

An open label, randomized, comparative study of antiscabietic drugs permethrin, gamma benzene hexachloride and ivermectin in patients of uncomplicated scabies

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ABSTRACT

Background: To determine efficacy and cost effectiveness of antiscabietic drugs (permethrin, gamma benzene hexachloride and ivermectin) in patients of uncomplicated scabies.

Materials and Methods: This was a prospective, randomized clinical study conducted in 210 diagnosed patients of scabies (>12years of age) from January 2011 to October 2011. They were randomly allocated into one of the three groups. Group A received topical permethrin (5% cream), Group B received topical gamma benzene hexachloride (1% lotion) and Group C received oral ivermectin (tab 200mcg/kg). All the three groups received treatment two times- at the time of first visit and one week later. The patients were followed up at the end of first and third week. At each visit, cure rate was assessed by clinical and itching grading score and compared to determine the efficacy. Cost effectiveness was compared on basis of cost in INR to treat one case successfully.

Results: Cure rate at the end of first week was 83.87% in Group A, 78.18% in Group B and 55.17% in Group C while cure rate in the three treatment groups at the end of third week was 93.55% in Group A, 80.00% in Group B and 98.28% in Group C. Thus at the end of first week Group A showed better cure rate while at the end of third week Group C was equally efficacious to Group A. The cost (INR) to treat one patient was 69.19 for permethrin, 37.50 for gamma benzene hexachloride and 24.42 for ivermectin.

Conclusion: A single application of permethrin is superior to both ivermectin and gamma benzene hexachloride while ivermectin in two dose regimen is equally efficacious to permethrin and more cost effective than the other two conventional antiscabietic drugs. Oral ivermectin can be used as an alternative to permethrin.

Key words: Antiscabietic, permethrin, gamma benzene hexachloride, ivermectin.

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INTRODUCTION

Scabies is a contagious skin disease caused by the mite *Sarcoptes scabiei* var. *hominis*, which is an obligate human parasite.^[1] It is estimated that nearly 300 million people worldwide are infected with this disease.^[2] Scabies is prevalent in almost all age groups. The spread of scabies is enhanced by overcrowding and poor hygiene. Drugs used for scabies has changed a lot from sulphur ointment to permethrin cream and ivermectin tablets orally. There are several currently available antiscabietic

drugs. There are lot of factors which determine the choice of therapy such as age, cost of treatment, efficacy etc.^[3]

There are various treatment modalities for scabies but still the search for ideal scabicide is going on. An ideal scabicide must be

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safe, effective and of low cost as this disease is more common in poor people.^[4] Several studies were conducted to compare various antiscabietic drugs for scabies. Bachewar et al., has compared benzyl benzoate, permethrin and ivermectin and found benzyl benzoate as first line intervention and ivermectin as best cost effective drug.^[5] Another study by Sunita B. Chhaya et al., suggests ivermectin as an alternative to permethrin.^[1] The present study was conducted to compare three commonly used antiscabietic drug (permethrin, gamma benzene hexachloride and ivermectin) to find out the best intervention at minimal cost. As fewer studies have been done to elucidate the extent of problem, this study would be helpful in providing some of the very basic data on the safest scabicide at the lowest affordable cost in our country, which is very necessary as the disease is quite prevalent in the major poor population in India.

MATERIALS AND METHODS

This prospective, comparative and randomized study was conducted on the patients of scabies attending the Out Patient Department of Skin & Venereal Diseases and Department of Pharmacology, Maharani Laxmi Bai Medical College, Jhansi for a period of January 2011 to October 2011. The diagnosis was made on basis of history and clinical examination. Ethical clearance was obtained from Institutional Ethics Committee of Maharani Laxmi Bai Medical College, Jhansi.

Eligibility Criteria

The eligibility criteria were decided on basis of inclusion and exclusion criteria. The inclusion criteria were any newly diagnosed patient of scabies of any gender and above 12 years of age and presence of diffuse itching and visible lesions associated either with at least two typical locations of scabies (interdigital folds, flexor aspect of wrist and elbow, genitals, anterior axillary folds) or with a household

member with itching.

