

# Comparison of Safety Of Oral Ivermectin with Topical Permethrin in the Treatment of Scabies: A Comparative Study

Rishabh Dev Tripathi<sup>1</sup>, Seema Sitaula<sup>2</sup>, Sanjeev Kharel<sup>3</sup>

<sup>1</sup>Om Hospital and Research Centre, Kathmandu

<sup>2</sup>Department of Dermatology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

<sup>3</sup>Intern, Maharajgunj Medical Campus, Tribhuvan University, Kathmandu, Nepal

## Abstract

**Introduction:** The mite *Sarcoptes scabiei* var. *hominis* is the cause of scabies, a skin illness. The Food and Drug Administration (FDA) approves permethrin cream (5%) for the treatment of scabies and is also recommended by the Centers for Disease Control and Prevention (CDC) as first-line topical therapy for scabies. Oral ivermectin, a novel antiparasitic agent that has been extensively used for several parasitic infections and can be used as an alternative approach for the treatment of scabies. This comparative study aimed to describe the adverse effects of ivermectin and permethrin and their comparison.

**Objective:** To compare the safety outcomes of ivermectin and permethrin for the use of scabies.

**Methods:** This is the prospective open-labeled randomized and comparative study carried out in the outpatient department of dermatology and venereology at Tribhuvan University Teaching Hospital, Kathmandu. In Group A, patients received oral Ivermectin tablets at a dose of 200 µg/kg on day 1 before breakfast, and in Group B, patients received topical Permethrin 5% cream to be applied all over the body below the neck at night twice a week apart.

**Results:** This study included 93 patients who met the inclusion criteria, with 45 patients belonging to the Ivermectin group and 48 patients belonging to the Permethrin group. In the ivermectin group, the most common side effect reported was nausea, followed by abdominal discomfort and headache. In the Permethrin group, the most common side effect was a burning sensation on the skin after application of the drug, followed by irritation and erythema, which were present in 3.2% and 2.2% of patients, respectively. The difference in overall side effects between the two groups was statistically not significant. ( $p=0.682$ )

**Conclusion:** Our study concludes that a single dose of oral Ivermectin given at a dose of 200 micrograms/kg is comparable to Permethrin cream 5% used twice a week in terms of safety standards. Neither drug caused any life-threatening adverse reactions in the patients.

**Key words:** Ivermectin; Permethrin; Scabies

## Introduction

The mite *Sarcoptes scabiei* var. *hominis* is the cause of scabies, a skin illness. The mite excavates beneath the skin, resulting in severe itching and a papular rash. Secondary skin infections caused by bacteria like *Staphylococcus aureus* and *Streptococcus pyogenes* can exacerbate infestations, resulting in invasive diseases, immune-mediated disorders, and more severe skin infections.<sup>1</sup> In addition to affecting sleep,

academic or job performance, and creating stigma, scabies significantly lowers quality of life.<sup>2,3</sup> Scabies is a neglected tropical illness that affects over 130 million people and imposes significant expenses on health-

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### Corresponding Author:

Sanjeev Kharel,  
Intern, Maharajgunj Medical Campus, Tribhuvan University,  
Kathmandu, Nepal  
ORCID ID: 0000-0001-9591-3168  
E-mail: [Kharelsanjeev1208@gmail.com](mailto:Kharelsanjeev1208@gmail.com)

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care systems worldwide. While effective treatments exist, it is unknown which treatment tactics produce the best results at the lowest cost, and how this varies between communities.<sup>2</sup>

Synthetic pyrethroids, including permethrin, represent one of the most important insecticides, accounting for over 25% of the world insecticide market. It demonstrates extremely low mammalian toxicity and has higher insecticidal activity than natural pyrethrins.<sup>4</sup> The USFDA approves permethrin cream (5%) for the treatment of scabies and is also recommended by the Centers for Disease Control and Prevention (CDC) as first-line topical therapy for scabies.<sup>5</sup> According to a recently updated Cochrane review, permethrin appears to be the most effective topical scabicide, significantly better than crotamiton and lindane.<sup>6</sup>

Oral ivermectin, a novel antiparasitic agent that has been extensively used for several parasitic infections, including onchocerciasis, lymphatic filariasis, and other nematode-related infestations, can be used as an alternative approach for the treatment of scabies. Ivermectin is thought to interrupt glutamate-induced and  $\gamma$ -aminobutyric acid-induced neurotransmission in parasites, leading to their paralysis and death. In humans, ivermectin does not cross the intact blood-brain barrier and thus has low CNS toxicity.<sup>7</sup> This comparative study aimed to describe the adverse effects of ivermectin and permethrin and their comparisons.

