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ORIGINAL ARTICLE

Efficacy and safety of oral ivermectin combined with topical permethrin in treatment of scabies.

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ABSTRACT… Objective: To determine the efficacy and safety of oral ivermectin and topical permethrin when given either alone or in combination in patients with scabies. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Dermatology, Sheikh Zayed Hospital, Lahore. **Period:** April, 2022 to September, 2022. **Material & Methods:** A total of 369 patients with scabies, age 18-60 years and both genders were enrolled after taking written informed consent and were randomly and equally divided into three groups. Group A received 5% topical permethrin, Group B received oral Ivermectin and Group C received a combination of topical permethrin and oral ivermectin. Efficacy and safety was assessed over 3 weeks. **Results:** The mean age of the patients was 41±10.9. There were 164 (44.4%) males and 205 (55.6%) females. The treatment in Group A, B and C was efficacious in 70.7%, 67.5% and 84.6% patients respectively and there was a significant difference between Group A versus C (p=0.009) and Group B versus C (p=0.002). In terms of side effects, 11.4% patients in Group A, 13% in Group B and 17% in Group C experienced side effects. **Conclusion:** The combination therapy was more efficacious than either treatment alone in patients with scabies, however, the side effects were more compared to single agent.

Key words: Efficacy, Scabies, Ivermectin, Permethrin.

INTRODUCTION

Scabies is among the commonest transmissible diseases round the globe.[1] It is a parasitic infection of the skin which is caused by a mite named Sarcoptes scabiei.[1] It is transmissible by direct contact and is characterized by intense itching and formation of nodules, papules and vesicles over the skin.[1] In few cases, specifically in immunocompromised patients, it can lead to formation of crusts over the skin and hyperinfestation that leads to superimposed bacterial infection which is associated with high rates of morbidity as well as mortality due to septicemia.[2] According to the study on the Global Burden of Disease, it was revealed that scabies was prevalent in 200 million people, globally.[3] The rate of prevalence of this skin disease is high in tropical areas, countries with poor resources and overcrowded zones[3]. Because of lower middle socioeconomic status, the Pakistani population is vulnerable to this virus.[4] It has been estimated that the prevalence rate of scabies among dermatological disorders in Pakistan is 38.15%.[4]

Scabies can be treated with either topical or oral treatments, or a combination of the two.[5] The first line of treatment frequently comprises topical neurotoxic insecticidal drugs (permethrin, ivermectin, malathion, spinosad, lindane, and benzyl benzoate), which cause mite paralysis and death.[5] Topical permethrin is the most generally recommended first-line therapy for classic scabies in most clinical practice guidelines and is currently utilized in local practice.[6] It operates by inhibiting sodium channels, causing mites and eggs to depolarize, paralyze, and die.[6] However, topical treatment is difficult because it needs whole-body application, which is costly and cumbersome, resulting in poor compliance and treatment failure due to insufficient application.[7]

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Furthermore, the presence of lesions which are eczematous or impetiginized may limit its use because irritation of skin may occur following application of permethrin topically.[7]

Ivermectin, an old broad-spectrum antiparasitic medicine, is the sole oral scabicide used in mass drug administration in endemic populations, and it is FDA-approved for scabies in various countries.[8] Combination oral and topical treatment has also been employed in crusted scabies, as well as recurring, widespread, or recalcitrant classic scabies in susceptible populations such as diabetics and inhabitants of nursing homes.[9] In a few randomized controlled trials (RCTs), the combination of oral ivermectin with topical permethrin demonstrated increased efficacy, while side effects were higher than with either treatment alone.[10]

The international and local data on efficacy and safety of combination of oral and topical agents in scabies is relatively less. Furthermore, it is not clear as to which therapy has superiority over the other in terms of achieving cure. Therefore, the aim of the current study is to determine the efficacy and safety of oral ivermectin and topical permethrin when given either alone or in combination in patients with scabies. The study will help in guiding about a better treatment strategy which is effective clinically and is associated with lesser side effects and thus can help in reducing patients distress and further morbidity associated with the condition by achieving early cure.

