SCABIES;
SAFETY OF PERMETHRIN AND IVERMECTIN

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ABSTRACT... Scabies is a common health problem worldwide. Most treatment modalities available are topical. Among them 5% Permethrin is the most effective scabicide with few side effects. Limiting factors are its high cost, cumbersome application and emerging resistance. Ivermectin is the only oral scabicide available. It is effective, inexpensive and easy to use drug with no known drug interactions and limited side effects. **Objective of study:** To compare the safety of topical Permethrin and oral Ivermectin in treatment of scabies. **Study design:** Quasi-experimental study. **Setting:** Department of dermatology Jinnah Hospital, Lahore. **Subjects:** 120 patients were enrolled and were randomly divided in 2 groups of 60 each. **Duration:-** 12-02-07 to 31-01-08. Non funded study (As ivermectin was not available in Pakistan during the study period, it was imported from India as tablet Ivecop 12 mg). **Methods:** Topical Permethrin and oral Ivermectin were used in groups A and B respectively. Patients were examined and certain investigations were carried out before dug administration, and at day 7 and day 14 to evaluate the safety of both drugs on the basis of appearing of side effects and change in baseline investigations. **Results:** In both groups, equal number of patients experienced side effects (n=15). In group A, side effects observed were burning (n=8), contact dermatitis (n=4) and stinging (n=3). In group B, we observed muscular pain (n=5), nausea (n=5), headache (n=2) and others (n=3). Significant rise of hepatic enzymes was noticed in only 1 patient of group B which improved on next follow up. **Conclusions:** We found no statistically significant difference regarding safety of use between permethrin and ivermectin.

Key words: Ivermectin, permethrin, scabies

INTRODUCTION

Scabies is one of the commonest infestations worldwide with a long historical background[1]. No race or social class is exempt although its prevalence is high in underdeveloped countries where it is an endemic, possible reason being overcrowding and poor hygiene which facilitates its spread[2,3]. However with the emergence of HIV, its prevalence is also on rise in developed countries[1,3].

Clinical diagnosis is made on history of generalized itch with nocturnal worsening with similar symptoms present in contacts[2]. Diagnosis confirmation is either by detection of burrow or microscopic finding of scabies mite, its egg shells or feces[1,2].

Various treatment modalities are available; most of them are topical e.g; lindane, permethrin, benzyl benzoate, crotamiton, etc[4,5]. They are cumbersome, messy and time consuming, leading to poor patient compliance. Topical Permethrin appears to be the most effective treatment for scabies[6]. It is available as a first line drug in UK and USA and is the most studied drug[7].

After a bath, 5 % Permethrin cream or lotion is applied over entire body from neck downwards to be washed off after 8-14 hours. Appropriate application ensures maximum concentration of the drug in the skin with minimal systemic absorption. In children less than 5 years, it must be applied to the head and neck as well[7]. Unless new lesions develop within 10 days, retreatment is unnecessary[7].

Permethrin is a photostable synthetic pyrethroid with potent insecticidal activity. It is cosmetically acceptable and easy to use without any unpleasant odor. Permethrin is about 20 times less permeable through human skin than Lindane. It is rapidly broken down by skin esterases to an inactive metabolite which is excreted in urine hence having very low mammalian toxicity[3].

It acts by disrupting the current in sodium channels of mite cells resulting in delayed repolarization, paralysis and death of the parasite. As sodium channels are

ubiquitous therefore it acts at all stages of the life cycle of mite[3,8].

The development of resistance has reduced the use of pyrethroids. The best recognized form of pyrethroid resistance, known as knockdown resistance (KDR), has been linked to specific mutations in the target organisms[9].

Permethrin may cause some side effects e.g; skin irritation, itching, stinging, rash, redness and swelling etc[7]. Dystonia or musculoskeletal adverse effects including muscle spasm may occur but only after inappropriate occupational or dermal exposure. Mechanism behind these adverse effects may be related to Permethrin's ability to delay sodium channel closure within nerve cells leading to a lowered threshold of nerve fibers causing further action potentials, leading to repetitive firing and hyperexcitation of the nervous system[10].

It is a pregnancy category B drug. However it had been used in pregnant women without any ill effects. Its safety in breastfeeding is unknown[11]. Its major drawback is high treatment cost[3].

The topical acaricides must remain on the entire body area for a certain period and later to be removed with soap and water. Same treatment may need to be repeated several times according to different schedules. Patients as well as all the contacts need to be treated in the same manner which may lead to high treatment cost[8]. This justifies the search for an easily administered treatment involving a single dose and with minimal adverse effects[3].

