in the study. Each subject was required to attend the clinic on two occasions during the study. In the first visit, the patient was screened for any excluding factor and demographic profile was recorded. Detailed medical history was taken and clinical examination of the potential subjects was done to make the diagnosis of tinea corporis. The patients were divided into two groups randomly using random number table. One group was allocated topical 1%clotrimazole cream and second group was given combination of 1% isoconazole and 0.1%diflucortolone valerate cream. The patients were instructed to apply the cream thinly to the affected area twice daily for 2 weeks. Patients enrolled for the study were not permitted to concomitantly use any other antifungal other than the trial drug or any other topical medication. No systemic antihistamine was

given. All the data was recorded on a specially designed performa by researcher separately for each case and duly verified by consultant and evidenced with detection of fungal hyphae in KOH in difficult cases. The second visit was on day 14 when the patient was called and compliance determined from the trial diary. Clinical examination was repeated and physical scores assessed based on efficacy parameters after evaluation of signs and symptoms. Clinical efficacy is the clearance of all the signs and symptoms of tinea corporis i.e., absence of pruritus, erythema and scaling at the end of two weeks of treatment.

Statistical analysis

Data was analyzed in SPSS version 16. The quantitative variables like age and duration of illness were calculated by taking means and standard deviation. The qualitative variables like gender and outcome variable like efficacy were calculated by taking frequency and percentages. Confounding factors like age, gender, site, size and duration of illness were controlled by stratification through Mantel Haenszel Chi square test. Comparison of efficacy in two groups was done by Chi-Square test. p value of <0.05 was considered as significant.

Results

A total of 380 patients were included in the study, amongst whom 190 were in group A receiving topical 1% clotrimazole cream and group B comprised of same number of patients received 1% isoconazole and 0.1% diflucortolone valerate cream. The mean age of all 380 patients was 35.25 ±12.65 years (range 14-60 years).Regarding gender, 185 (48.7%) were males while 195 (51.3%) were females. Out of 343 patients, mean duration of illness was found to be 18.81 days (SD± 7.17 days; range 8 to 48 days). Out of 375 patients, the mean size was recorded as 3.55 cm (SD±0.99 cm; range (2- 8cm). Briefly discussing group characteristics, no statistically significant difference was found in both study groups regarding age (p=0.87), sex (p=0.60), duration of illness (p=0.89),size of lesion (p=0.62) as shown in Table 1 and site of lesion (p=0.62) shown in Table 2. Both male and female are equal in group A whilein group B, 52.63% were females and 47.37% were males, this difference was not statistically significant (chi statistic 0.263, p-value 0.60).

Table I. Comparison of age, duration of illness & size of lesion in study groups

CHARACTERISTICS	STUDY GROUPS	n (number of patients)	MEAN	STANDARD DEVIATION	t-VALUE	p-VALUE
AGE IN YEARS	Group A	190	35.15	12.79	-0.15	0.87
	Group B	190	35.35	12.55		
DURATION OF ILLNESS IN DAYS	Group A	174	18.76	7.56	-0.12	0.89
	Group B	169	18.86	6.76		
SIZE OF LESION IN CENTIMETERS	Group A	187	3.58	0.96	0.49	0.62
	Group B	188	3.53	1.02		

The treated lesions were located in arms in 96 patients (25.3%), legs in 111 patients (29.2%),while majority had lesions in trunk 173 (45.5%). The sites of lesion were compared in both study groups as displayed in table II and no statistically significant difference was observed in both study groups (d.f. 2, χ statistic 0.94, p- value 0.62)

Table II Comparison Of Sites Of Lesion In Study Groups

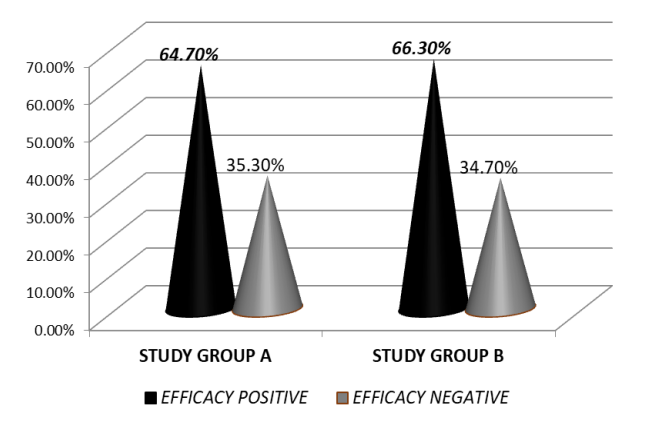
SITE OF LESIONS	*STUDY GROUPS*					
	GROUP A (n=190)		*GROUP B(n=190)*		*TOTAL*(N=380)	
	Frequency	*Percentage*	Frequency	*Percentage*	Frequency	*Percentage*
ARMS	**44**	*45.8%*	**52**	*54.2%*	**96**	*100.0%*
LEGS	**58**	*52.3%*	**53**	*47.7%*	**111**	*100.0%*
TRUNK	**88**	*50.9%*	**85**	*49.1%*	**173**	*100.0%*