MATERIAL & METHODS

It was a randomized controlled trial. The study was carried out at the Department of Dermatology, Sheikh Zayed Hospital, Lahore, from April, 2022 to September, 2022 after taking approval from the Ethical review committee (ERC letter number SZMC/FCPS/169/2022). A total of 369 patients with newly diagnosed scabies, of age 18-60 years and both genders were enrolled in the study, after taking written informed consent. The sample size was calculated keeping the expected percentage of scabies as 38.15%[4] with 5% margin of error and 95% confidence interval. Non-probability consecutive sampling technique was used. Patients who presented with atypical symptoms such as crusted scabies, scabies incognito, those allergic to permethrin or ivermectin, those with a history of treatment previously and with comorbid diseases such as diabetes, hypertension, liver and kidney disorders were excluded from the study.

The diagnosis of scabies was established clinically if there was a history of intense itching at night in the patient as well as there were similar complaints in the close member of the family or contacts and on clinical examination, there was presence of lesions which were typical of scabies such as burrows, papules, pustules, vesicles or nodules at body sites which are classical of scabies i.e. at interdigital folds of the hands, the flexor sides of the elbows and wrists, the axillary folds both anteriorly and posteriorly, waist, the periumbilical areas, shaft of penis, vulva, gluteal region and the lateral aspects of the feet.

The primary outcome measure to be assessed was efficacy of the treatment. Treatment efficacy was labeled if on follow up i.e. at 3 weeks following treatment, the disease was cured i.e. there were no new lesions clinically such as papules, classical burrows and vesicles, there was improvement in old lesions as well as in the severity of itching. Secondary outcome measures that were assessed were adverse effects related to the treatment i.e. presence of burning sensation on skin, worsening of itching, skin rash, numbness, headache, dizziness, muscle pain, nausea and diarrhea.

Detailed demographic history, clinical history and physical examination of all patients was carried out and findings were noted down on a predesigned proforma. Scabies was graded into four grades and four degrees of severity depending on the lesions found on examination i.e. Grade 0 (No lesion)-if the patient was free of any lesions were present, Grade 1 (mild severity)-if 10 or fewer lesions were present, Grade 2 (moderate severity)- if 11 to 49 lesions were present and Grade 3 (Severe severity)-if 50 or more lesions were present. Furthermore, the severity of itching was assessed in all patients

using Visual Analogue scale (VAS) score, where 0 showed no itching and 10 showed worst itching. The itching was further categorized as mild if the score was 1-3 on VAS, moderate if the score was 4-6 on VAS and severe if the score was 7-10.

Following evaluation, all patients were then divided into three groups of equal number i.e. 123 in each group, by block randomization technique. Patients in Group A received 5% topical permethrin, those in Group B received oral Ivermectin and those in Group C received a combination of topical permethrin and oral ivermectin. In Group A, patients were given 30g of 5% permethrin cream and were instructed to apply it to their entire body, from neck to toe, and to leave it on their skin for at least 8 hours. Participants were advised to take a warm water scrub bath before application and the following morning. After 7 days, a repeat application of the same treatment was recommended. In Group B, patients were given ivermectin orally in a single dose of 200mcg/kg body weight with meals, which was repeated after 10 days. In Group C, both treatments were given as a combination in similar doses as given alone.

During the trial, patients were told not to use any additional medications, including antipruritic medicines. During the initial appointment, participants were counseled regarding the treatment of family members and close acquaintances. They were also instructed to avoid fomite transmission by washing and drying all contaminated garments and bedding in the sun. All patients were followed over a period of 3 weeks i.e. they were assessed at 1st, 2nd and 3rd week after initiating treatment. All participants were assessed for the efficacy as well as safety of the treatment. During follow up visits, patients were examined again thoroughly and the findings were compared to the baseline and were subjected to statistical analysis.

Patients were called for follow up at 1st, 2nd and 3rd week for assessment of compliance and for evaluation of treatment efficacy as well as safety of treatment. Each of the three visits included a thorough inspection of the full body surface, which was compared to the baseline clinical grading score and itching grading score. At the end of the trial, those patients who were not cured as assessed clinically were shifted to the intervention which showed better efficacy.