## Materials and Methods

This is the prospective open label randomized and comparative study carried out in the outpatient department of dermatology and venereology in Tribhuvan University Teaching Hospital, Kathmandu. The study was approved by the institutional review committee of the Institute of Medicine. Keeping significance level  $\alpha = 5\%$  and power of study  $(1 - \beta) = 95\%$ , the minimum sample size calculated was 48 with 24 patients in each group. In this study, a total of 93 patients were enrolled, with 45 patients in the Ivermectin group (A) and 48 patients in the Permethrin group (B).

### Inclusion Criteria:

Patients meeting the criteria mentioned below were selected as eligible participants for our study:

- All the patients diagnosed with scabies who are more than 5 years old / >15kg have been included.
- Only those patients who have given written consent have participated in the study.

### Exclusion Criteria:

Patients meeting the following criteria have been excluded from the study:

- Pregnant and lactating women,
- Patients with immunodeficiency or severe systemic disease
- Heavily crusted or nodular scabetic lesions
- Received prior treatment with anti-scabies or topical steroid therapy.

## Data collection and synthesis

At the initial visit, all the study patients underwent the necessary physical and cutaneous examinations, the details of which were recorded in a pre-designed pro forma. The diagnosis of scabies was made based on the presence of at least three of the following clinical criteria:

- Presence of a burrow;
- Presence of scabetic lesions at the classical sites\*
- Nocturnal pruritus and
- Family history of similar illnesses.

\* The classical sites of scabetic lesions consist of the interdigital folds of the hands, the flexor aspects of the forearms, the axillary folds, the nipple areaola, the periumbilical area, and the genitalia.

Patients were randomized into two groups: A and B

**In Group A:** Patients received an oral Ivermectin tablet at a dose of 200  $\mu\text{g}/\text{kg}$  on day 1 before breakfast.

**In Group B:** The patients received topical Permethrin 5% cream to be applied all over the body below the neck at night, twice a week apart. It was explained that the cream must remain in contact with the skin for at least 8 hours. They were advised to take a bath with warm water not earlier than 8 hours after application. Patients in both groups were followed up at 2-week intervals (minimum 2 visits) to assess the cure rate. During follow-up visits, patients underwent clinical assessments, which included examination of the whole body for the presence of new lesions. Patients were asked to quote 0/25/50/75/100% on the VAS (Visual Analogue Scale) about the subjective status of pruritus, considering the status of pruritus at their first visit to be 100%.

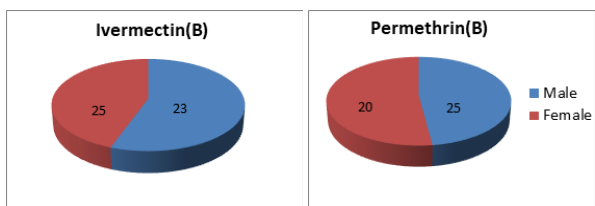
The details of the patient's demographic features (age, gender), mean weight, mean duration of illness, severity of pruritus, and common adverse effects in both groups. The raw data was compiled and entered for data analysis in SPSS in different phases, until the end of the study. All the raw data was collected in Microsoft Excel (Ver. 2016) in different phases, until the end of the study. Statistical analysis was performed using SPSS 21 (IBM Corp., Released 2012). IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Continuous data was presented as the mean and standard deviation. Categorical data was presented as frequency and percentage, and for the test, a p-value of 0.05 or less is considered statistically significant. Regression analysis was conducted to adjust confounders.

**Results**

This study included 93 patients who met the inclusion criteria, with 45 patients belonging to the Ivermectin group (A) and 48 patients belonging to the Permethrin group (B). In terms of clinical and demographic data, there was no significant difference between the two groups (Table 1). The patient's age ranged from 6 to 45 years of age, with a mean age of 23.69. Out of 45 patients in group A, 25 were male and 20 were female; out of 48 patients in group B, 23 were male and 25 were female (Figure 1). The weights of the patients in both groups were comparable as well. The mean weight in group A was 50.26, while it was 47.72 in group B. The mean duration of illness was 19.33; the difference in the mean duration of illness between the two groups was statistically insignificant (Table 1).

