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Research Article

Scabies complete clearance as a treatment efficacy: in Permethrin alone and in combined with oral Ivermectin: South Iraq-2019

DR. AHMED ABDULHUSSEIN KAWEN
Assistant Professor, MBChB; FICMS. Department of dermatology, College of Medicine , University of Thi-Qar, Iraq
Email ID: ahmedpath@yahoo.com
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ABSTRACT

Background: Scabies as an intense itching disease, worldwide occurrence, where poorly sanitation region experience badly natural history of illness, with real problematic impact, had multi management stratigies of different efficacy, response rate and adverse effect.

Aim: compare the topical Ivermectin combination with the permethrin 5% efficacy against permethrin 5% cream only as a scabies treatment**.**

Materials and Methods: Interventional comparative study as a randomized controlled trial. Between April 2019 and April 2020, any patients with scabies who were older than 5 years of age and attending the Dermatology outpatient clinic, who visiting the outpatients of dermatology and venereology in Al-Hussein Teaching hospital- Thi-Qar province were assessed for enrolment in the study. Statistical and epidemiological analysis done by SPSS version 25, P value<0.05considersignificant.

Results: The study including 373 scabies patients, according to type of treatment they devided into 2 group A: who take combination of oral Ivermectin and topical permethrin (189 patients) with mean age of 27.5 ±11.5years for male, 24.8 ±11.1 while for group B (Permethrin only) the mean age of 28. ±11.7years for male and 24.5 ±10.9years for female, where there was no significant difference between these groups regarding gender distribution according to their age and according to their duration of disease from the time diagnosis measured by days the P value for such difference was of >0.05, mean size of the of the lesion at different occasions of measure, the paired t- test , which proved that at all comparison stage there was significant statistical difference, where P values (0.001), correlation was nearly of medium positive correlations. Lesion categories in crossly matched different types of lesion according to the three different times of measure show very high significant statistical differences.

Conclusion: Combined effect of both lines of treatment show significant reduction in the time of treatment and higher complete clearance rate of lesion with full recovery rate without considerable side effect

Keywords: Scabies, Permethrin, Ivermectin, South-Iraq, 2019

INTRODUCTION

Sarcoptes scabiei cause a mite skin infestation named as scabies, which characterized by intense itching, it is of worldwide occurrence, poorly sanitation region experience badly natural history of illness, with real problematic impact, crowding in over way, disruption of society had also a big role in the disease entity. Big wide period prevalence range globally extended from (0.2% - 71.4%),also the distribution express large geographical variations [1,2]. Pacific & South - Central Americas experience highest point prevalence of scabies. peak age group of effect during the childhood [3]; 119 outbreaks in Germany through 10 years of the last decade (2004- 2014) reflecting 19% of the infectious diseases is scabies [4]. The worldwide for "Global Burden of Disease Study" at 2015 (scabies causing 0.21% of DALY) [5]. Cyclical epidemics wave of scabies had been noted in high economics and resource-rich countries, nursing homes and living institution also experiencing scabies epidemics [6], army institutions and defense military affaires also a target for scabies [7]. seasonal variation also noticed, where high incidence during winter than summer, which might be explained by overcrowding indoor, and mite survive long in cold weather [8]. In communities of limited resource the endemic situation of scabies is the main pattern of its distribution [9]. This big variation influenced by social attitudes changes , immune status and susceptible pool movements of population, misdiagnosis, wars, and inappropriate treatment strategy, Although this infection is non- life-threatening but of big economic and health burden with widespread misery & debilitation [10]. Person to person direct skin contact even sexual form is the main mode of transmission, objects (inanimate) or even furnishings a possible