Ivermectin is the only available oral scabicide till date[3,8,9]. It is a synthetic antihelminthic being used in various parasitic disorders[8]. Chemically it is 22, 23 dihydro-derivative of avermectin B, similar to macrolides but without any antimicrobial action.12 It was discovered in 1975 by people working in Merck laboratories for veterinary use. It is rapidly absorbed and excreted through feces[8].

Ivermectin is an agonist of ligand-gated chloride ion-driven peripheral neurochannels. It simulates the ligand by "opening the gate" and allowing an efflux of chloride ions, which generates sufficient current to allow the release of the associated neurotransmitter, γ-aminobutyric acid (GABA). In higher doses continual neuronal discharge would be expected to paralyze the organism completely[12]. These chloride channels are present in nerve and muscle cells of invertebrates. In mammals, analogous GABA-secreting neurons are found only in the central nervous system, a region not readily penetrated by this agent by virtue of blood brain barrier in collaboration with MDR gene. It should be cautiously administered to young children as blood brain barrier is partially weak in them[3].

Many researchers believe that Ivermectin primarily interferes with the function of the gastrointestinal tract of target parasites starving them to death[7,12].

Ivermectin is not ovicidal as nervous system containing chloride channels has not yet developed in younger stages of development[3].

Various studies have proved efficacy of ivermectin. Khan I et al found it comparable with Permethrin in the treatment of common scabies[13]. Its compliance is found better than topical treatment. Monitoring of urine or plasma parameters during treatment is not necessary. Mass treatment of scabies with Ivermectin in an endemic population is more efficacious as compared to topical permethrin application in reducing the baseline prevalence, decreasing the chain of transmission and chances of reinfection[7].

Toxic effects of ivermectin after a single dose for scabies appear to be insignificant[9]. It may cause transient increase in intensity of itch after one week of administration which may be due to hypersensitivity reaction caused by destruction of the mite and release of antigens. Occasional patients might develop transient tachycardia, flushing and nausea[12]. Rarely fever, pruritus, headache, myalgia, maculopapular rash and lymphadenopathy have been seen and very rarely hypotension may occur. Side effects are seen mainly in

patients of filariasis, rarely in scabies[3]. Ivermectin does not appear to induce allergic reaction such as Mazotti reaction in onchocerciasis and scabies, which is frequently seen in filariasis.

There are reports of resistance developing to ivermectin[14]. Possible mechanism is through ABC transporters such as P-glycoprotein.

Ivermectin should not be used in atopic patients, those with nervous system disorders, or in children of body weight less than 15kg or aged < 5 years[21,22]. It is a pregnancy category C drug and is excreted in low concentration in breast milk. However in third world countries, it has been used to treat Onchocerciasis in pregnant and nursing women with no teratogenic effects observed[15].

Ivermectin was approved by FDA for the treatment of strongyloidiasis and onchocerciasis in 1996[12,15]. It is effective against certain ectoparasites e.g. Sarcoptes scabiei, Pediculosis humanus, Demodex folliculorum and Cheyletiella sp[17,18]. Other off label indications are Filariasis, Larva migrans[12,14], Rosacea[22], and Myiasis[18].

Most frequently used dose of Ivermectin in treatment of scabies is a single oral dose of 200 µg/kg bodyweight[22]. Many authorities recommend a second dose 4-14 days after the 1st dose[61,18]. Some researchers suggest single dosing regimen of 400 mg/kg[14,18].

Since 1992 several clinical trials evaluated the role of Ivermectin in the treatment of human scabies. They revealed high cure rates (70% - 100%) for both the classic form, as well as crusted Norwegian scabies[3,13,16]. For last few months it is available in Pakistan and is increasingly being used to treat scabies. Keeping this in mind we conducted a clinical trial, aim of which was to compare safety of oral Ivermectin in a single dose of 200 µg / kg with that of topical 5% Permethrin.

Objective
To compare the safety of topical Permethrin 5% and oral Ivermectin in the treatment of scabies.

Safety was measured on the basis of non-appearance of undesirable effects and absence of any significant change in the baseline investigations.

Inclusion Criteria
Patients of either sex with clinical diagnosis of scabies aged 5-60 years

Exclusion Criteria
1. Pregnant or lactating patients.
2. History of hypersensitivity to permethrin or ivermectin.
3. Used topical or systemic scabicide in last 4 weeks.
4. Taking steroids or other immunosuppressive therapy or radiotherapy for any systemic or cutaneous indication.
5. History of epilepsy, seizures, syncope or coma.
6. Patients with evidence of hepatic or renal dysfunction (On history or relevant investigations).
7. Patients with chronic debilitating disorders or neoplasia.

MATERIALS AND METHODS

Study Design
Quasi Experimental study

Setting
Department of dermatology Jinnah Hospital, Lahore.

Sample Size
We enrolled 120 otherwise healthy patients with clinical diagnosis of scabies

Sampling Technique
Purposive sampling with random allocation.

