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Systemic Ivermectine plus Intralesional Antimony Compared with Antimony Alone in Treatment of Cutaneous Leishmaniasis

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Abstract

Background: About (1.5 million) cases of CL annually all-over the world, there are many treatment strategies are applicable; some are topical other is systemically given

Rationale: Many management modalities are of good final result, but the durable effect might be of golden hope for the patients.

Aim: Estimate the effectiveness of intralesional sodium Stibo-gluconate (ILSSG) augmented by orally administered Ivermectine to decrease the number of injection sessions and its complications, increase the efficacy of pentavalent antimony, shorten the therapy duration and minimize or prevent the resultant scar.

Methodology: An evaluative prospective study had been conducted from September 2018 to the march of 2020 to recruit eighty nine patients with typical cutaneous leishmaniasis, who visiting the outpatients of dermatology and Venereology in Al-Hussein Teaching hospital- Thi-Qar province. After full consent, two groups, well crossly matched regarding age, gender, the type and size of the lesions: group a received ILSSG plus oral Ivermectine weekly and group B whom received ILSSG weekly alone.

Results: high rate of complete response in group A in six week (81.39%) compared to 1st week (2.23%) when it compared with group B which was with very good response rate in 6th week (67.39%) while no response in 1st week. The complete response A and B was relatively equal (93.02%) and (91.3%) respectively in third month. The highest rate of partial response was observed in the first week 16(37.20%) and then reduced in the third week (27.90%) and sixth week (16.27%) while the percentage of reduction of group B- partial response in was higher than group A as a compared group. The group A -poor responses were (60.46%), (9.30%) and (2.32%) in the 1st, 3rd, 6th week respectively, which showing obvious decrement, while group B -poor responses were high especially in the week (97.82%) and (43.47%) first and third week respectively. There was significant statistical difference in response rate within the 1st and 3rd weeks of follow-up, while 6th week and 3rd months which showing the differences in response rate.

Conclusion: Addition of Ivermectine as Combined type of treatment show early good and partial response than ILSSG alone with significant durable effect.

Keywords: Cutaneous Leishmaniasis; ILSSG; Ivermectine; Thi-Qar

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Introduction

A different *leishmaniasis species* causing cutaneous leishmaniasis (CL), which labeled asking macrophages parasitic infestation, for about sixty percent by *L. major* & forty percent by *L. tropical* where had been as the most prevalent Iraqi species in as detected by PCR technique [1]. WHO estimate about (1.5 million) cases of CL annually all-over the world, also (350 million) individuals nominated as a risky for CL disease acquiring in about (eighty eight) endemic countries, Iraq one of them, in which CL might create a health emergency and one of the main health problem [2]. Even though It seemly to be disease of self-limiting pattern, but, there were many nagement modalities with different durations, the disease also may lasting months or years.

Main complications are secondary bacterial infection, cosmetically important sites as the face with risk of serious disfigurement, immune suppression and psychological impact on patient [3]. Many treatment strategies are applicable; some are systemically given such sodium Stibo-gluconate but main limitation are systemic toxicities, painful injections, and case resistance [4,5] ketoconazole is another example of systemic agents, that used to overcoming and or to avoid adverse effect of the 1st systematic regimen [6,7]. Zinc sulfate is another choice of treatment [8] and further option is the Dapsone [9]. Limited form of CL is preferably to treated by either Promomycin (topical) [10] or Trichlore Acitic Acid (50%) [11], or by Cryotherapy (as physical methods) [12] cauterization and application of heat and [13] or sodium



Stibo-gluconate (intra-lesion) injection of [14], 2%- Zinc sulfate [15], although the sodium Stibo-gluconate (intra-lesion)-ILSSG is the main role of CL management strategy. But the tendency for the systematic treatment not always, it indicated in some situation such treatment for immunosuppressed patient; >4 lesions of size substantially more than 1 cm or individual lesion(s) measuring equal or more than five cm; regional lymphadenopathy (hugely enlarged, of the, facial, auricular, genital mucosal involvement, skin of fingers or toes, or overlying joint skin [16-18], pain, swelling and erythema decrease in dramatic way for the sessions of intra-lesional therapy [19]. In children this type of treatment might be problematic. For that reason, the present study was designed to estimate the effectiveness of intralesional sodium Stibo-gluconate augmented by orally administered Ivermectine to decrease the number of injection sessions and its complications, increase the efficacy of pentavalent antimony, shorten the therapy duration and minimize or prevent the resultant scar.