another mode of infection [8]. Mites number is the determinant of infectiousness that ranges from (1-1000000 (s) mites) [9]. Varieties of distinct genetic animal is another determinant [11] , wrists, between fingers, axillary and elbow joints often intense itch or skin night discomfort, popular irritation or vesicular eruptions is the main clinical presentation that reflecting debilitates and depression [1,12]. Genitalia, buttocks, breasts (female nipples), and peri-umbilical area are another sites of affection. In infancy (scalp, face, soles & palms), where e immune reaction of host is the main modulator of the pathophysiology of the disease, and initial infection symptoms appear within several weeks but reinfection (1-2 days) [1]. hyperkeratotic dermatosis, disturbed immune system response is one of the main sequel hospitalization in some situation is mandatory [13]. Streptococcus superadded infection complicated by acute glomerulonephritis is one of the crippled complication of scabies [14,15]. Diagnosis of scabies must include full detailed travelling history in addition confirmed by microscope exam identifying a egg, mite, or feces of mite in a skin burrow [9]. Compounds of sulfur, crotamiton, benzyl benzoate, malathion, hexachlorocyclohexane, ivermectin and permethrin. are the main lines for treatment [16-18] . Recently oral ivermectin & topical permethrin become the relevant options of scabies treatment [19,20]. Topical permethrin 5% approved in Germany (at 2004) [21,22]. And US FD A approval [23]. In L & MIC (India) approved at 1995 [24], but it is expensive, but oral ivermectin cheaper [25] introduce as the second choice. Which approved firstly France (2001) [23]; Australia [26] & Netherlands;[27]. and Germany [28], USA still off-label [10].

While FDA (2012) approved topical Ivermectin (0.5% lotion) for head lice treatment and for rosacea lesions (1% cream), [9]. Permethrin is applied from the neck down usually before bedtime and left on for about eight to fourteen hours, then showered off in the morning. One application is normally sufficient for mild infections. For moderate to severe cases, another dose is applied seven to fourteen days later [30,31]. Ivermectin, as antiparasitic oral medication, also consider as scabicide, although FDA not approved it's usage for this purpose, A studies recommend it's single dose as (two hundred Mgm)/ kg- BW , followed 2 doses repeated weeks later [32,33].

Study aimed to compare the topical ivermectin combination with the permethrin 5% efficacy against permethrin 5% cream only as a scabies treatment

MATERIALS AND METHODS

This was an interventional comparative study as a randomized controlled trial. Between April 2019 and April 2020, any patients with scabies who were older than 5 years of age and attending the Dermatology outpatient clinic, who visiting the outpatients of dermatology and venereology in Al-Hussein Teaching hospital- Thi-Qar province were assessed for enrolment in the study.

age < 5years , current pregnancy and or lactation, seizure history, systematic diseases, immune-compromised patients and on anti-scabies 1 month before study were excluded. Patients verbal consent had been taken, with full ethical consideration.

Patients full identity , history , infestation history and physical examination, specific laboratory investigation had been done for all patients with full recording were given a physical examination and their history of infestations, antibiotic treatment and other pertinent information was recorded. photographs were taken for later clinical comparison. Exclusion criteria regarding treatment for the last month with pediculicides, scabicides or other topical agents. diagnosis depend on: 1- presence of a typical scabietic lesions and/or burrow in the infestation classical sites of. 2- patients reporting of nocturnal pruritus and similar symptomatic history for patient's in the same family or among close contacts.3- Confirmed infestation: by mites, eggs , larvae demonstration or some time fecal material under light microscopy. Patients who satisfied the above criteria were randomly divided into two groups: group A were to receive combination of topical ivermectin and permethrin 5% cream , and group B were to receive permethrin 5% cream alone .

Randomization and treatment: In total, 400 patients were initially enrolled. Of these, 27 patients were not able to return after the first follow-up examination, and were therefore excluded from the study. The remaining 373 patients (228 male, 145 female) constituted the final study population.

The first group received 1% ivermectin in a solution of propylene glycol applied topically at morning (up to 8 hrs) to the affected skin(The dose employed was 400 microg/kg) and wash at night ,then apply the permethrin 5% cream (over night upto 12 hrs), repeated once the following week) and , while the second group received permethrin 5% cream over night upto 12 hrs and were told to apply this twice with a one-week interval. Patient adviced to not use any other types of treatment other than described

Evaluation: After treatment; blinded (to treatment type) experienced investigators made clinical evaluation. Patients were assessed at 2 and 4

weeks after the first treatment. investigators assessment done by sites of lesions recording by sheets diagram , the lesions compared with pretreatment visible photograph.

Scraped for new lesions by microscopic is another tool of evaluation, specific defined criteria were used for evaluation where cure from scabies defined by new lesions absence and old lesions healing, while treatment failure" was defined " presence of microscopically confirmed new lesions at the 2-week follow- up" where the repeated treatment at the end of week two, these patients were at week four evaluated again. Re-infestation nominated as full cure at week two and reoccur within the 1st month of treatment . patients who experience any scabies sign, whether due to failure of treatment or re-infestation, they were treated with lotion of 1% lindane.