Data was analyzed using SPSS version 25.0. Quantitative data such as age of the patients, VAS score for itching was presented as mean and standard deviation. Qualitative data such as gender, severity of scabies, severity of itching, efficacy of treatment and side effects were presented as frequency and percentages. Chi square test was applied to compare the outcomes between the three groups and a p value of ≤ 0.05 was considered as significant statistically.

RESULTS

The mean age (in years) of the patients was 41 $\pm$10.9, the mean number of lesions were 37$\pm$ 16.57 and mean VAS score for itching was 7$\pm$ 1.95(Table-I). There were 164 (44.4%) males and 205 (55.6%) females (Table-II). The severity of scabies was mild in 58 (15.7%) patients, moderate in 206 (55.8%) patients and severe in 105 (28.5%) patients. Itching was mild in severity in 33 (8.9%), moderate in severity in 142 (38.5%) and severe in intensity in 194 (52.6%). The treatment in Group A, B and C was efficacious in 70.7%, 67.5% and 84.6% patients respectively (Table-II). Comparison of all three groups in terms of efficacy revealed that there was no significant different in the efficacy of Group A versus B as indicated by a p value of >0.05, however, there was a significant difference between Group A versus C ($p=0.009$) and Group B versus C ($p=0.002$), thus denoting that combination therapy was more efficacious than either treatment alone (Table-III). In terms of side effects, 11.4% patients in Group A, 13% in Group B and 17% in Group C experienced side effects i.e. combination treatment was associated with more side effects compared to either drug given alone (Table-IV).

Variable	Mean and Standard Deviation
Age (in years)	41$\pm$10.9
Number of lesion	37$\pm$16.57
Visual analog scale score	7$\pm$1.95

Table-I. Mean of quantitative variables

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Variables	Frequency (Percentage)
Gender:	
Males	164 (44.4%)
Females	205 (55.6%)
Severity of scabies:	
Mild	58 (15.7%)
Moderate	206 (55.8%)
Severe	105 (28.5%)
Severity of itching/pruritus:	
Mild	33 (8.9%)
Moderate	142 (38.5%)
Severe	194 (52.6%)
Efficacy of Topical Permethrin alone (Group A):	
Yes	87 (70.7%)
No	36 (29.3%)
Efficacy of Oral Ivermectin alone (Group B):	
Yes	83 (67.5%)
No	40 (32.5%)
Efficacy of Combined Topical Permethrin and oral Ivermectin (Group C):	
Yes	104 (84.6%)
No	19 (15.4%)

Table-II. Frequency of qualitative variables

Efficacy	Group			P-Value
	A n=123	B n=123	C n=123	
Yes	87 (70.7%)	83 (67.5%)	104 (84.6%)	0.581[1] 0.009[2] 0.002[3]
No	36 (29.3%)	40 (32.5%)	19 (15.4%)	

Table-III. Comparison of efficacy between three groups

[1]p value for intergroup comparison of group A and B
[2]p value for intergroup comparison of group A and C
[3]p value for intergroup comparison of group B and C

DISCUSSION

The current study results revealed that in patients with scabies, the combination of oral ivermectin and topical permethrin was superior in efficacy compared to either treatment alone. However, in terms of side effect profile, the combination therapy led to more side effects compared to either treatment alone in patients with scabies. When single treatments were compared with each other, there was no statistically significant difference between both in terms of efficacy i.e. topical permethrin alone and oral ivermectin alone were similar in efficacy.