The exclusion criteria were any pregnant or lactating females, any history of diabetes, hypertension or any chronic disease, any psychiatric illness or neurological disorder and any other associated skin disease which can affect the study due to same presentation like atopic dermatitis, dyshydrotic eczema, insect bite reaction etc.

Sample size

A total of 210 patients of scabies attending the OPD of Skin and Venereal Diseases were included in the study. The patients were informed and written consent was taken. The selected patients were allocated to any one of the three treatment groups randomly on basis of a computer generated random table.

Interventions

The participants were randomly allocated one of the following groups-

GROUP A- Single application of half tube i.e. 15g of permethrin 5% cream was applied over whole body below neck and scrub bath was taken 12 hours later. This process was repeated after one week. The 30 g tube contains permethrin 5% and 1 mg formaldehyde and was priced at INR65.

GROUP B-Single application of half bottle i.e. 25ml of gamma benzene hexachloride (GBH) 1% lotion was applied over whole body below neck and scrub bath was taken 12 hours later. This procedure was repeated after one week. The 50 ml bottle contains GBH 1% and was priced at INR30.

GROUP C- Tab Ivermectin 200 mcg/kg consumed as single dose anytime of the day and repeated after one week. The single tablet was priced at INR12.

Participants of Group A and Group B were instructed to take warm water bath before application of medicine and then after application of medicine next morning. They were

advised about treating the family members also and prevention of transmission by washing all clothes and bedding that came in contact. They were also advised not to take any other medicine for this disease during the study period.

Grading scores

At the initial visit, of all the patients included in the study a thorough history was taken and they underwent physical and cutaneous examination. The baseline itching and clinical grade scoring was done. All the details were recorded. The efficacy was assessed on basis of two parameters^[1].

Clinical grading score

The primary efficacy parameter was lesion subsidence. Severity of lesions was clinically graded on a scale of 0 to 3 arranged as follows: 0 = Free of lesions (no lesions) , 1= 10 or fewer lesions (mild), 2= 11- 49 lesions (moderate), 3= 50 or more lesions (severe).

Itching grading score

The secondary efficacy parameter was assessment of reduction in severity of pruritus, considering the pruritus at first visit as 100%. The patient was asked for reduction in pruritus on subsequent visit and on basis of that grading was done on the given scale by the observer. Pruritus was graded on a scale of 0 to 4 on basis of severity. Grading was done as: 0=0% (no pruritus), 1=1-25% (mild pruritus), 2=26-50% (moderate pruritus), 3=51-75% (severe pruritus), 4=76-100% (very severe pruritus).

Efficacy Assessment

Patients of all the three groups were followed-up at the end of first and third week and patients were examined to assess safety (no appearance of any adverse effects or intolerability to the drug) and efficacy. At each of the two follow ups, a detailed examination of the entire body was performed. All remaining suspected scabies lesions were examined and compared

with baseline clinical grading score. The patient were asked for any remaining pruritus and compared with baseline itching grading score.

The treatment was considered effective if at the end of three weeks, the pruritus was reduced and lesions were improved without appearance of any new lesions from initial visit.

Improvement was graded as: ^[6] Mild= clinical grading score (grade 2 or 3)+itching grading score (grade 3 or4). Moderate= clinical grading score (grade 1)+itching grading score (grade 1or2). Good = clinical grading score (grade 0)+itching grading score (grade 0). Complete clinical cure was defined as reduction both in clinical grading score (up to grade 0 or 1) and itching grading score (up to grade 0, 1 or 2). Patient was considered to be not cured if at the end of three weeks there was no improvement in the pruritus and not healing of old skin lesions or appearance of new lesions. Also patients with mild improvement were also included in the criteria for not cured.

At the end of each visit, patients were observed for these end points; Cured- patients showing moderate or good improvement. Not cured- patients showing no or mild improvement.

Cost effectiveness assessment

The cost effectiveness was calculated on basis of total expenditure on medicine (in INR) at the end of the third week and cure rate (in %) and the three drugs were compared on the basis of amount needed to treat one case successfully.^[5]

Statistical analysis

The percentage of improvement was compared between the three groups. Intergroup comparison between two groups was done using unpaired 't' test. For all statistical tests, p value ≤ 0.05 were considered to be statistically significant.

RESULTS

The current study was planned with an objective to study different available treatment modalities in scabies. Baseline characteristics of the patients in three treatment groups were comparable (Table 1).

Table 1: Baseline characteristics of the patients in three treatment groups

Parameters	Group A (n=70)	Group B (n=70)	Group C (n=70)
Mean age (years)	23.55	28.89	27.74
Gender (male/female)	49/21	51/19	41/29
Geographical distribution (urban/rural)	37/33	42/28	36/34
Socio economic status (lower middle /upper lower/lower)	10/40/20	12/36/22	11/40/19
Nocturnal pruritus(%)	100	100	100
Family history of pruritus(%)	72.00	84.00	78.00
Itching grading score (very severe/severe/moderate/mild/no itching) (%)	100/0/0/0/0	100/0/0/0/0	100/0/0/0/0
Clinical grading score (severe/moderate/mild/no lesions) (%)	20.97/43.55/32.26/03.22	21.82/25.45/41.82/10.91	20.69/41.38/32.76/05.17

Since the current study was an OPD based study, several patients were lost during follow up. Any patient who didn't turn up in any or both follow up was excluded from study. Thus only those patients who completed both follow ups and were compliant were included in study. Clinical cure rate was assessed on basis of clinical grading score and itching

grading score. Patients showing improvement in both scores were considered as cured (Table 2 and Fig.1-2).

At the end of first week, permethrin and gamma benzene hexachloride shows no significant difference ($p > 0.05$) while ivermectin was less efficacious to both permethrin ($p < 0.001$) and gamma benzene hexachloride ($p < 0.01$). At the end of third week there was no significant difference between permethrin and ivermectin ($p > 0.05$) while both permethrin ($p < 0.05$) and ivermectin ($p < 0.01$) were more efficacious than gamma benzene hexachloride (Table 2).

When cost effectiveness was compared, ivermectin(INR 24.42 per patient) was much more cost effective than both permethrin (INR 69.19 per patient) and gamma benzene hexachloride (INR 37.50 per patient) (Table 3). No adverse effects were noted in any of the three groups by the patients or investigators.

DISCUSSION

Scabies is the common parasitic infestation of human beings. It is more common in poor people due to overcrowding and unhygienic conditions which helps in transmission. All age group and both sex are susceptible.^[7]

The mainstay of therapy currently is topically applied medicines such as benzyl benzoate, gamma benzene hexachloride, permethrin etc.^[8] In addition, recently an oral drug ivermectin in dose of 200mcg/kg has been found to be an effective scabidicidal agent.^[9] The main aim of this study was to determine

Table 2: Number of patients included, dropouts and cured on basis of clinical grading score (0 or 1) + itching grading score (0, 1 or 2) in each groups.

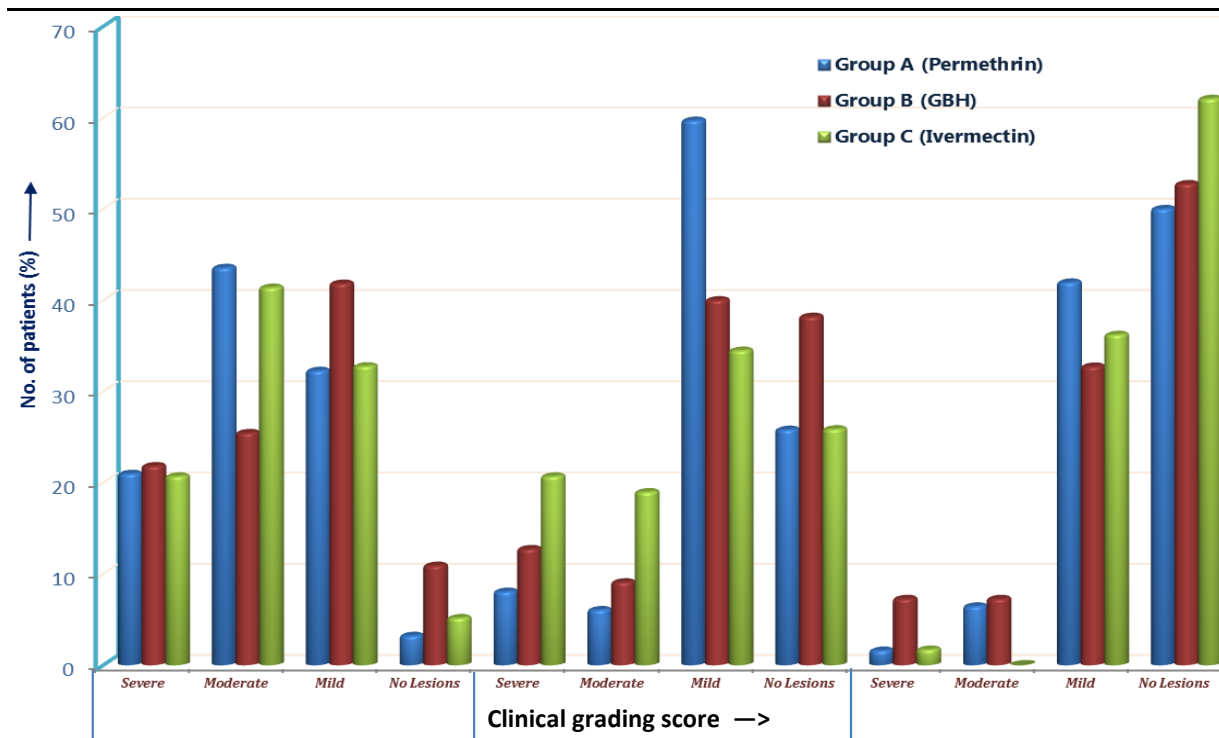
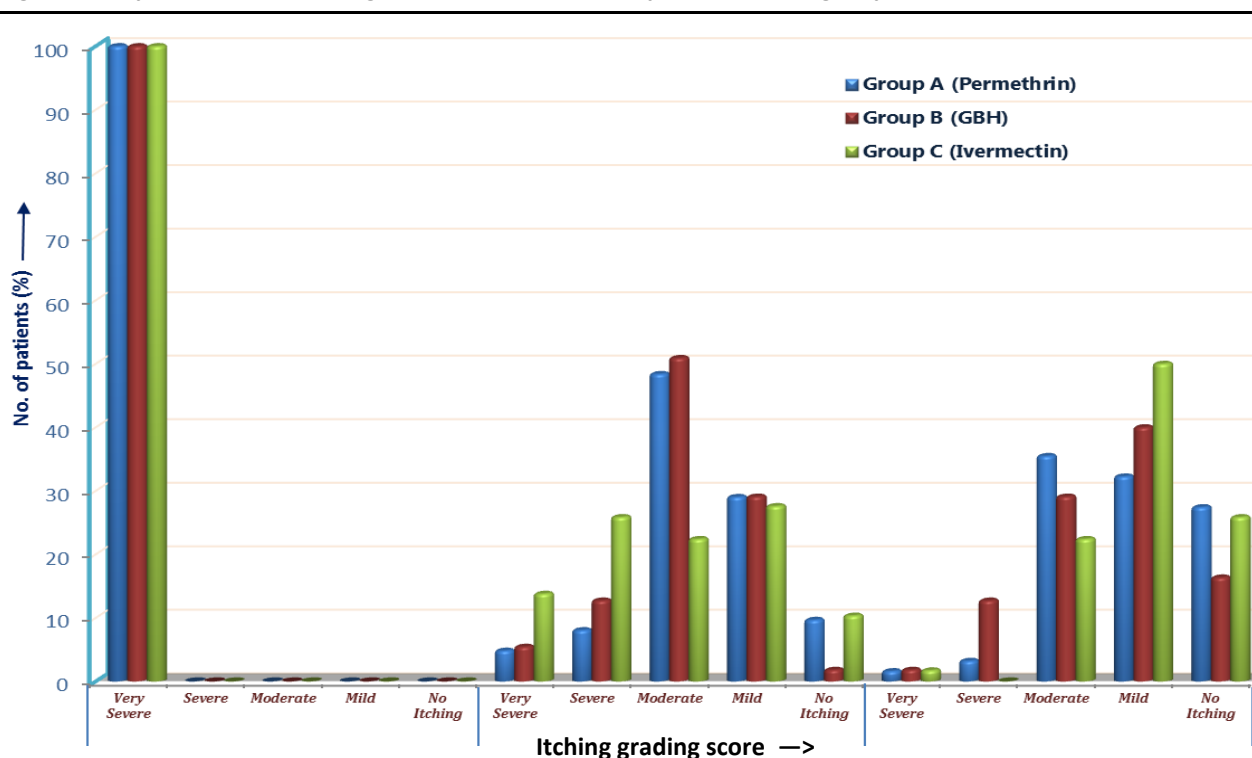
Group. drug	Subjects included (no., %)	Lost to follow-up (no., %)	Non-compliance (no., %)	Dropouts (no., %)	Completed both follow up	Cure rate at the end of first week (no., %)	Cure rate at the end of third week (no., %)
A. Permethrin	70, 100	07, 10.00	1, 1.43	08, 11.43	62	52/62 (83.87)*	58/62 (93.55) [§]
B. GBH	70, 100	13, 18.57	2, 2.86	15, 21.43	55	43/55 (78.18) [†]	44/55 (80.00) [†]
C. Ivermectin	70, 100	11, 15.71	1, 1.43	12, 17.14	58	32/58 (55.17) [‡]	57/58 (98.28) [¶]