Comparison of clinical efficacy in both study groups

Amongst 190 patients of study group A, where 123 (64.70%) patients showed positive clinical efficacy and in group B, 126 (66.3%) patients showed positive clinical efficacy. Even though the clinical efficacy showed slightly better results with ISN and DFV group, the difference was also not statistically significant. (d.f. 1, χ statistic 0.10, p- value 0.74) as shown in Table III and Graph 1.

Table III: Comparison of Efficacy between both groups

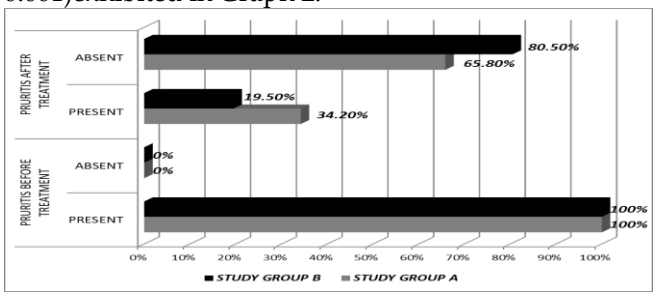
Group	Efficacy		Total
	Positive	Negative	
Group A (clotrimazole)	123 (64.7%)	67 (35.3%)	190
Group B (isoconazole +diflucortolone valerate)	126 (66.3%)	64 (34.7%)	190
Total	249	131	380



Graph 1: Comparison Of Clinical Efficacy In Both Study Groups

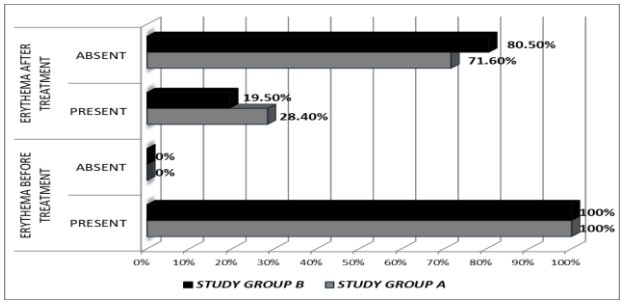
Disappearance of individual features of tinea corporis

Taking each of the features of tinea corporis individually, following statistics are shown. Prurius was observed to have disappeared in greater number of patients in group B i.e.,153 (80.5%) comparable to 125 (65.8%) patients of study group A and this difference was highly statistically significant in both study groups (d.f. 1, χ statistic 10.50, p- value 0.001)exhibited in Graph 2.



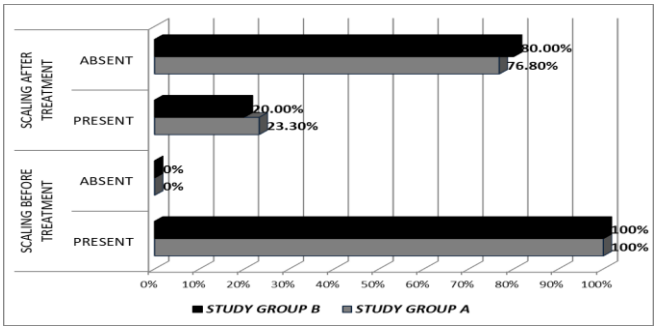
Graph 2: Comparison Of Pruritus At Baseline With Pruritus After Treatment In Both Study Groups

Erythema was found to have disappeared in 136 (71.6%) patients of group A and 153 (80.5%) patients of group B. This difference was also statistically significant (d.f. 1, χ statistic 4.17, p- value 0.04) and is graphically shown in Graph 3.