Data Collection Procedure
After approval from hospital ethical committee and written informed consent from patients or their care-takers, patients fulfilling the inclusion criteria were enrolled. A detailed history was taken and dermatologic examination was then carried out and investigations were done. The following laboratory tests of patients

were carried out

1. Hemoglobin and total leukocyte count
2. Serum creatinine
3. Bilirubin and SGPT

These were recorded on a predesigned proforma.

Intervention
Patients were randomly divided in 2 groups of 60 patients each. Randomization was done using random number table in SPSS version 10. In group A, "topical 5% Permethrin" in lotion form and in group B, "oral Ivermectin" in the form of tablets was used. Both drugs were given free of cost to all the patients and contacts.

In "group A" patients received explicit written instructions about topical application. It had to cover the entire body and be kept there for 8-10 hours followed by a bath. In "group B" ivermectin tablets were taken by the patient in the presence of the investigator.

In both groups patients were advised not to use any other antiscabietic medicine during the study period. Bed covers and personal clothes had to be washed with soap and water after completion of therapy. All the patients were given antihistamines at bed time during 1st week. Secondary infection, if present, was treated with a 7-day course of antibiotic.

Evaluation
All the patients were followed up at day7 and day 14. History, examination and investigations were repeated on these visits.

Data Analysis Procedure
Data analysis was computer based. Statistical package for social sciences (SPSS) version 10 was used for analysis. Descriptive statistics were calculated. Age was presented as Mean ± SD. Gender, socioeconomic status and diagnostic tests were calculated as frequencies / percentages. To account for statistical difference in 2 groups, Chi square test, Student t test and the Fisher's exact test were used, as appropriate. A p-value of < 0.05 was considered significant.

RESULTS

All 120 patients completed the study. Mean age of all patients in both groups was 20.45+9.75 years. [Mean difference in 2 groups = 2.0 (95% difference = -2.10 to 6.10 years), two-tailed p-value = 0.33 (>0.05)]. Males were 55% of the sample size. There was no statistically significant difference in age as well as in other clinical parameters regarding severity of disease, between the two groups. All statistical comparisons at baseline were nonsignificant between the 2 groups except that the history of scabies in contacts was present more in the Permethrin group than in the Ivermectin group, and the difference was statistically significant.

At day 7, side effect profile of both groups was mild, although maximum side effects were observed on this visit. The group treated with Ivermectin, observed nausea and muscular pain (n=5 for each symptom, 8.3%, $p < 0.05$), vomiting (n=1, 1.7%) and headache (n=2, 3.3%), whereas the group treated with Permethrin had encountered burning as the most common side effect in the initial 2-3 days (n=8, 13.3 %), followed by contact dermatitis (n=4, 6.7%) and stinging sensation (n=3, 5%).

Laboratory test results showed no significant difference between the 2 treatments except significant rise of SGPT (258 IU [Normal range was upto 35 IU]) in 1 patient and upto 20% of reference value in 4 patients of group B.

Final assessment was made at day 14. In Ivermectin group, 4 patients (6.66 %) had severe itch vs 3 patients (5.0%) in Permethrin group. Only side effect found in second week post-therapy was complaint of headache in only 1 patient in group B, (p-value was 1.0 for Fischer's exact test). Rest of the patients remained well in both groups.

Investigations revealed no significant difference between the 2 groups. Increase in SGPT values at day 7 in some patients of group B was settled.

DISCUSSION

Scabies is a common endemic disease of tropical areas[16]. Burden of disease is high due to failure to break the cycle of reinfestation, as treatment of contacts remains the problem[2]. Currently most antiscabietic drugs

Table-I. Baseline characteristics of the patients

Parameters	Permethrin	Ivermectin	p-value
Mean age	21.45±9.78	19.45±9.72	0.14
Nocturnal pruritus (%)	88.3	83.3	0.432
Similar symptoms in contacts of patients (%)	75	66.6	-
No. of contacts	155	107	-
Severity of itching, mild/moderate /severe (%)	20/70/10	30/53.3 /16.7	0.72/0.06 /0.16
Socioeconomic status, upper/ middle/lower (%)	10.0/53.3 /36.7	1.7/68.3 /30.0	-

Table-II. Comparison of baseline laboratory profile (Day 0) with t-test

Quantitative investigations	Group A (n=60)		Group B (n=60)		p-value
	Mean	SD±	Mean	±	
Hb	14.6	2.2	13.3	2.1	0.43
TLC	7.24	1.97	7.28	2.07	0.90
Bilirubin	1.10	0.14	1.1	0.17	0.42
SGPT	24.7	6.4	25.0	5.7	0.8
Creatinine	0.89	0.11	0.90	0.11	0.57

Table-III. Comparison of laboratory profile after one week treatment (Day 7)