GBH - Gamma Benzene Hexachloride, unpaired 't' test was used to compare the percentage of cure rates.

* $p > 0.05$ vs. group B, [†] $p < 0.01$ vs. group C, [‡] $p < 0.001$ vs. group A, [§] $p < 0.05$ vs. group B, [¶] $p > 0.05$ vs. group A.

Table 3: Cost- effectiveness analysis of each drug at end of third week

Group. drug	Cost in INR for 100 participants	Cure rate (%)	Cost effectiveness	Cost (INR) to treat one case
A. Permethrin	65 X 100 = 6,500	93.95	INR 6,500 for 93.95 participants	69.19
B. Gamma Benzene Hexachloride	30 X 100 = 3,000	80.00	INR 3,000 for 80.00 Participants	37.50
C. Ivermectin	24 X 100 = 2,400	98.28	INR 2,400 for 98.28 participants	24.42

Figure 1: Improvement in Clinical Grade at each follow up visit in three groups**Figure 2: Improvement in Itching Grade at each follow up visit in three groups**

the better treatment option for scabies at minimal cost.

Gamma benzene hexachloride is a neurotoxin that interacts with the GABA-A receptor chloride channel complex at the picrotoxin binding site and disrupts GABA neurotransmission. This results in death of mite.^[10] Since it acts only on GABA-A receptors, so its ovicidal effect cannot be established. Thus a second course of treatment must be given after one week to destroy any newly hatched larvae. Its selective action on single receptor may explain its low efficacy in comparison to permethrin and ivermectin. Similarly, Zargari O et al., in their study found that permethrin provided an improvement rate of 84.60% after two weeks, whereas gamma benzene hexachloride was effective only in 48.90% of patients.^[11]

Permethrin is a neurotoxin and it blocks the movement of sodium ions from outside to inside of the nerve cells. This causes delayed repolarisation and paralysis and death. Permethrin acts on ubiquitous sodium channels so it acts at all stages of the life cycle of the mite. Neither gamma benzene hexachloride nor ivermectin has this effect.^[12] Permethrin has rapid onset of action. It may be due to its topical application which ensures maximum concentration of drug in skin and action at all stages of the life cycle of the parasite.

Ivermectin acts against the scabies mite through two channels- It has high affinity for the glutaminated gated chloride ion channels which is found in the peripheral nervous system of invertebrates. This causes hyperpolarisation by increasing intracellular chloride concentration and results in paralysis of parasite.