Graph 3: Comparison of Erythema at Baseline with Erythema after Treatment in Both Study Groups

Scaling was found to have disappeared in 146 (76.8%) patients of group A however in 152 (80.50) patients of group B. This difference was not statistically significant (d.f. 1, χ statistic 0.56, p- value 0.45) and this comparison is graphically displayed in graph 4.



Graph 4: Comparison of Scaling at Baseline With Scaling After Treatment In Both Study Groups

Concominant existence of two or more features of tinea corporis after treatment

After two weeks of treatment, concomitant existence of any two or all the three features of tinea corporis was also looked for in both study groups and results are displayed in Table III.

Table Iii Comparison of Concomitant Existence Of Erythema, Pruritus And Scaling, Either Any Two Or All Three In Study Groups

CONCOMITANT PRESENCE OF FEATURES OF TINEA CORPORIS AFTER TREATMENT	STUDY GROUPS		
	Group A	Group B	Total
Both Pruritus & Erythema	54 (62.0%)	33 (37.9%)	87 (100%)
Both Pruritus & Scaling	42 (76.4%)	13(23.6%)	55(100%)
Both Erythema & Scaling	38 (73.1%)	14 (26.9%)	52 (100%)
Pruritus, Erythema & Scaling	38 (76.0%)	12 (24.0%)	50 (100%)

Stratified analysis to control any confounding effect of age, gender, site and size of lesion and duration of illness:

To further control any potential confounding effect of these variables, stratified analysis was also performed. First the occurrence of clinical efficacy was not statistically significant based on Pearson chi square test, for gender (p-value 0.30), age (p-value 0.32), duration of illness (p-value 0.45), site of lesion (p-value 0.23) and size of lesion (p-value 0.59).

Stratified analysis was also done through Mantel Haenszel Chi square test, to get exclusive association of treatment type and clinical efficacy after controlling for gender, age, duration of illness, size and site of lesion.

The p values of less than 0.05, showed no association of treatment type with clinical efficacy, after controlling, as shown in Table IV.

Table IV: Stratified Analysis After Controlling For Gender, Age, Duration Of Illness, Size And Site Of Lesion

VARIABLES CONTROLLED	STUDY GROUPS	EFFICACY POSITIVE	EFFICACY NEGATIVE	PEARSONS CHI SQUARE	MANTEL HAENSZEL CHI SQUARE
MALES	A	66	29	χ statistic 1.68 d.f 1	χ statistic 0.05 p-value 0.80
	B	60	30	p-value 0.68	
FEMALES	A	57	38	χ statistic 0.75 d.f 1	
	B	66	34	p-value 0.38	
AGE UP TO 30 YEARS	A	55	38	χ statistic 1.21 d.f 1	χ statistic 0.03 p-value 0.85
	B	59	29	p-value 0.27	
AGE ABOVE 30 YEARS	A	68	29	χ statistic 0.44 d.f 1	
	B	67	35	p-value 0.50	
ILLNESS UPTO 30 DAYS	A	104	53	χ statistic 0.02 d.f 1	χ statistic 0.04 p-value 0.83
	B	105	53	p-value 0.96	
ILLNESS >30 DAYS	A	19	14	χ statistic 0.44 d.f 1	
	B	21	11	p-value 0.50	
LESION ON ARMS	A		18	χ statistic 0.06 d.f 1	χ statistic 0.06 p-value 0.79
	B	32	19	p-value 0.80	
LESION ON LEGS	A	40	18	χ statistic 1.81 d.f 1	
	B	30	23	p-value 0.17	
LESION ON TRUNK	A	57	31	χ statistic 2.27 d.f 1	
	B	64	21	p-value 0.13	
SIZE OF LESION UPTO 3 CM	A	43	23	χ statistic 0.09 d.f 1	χ statistic 0.05 p-value 0.80
	B	47	28	p-value 0.75	
SIZE OF LESION > 3 CM	A	80	44	χ statistic 0.46 d.f 1	
	B	79	36	p-value 0.49	

Discussion

Dermatophytosis, rarely dangerous or life threatening, are important because of their worldwide distribution, frequency, person-to-person transmission, and morbidity. Furthermore, severe infections or those refractory to treatment may be the first indication of an underlying immunodeficiency[1].

