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OMPARING THE EFFICACY OF SYSTEMIC IVERMECTIN VERSUS COMBINED MODALITY

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ABSTRACT

Background: Scabies is a contagious parasitic infestation. It is significant health problem worldwide. Various treatment options have been existed but the ideal management modalities are ongoing. **Objectives:** To evaluate the efficacy of oral ivermectin versus topical permethrin with the aim of determination suitable regimen for scabies in Mosul city. **Methods**: The diagnosis was established by dermatologists. 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 with 2 doses ivermectin. All family contacts were simultaneously treated with permethrin. Patients were followed after 2 and 4 weeks interval. **Results:** At second week post therapy, 75% of the patients in group I and 88% in group II achieved a statistically significant improvement in pruritus as compared to baseline ($P< 0.05$). None had severe lesions; the improvement in severity score was significantly greater in group II ($P < 0.05$). At 4 weeks, the overall cure rate was 82% in group I and 90% in group II (no significant different). Both ivermectin tablets and permethrin cream were well tolerated and no major side effects were demonstrated. **Conclusion:** Combination of oral ivermectin with topical permethrin represents a useful alternative option with higher cure rate than single therapy. Oral ivermectin is a magic remedy for epidemics and large scales, however, permethrin shows rapid onset of action. Simultaneous treatment of all close contacts and improving personal hygiene can control spreading of scabies.

Keywords: Ivermectin, Permethrin, Scabies, Topical.

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] It affects both sexes of all age groups, races and social classes. However, it particularly problematic in areas with poor hygiene

and overcrowding where there is frequent skin to skin contact as hospitals, or prisons.[2]

The Sarcoptes scabiei mite is a tiny parasite 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.[3] The classical sites are found in body crevasses as those between fingers and toes, elbows, axillary, genital, the periumbilical area, under the female breasts and nipples areolas. Apart from infants and young children, the face, neck, palms, and soles are unaffected.[4]

Clinical infestation with the scabies results in intense itching with irritating papular eruptions and discomfort. Severe itching, particularly at night, is considered the commonest symptom of scabies.[5] Much of the symptoms are as a result of the host`s immune "allergic" reaction last several weeks to appear following initial infection in a subject exposed for the first time. Sever itching results in frequent scratching that make the skin prone to secondary infections.[6] 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.[7] In most of the 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.[8]

Various treatment options for scabies are exist. Topical therapy has the disadvantages of being time-consuming, cumbersome, treatment failure results from poor compliance, inadequate scabicide application, frequency or technique of application. In addition to inadequate management of close contacts, 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. 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. 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. Ivermectin is not recommended for use during pregnancy, lactation or for children less than 6 years of age. 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.[9]

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.[10]

As Iraqi population being frequently affected by scabies in addition to the rising resistance to topical antiscabies, hence, it is decided to conduct this study to evaluate the efficacy of using combination therapy of systemic ivermectin with topical permethrin 5% cream with the aim of determination better management and suitable regimen option for scabies in Mosul city.

PATIENTS AND METHOD

This study was conducted from December 2021 to May 2022, at Al-quds Health Center in Mosul city. All patients with scabies, who attending the dermatology outpatient clinic were assessed for enrolment; the diagnosis was established by taking detailed history along with meticulous examination by dermatologist. The study protocol was approved by the Heath Center ethics committee. All patients agreed for contribution after full explanation regarding the study aim and protocol.

Any patient with scabies of either sex, aged > 6 years, experiencing serious pruritus that increases during night, were enrolled; Demonstration of

classical burrows or characteristic lesions of scabies as papules, pustules or nodules on at least 3 body sites of scabies predilection. With the history of involvement in other family members, subjects were excluded if: Patients < 6 years or > 65 years, pregnant or lactating, hypersensitivity to ivermectin or permethrin and history of scabies treatment in the last 4 weeks. Eligible patients were alternately divided into 2 groups. Group I received oral ivermectin (SCAV; Snow Pharmaceuticals Halstenbek, Germany), 2 doses (200 µg/kg) separated by 1 week. Patients were advised to take the tablet before breakfast. Group II applied permethrin 5% cream (Permesol; TSL. Company, Turkey) repeated after 1 week. In addition to 2 doses oral ivermectin, topical therapy composed of a thorough bath of sulfur soap, application of permethrin 5% cream (group II) from chin downwards, at night. All family contacts, in both groups, were treated simultaneously with permethrin cream, but not enrolled. Itching was treated by oral antihistamine (loratidine). Additionally, Crotaphil-H cream 25g (Crotamiton 10% + Hydrocortisone) was applied as adjuvant antiscabietic and antipruritics for both groups. Any adverse events were recorded. Standard instructions for all participants to enhance management successfulness as drugs using, management all close contacts and washing clothes and bedding in hot water.

