

Original papers

The efficacy of oral ivermectin vs. sulfur 10% ointment for the treatment of scabies

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ABSTRACT. Human scabies is caused by an infection of the skin by the human itch mite (*Sarcoptes scabiei* var. *hominis*). There are different medications for the treatment of scabies. This study aimed at comparing the efficacy and safety of oral ivermectin vs. sulfur 10% ointment for the treatment of scabies. In total, 420 patients with scabies were enrolled, and randomized into two groups: the first group received a single dose of oral ivermectin 200 µg/kg body weight, and the second group received sulfur 10% ointment and were told to apply this for three successive days. Treatment was evaluated at intervals of 2 and 4 weeks, and if there was treatment failure at the 2-week follow-up, treatment was repeated. A single dose of ivermectin provided a cure rate of 61.9% at the 2-week follow-up, which increased to 78.5% at the 4-week follow-up after repeating the treatment. Treatment with single applications of sulfur 10% ointment was effective in 45.2% of patients at the 2-week follow-up, which increased to 59.5% at the 4-week follow-up after this treatment was repeated. A single dose of ivermectin was as effective as single applications of sulfur 10% ointment at the 2-week follow-up. After repeating the treatment, ivermectin was superior to sulfur 10% ointment at the 4-week follow up. The delay in clinical response with ivermectin suggests that it may not be effective against all the stages in the life cycle of the parasite.

Key words: scabies, *Sarcoptes scabiei*, oral ivermectin, sulfur 10% ointment

Introduction

Scabies is a contagious skin infection caused by the mite *Sarcoptes scabiei*. The mite is a tiny and usually not directly visible parasite, which burrows under the host's skin, causing intense allergic itching [1,2]. The infection in animals is caused by a different but related mite species, and is called sarcoptic mange. The characteristic symptoms of a scabies infection include intense itching and superficial burrows [3,4]. The burrow tracks are often linear, to the point that a neat „line" of four or more closely placed and equally developed mosquito-like „bites" is almost diagnostic of the disease [5,6]. The symptoms are caused by an allergic reaction of the host's body to mite proteins, though exactly which proteins remains a topic of study. The mite proteins are also present from the gut, in mite feces, which are deposited under the skin [7,8]. The allergic reaction is both of the delayed (cell-mediated) and immediate (antibody-mediated) type, and involves IgE. The allergy-type symptoms continue for some days, and even several weeks, after all mites are killed [9,10]. New lesions may appear for a few days after mites are eradicated. Nodular lesions from scabies may continue to be symptomatic for weeks after the mites have been killed [11,12]. Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or there is itchiness of another household member [13,14]. The classical sign of scabies is the burrows made by the mites within the skin. A number of medications are effective in treating scabies; however, treatment must often involve the entire household or community to prevent re-infection [15,16]. Options to improve itchiness include antihistamines. The usual scabies treatment is with permethrin 5% dermal cream. Permethrin is an insecticide that kills

the mites [17,18]. Sulfur ointment (precipitated sulfur) 5% to 10% is considered a safe treatment for scabies. There is not clear evidence from studies showing how well it works. But it sometimes cures scabies, especially Norwegian scabies. Topical sulfur ointment is a cost-effective and safe therapeutic agent. It is often applied for the whole body for three successive days [9,19]. Ivermectin is an oral medication shown by many clinical studies to be effective in eradicating scabies, often in a single dose. It is the treatment of choice for crusted scabies and is often used in combination with a topical agent [20,21]. It has not been tested on infants and is not recommended for children under six years of age. Topical ivermectin preparations have been found to be effective for scabies in adults and are attractive due to their low cost, ease of preparation, and low toxicity. It has also been useful for sarcoptic mange (the veterinary analog of human scabies) [22]. This study aimed at comparing the efficacy of oral ivermectin vs. sulfur 10% ointment in the treatment of scabies.

Materials and Methods

This was a single-blind, randomized controlled trial. Between January 2011 and January 2015, any patients with scabies who were older than 2 years of age and attending the dermatology outpatient clinic, Sari, were assessed for enrolment in the study. Exclusion criteria were age younger than 2 years; pregnancy or lactation; history of seizures, severe systemic disorders, immunosuppressive disorders and presence of Norwegian scabies; and use of any topical or systemic acaricide treatment for 1 month before the study. Written consent was obtained from all the patients.