Topical azoles treatments are effective in tinea corporis in terms of clinical and mycological cure rates. Regarding combinations therapy of topical steroids and antifungals though there is no standard guideline. There is insufficient evidence to confidently assess relapse rates in the individual or combination treatments.[15] In a randomized double-blind study of 294 patients in Thailand, 0.1% diflucortolone was combined with 1.0% isoconazole nitrate was compared with a plain 1.0% clotrimazole formulation. The results were significantly better for the diflucortolone plus isoconazole nitrate combination in terms of remission of symptoms, and after 1 week the mycological cure rates were also better, as shown in potassium hydroxide and culture investigations.[16]

In another multicenter, retrospective study on 58 patients of tinea inguinalis (another form of dermatophytosis) mycological, clinical efficacy and tolerability of isoconazole nitrate alone vs isoconazole nitrate and diflucortolone valerate was compared.

Treatment results with the combination of isoconazole nitrate and diflucortolone valerate were superior regarding erythema and pruritus. Mycological cure rates were similar in both groups of patients.[17]

There continues to be a number of patients receiving combination antifungal/corticosteroid creams. One of the reason is that the non-dermatologists prescribe them as they lack the experience in recognizing and differentiating a fungal infection from a noninfectious inflammatory dermatitis, so they choose to use a combination agent in an attempt to cover both diagnoses. However, superficial fungal infections generally can be treated successfully with a single-agent topical antifungals. Many authors recommend against the use of combination antifungal/corticosteroid creams because of the greater cost, lower efficacy, and greater risk of adverse effects. However, patients who complain of intense pruritus in association with an infection-induced dermatitis are best treated by simultaneous application of a low- or medium-potency topical corticosteroid for a limited period of 7-10 days, along with a topical antifungal agent that will be continued until clinical findings resolve.[14]

Similarly, experts from India, considering the misuse of topical steroids already prevailing in their country, vetoed its use in tinea corporis.[17]Similar situation of topical steroids exist in our country.

In this study, isoconazole 1% is given in combination with 0.1% diflucortolone valerate and its clinical efficacy is compared with 1% clotrimazole (another member of imidazole group). The results however showed no significant difference in clinical efficacy in both groups at the end of 2 weeks of treatment.

In the present study, though clinical efficacy was not different in both groups, but erythema and pruritus disappeared in a significant number of patients with combination therapy. Erythema was found to have disappeared in 136 (71.6%) patients of clotrimazole group but in 153 (80.5%) patients of ISN and DFV group. This difference was statistically significant (d.f. 1, χ statistic 4.17, p- value 0.04). Similarly, pruritus resolved in 153 (80.5%) of ISN and DFV group as compared to 125 (65.8%) patients of clotrimazole group and this difference was highly statistically significant in both study groups (d.f. 1, χ statistic 10.50, p- value 0.001). this showed steroid component has got a beneficial effect on the resolution of erythema and pruritus as compared to topical azole alone.

Primary outcome in my study was the disappearance of all the three signs (erythema, pruritus and scaling) of tinea corporis. However if we consider any two signs together instead of three, results also show a favourable outcome of ISN and DFV group. After treatment, both pruritus & erythema were still present in 54 (62.0%) of clotrimazole group as compared to only 33 (37.9%) of ISN and DFV group. Similarly, both pruritus & scaling persisted in 42 (76.4%) of clotrimazole while just in 13 (23.6%) of combination group. Erythema and scaling if studied in combination resisted to treatment in 38 (73.1%) of clotrimazole group while only in 14 (26.9%) of ISN and DFV group. All the 3 signs (pruritus, erythema and scaling) after treatment persisted in 38 (76.0%) of clotrimazole users while only in 12 (24.0%) of ISN and DFV users.

One of the limitations of our study is that efficacy is mainly based on clinical signs and symptoms and mycological examination (KOH examination or culture) is only done for selected patients. However, as the clinical features of tinea corporis are very typical, so it is the usual practice in busy outpatient department of developing countries. Another limitation is that patients are only followed up for 2 weeks and no follow up beyond that period is done.

Despite showing greater improvement in erythema and prorates with ISN and DFV than with clotrimazole group, there is no significant difference in the overall efficacy in both groups. Considering the high cost of corticosteroid azole combinations, azole monotherapy should be considered as first line treatment in patients on tinea corporis.

Conclusion

Topical Isoconazole nitrate with diflucortolone valerate and topical clotrimazole are effective treatments for tinea corporis and there is no significant difference in their clinical efficacy.

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B. Experimentation/Study Conduction
C. Analysis/Interpretation/Discussion
D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis