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THE EFFICACY OF ORAL IVERMECTIN AND COMBINED MODALITY IN THE MANAGEMENT OF SCABIES

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ABSTRACT

Background: Scabies is significant global health problem. Various theraputic options have been existed but the ideal treatment modalities is ongoing. **Objectives**: To assess oral ivermectin efficacy versus concomitant oral ivermectin with topical permethrin with the aim of determination suitable regimen for scabies. The diagnosis was established by dermatologist at Al-Quds Health Center in Mosul city. In total, 220 patients were allocated into two groups. Group I received oral ivermectin, two doses of 200 µg/kg separated by 1 week. Group II applied permethrin 5% cream overnight, repeated after 1 week in addition to 2 doses ivermectin. Patients were seen 2 and 4 weeks interval. **Results**: At second week, 75% of the patients in group I and 88% in group II achieved a significant improvement in pruritus as compared to baseline ($P< 0.05$). The improvement in severity score was significantly greater in group II than group I ($P < 0.05$). At 4 weeks, the overall cure rate was 82% in group I and 90% in group II (no significant different). Though permethrin showed somewhat more effective, both ivermectin and permethrin were well tolerated and no major side effects were demonstrated. **Conclusion**: The concomitant ivermectin orally and topical permethrin represents a useful alternative with higher cure rate than single therapy. Both medications are almost similarly effective but permethrin shows rapid onset of action. Oral ivermectin is a magic remedy in epidemics and large scale. Treatment of all close contacts simultaneously and personal hygiene can control spreading of scabies.

KEYWORDS: Scabies, Ivermectin, Permethrin.

INTRODUCTION

Scabies is an intensely itchy, highly contagious ectoparasitic infestation caused by the mite Sarcoptes scabiei. It is a globally significant public health dilemma.[1,2] It affects both sexes of all age groups, races and social classes. However, it particularly problematic in areas associated with poor hygiene and overcrowding where there is frequent skin to skin contact as child care centers, hospitals, nursing homes, or prison.[3,4] There is seasonal variation with scabies incidence being higher in winter than summer, possibly due to the tendency to indoor overcrowding in cold climate.[5] The Sarcoptes scabiei mite is a tiny, not directly visible parasite that burrows under the skin, which in most cases results in an severe itching due to an allergic reaction. Lesions contain tiny gray specks, slightly raised tortuous burrow, papules, itchy excoriation and crusts.[6] The classical sites of the lesions are found in body crevasses as those between the fingers and toes, the elbows, axillary areas, the buttocks, the genital, the waist area, the periumbilical area, under the female breasts and nipples areolas. Apart from infants and very young children, the face, neck, palms, and soles are usually unaffected.[7,8] Clinical infestation with the scabies mite results in intense itching (pruritus) with irritating papular eruptions and discomfort. Severe itching, particularly at night, is considered the earliest and commonest symptom of scabies.[3,6] Much of the symptoms associated with scabies are as a result of the host`s immune “allergic” reaction that can last several weeks to appear following initial infection in a subject exposed for the first time. While, the symptoms appear after a shorter interval (1 to 2 days) after reinfestation. Sever itching results in frequent scratching that make the skin prone to secondary infections.[9,10] Scabies typically transmitted through prolonged personal contact(skin-to-skin contact of a social or sexual nature) and transfer via inanimate things as sharing personal items as clothing, bedding,

towels or furnishings may also possible.[11] In most cases, a physician can identify scabies depending on the rash appearance and on the history of generalized itching with nocturnal worsening as well as presence of similar symptoms in close contacts. Diagnosis confirmation is either by burrow detection or microscopic finding of the mite or its egg shells.[12] Various treatment options for scabies are exist. Topical therapy has the disadvantages of being time-consuming, cumbersome, treatment failure that results from poor compliance, inadequate scabicide application, frequency or technique of application. In addition to inadequate management of close contacts.[9,13] Scabies management involves eradicating the mite with medication. All people in the household that have had close contact with an infected person during the past month should be treated, even if they lack symptoms.[14] Scabies is mostly treated with permethrin 5% cream or lotion. It is an insecticide which kills the mite causes scabies. Permethrin should be washed after 8–14 hours and it can be repeated 1–2 weeks later.[15] Ivermectin is an effective oral medication to eradicate scabies, often with a single dose. It is safe and easy to use in families and individuals on a large scale. It is the drug of choice for treatment of crusted scabies, it is often used in addition to topical agent. Ivermectin is not recommended for use in pregnancy, lactation or children less than 6 years of age.[16,17] Topical ivermectin preparations, also, have been established to be effective for treatment of scabies in adults, they are appeal due to their ease of preparation, low cost, and low toxicity.[18] Although scabies is endemic in various developing countries, few studies compared ivermectin with topical agents in these countries. Usha and Nair demonstrated ivermectin efficacy to be comparable to topical permethrin 5% when administered in a dose of 200µg/kg.[19] As Iraqi population being frequently affected by scabies, hence, it is decided to conduct this study to evaluate the efficacy of therapies composed of systemic ivermectin versus concomitant use of systemic ivermectin with topical permethrin 5% cream in addition to adjuvant crotamiton cream with the aim of determination better management and suitable regimen option for scabies in Mosul city.