Patients were seen 2 and 4 weeks interval for evaluation of management and determination of cure. Assessment included lesions counting assigned as: mild (10 or less lesions), moderate (11- 49), and severe (50 or more) and scoring of pruritus by visual analogue scale (VAS) 0-10 score. The management was successful if at the end of the four weeks was improvement in pruritus and improvement in the skin lesions. While it failed if either lack of initial cure or appearance of new lesions, at the end of four weeks.

Statistical analysis: Statistical analysis was 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 A and 7 from group B) 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 wakeup patient from sleep. Classical burrow, pruritic papules and vesicles were demonstrated in all patients (Table 1).

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	19	21

>5	**93**	**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**

Table1: Baseline characteristics of the enrolled patients at time of presentation prior to treatment

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).

Mean of pruritus (VAS)	Baseline	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

Table 2. Baseline, 2-week and 4-week outcome measurements of pruritus as assessed by VAS (0-10), together with the percentage of improvement

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).

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

Table 3. Assessment of severity of disease (number of lesions) in both groups after 2-week and 4-week

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.

DISCUSSION

Though patients do not die of scabies, it would be wrong to say it is of minor importance. Itching is often extremely severe, resulting in sleep loss, unhappiness and bacterial infection complications.[11] 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 versus oral ivermectin for scabies therapy. In 2019, Ibraheem[12] studied combined topical drugs modalities. The findings of our study confirm that the combination oral antiparasitic with topical scabicide is an important therapeutic choice.

None of the topical agents be conventional by several patients, because they have to be applied all over the body for nights, time consuming and cumbersome.[13] Currently, permethrin is considered as the" gold standard" in the treatment of scabies, with minimal toxicity. It is cosmetically elegant and well accepted by our patients. In general, all topical therapies are unsuitable for epidemics and scabies outbreaks. However, pill form may be preferred as an alternatives for families and individuals on a large scale, in case of resistance to topical antiscabies and it can be better tolerated by patients with eczema and ulcerations where topical scabicides result in serious cutaneous reactions.[14]

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 with topical permethrin was superior to oral ivermectin. As group II get faster and better efficacy against pruritus compared with group I ($P < 0.05$). Previous studies also proved that permethrin was more effective in relieving pruritus than oral ivermectin.[15] As a drug with quicker effect in alleviating pruritus is much more tolerable and it lessen the requirement to antihistamines.[16] Most patients in this study decreased the antihistaminic intake after the second week of treatment.

Itching and number of lesions were the main efficacy outcome measures for the management effectiveness. Regarding number of lesions, both treatment modalities demonstrated comparable efficacy with the end of fourth week ($P > 0.05$). Complete lesions resolution was observed in 83% and 90% for group I and group II, respectively. This demonstration is consistence with observation of Bachewar et al who found that, 86.6% of ivermectin group and 90% of permethrin were cured completely.[17] Of notice, sever lesions were cleared for all patients with the first follow up and the remained lesions were mild and didn't need 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 alleviate itching which achieved with oral antihistamine administration plus crotamiton cream which is a weak scabicidal, antipruritic cream. Accordingly, it is a good therapy for persistent post scabietic itch.[18]

As a result of symptomatic treatment, itching duration were subsided in the first week of treatment. While in previous study, itching continued for up to 6 weeks as they depended on application of scabiecides alone.[19] Additionally, Crotaphil-H cream protects patients skin from crusting and unsightly looking that caused by sever itching.

Although the persistence of itching for several weeks after therapy was a common finding; It results from the body reaction to the dead mites and their waste products.[1,20] Moreover, topical scabicides may result in contact dermatitis, therefore; patients should be discouraged from excessive using topical scabicides.[26] Scabies management is theoretically simple, yet, failure is caused by inadequate application or due to reinfestation from failure to treat close contacts.[20] In

this study, we emphasized the management of all family members simultaneously, as they might be infested but symptomless. Moreover, disease control requires following the treatment instructions and personal hygiene that prevent spreading of scabies. With regard to safety concerns, no serious side effects and no treatment failure or resistance had been reported.

CONCLUSION

The combination therapy of oral ivermectin with topical permethrin should be welcomed in the treatment of scabies as a useful alternative option with higher cure rate than single therapy. 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 familiar, so, we emphasize to treat all close contacts simultaneously and improving personal hygiene can control the spreading of scabies infestation.

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