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Better Disease Control by Multidrug Regimen in Scabies: A Randomized Controlled Trial

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Abstract

Background: Scabies is ahighly contagious skincondition with varying morbidity worldwide. The most widely used treatment options for the scabies include topical permethrin 5% and oral Ivermectin with similar efficacy. Treatment failure due to non-compliance is a major problem with the current treatment modalities.

Aim: This study was designed to compare the efficacy of combination treatment to the standard treatment regimen for scabies.

Materials and Methods: A randomized controlled trial was done with 212 patients, divided randomly into two groups Group 1 and Group 2. Group 1 were treated with two-time application of 5% permethrin one week apart while Group 2 were treated with a combination of 5% permethrin and oral ivermectin (200□g/kg) on a single day. Patients were followed up every week for 4 weeks to assess the efficacy and adverse events.

Results: The treatment efficacy in Group 2 was more compared to Group 1 after 2 weeks of follow up (72.6% vs 65.1% after 1 week; 89.6% vs 80.2% after 2 weeks) however, it was not statistically significant. After 4 weeks of follow up, the treatment efficacy in both groups was similar. The reduction in the intensity of itching was almost similar in both the groups at every follow up.

Conclusion: The combination of 5% topical permethrin and oral ivermectin showed earlier resolution of clinical symptoms compared to 5% topical permethrin alone repeated in 1 week. The reduction in the intensity of itch was similar in both groups..

Key words: Combination regimen; Ivermectin; Permethrin; Scabies

Introduction

Scabies-related morbidity varies among the population and is fairly common.[1] Association with STI in adults and secondary infection, impetiginization and rarely Streptococcal pyogenes toxin mediated scarlet fever, and post-streptococcal glomerulonephritis in children may also be seen, though the clinical diagnosis is easy with a classical presentation.[2-5] The treatment options commonly used for this disease include topical permethrin 5% and oral ivermectin 200 μg/kg with similar efficacy.[6, 7] The emergence of resistance and lack of compliance of the patients are the major problems with the current treatment modalities,[8, 9] particularly the standard regimen of repeat application of topical permethrin 5% 1 to 2 weeks apart. We hypothesized that a single use regimen would be equally or more superior to the repeat use regimen due to better patient compliance. The objective of this study was to identify if the combination regimen of topical permethrin 5% along with oral ivermectin 200 μg/kg given on a single day only is equally or more efficacious than the standard regimen of repeat application of topical permethrin 1 week apart.

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Materials and Methods

This was a single center, open labeled, equal randomization [1:1], assessor blinded, double sided, comparative, parallel group clinical study conducted after receiving ethical clearance from the Institutional Review Committee.

Willing patients of either sex, aged 5 to 80 years with a clinical diagnosis of scabies were included. BPKIHS is a tertiary level hospital in Eastern Nepal providing service to patients in nearby 5 districts and from across the border in India. As a teaching hospital, it serves thousands of patients daily on an outpatient basis. The study was conducted at the Department of Dermatology and Venereology from January 2017 to December 2017. After taking written consent, basic demographic and disease related information were inquired and patients were divided randomly into two groups in equal ratio. Group 1 were treated with two applications of 5% permethrin one week apart as standard therapy while Group 2 were treated with the combination of 5% permethrin and oral ivermectin (200μg/kg) on a single day only.

Patients were followed up every week for 4 weeks and assessed for efficacy and adverse events. Physician global assessment scale and visual analog scale was used to record progress. The primary outcome was a reduction in pruritus and the secondary outcome was disappearance of cutaneous lesions.

Sample size with a difference of 10%, power of 80%, and considering alpha error at 5% was estimated at 101 patients in each group, based on similar studies.[5,6] Considering the drop out error of 5% a further 10 patients were added, making 106 patients in each group with a total of 212 cases, 12 months' time period was estimated to reach this number. Patients were shifted to standard treatment in case of treatment failure.

Online randomizer (https://www.randomizer.org/) was used to generate a single factor block randomization with 1:1 allocation using random block sizes 4, 6, and 8. The patient allocation number was provided serially from a closed opaque envelope after getting all prior information about the patient and the disease from the assessor. The details of series were not known to the patients or the assessor.

Statistical analysis was performed using the IBM SPSS software version 11.5. Continuous variables were expressed as the mean or medians whereas categorical variables were expressed as a number. The normality of continuous variables was analyzed by using a Kolmogorov–Smirnov test. The Pearson's correlation analysis was used to statistically analyze to compare the efficacy of the treatment modalities in patients among Group 1 and Group 2. A 95% confidence interval was used and *p*-value of <0.05 was considered statistically significant.

Results

Patients meeting the eligibility criteria were enrolled in the study. Enrollment was done for 1 year from January to December 2017. Each patient was followed up for 4 weeks. Information about the progress was taken over the phone for patients who were lost to follow up to complete the record. The statistical analysis included all the participants who were randomly assigned equally to the 2 groups (n=212) (Figure 1).

The mean age with 2 standard deviations of the patients in Group 1 was 13.40 ± 10.86 years with a median of 13 years. Similarly, the mean age with 2 standard deviations of the patients in Group 2 was 12.75 ± 10.96 years with a median age of 12.5 years. The basic demographic characteristics of the patients in both groups were similar (Table 1). The characteristics of the disease in regard to the duration of disease, nocturnal exacerbation, family history, morphology, and distribution of lesions were similar in both the groups (Table 2). The efficacy of treatment was assessed using a clinical grading assessment of the patients at baseline and at weekly follow up for 4 weeks. The treatment efficacy in group 2 was more compared to group 1 after 2 weeks of follow up (72.6% vs 65.1% after 1 week; 89.6% vs 80.2% after 2 weeks) however, it was not statistically significant. After 4 weeks of follow up, the treatment efficacy in both groups was similar (Table 3). Hence, the patients in Group 2 achieved earlier clinical improvement compared to those in Group 1. However, after a month, the clinical efficacy was similar in both the groups. The reduction in the intensity of itching was almost similar in both the groups at every follow up (Table 4). Adverse events were noted in 5 (4.7%) patients in group 1 and 7 (6.6%) patients in group 2 and were mild in nature not requiring termination of treatment or hospital admission.

Discussion

The problems during treatment of scabies include treatment failure, lack of compliance and delayed resolution of the clinical symptoms. The rate of treatment failure with topical permethrin and oral ivermectin are 10% and 14 % respectively.[7] There is a lack of compliance for topical application compared to oral medication. Delayed hypersensitivity reaction to mite and its product may persist for weeks after the completion of the proper treatment[7] which further contributes to the associated stigma.[4]

In this study, we found that a combination of topical permethrin and oral ivermectin had better efficacy compared to topical permethrin in the first 2 weeks however it was not statistically significant. At the first week, the efficacy of the combination regimen was 72.6% and that of a single agent was 65.1% and in the second week was 89.6% and 80.2% respectively. However, at the end of the third and fourth weeks, the efficacy was almost similar. The combination regimen was seen to have an earlier clinical resolution compared to topical permethrin. However, on comparing the reduction of the intensity of itch, the combination regimen proved not superior to the standard regimen.

The combination agents that we used have different mechanisms of action. Among the topical preparations, considering the efficacy and side effects, 5% permethrin was included in our study. It inhibits sodium channels and results in neurotoxicity in mites. It is also ovicidal.[8, 10] The efficacy is around 90%. Adverse effects include erythema and itching which are rare.[11-13] The only oral medication available is ivermectin which interrupts the GABA-induced neurotransmission of mites. It is not ovicidal however it has a persistent presence in the skin for a longer duration. It has a mild side effect of gastrointestinal intolerance.[7] None of the participants showed severe side effects requiring termination of therapy.

This is the first study comparing the topical medication with the combination of topical and oral medication. The Cochrane review had concluded equal efficacy of 5% permethrin and oral ivermectin which is about 90%.[7, 14, 15] The risk of treatment failure is high with oral ivermectin compared to 5% permethrin with the rates variable in different studies.[16-18]

Conclusion

The efficacy of treatment apparently increased with the combination of oral and topical medication. The different mechanisms of action of the combination drugs used may have contributed to the earlier resolution of symptoms. Single use regimen as compared to repeat application may also have contributed to better patient compliance. However, a study with a larger sample size is required to confirm the findings and evaluate the statistical significance.