Quantitative investigations	Group A (n=60)		Group B (n=60)		p-value
	Mean	SD±	Mean	±	
Hb	12.9	1.8	13.4	2.0	0.13
TLC	7.0	1.6	7.2	1.8	0.630
Bilirubin	1.0	0.2	1.1	0.2	0.45
Creatinine	0.91	0.12	0.95	0.12	0.153

Table-IV. Comparison of laboratory profile (Day 14) with t-test

Quantitative Invest.	Group A (n=60)		Group B (n=60)		p-value
	Mean	SD±	Mean	±	
Hb	12.9	1.9	13.4	2.04	0.119
TLC	6.7	1.5	6.6	1.2	0.649
Bilirubin	1.08	0.118	1.06	0.14	0.482
SGPT	26.88	5.84	27.31	7.44	0.72
Creatinine	0.92	0.12	0.94	0.11	0.388

are topical. Their application is cumbersome and messy which leads to poor compliance. Cost of total treatment is also high[8,12]. Ivermectin, a synthetic macrolide, has been used for treating human scabies by different researchers since early 1990's. When used properly, it can avoid some concerns regarding the apparent development of Lindane- or Permethrin-resistant strain[8].

Since Ivermectin has become recently available in Pakistan and is freely used for scabies treatment, it is important to evaluate its safety and compare it with standard topical therapy already being used.

In our study we found no statistically significant difference in the safety of Permethrin and Ivermectin when used as a single therapy in scabies treatment. A total of 8 patients in our study became reinfested with S. scabiei two weeks after treatment, n=4 in each group. This relapse may be due to development of increasing resistance against both drugs[9,14]. The results of Abedin S et al are also comparable with our results, in terms of its efficacy[6]. At completion of 2 weeks post-therapy, contrary to Usha et al and Akhtar SJ, none of our patients complained of aggravation of pruritus after taking the medicine in the Ivermectin group. This may be due to difference in inclusion criteria. Muscular pain was reported by 5 patients each (8.3%) and the same number reported nausea during the initial few days after taking Ivermectin tablet. The complaint by 2 patients, of mild to moderate headache in the first week of therapy, subsiding after a couple of days without any medication,

is a finding similar to that of others such as Madan et al[16]. Only 1 patient (1.7%) had persistent headache at second follow up at 2 weeks. These results compared well with the results by Akhtar SJ et al[17].

In Permethrin group, burning sensation was the most common side effect seen, 8 patients (13.3 %), similar to Bukhari et al (10.0%)[4]. This was followed by contact dermatitis and stinging sensation seen in 4 (6.7%) and 3 (5%) patients respectively. After 7 days, a total of 15 patients (25%) experienced side effects in each group, which indicates that there is no difference in occurrence of side effects. The laboratory profile was within reference ranges in all patients. Only one patient in Ivermectin group, had significant rise in serum SGPT, which settled to baseline on next follow up after a week. This may be due to hepatic metabolism of the drug[7,15].

When we compared our results with other similar studies we found them compatible with those shown by Khan I and Yasmin R. They concluded that Ivermectin is as safe and effective as Permethrin in the treatment of scabies. Efficacy was 100% in all 30 patients studied. There was no side effect observed in that study[13].

Akhtar SJ et al used Ivermectin to decrease burden of disease by increasing compliance of contacts to multiple doses of the drug. They used it at higher doses of 300 µg/kg in 60 patients, regardless of age. No major side effect was observed and treatment was 100% effective[17]. These observations are useful concerning the safety of drugs in older people who are generally receiving multiple drugs and live together in close groups[19].

Ivermectin is not approved for use in children under five years of age.

However Abedin S et al documented excellent efficacy of 2 doses of oral Ivermectin in treatment of endemic scabies in a pediatric population in India, concluding its safety in children[6].

Regarding its use in pregnancy, Ivermectin has been used in about 400 pregnant women inadvertently received the drug in the first trimester as the mainstay of treatment in the onchocerciasis control program. No significant increase in teratogenicity was observed[2].

The main limitation of our study was that Ivermectin was not given to children below 5 years of age (or < 15kg) and to pregnant or lactating women due to concerns regarding its use in these conditions keeping in mind possibility of increased penetrance of drug through the immature blood-brain barrier. Another limitation was inability to trace all the contacts and treat them. Further studies are required to evaluate safety of this drug in children.

CONCLUSIONS

We found oral Ivermectin in a single dose as safe as topical Permethrin for the treatment of most cases of human scabies. It is a promising tool to improve compliance and may be a convenient alternative to conventional topical scabicides with no additional side effect hazards associated with oral drugs. It can be used safely in all age groups to achieve control of scabies more efficiently.

However additional large-scale studies are required to further evaluate its adverse effects especially long-term side effects.

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