**Table 1:** Comparison of clinical demographic characteristics

Variables	Ivermectin (A)	Permethrin (B)	Total
Age ( 6-45yrs) (p=0.163; t=1.408)	25.15 ±9.05	22.37 ± 9.57	23.69 ± 9.41
Male	25	23	48
Female ( p= 0.461; t=0.543)	20	25	45
Mean Weight (kg) (p=0.076; t=1.794)	50.26 ± 12.63	45.33 ± 13.80	47.72 ± 13.41
Mean duration of illness (days) (p=0.44; t=0.776)	22.11± 10.07	18.60 ± 8.52	19.33 ± 9.28

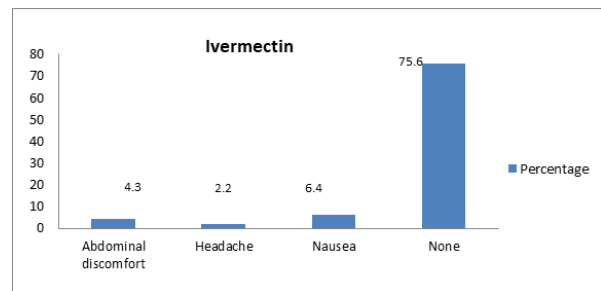


**Figure 1:** Pattern of sex distribution in each group  
The difference in the severity of pruritus between the two groups was, however found to be statistically significant (Table 2). In group A, out of 45 patients, 4, 23, and 18 had mild, moderate, and severe pruritus, respectively. In group B, out of 48 patients 8, 11, and 29 had mild, moderate and severe pruritus, respectively.

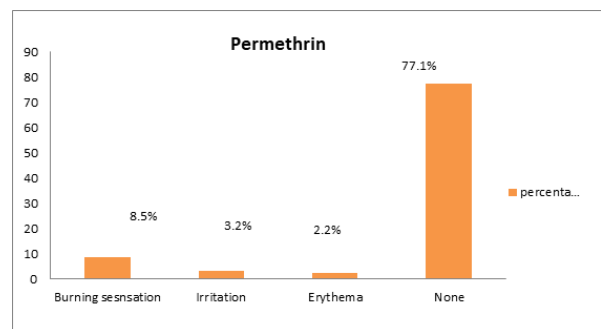
**Table 2:** Comparison of the severity of pruritus between the groups

Severity of Pruritus	Treatment group (χ2=8.055; P=0.018)		Total
	Ivermectin (A)	Permethrin (B)	
Mild	4	8	12
Moderate	23	11	34
Severe	18	29	47
Total	45	48	93

In the ivermectin group (A), the most common side effect reported was nausea, reported by 6 patients (6.4%). Abdominal discomfort and headaches were reported by 4.3% and 2.2% of patients, respectively, during follow-up visits (Figure 2). In the permethrin group (B), the most common side effect was a burning sensation on the skin after application of the drug, which was reported by 8 patients (8.5%) during follow-up visits. Other side effects include irritation in 3.2% of patients and erythema in 2.2% of patients (Figure 3).



**Figure 2:** Common adverse effects in the Ivermectin group

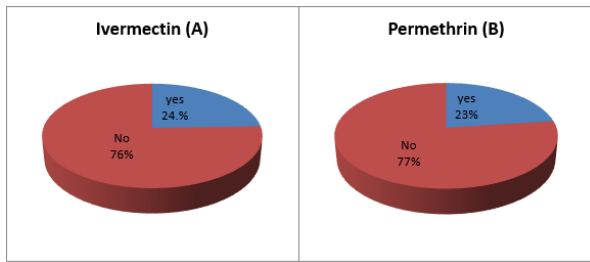


**Figure 3:** Common adverse effects in the Permethrin group

Out of 93 patients enrolled in the study, 22 (23.7%) reported at least one side effect after the treatment. In group A, out of 45 patients, 11 (24.4%) reported at least one side effect, and in group B, 11 out of 48 patients (22.9%) reported at least one side effect due to the treatment (Figure 4)) The difference in overall side effects between the two groups was statistically not significant when compared by the chi-square test (P=0.862; χ2=0.03). (Table 2)

Treatment group (P= 0.862; χ2=0.03)	Presence of at least one side effect after treatment		Total
	No	yes	
Ivermectin (A)	34	11	45
Permethrin (B)	37	11	48
Total	71	22	93

**Table 2:** Comparison of adverse effects between two groups



**Figure 4:** Comparison of adverse effects between two groups

## Discussion

Our study showed few common adverse effects in both groups, no difference in overall side effects between the two groups, and no serious complications.

No major life-threatening side effects have been observed in either group. Out of 45 patients in the Ivermectin group, 11 experienced minor side effects such as nausea, abdominal discomfort, and headache. Similarly, in the Permethrin group, 11 out of 48 patients experienced minor adverse effects such as erythema, irritation, and burning sensations. In this study, pregnant ladies, lactating women, children below 6 years, and immunocompromised patients were not included because of safety concerns. Ivermectin is the mainstay of treatment in the onchocerciasis control program, with about 19 million doses distributed over the world without any major side effects. In the same control program, 400 pregnant women inadvertently received the drug in the first trimester, but no significant increase in teratogenicity was observed.<sup>8</sup>