RESULTS

The study including 373 scabies patients, according to type of treatment they devided into 2 group A: who take combination of oral Ivermectin and topical permethrin (189 patients) with mean age of 27.5 ±11.5years for male, 24.8 ±11.1 while for group B (Permethrin only) the mean age of 28. ±11.7years for male and 24.5 ±10.9years for female, where there was no significant difference between these groups regarding gender distribution according to their age and according to their duration of disease from the time diagnosis measured by days the P value for such difference was of >0.05.

Table 1: Biographical difference among studied group

	sex	N	Mean	S. D	Levene's Test for Equality of Variances
Group B Age	Male	109	28.0183	11.775	1.454,0.229
	Female	75	24.5733	10.918	
Duration	Male	109	23.9266	4.992	4.478
	Female	75	22.4400	6.329	.036
Group A					
Age	Male	119	27.5882	11.466	.701
	female	70	24.8286	11.138	.404
Duration	male	119	24.2689	5.045	.173
	female	70	21.4429	6.02564	.678

Table 2: Distribution of lesion types according treatment duration

Groups and time	No lesion		Mild		Moderate		sever	
	No.	%	No.	%	No.	%	No.	%
GA-1st W			40	21.2	48	25.4	101	53.4
GA-2W	166	87.8	23	12.2				
GA-4W	189	100						
GB-1stW			40	21.7	48	26.1	96	52.2
GB-2W	119	64.7	4	2.2	32	17.4	29	15.8
GB-after4W	154	83.7	6	3.3	20	10.9	4	2.2

The distribution seems to be comparable among the studied group according to their initial criteria of engagement with in study, where nearly half of all with sever type of disease, but the distribution differ with the progression of disease treatment time as shown in table 2.

Table 3: Comparison of the paired difference according to the lesion size

Pairs	Groups of comparison	T test	P	Correlation
Pair 1	GB. at1stW & GB. after2ndW	17.399	0.001	0.407
Pair 2	GB.at1stW & GB.after4W	27.207	0.001	0.192
Pair 3	GB. after2ndW &GB. after4W	7.213	0.001	0.565
Pair 4	GA & GA after 2W	39.494	0.001	0.315
Pair 5	GA & GA after4W	39.752	0.001	
Pair 6	GAafter2W & GAafter4W	5.104	0.001	
Pair 7	G.B.after2ndW & GA after 2W	9.056	0.001	0.490
	Pair 8 GB. after4W & G1after4W	5.680	0.001	

According to mean size of the of the lesion at different occasions of measure, the paired t (student) test done, which proved that at all comparison stage there was significant statistical difference, where P values (0.001), correlation was nearly of medium positive correlations.

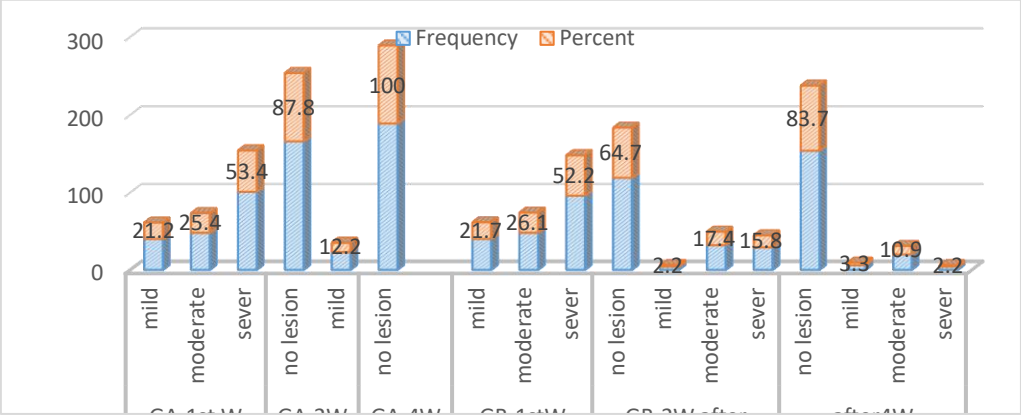

Fig.1: Pattern of cases lesion types according to time of treatment

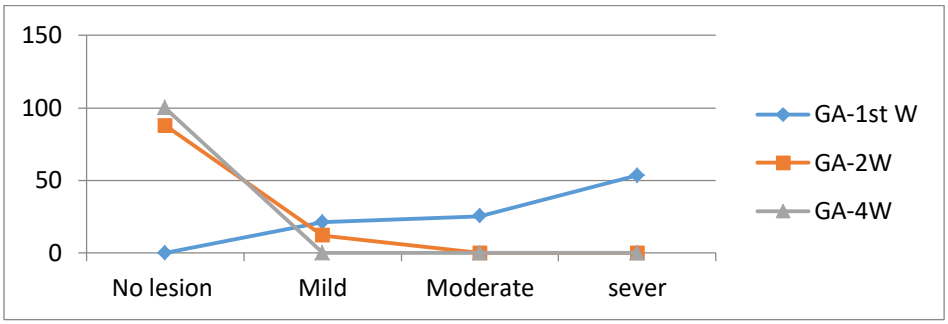

Fig.2: pattern of group A lesion types according to time of treatment

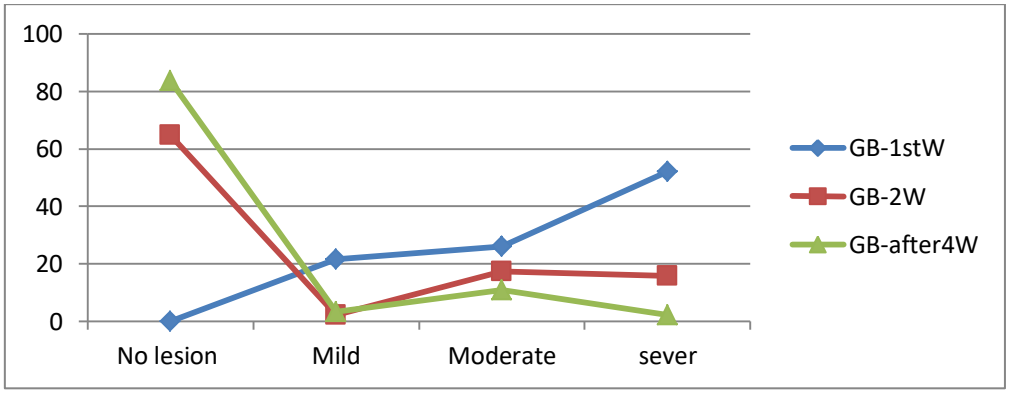

Fig.3: pattern of group B lesion types according to time of treatment

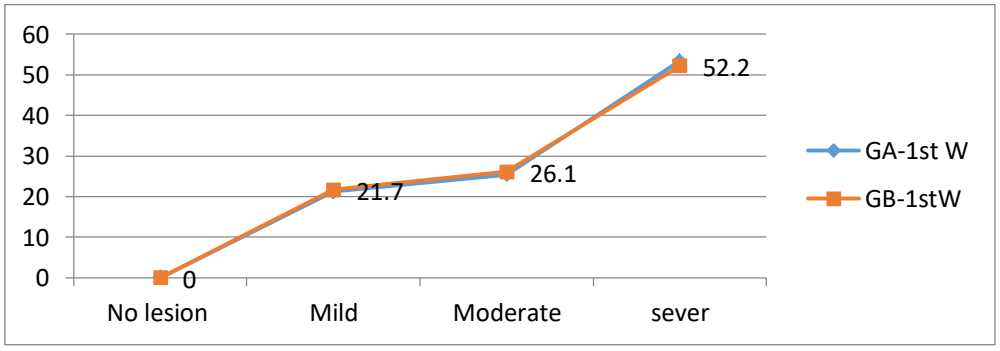

Fig.4: pattern of both group lesion types at 1st week of study

Table4-A: Management strategies impact on types of lesions according to the duration of treatment (at1stW, after 2ndW and after4W *) for Permethrin group-Intergroup comparison

At 1st Week				After 4 Weeks				Total	X2 or FE
				no lesion	mild	moderat	sever		P value
Mild	After 2nd Week	No lesion	N	37		0		37	40.000b
			%	100.0%		0.0%		100.0%	0.0001
		Mild	N	2		0		2	
			%	100.0%		0.0%		100.0%	
		Moderate	N	0		1		1	
			%	0.0%		100.0%		100.0%	
	Total		N	39		1		40	
			%	97.5%		2.5%		100.0%	
Moderate	After 2nd Week	no lesion	N	34	0	0		34	26.901c
			%	100.0%	0.0%	0.0%		100.0%	0.0001
		moderate	N	5	3	6		14	
			%	35.7%	21.4%	42.9%		100.0%	
	Total		N	39	3	6		48	
			%	81.3%	6.3%	12.5%		100.0%	
Sever	After 2nd Week	No lesion	N	48	0	0	0	48	44.323
			%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0001
		Mild	N	2	0	0	0	2	
			%	100.0%	0.0%	0.0%	0.0%	100.0%	
		Moderate	N	8	3	6	0	17	
			%	47.1%	17.6%	35.3%	0.0%	100.0%	
		Sever	N	18	0	7	4	29	
			%	62.1%	0.0%	24.1%	13.8%	100.0%	
	Total		N	76	3	13	4	96	
			%	79.2%	3.1%	13.5%	4.2%	100.0%	
Total	After 2nd Week	no lesion	N	119	0	0	0	119	106.632
			%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0001
		Mild	N	4	0	0	0	4	
			%	100.0%	0.0%	0.0%	0.0%	100.0%	
		Moderate	N	13	6	13	0	32	
			%	40.6%	18.8%	40.6%	0.0%	100.0%	
		Sever	N	18	0	7	4	29	
			%	62.1%	0.0%	24.1%	13.8%	100.0%	
	Total		No.	154	6	20	4	184	
			%	83.7%	3.3%	10.9%	2.2%	100.0%	

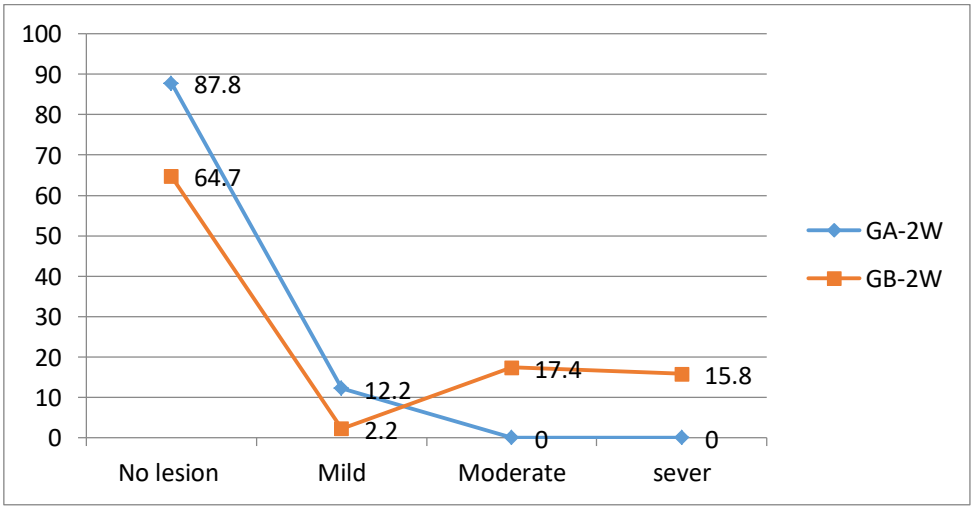

Fig.5: pattern of both group lesion types after 2nd week of study

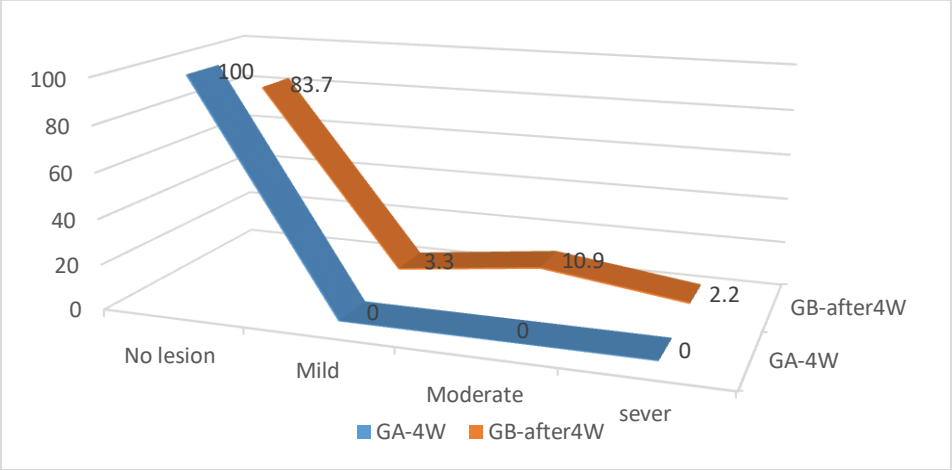

Fig.6: pattern of both group lesion types at 4th week of study

Crossly matched different types of lesion according to the three different times of measure show very high significant statistical differences

Table 4-B: Management strategies impact on types of lesions according to the duration of treatment (at 1st, after 2nd and after 4 weeks *) for Permethrin group-Intragroup comparison –I

At 1st W		After 2nd Week				Total	FE
		no lesion	mild	moderate	sever		
Mild	No.	37	2	1	0	40	46.299a 0.0001
	%	92.5%	5.0%	2.5%	0.0%	100.0%	
Moderate	No.	34	0	14	0	48	
	%	70.8%	0.0%	29.2%	0.0%	100.0%	
Sever	No.	48	2	17	29	96	
	%	50.0%	2.1%	17.7%	30.2 %	100.0%	
Total	No.	119	4	32	29	184	
	%	64.7%	2.2%	17.4%	15.8 %	100.0%	
At 1st Week		After 4th W					10.798a 0.009
mild	No.	39	0	1	0	40	
	%	97.5%	0.0%	2.5%	0.0%	100.0%	
moderate	No.	39	3	6	0	48	
	%	81.3%	6.3%	12.5%	0.0%	100.0%	
sever	No.	76	3	13	4	96	
	%	79.2%	3.1%	13.5%	4.2%	100.0%	
Total	No.	154	6	20	4	184	
	%	83.7%	3.3%	10.9%	2.2%	100.0%	
after2ndW			After four week				
No lesion	No	119	0	0	0	119	106.632a 0.0001
	%	100.0%	0.0%	0.0%	0.0%	100.0%	
Mild	No	4	0	0	0	4	
	%	100.0%	0.0%	0.0%	0.0%	100.0%	
Moderate	No	13	6	13	0	32	
	%	40.6%	18.8%	40.6%	0.0%	100.0%	
Sever	No	18	0	7	4	29	
	%	62.1%	0.0%	24.1%	13.8 %	100.0%	
Total	No	154	6	20	4	184	
	%	83.7%	3.3%	10.9%	2.2%	100.0%	

Table 5: Management strategies impact on types of lesions according to the duration of treatment (at1stW, after 2ndW and after4W *) for combination treatment group

Combination group		after2W		Total	FE
		no lesion	mild		P
1st Week					
Mild	Count	40	0	40	
	% within G1	100.0%	0.0%	100.0%	22.816a
Moderate	Count	48	0	48	0.001
	% within G1	100.0%	0.0%	100.0%	
Sever	Count	78	23	101	
	% within G1	77.2%	22.8%	100.0%	
4th Week					
Mild	Count	40	40	189	No statistics are computed because G1after4W is a constant.
	% within G1	100.0%	100.0%	100.0%	
Moderate	Count	48	48		
	% within G1	100.0%	100.0%		
Sever	Count	101	101		
	% within G1	100.0%	100.0%		

There was highly significant statistical differences in the response of the scabies lesion types between 1st and 2nd week of treatment in combination types of treatment.

Table 6: Management strategies impact on types of lesions according to the duration of treatment (at 1st , after 2nd and after 4th W *) for both group

		Groups		Total	FE
		Permtherin	Combination		P
At 1st Week	Mild	40	40	80	0.60
		50.0%	50.0%	100.0%	0.970 RR=1
	Moderate	48	48	96	
		50.0%	50.0%	100.0%	
	Sever	96	101	197	
		48.7%	51.3%	100.0%	
After 2nd W	No lesion	119	166	285	82.069 0.0001 RR=0.71
		41.8%	58.2%	100.0%	
	Mild	4	23	27	
		14.8%	85.2%	100.0%	
	Moderate	32	0	32	
		100.0%	0.0%	100.0%	
	Sever	29	0	29	
		100.0%	0.0%	100.0%	
After 4th W	No lesion	154	189	343	30.502 0.001 RR=0.814
		44.9%	55.1%	100.0%	
	Mild	6	0	6	
		100.0%	0.0%	100.0%	
	Moderate	20	0	20	
		100.0%	0.0%	100.0%	
	Sever	4	0	4	
		100.0%	0.0%	100.0%	
Total		184	189	373	
		49.3%	50.7%	100.0%	

There was highly significant statistical differences in the response of the scabies lesion types according to 2 main different types of treatment

DISCUSSION

Selection bias had been overcame , and other sources of bias had been minimized with well cross matching of the studied population, where the study including 373 scabies patients, 189 patients take combination of oral Ivermectin and topical permethrin, with mean age of 27.5 ±11.5years for male, 24.8 ±11.1 while for group B (Permethrin only) the mean age of 28. ±11.7years for male and 24.5 ±10.9years for female, so that no significant difference between these groups regarding gender distribution according to their age and according to their duration of disease from the time diagnosis measured by days the P value for such difference was of >0.05 had been noticed. It was comparable to Bachewar 2009 and Rohatgi 2013 [35,36] studies, where risk of bias was low. While other studies show divergent rates of bias.