Side Effects	Group		
	A (topical permethrin alone) n=123	B (Oral ivermectin alone) n=123	C (topical permethrin and oral ivermectin) n=123
No Side Effect	109 (88.6%)	107 (86.9%)	102 (82.9%)
Burning Sensation On The Skin	10 (8.1%)	0 (0%)	4 (3.3%)
Worsening Of Itching	2 (1.6%)	0 (0%)	1 (0.8%)
Skin Rash	2 (1.6%)	0 (0%)	3 (2.4%)
Numbness	0 (0%)	0 (0%)	1 (0.8%)
Headache	0 (0%)	3 (2.4%)	2 (1.6%)
Muscle Pain	0 (0%)	4 (3.3%)	4 (3.3%)
Nausea	0 (0%)	4 (3.3%)	3 (2.4%)
Diarrhea	0 (0%)	3 (2.4%)	2 (1.6%)
Dizziness	0 (0%)	2 (1.6%)	1 (0.8%)

Table-IV. Comparison of side effects between three groups

There is variable evidence of the effectiveness as well as safety of topical permethrin and oral ivermectin for treating patients who have scabies.[11,12] The evidence is limited for suggesting that the combination of topical permethrin and oral ivermectin has higher efficacy compared to either treatment given alone.[13,14]

In a systematic review, it was revealed that the combination therapy i.e. oral ivermectin and topical permethrin showed higher efficacy compared to permethrin alone or ivermectin alone. However, the rates of side effects were higher in the combination treatment compared to when single agent was used.[2] The current study similarly assessed the efficacy of combination therapy versus single therapy alone and revealed

that combination of topical permethrin and oral ivermectin was more effective compared to single treatment. The results of our study are consistent with findings of previous studies. Dey in his study compared oral ivermectin alone, topical permethrin alone and combination of both in patients with scabies and revealed that the combination of both agents yielded better efficacy compared to oral ivermectin i.e. efficacy of combination therapy was 97% at 4 weeks for improving lesions compared to 91% in the ivermectin group, however, the efficacy of topical permethrin alone was similar to combination therapy i.e. 97%.[15] These findings are inconsistent with our study findings probably because we assessed patients only for a period of 3 weeks whereas Dey assessed them over 4 or more weeks.

Our study revealed that permethrin alone when applied topically was effective in 70.7% patients.

Das *et al.*[16] revealed that topical permethrin when applied alone was effective in curing 93.3% patients and Meenakshi *et al.* revealed that the cure rate was 93.5%.[17] These rates are higher as compared to the results shown by the current study. This difference in the rates of efficacy of topical permethrin may be due to the fact that in our study, the follow up was done for maximum 3 weeks, whereas these researchers assessed the efficacy of treatment over a period of 4 weeks or more.

The efficacy of oral ivermectin alone in our study was 67.5%. In a study by Dey DS, oral ivermectin alone was found to be efficacious in 81% of the patients by the end of two weeks.[15] These rates are much higher compared to our study. This may be because Dey DS enrolled very few patients in the study groups whereas the sample size in our study was comparatively large which could have yielded lesser rates. Goldust *et al.* revealed that at a follow up period of 2 weeks, ivermectin was effective in 85.9% patients and topical permethrin was effective in 92.5% patients and this difference was not significant (p= 0.42).[18] These findings are in line with current study findings in that our study similarly reported that permethrin was more effective compared to oral ivermectin alone, however, the difference was not statistically significant and both can be used for treating scabies when only a single treatment is needed.

The current study supports the use of combination of topical permethrin and oral ivermectin for treating patients with scabies. More trials must be carried out clinically on the new treatment strategies for treating this distressing disease in order to find a treatment which is highly efficacious, has less adverse effects and is cost effective.[19] General public must be educated about it by creating awareness programs especially in high risk people about its control, transmission, prevention and correct topical application.[20]

The current study had certain limitations. Firstly, as the study was single centered so the results cannot be generalized. Secondly, the cost-effectiveness of the treatment was not assessed. Lastly, patients of varying severity were enrolled in the study and the effect of symptoms severity was not assessed so bias can occur.

CONCLUSION

The current study concludes that the combination of topical permethrin and oral ivermectin was more efficacious compared to either treatment given alone. However, the side effect profile of combination therapy was more compared to when single agent was used. Future studies must be carried out on a large sample size and must incorporate comparison with other treatment options as well in order to validate the findings of current study.

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3	Beenish Jabeen Bajwa	Literature review, Data analysis.	
4	Beenish Rahat	Literature review, Data collection.	
5	Tassmia Afzal	Analysis and interpretation of data, drafting of manuscript.	
6	Riffat Naseem	Revisions of final manuscript, approval of final version.