Before entry into the study, patients were given a physical examination and their history of infestations, antibiotic treatment and other pertinent information was recorded. Age, gender, height and weight were recorded for demographic comparison, and photographs were taken for later clinical comparison. None of the patients had been treated with pediculicides, scabicides or other topical agents in the month preceding the trial. The diagnosis of scabies was made primarily by the presence of the follow three criteria: presence of a burrow and/or typical scabietic lesions at the classic sites of infestation, report of nocturnal pruritus and history of similar symptoms in the patient's families and/or close contacts. Infestation was confirmed by demonstration of eggs, larvae, mites or fecal material under light microscopy. Patients who satisfied the above criteria were randomly divided into two groups: group A were to receive ivermectin, and group B were to receive sulfur 10% ointment.

Randomization and treatment. In total, 480 patients were initially enrolled. Of these, 60 patients were not able to return after the first follow-up examination, and were therefore excluded from the study. The remaining 420 patients (240 male, 180 female; mean±SD age 42.18±12.86 years, range 4–72) constituted the final study population.

The first group received a single dose of 200 μg/kg body weight oral ivermectin and the second group received sulfur 10% ointment and were told to apply this for three successive days. The treatment was given to both patients and their close family members, and they were asked not to use any antipruritic drug or any other topical medication.

Evaluation. The clinical evaluation after treatment was made by experienced investigators who were blinded to the treatments received. Patients were assessed at 2 and 4 weeks after the first treatment. At each assessment, the investigators recorded the sites of lesions on body diagram sheets for each patient, and compared the lesions with those visible in the pretreatment photograph. New lesions were also scraped for microscopic evaluation. Patients were clinically examined and evaluated based on the previously defined criteria (see 'Patient recruitment'). 'Cure' was defined as the absence of new lesions and healing of all old lesions, regardless of presence of postscabietic nodules. 'Treatment failure' was defined as the presence of microscopically confirmed new lesions at the 2-week follow-up. In such cases, the treatment was repeated at the end of week 2 and patients were evaluated again at week 4. 'Re-infestation' was defined as a cure at 2 weeks but development of new lesions with positive microscopic findings at 1 month. Any patients with signs of scabies (whether as a result of treatment failure or re-infestation) would then be treated with permethrin.

Statistical analysis. The χ^2 test or the Fisher exact test was used, as appropriate to examine difference between groups, and $P<0.05$ was considered significant. SPSS software (version 16; SPSS Inc., Chicago, IL, USA) was used for all analysis.

Table 1. Demographic characteristics of the study population

	Ivermectin (n=210)	Sulfur 10% (n=210)
Age	36.94±17.56	32.89±11.76
Male	165	155
Female	55	65
Height (cm)	170±34	172±76
Weight (kg)	72±54	73±3=59

Table 2. Severity of infection pretreatment of all patients

Lesions	Ivermectin	Sulfur 10%	Total subjects
Mild <50	30	35	75
Moderate 50-100	60	55	115
Severe > 100	120	130	250
	n=210	n=210	420

Results

There were no significant differences in age or gender between the two groups (Table 1). On entry into the study, the number of patients in each treatment group who were graded as having mild, moderate or severe infection was also not significantly different (Table 2).

At the 2-week follow-up, the treatment was effective in 130 (61.9%) patients in the ivermectin group and 95 patients (45.2%) in the sulfur 10% ointment group, with no significant difference between the groups (P=0.42). The treatment was repeated for the 195 patients (110 male, 85 female; 80 in the ivermectin group and 115 in the sulfur 10% ointment group) who still had infestation.

At the second follow-up, at 4 weeks, only 45 of the 80 patients in the ivermectin group still had severe itching and skin lesions, compared with 85 of the 115 patients in the sulfur 10% ointment group. Thus, the overall cure rate was 165/210 patients (78.5%) in the ivermectin group and 125 of 210 (59.5%) in the benzyl benzoate 25% lotiongroup (P<0.05).