This trial is registered at ClinicalTrials.gov, ID NCT05198947

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Table 1

Characteristics	Category	Group 1 n (%) n=106	Group 2 n (%) n=106	X^2	p-value
Age group	5-20	68 (64.2)	69 (65.1)	0.874	0.646
	21-40	32 (30.2)	28 (26.4)		
	>40	6 (5.7)	9 (8.5)		
Religion	Hindu	69 (65.1)	73 (68.9)	0.437	0.804
	Buddhist	28 (26.4)	26 (24.5)		
	Others	9 (8.5)	7 (6.6)		
Education	Illiterate	8 (7.5)	12 (11.3)	4.334	0.115
	School level	60 (56.6)	45 (42.5)		
	High school and above	38 (35.8)	49 (46.2)		
Occupation	Unemployed	8 (7.5)	10 (9.4)	4.359	0.360
	Housewife	15 (14.2)	14 (13.2)		
	Student	71 (67)	60 (56.6)		
	Farmer	6 (5.7)	9 (8.5)		
	Others	6 (5.7)	13 (12.3)		
Marital Status	Married	35 (33)	31 (29.2)	0.352	0.553
	Unmarried	71 (67)	75 (70.8)		
Family size	≤ 5	36 (34)	26 (24.5)	2.280	0.131
	>5	70 (66)	80 (75.5)		
Economical class	Lower class	74 (69.8)	72 (67.9)	0.088	0.767
	Middle class	32 (30.2)	34 (32.1)		

[Table 1 showing the basic demographic characteristics of patients in Group 1 and 2.]

Table 2

Characteristics	Category	Group 1 n (%) n=106	Group 2 n (%) n=106	X^2 /Fischer's exact test*	p-value
Duration of disease	≤ 4	83 (78.3)	84 (79.2)	0.028	0.867
	>4	23 (21.7)	22 (20.8)		
H/o Atopy	Yes	9 (8.5)	5 (4.7)	1.224	0.269
	No	97 (91.5)	101 (95.3)		
Nocturnal exacerbation	Yes	81 (76.4)	86 (81.1)	0.705	0.401
	No	25 (23.6)	20 (18.9)		
Family History	Yes	95 (89.6)	96 (90.6)	0.053	0.818
	No	11 (10.4)	10 (9.4)		
Morphology of lesion	Burrow	13 (12.3)	19 (17.9)	1.325	0.250
	Papule	104 (98.1)	103 (97.2)	2.005	0.367
	Pustule	12 (11.3)	13 (12.3)	1.040	0.595
	Nodule	4 (3.8)	8 (7.5)	1.413	0.235
	Vesicle	5 (4.7)	7 (6.6)	0.353	0.552
	Bulla	1 (0.9)	0 (0)	*	1.000
Distribution of lesion	Head and neck	23 (21.7)	28 (26.4)	0.645	0.422
	Extremities	72 (67.9)	75 (70.8)	0.200	0.655
	Trunk and abdomen	70 (66)	73 (68.9)	0.193	0.660
	Genitalia	65 (61.3)	64 (60.4)	0.020	0.888

[Table 2 showing the characteristics of disease]

Table 3

Time of assessment	Category	Group 1 n (%)	Group 2 n (%)	X2/ Fischer's Exact	p-value
Baseline	No lesion	1(0.9)	0(0)	3.420	0.331
	Mild	36(34)	29(27.4)		
	Moderate	34(32.1)	45(42.5)		
	Severe	35(33)	32(30.2)		
First follow up					
(After 1 week)	No lesion	69(65.1)	77(72.6)	1.412	0.703
	Mild	10(9.4)	8(7.5)		
	Moderate	13(12.3)	10(9.4)		
	Severe	14(13.2)	11(10.4)		
Second follow up					
(After 2 weeks)	No lesion	85(80.2)	95(89.6)	3.915	0.271
	Mild	8(7.5)	5(4.7)		
	Moderate	10(9.4)	5(4.7)		

	Severe	3(2.8)	1(0.9)		
Third follow up (After 3 weeks)	No lesion	99(93.4)	101(95.3)	0.353	0.552
	Mild	7(6.6)	5(4.7)		
	Moderate	0(0)	0(0)		
	Severe	0(0)	0(0)		
Fourth follow up					
(After 4 weeks)	No lesion	104(98.1)	105(99.1)	0.338*	1
	Mild	2(1.9)	1(0.9)		
	Moderate	0(0)	0(0)		
	Severe	0(0)	0(0)		

[Table 3 showing Clinical Grading assessment in both groups at baseline and follow-up]