It also blocks neurotransmission across the nerve synapse that uses gamma-aminobutyric acid thus resulting in the paralysis and death of mite.^[2,13] Ivermectin is an oral drug, so concentration achieved in skin is variable. Due to its specific site of action, ivermectin may not be effective against the younger stages

of parasite inside egg because the nervous system has not yet developed.^[1] So it acts only as miticidal drug. This is the probable reason for its lower efficacy at the end of first week but as it acts through two channels its efficacy becomes equal to permethrin at the end of third week.

When cost effectiveness of the three drugs were compared, it was found that ivermectin (INR 24.42 per patient) was much more cost effective than both permethrin (INR 69.19 per patient) and gamma benzene hexachloride (INR 37.50 per patient). Bachewar NP et al., found similar results that permethrin gave the fastest symptomatic relief but ivermectin was most cost effective.^[5]

Thus, Ivermectin is most suitable drug closely followed by permethrin. Although permethrin has rapid onset of action and at the end of first week its improvement rate was far greater than ivermectin but at the second follow up ivermectin was equally efficacious but exceeds in cost effectiveness in comparison to permethrin.

As far as safety of antiscabietic drugs is concerned, in our study, no adverse effects were observed with any of the drugs. All the three drugs are neurotoxins and selectively act on ion channels found only in nervous system of invertebrates. Therefore they possess minimal effect on the nervous system of humans. Further, permethrin and gamma benzene hexachloride are used topically so their systemic effects are almost null.^[5,14] Guzzo CA et al., in their study found that the patients who were treated with ivermectin does not show any serious adverse effects.^[14]

Thus it can be concluded that ivermectin is preferable drug owing to its oral administration, high efficacy, minimum side effects and low cost in comparison to permethrin which is equally efficacious but has cumbersome topical application and high cost.

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Not reported.

REFERENCES

1. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol* 2012;78:605-10.
2. Stone SP, Goldferb JN, Bacelieri RE. Scabies, Other Mites, and Pediculosis. In: Goldsmith L, Katz S, Gilchrist B, Paller A, Leffell D, Wolff K, editors. *Dermatology in General Medicine*. New York: McGraw Hill; 2008; p.2029-32.
3. Burns DA. Diseases Caused by Arthropods and Other Noxious Animals. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. *Textbook of Dermatology*. Wiley-Blackwell; 2010;38.36-38.45.
4. Karthikeyan K. Treatment of scabies: Newer perspectives. *Postgrad Med J* 2005;81:7-11.
5. Bachewar NP, Thawani VR, Mali SN, Gharpure KJ, Shingade VP, Dakhale GN. Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. *Indian J Pharmacol* 2009;41:9-14.
6. Sharma R, Singal A. Topical permethrin and oral ivermectin in the management of scabies: A prospective, randomized, double blind, controlled study. *Indian Journal of Dermatol Venereol and Leprol* 2011;77:581-6.
7. Scheinfeld N. Controlling scabies in institutional settings: A review of medications, treatment models, and implementations. *Am J Clin Dermatol* 2004;5:31-7.
8. Roos TC, Alam M, Roos S, Merk HF, Bickers DR. Pharmacotherapy of ectoparasitic infections. *Drugs* 2001;61:1067-88.
9. Usha V. Review of ivermectin in scabies. *J Cutan Med Surg* 2001;5:496-504.
10. Taplin D, Rivera A, Walker JG, Roth WI, Reno D, Meinking R. A comparative trial of three treatment schedule for eradication of scabies. *J Am Acad Dermatol* 1983;9:550-4.
11. Zargari O, Golchai J, Sobhani A, Dehpour AR, Sadr-Ashkevari S, Alizadeh N, et al. Comparison of the efficacy of topical 1% lindane v/s 5% permethrin in scabies: A randomized, double-blind study. *Indian J Dermatol Venerol Leprol* 2006;72:33-6.
12. Campbell WC. Ivermectin, an antiparasitic agent. *Med Res Rev* 1993;13:61-79.
13. Tripathi KD. *Essentials of Medical Pharmacology*. 6th ed. New Delhi: Jaypee; 2010.
14. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 2002;42: 1122-33.