The remaining 130 patients who were considered treatment failures in the study were retreated with open-label permethrin cream, which cured the infection in 2–3 weeks.

Adverse events. The treatments were considered cosmetically acceptable by both patients and parents. None of the 400 participants experienced allergic reactions. The main adverse event (AE) was irritation, reported by 70 patients (40 in the ivermectin group and 30 in the benzyl benzoate 25% lotion group), but this was not serious and did not affect compliance. None of the patients experienced worsening of the infestation during the study; even the treatment failures were improved compared with their pre-treatment status, and none had > 50 new lesions.

Discussion

A number of medications are effective in treating scabies; however, treatment must often involve the entire household or community to prevent re-infection. Options to improve itchiness include antihistamines [23,24]. Oral ivermectin is an effective and cost-comparable alternative to topical agents in the treatment of scabies infection. It has been used extensively and safely in the treatment of other parasitic infections, but the U.S. Food and Drug Administration has not approved the drug for the treatment of scabies infection. The safety of oral ivermectin in pregnant and lactating women and young children has yet to be established [25,26].

In this study, application of sulfur 10% ointment was as effective as a single oral dose of ivermectin by 2 weeks (P>0.05). The lack of efficacy of a single dose of ivermectin in some patients may be due to the lack of ovicidal action of ivermectin. Ivermectin, because of its specific site of action, may not be effective against the younger stages of the parasite inside the egg because the nervous system has not yet developed [27,28]. The concentration achieved in the skin may also be variable because ivermectin is orally administered. These factors could also explain the temporal delay in complete recovery observed in the ivermectin group. Because ivermectin has not been proven to be ovicidal, a single dose of 200 μg/kg body weight may be inadequate to eradicate the different stages of the parasite, and a higher dose or a second dose may be required within 1 to 2 weeks for higher cure [29,30]. In our patients we found that oral ivermectin was superior to sulfur 10% ointment when used in two doses over a period of 4 weeks. The data from the 4th week showed that ivermectin continued to decrease both the lesions and the degree of pruritus as compared to sulfur 10% ointment and this difference was statistically significant (P<0.05). This finding was in accordance to Goldust et al. [31] that concluded, a single dose of ivermectin was as effective as one

application of crotamiton 10% cream at the two-week follow-up. After repeat treatment, ivermectin was superior to crotamiton 10% cream at the four-week follow up. The delay in clinical response with ivermectin suggests that it may not be effective against all the stages in the life cycle of the parasite. In the study carried out by Usha et al. [32] higher number of patients showed clearance of lesions as compared to our results. This could be explained due to the longer follow up.

Ivermectin has several clinical advantages that make it superior to topical treatment in developing countries. It is safe, inexpensive, simple to administer, easily supervised, and treats the entire skin surface without neglected areas [33,34]. Ivermectin is better tolerated than topical treatment in those with excoriations or open ulcerations. The drug has successfully been used for mass treatment and in epidemics. It also has the additional benefit of reducing the prevalence of other human parasitic infections common in the tropics, including onchocerciasis, *Ascaris* infection, lymphatic filariasis, pediculosis, cutaneous larva migrans, and strongyloidiasis. Ivermectin is also superior to topical agents in treating immunocompromised persons with scabies [35,36]. Even when equivalent efficacy with sulfur 10% ointment is assumed, these additional advantages of ivermectin make it a superior choice in developing countries, like Iran, where conditions favor rapid spread that can quickly reach epidemic proportions. Long-term evaluation of the risk of re-infection and rates of disease in close contacts warrants further study [37–39]. Regarding side effects, sulfur 10 % ointment was found to be significantly more safe than ivermectin (P<0.05).

Conclusions

Although ivermectin was more effective than sulfur 10% ointment, it has few outweighing advantages over the topical sulfur. It is cost-effective and as treatment can be given to masses with better compliance with or without supervision. It can also be given safely in patients of scabies with secondary eczematization, erosions or ulcers where topical therapies such as permethrin, lindane and benzyl benzoate can cause serious cutaneous and systemic side effects in addition to the problem of compliance.

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