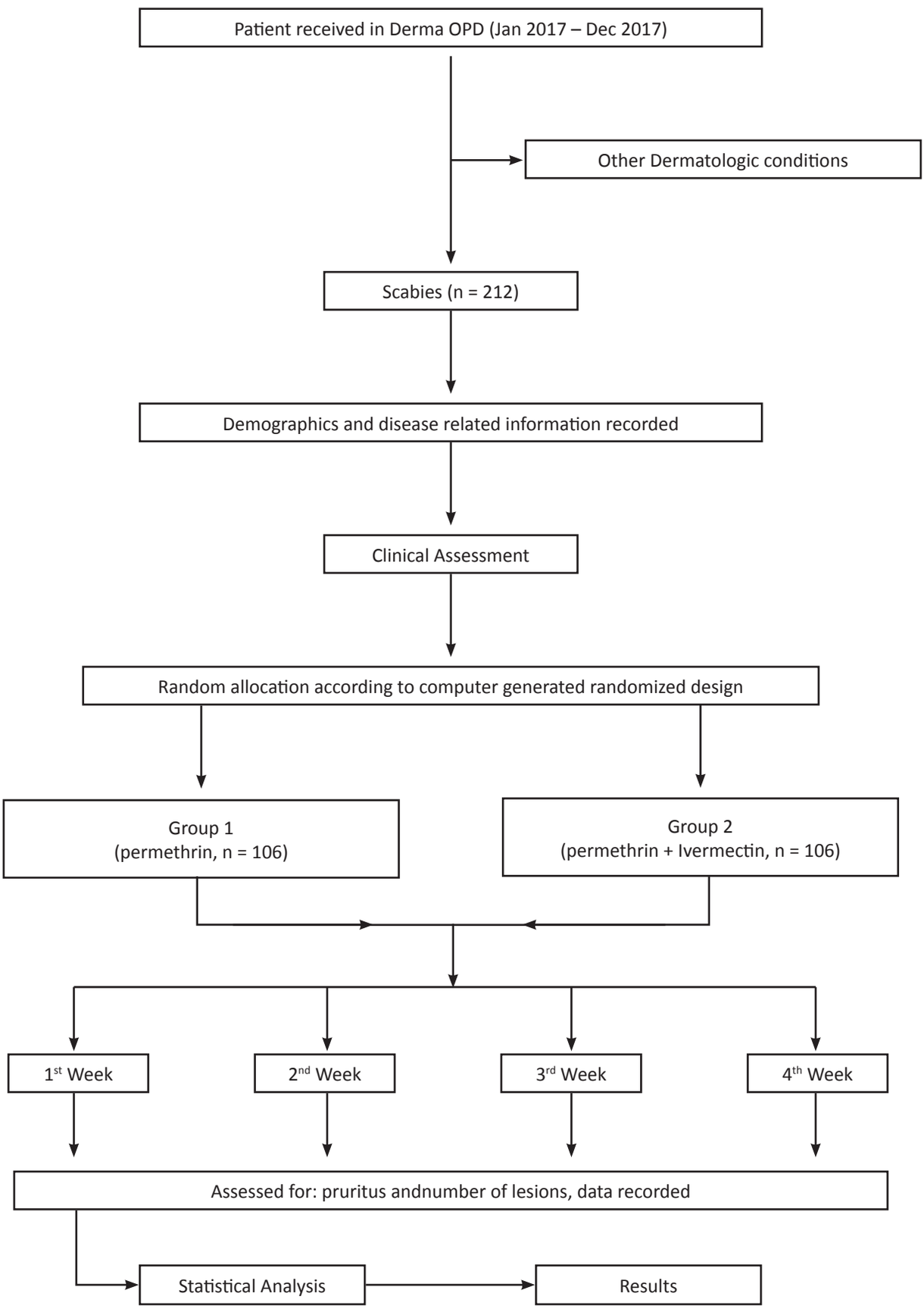
Table 4

Time of assessment	Category	Group 1 n (%)	Group 2 n (%)	X2/ Fischer's Exact	p-value
Baseline	No itch	0(0)	0(0)	3.702	0.157
	Mild	6(5.7)	1(0.9)		
	Moderate	67(63.2)	71(67)		
	Severe	33(31.1)	34(32.1)		
First follow up (After 1 week)	No itch	12(11.3)	13(12.3)	0.610	0.894
	Mild	18(17)	22(20.8)		
	Moderate	45(42.5)	42(39.6)		
	Severe	31(29.2)	29(27.4)		
Second follow up (After 2 weeks)	No itch	33(31.1)	38(35.8)	1.887	0.596
	Mild	29(27.4)	27(25.5)		
	Moderate	17(16)	21(19.8)		
	Severe	27(25.5)	20(18.9)		
Third follow up (After 3 weeks)	No itch	93(87.7)	95(89.6)	0.402	0.818
	Mild	11(10.4)	10(9.4)		
	Moderate	2(1.9)	1(0.9)		
	Severe	0(0)	0(0)		
Fourth follow up (After 4 weeks)	No itch	104(98.1)	106(100)	2.019*	0.498
	Mild	2(1.9)	0(10)		
	Moderate	0(0)	0(0)		
	Severe	0(0)	0(0)		

[Table 3 showing Clinical Grading assessment in both groups at baseline and follow-up]

Figures and Tables:

Figure 1: Flow Chart of the study



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