MATERIALS AND METHODS

This study was conducted from January to April 2023 at Al-quds Health Center for Family Medicine and at private Dermatology Clinic in Mosul city. All consecutive patients with scabies who attending the dermatology outpatient clinic were assessed for enrolment in the study.

The diagnosis of scabies was established by taking detailed history, including that of family and close contacts, along with meticulous examination of typical lesions by dermatologist and experienced family physician. The study protocol was approved by the local Heath Center ethics committee. All the patients agreed for contribution after full explanation regarding the aim and protocol of the study. Inclusion criteria: Any patients with scabies of either sex, aged above 6 years old who were experiencing serious pruritus all over the body that increases during night; Demonstration of classical burrows (identified with a magnifying lens) or secondary lesions which are characteristic of scabies as papules, vesicles, pustules or nodules on at least 3 typical body sites of predilection for scabies including finger webs of the hands, wrists, elbows, nipple areolas in women, axillary folds, periumbilical regions, buttocks, and genital areas. In addition to history of involvement of similar symptoms in other family member or contacts. Subjects were excluded for any of the following causes: Patients below 6 years or above 65 years of age, pregnant or lactating women, serious chronic illness, hypersensitivity to ivermectin or permethrin, suspicious cases and history of treatment of scabies or patient treated with corticosteroids in the last 4 weeks before the consultation. Eligible patients were alternately divided into 2 equal groups. Group I received oral ivermectin (SCAV; Snow Pharmaceuticals Halstenbek, Germany), 2 doses of 200 µg/kg separated by 1 week (weight of the patients was estimated to determine ivermectin dose). Patients were advised to take the tablet with a full glass of water before breakfast. While group II applied permethrin 5% cream (Permesol; TSL. Company, Turkey) topically overnight, and repeated once after 1 week. In addition to 2 doses oral ivermectin of 200 µg/kg separated by 1 week. Topical therapy in both groups composed of a thorough bath using sulfur soap. Followed by topical application of permethrin 5% cream (group II) to the all body parts, from chin downwards including under fingernails using a soft brush. The application of scabicide is best done at night. Also, all family contacts, in both groups, were treated simultaneously with topical permethrin 5% cream for single overnight application, but they were not enrolled in the study. Itching treated by oral antihistamine (loratidine), or by short oral steroids in severe cases. In addition, topical management involved application of Crotaphil-H cream 25g (Crotaphil-H; Philadelphia Pharmaceuticals, Amman-Jordan) (Crotamiton 10% + Hydrocortisone) as adjuvant antiscabietic treatment and antipruritics for both groups. Any adverse events of the treatment were recorded. Standard instructions for all participants were given about the disease nature and other measures which enhance successfulness of therapy as mode of drugs using and the importance of management all the close contacts to prevent recurrence as well as the importance of washing patients clothes and bedding in hot water and drying them in the sun. They were further advised about the opportunity of continuous itching even following successful therapy for up to two weeks. And, not to ingest or apply any other medicines for this disease other than those prescribed in this study. Patients were seen 2 and 4 weeks interval after the first visit, at each follow-up visit, patients were assessed clinically for evaluation of management and determination of cure or relapses. Clinical assessment of the cases included counting the lesions and scoring of pruritus by the patients. For the severity, it was assessed by counting the lesions and assigned as: mild (10 or less lesions), moderate (11-

49 lesions), and severe (50 or more lesions). And by using visual analogue scale (VAS) 0-10 score. The management was considered successful if at the end of the four weeks, there was improvement in the pruritus as evaluated by the VAS and clinical improvement in the skin lesions as well as no new lesions at day 14. Relapse was identified by signs and symptoms of scabies and appearing after one month of an initial cure. While the treatment was considered to be failed if either lack of initial cure, relapse, or appearance of new lesions, at the end of four weeks.

Statistical analysis were done using SPSS (V24; IBM SPSS Statistics USA).Results were illustrated as mean, range and percentage. Responses to treatment at 2 and 4 weeks post therapy were compared with baseline. Normality for data distribution was evaluated by Shapiro-Wilko test. Differences between means were tested for significance by student t –test, when data followed normal distribution, or Mann - Whitney U test. P value ≤ 0.05 was considered significant.

RESULTS

A total of 235 patients were enrolled in this study. Fifteen patients (8 from group I and 7 from group II) were unable to return to the follow-up examination after the initial management. Therefore, they were excluded from the study. The remaining 220 patients consisted of 130 males (59%) and 90 females (41%). Their mean ages was 30.5±12.05 (range: 7- 63 years). The mean disease duration was 9.4±2.05 (range: 1-18 weeks). The demographic characteristics of the 2 groups showed no significant difference. Itching was reported in all patients, which varied in severity from moderate 68(31%) to severe 152 (69%) that wake up patient from sleep. Classical burrow, pruritic papules and vesicles were demonstrated in all patients (Table 1).

Table No. 1: Baseline characteristics of the enrolled patients at time of presentation prior to treatment.

Characteristics	Group I N=112	Group II N= 108
Sex (Male/Female)	68/44	62/46
Mean age (years) ±SD	29.6 ± 11.9	31.4 ± 12.2
Mean duration of disease ±SD	9.1±2.2	9.7±1.9
History of contact	112	108
No of family members with scabies ≤ 5 >5	 19 93	 21 87
Nocturnal pruritus	112	108
Mean number of lesions	72±44	78±41
Severity of lesions: Mild/Moderate/Severe	0/32/80	0/36/72

The criterion of judging the effectiveness of management was the complete disappearance of lesions and itching at 4 weeks post treatment. Also, treatment compliance and tolerability were assessed by questioning the patients. Clinical assessment included scoring of pruritus by the patients (assessed by VAS) and counting the lesions.

In general, 75% of the patients in group I and 88% in group II achieved a statistically significant improvement in pruritus (assessed by VAS) as compared to baseline. The reduction in pruritus VAS score was highly significant ($P < 0.001$ and $P \leq 0.0001$ after 2 and 4 weeks post therapy, respectively) over the time for both groups. The difference between the 2 groups was significant ($P < 0.05$) (Table 2).

Table No. 2: Baseline, 2-week and 4-week outcome measurements of pruritus as assessed by VAS (0-10), together with the percentage of improvement. Data are mean (range).

Mean of pruritus (VAS)	Baselin	2 Weeks	Improvement %	4 Weeks	Improvement %
Group I(N=112)	8 (6-9)	6* (6-8)	25	2** (0-4)	75
Group II (N=108)	8 (5-9)	5* (4-7)	38	1** (0-3)	88

*P <0.001, **P < 0.0001. VAS: visual analogue scale for patient's global assessment. N: number of patients.

Regarding number of lesions, on follow up at 2 weeks post treatment, in group I, 41(36%) had mild lesions, 50 (45%) had moderate lesions, and none had severe lesions. For group II, 49 (45%) had mild lesions, 33(31%) had moderate lesions, also, none had severe lesions. The improvement in severity score was significantly greater in the group II than in the group I ($P < 0.05$). At 4 weeks, 12 (11%) had lesions (all mild) in group I, compared with 9 (8%) in group II had mild lesions, too. The overall cure rate after 4 weeks was 82% in group I and 90% in group II (there was no significant different in both groups $p > 0.05$) (Table 3).

Table No. 3: Assessment of severity of disease (number of lesions) in both groups after 2-week and 4-week.

Group	No. of cured cases (%)		Total no. of cured cases (%)
	After 2 Weeks	After 4 Weeks	
Group I (N=112)	63* (56%)	30**(26%)	93(82%)
Group II (N=108)	78* (72%)	19**(18%)	97(90%)

*P <0.001 **P < 0.0001

At the end of therapy, it has been observed that the patients in group II were much relieved as compared to group I, number of lesion clearance was less in group I as compared to group II. This was based on the relief of symptoms with clinical resolution of the lesions. Of note, both ivermectin tablets and permethrin cream were well tolerated and no major adverse effects were demonstrated during interview or at follow up visit. None of the participants deteriorated during the study. Finally, treatment failure was not observed in any patient. Nine patients in group I and 11 patients in group II were left with mild lesions and they reduced their antihistamine intake.