The distribution seems to be comparable among the studied group according to their initial criteria of engagement with in study, where nearly half of all with sever type of disease, but the distribution differ with the progression of disease treatment time. It was consistent with Ahmad 2016 study [37], where there was no statistical difference of studied groups (RR: 84), also with in one week of the study, there was no differences.

According to mean size of the of the lesion at different occasions of measure, the paired t (student) test done, which proved that at all comparison stage there was significant statistical difference, where P values (0.001), correlation was nearly of medium positive correlations.

Complete clearance is simply defined as no cutaneous lesions and or burrows no itching, and microscopy is negative regarding parasitological examination.

The current study show complete clearance for the permetherin group in about 42% , which of lesser percentage than complete clearance for the combination group which was 58%, these result was lower than Chhaiya 2012 study [31] who reporting that 63.0% of patient getting complete clearance in the 2nd week of the study also and lower than Sharma 2011; Rohatgi 2013 studies [32,36] after 2 weeks of treatment , that reported complete clearance' as an outcome with higher percentages.

Combined effect of both lines of treatment in the current study show significant reduction in the time of treatment and higher clearance rate of lesion with full recovery rate without mentioned side effect

Chhaiya 2012 study [31] revealed that combined effect show no difference between the treatment groups (Relative Risk 0.91) this explained by the difference in the permethrin concentration.

Crossly matched different types of lesion according to the three different times of measure show very high significant statistical differences

There was highly significant statistical differences in the response of the scabies lesion types between 1st and 2nd week of treatment in combination types of treatment, Which was higher than Ahmad 2016 study, where was no significant difference among studied groups two weeks follow-up (RR 1.00);

The combined treatment show complete clearance of scabies lesion where all cases labeled as a (non-lesion) criteria which was compatible and consistent with many studies [31,32,36,38,39].

Two trials by Das (2006) and Shama 2011 using two doses of ivermectin (initial treatment and at two weeks' follow-up) compared to one application of permethrin 5% cream. After four weeks, no difference (RR 0.97) [32].

Our finding is differ from Saqib 2012 study, when he find no difference in the 2 groups of comparison for the only the ivermectin or permethrin 5% as a single dose of treatment weekly, this might because differences in the bases of comparison.

But Abdel-Raheem 2016 as another study find some sort of difference RR(0.70) for 107 patients after 2 weeks of treatment , and no difference in AE, found by Abdel-Raheem 2016 [40]

In recent years, topical permethrin and oral ivermectin have become the most relevant treatment options for scabies [19,20].

Adverse events: The treatment lines were acceptable cosmetically for all patients and their parents, where no one of them suffer from allergic reactions. Except mild adverse event (AE) in form of irritation that reported by forty patients 20 in the group A and 20 in the group B), where it was non- serious and also didn't affect patients compliance and adherence to therapy. Consistent with Bachewar 2009, (35) where adverse events not noticed by any one of participants.

Our study dosnt extended to more than 4 weeks which differ from Usha ,[39] who evaluate patients after eight weeks. 7.5% of them experienced at least 1 AE among Ivermectin group, zero percent in permethrin patients experienced an event.

Mushtaq [31]; Sharma [32] 2011; [38] ; Wankhade [41] studies(31,32,38,41) for 502 patients experiencing at least one AE, four weeks

after. Ivermectin leading larger percent with one AE (R.R= 1.3), zero events had been reported by [36]

Reinfection and exacerbation of infection was also not experienced by any patients during the course of treatment ; regarding the failures of treatment stratigy in group B, it was not full failure, through which the lesions were dropped in their size to less than 50 as compared with their pre-treatment status.

Current study show 0% of with draw that agree with [42] who report no one withdrew due to side effect (120 participants) also [41,42] finding show the same thing

CONCLUSION

Combined effect of both lines of treatment show significant reduction in the time of treatment and higher complete clearance rate of lesion with full recovery rate without considerable side effect

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