The safety of ivermectin has been documented in millions of people with microfilaria diseases. Only 1-8% of the 150,000 adverse reports caused by ivermectin were severe. Common side effects include anorexia, asthenia, headache, arthralgia, myalgias, fever, eosinophilia, and maculopapular rashes. Pruritus may occur in up to 30% of treated patients. The Mazzotti reactions may occur while treating patients with onchocerciasis with ivermectin within seven days of treatment.<sup>9</sup> Ivermectin does not normally penetrate the blood-brain barrier, and consequently, there is no risk of seizures. Because of limited safety data, and also due to concern that the blood-brain barrier is not fully developed in small children, ivermectin should not be used in children younger than 5 years of age or during pregnancy or lactation. However, no genotoxicity or teratogenicity has been observed to date, and the concentration in human milk is minimal.<sup>10</sup> The drug is rapidly metabolized in the liver, where the molecule undergoes oxidation by the cytochrome P450 system, as well as hydrolysis into metabolites. Elimination of these metabolites occurs via urinary excretion. Since the drug has a very stable chemical structure, having a half-life of 51–71 days in an aqueous environment and showing high toxicity to aquatic organisms, it is listed as a "restricted use" substance by the US Environmental

Protection Agency.<sup>11</sup>

Similarly in different comparison study and a randomized clinical trial conducted by Sunita B Chhaya et al., in 315 patients, the clinical efficacy of permethrin 5% cream as a single application, tablet ivermectin 200 mcg/kg as a single dose, and ivermectin 1% lotion as the single application was compared.<sup>12,13</sup> At the end of the first week, the cure rate obtained was 74.8% in the permethrin group, 30% in the oral ivermectin group, and 69.3% in the topical ivermectin group ( $P < 0.05$ ). At the end of the second follow-up, the cure rate increased to 99% in the permethrin group, 63% in the oral ivermectin group, and 100% in the topical ivermectin group ( $P < 0.05$ ). At the end of the third follow-up, a 100% cure rate was observed in both the permethrin and topical ivermectin groups, while a 99% cure rate was obtained in the oral ivermectin group ( $P = 0.367$ ). No serious adverse events were observed.<sup>12,13</sup> Pramod Kumar Majhi et al, in their study, compared single-dose oral ivermectin (200  $\mu\text{g}/\text{kg}/\text{dose}$ ) with various other topical anti-scabidicidal medications including permethrin 5%, Gamma Benzene Hexachloride 1%, and topical Benzyl Benzoate 25%. This study included 60 patients in four different groups and was followed up in the 1<sup>st</sup> and 6<sup>th</sup> weeks to note the status of disease severity and pruritus. In terms of side effects, oral ivermectin showed a safe therapeutic response without causing skin irritation, or CNS side effects.<sup>14</sup> The frequency of treatment failure varied significantly amongst the medications used to treat scabies, with ivermectin and permethrin exhibiting the lowest rates. When oral ivermectin was taken in two doses as opposed to one, there was a notable decrease in treatment failure. Over time, treatment failure has gradually grown at a rate of 0.2% annually.<sup>15</sup> Ivermectin has several clinical advantages that can make it superior to topical treatments in developing countries. Despite being safe and inexpensive, it is also simple to administer, easily supervised, and treats the entire skin surface without neglecting areas, which increases both its compliance and feasibility.<sup>16</sup> Ivermectin is better tolerated and causes less discomfort than topical treatment in those with excoriations or open ulcerations. For mass treatment and control of the epidemic, the drug has been successful. Besides, it also has the additional benefit of decreasing the prevalence of other parasitic infections such as onchocerciasis, *Ascaris* infection, lymphatic filariasis, pediculosis, cutaneous larva migrans, and strongyloidiasis. Ivermectin is also superior to topical agents in treating immunocompromised persons with scabies.<sup>17</sup> There have been a few reports of serious adverse effects with oral ivermectin, including death and convulsion, but these are rare. Permethrin has been linked to death, dystonia (after labeled use), and congenital leukemia.<sup>18</sup>

Even when equivalent efficacy with Permethrin 5% cream is assumed, these additional advantages of ivermectin make it a superior choice in developing

countries, like Nepal, where the environment favors rapid spread that can quickly reach epidemic proportions. However, long-term evaluation of the risk of re-infection and rates of disease in close contacts warrants further research, which has been the major limitation of this study.

## Conclusion

Our study concludes that a single dose of oral Ivermectin

given at a dose of 200 micrograms/kg is comparable to Permethrin cream 5% in terms of safety standards. Permethrin cream 5% is to be applied two times at an interval of one week. Neither drug caused any life-threatening adverse reactions in the patients. The participants in either group experienced only minor side effects, such as nausea, abdominal discomfort, and erythema irritation. Further studies with a larger sample size are needed.

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