DISCUSION

Scabies infestation is one of the most common endemic diseases worldwide, primarily in the developing countries including Iraq as a result of the increasing numbers of prisoners.[20] Though patients do not die of scabies, it would be wrong to say that such condition is of minor importance. Itching is often extremely severe, resulting in much loss of sleep and unhappiness as well as bacterial infection complications such as impetigo, pyoderma, bacteremia and glomerulonephritis.[14] To the best of our knowledge, this is the first study in Iraq to assess the response to concomitant use of oral ivermectin with topical permethrin 5% cream versus oral ivermectin in the treatment of scabies infestation. The findings of the present study confirm that the combination treatment of oral antiparasitic agent with topical scabicide is an important therapeutic choice. Itching and number of lesions were the main efficacy outcome measures for evaluation of the management effectiveness. Of notice, many therapeutic options, both topical and systemic, have been used in treatment of scabies. None of the topical agents might be conventional by several patients, because they have to be applied all over the body for nights.[21] Moreover, this type of management has the disadvantages of being time consuming, cumbersome, and associated with failure to treatment as a result of poor compliance, insufficient application and inadequate management of close contacts.[22] Currently, permethrin has been reported to be the most effective scabicide with minimal toxicity since it is not absorbed when used topically. It is considered as the "gold standard" in the treatment of scabies.[23] It is cosmetically elegant and well accepted by our patients. In general, all topical therapies are unsuitable for epidemics and scabies outbreaks. However, a pill form may be preferred as an alternative to the topical agents in the treatment of scabies in families and individuals on a large scale, for patients who are unlikely to utilize topical medications properly and in case of resistant to topical antiscabies.[24,25] Ivermectin can be better tolerated and safely given to patients of scabies with secondary eczema, excoriations or open ulcerations where topical scabicides can result in serious cutaneous reactions.[26] Interestingly, both systemic and topical medications were effective and well tolerated by our patients. However, it was noticed that the concomitant use of oral ivermectin tablets with topical permethrin 5% (group II) was superior to oral ivermectin (group I). Asgroup II get faster and better efficacy against pruritus compared with group I (P < 0.05). A previous studies also proved that topical permethrin was more effective in relieving pruritus than ivermectin.[19,27] As a drug with quicker effect in alleviating pruritusis much more tolerable to patients. Furthermore, such drug will also lessen the requirement to antihistamines.[19] Most patients in this study in both groups decreased the use of antihistaminic intake after the second week of treatment. Regarding severity of disease (number of lesions), both treatment modalities demonstrated comparable efficacy with the end of fourth week (P > 0.05). Complete resolution of lesions was observed in 83% and 90% for group I and group II, respectively. This demonstration is consistence with prior observation of Khan et al who found that 86.6% of treated patients with ivermectin and 90% of topical permethrin were cured completely.[28] Whereas Indian study reported 95% cure rate with ivermectin,, 97% with permethrin for the treatment of scabies.[19] While Chhaiya reported much lower cure rate 63% in oral ivermectin and 99% for permethrin group.[17] Of notice, sever lesions were cleared for all patients in both groups with the first follow up at the second week post therapy. Additionally, all the remained lesions in 11% in group I and 8% group II, respectively, were mild and didn't need treatment other than crotamiton cream. Generally, scabies management not includes a scabicidal only but also symptomatic treatment of itching. In the present study, one of our aims was to stop itching which achieved with oral antihistamine administration plus short course oral steroids for severe cases, along with crotamiton cream. Crotamiton is a weak scabicidal agent, non-greasy, odorless, non-irritating antipruritic cream. Accordingly, it is a good therapy for persistent post scabietic itch.[14] As a result of this symptomatic treatment, itching duration were subsided in the first week of treatment. While in other previous studies, itching continued for up to 6 weeks as they depended on the application of scabiecides alone.[29] Additionally, Crotaphil-H cream protects patients skin from crusting, scaling, and unsightly looking that caused by sever itching.[30] Although the persistence of itching for several weeks after successful therapy is not uncommon. This is unnecessarily predictive of management failure or reinfestation. It results from reaction of the body to the

dead mites remaining in the skin and their waste products.[1] Moreover, topical scabicides may result in allergic contact dermatitis causing sever itching, therefore; patients should be discouraged from excessive using topical scabicides.[31] Scabies management is theoretically simple, yet, failure is commonly caused by inappropriate or inadequate application and might be due to reinfestation that results from failure to treat close contacts.[9] Importantly, disease control requires following the treatment instructions that emphasized the management of all family members and close contacts simultaneously, whether they are itchy or not, as they might be infested but symptomless.[14] In this study no treatment failure was reported due to well patients compliance with treatment regimen.

With regard to safety concerns, no side effects were reported in all patients utilizing oral ivermectin. However, previous reports had been published headache, fever, rash arthralgia and anorexia, with oral ivermectin.[32] A hot wash for clothes and bedding is advised during scabies management because mites can be destroyed by insecticide and heat, at a temperature of 60^{o} C for 5 minutes, as well as improved personal hygiene that may control or prevent spreading of scabies.[14] In conclusion, the combination therapy of oral ivermectin with topical permethrin represents a useful alternative option with higher cure rate than single therapy and with no major side effects. Both ivermectin and permethrin are almost similarly effective but permethrin shows rapid onset of action. Oral ivermectin considered as a magic remedy in situation of epidemics and large scale or when topical treatment has failed. Scabies is familial, so, we emphasize to treat all close contacts simultaneously and improving personal hygiene can control the spreading of scabies infestation.

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