Patients and Methods

An evaluative prospective study had been conducted from September 2018 to the march of 2020 to recruit eighty nine patients with typical cutaneous leishmaniasis, who visiting the outpatients of dermatology and venereology in Al-Hussein Teaching hospital, Thi-Qar province and Merjan teaching hospital. Where the diagnosis of each case based on the clinical examination, direct smear and a histopathological examination for the query cases in whom the smear was negative. A full verbal consent had been taken from patients, and full ethical consideration was on a values implemented carefully, where explanation was done to each patient or their next of kin (for children) regarding their disease and its natural history, prognosis, possible complication and available treatment options. Lastly, a formal consent was taken from each participant. A questionnaire for demographic and clinical data was designed to include the patients age by years, gender, address emphasizing on whether they live in rural or urban areas, number of lesions and its sites, duration, any previous systemic, topical or intra-lesional therapy taken, past medical, surgical and drug history specially allergy to the drug used in this study. An examination was done to evaluate each lesion regarding the size in centimeters, indurations, color, whether it is of dry or wet type, any signs of secondary bacterial infection and regional lymphadenopathy. Exclusion criteria: systemic pentavalent antimonies drugs patient (according to its indications) chronic debilitated patients, <5 years aged children, lactating or pregnant women.

Design and Work Field

The diagnosis was established by history, examination and The sample was divided into two groups, well crossly matched regarding age, gender, the type and size of the lesions: group A received intralesional sodium Stibo-gluconate (0.1 ml per 1 cm² of 100 mg per ml vial) weekly plus oral Ivermectine 200 ug/kg given weekly and group B whom received intra-lesional sodium Stibo-gluconate (0.1ml per 1 cm² of 100 mg per ml vial) weekly alone. A photograph was taken each visit and the lesion's dimensions, color and indurations were recorded, the following parameters were checked at zero time then weekly until healing which are lesion size, color, indurations and ulceration, also the patients were asked and examined for any possible adverse drug reactions. Weekly, the patients evaluated according to the following criteria: cure was defined as no indurations, reappearance of epidermal creases and no ulceration or cru station, partial improvement was defined as decrease the lesion's size, flattening, change of color from bright red to dusky red or brown but no epidermal creases seen, no and

poor responses were defined as no change in color, size or indurations. Also, a biochemical assessment of all participants was conducted at zero time, and then at first week and monthly thereafter in form of complete blood count, liver function test and renal function test. Chi-square test was used in analysis of the results using SPSS program version 25 had been used, where P<0.05 consider as significant.

Results

A total of 89 patients were enrolled in the study and were divided into two groups; group A included 43 patients of them 19 males and 24 females with total number of lesions was 96, while group B included 46 patients (24 males and 22 females) and the total number of lesions was 105, all were treated and evaluated weekly. The mean patients' age was 27±12 years for group A and 29±14 years in group B, while the mean disease duration was 1.9±0.5, 1.7±0.6 months for group A, B respectively. The most observed clinical presentation was plaque type in both groups (60.41% in group A and 49.52% in group B), followed by nodular type (25% in group A and 30.47% in group B) and, lastly, the popular type (14.58% in group A and 20% in group B) with no significant differences (P=0.261). 57% of patients had more than one lesion. The most common site of involvement was the face in both groups (35.41% in group A and 39.04% in B) followed by lower and upper limbs as a less common site lastly trunk was the uncommon site for CL in both groups, there was no significant statistical difference where P>0.05 and it was equal to 0.605 (Table 1).

Weekly the patient was evaluated (till healing) for complete, partial and poor responses to the given therapy. The present study recorded that high rate of complete response in group A in six week 35(81.39%) and fewer rates was in one week 1(2.23%) when as compared with group B which recorded high rate in six week 31(67.39%) while did not show any response in one week. The complete response in both group A and B was relatively equal 40(93.02%) and 42(91.3%) respectively in third month. The highest rate of partial response was observed in the first week 16(37.20%) and then reduced in the third week 12(27.90%) and sixth week 7(16.27%) while the percentage of reduction of group B-partial response in was higher than group A as a compared group. The group A poor responses were 26 (60.46%) 4(9.30%) and 1(2.32%) in the 1st, 3rd, and 6th week respectively, which showing obvious

Table 1: Demography and lesions character of two comparative groups.

Participant characters	Group A (trial) N=43	Group B (control) N= 46	P. value
Average age (year, mean ± SD)	27±12	29±14	NS
Duration of lesions (mean ± SD)	1.9±0.5	1.7±0.6	NS
Gender			
Male	19 (44.18%)	24 (52.17%)	0.451
Female	24 (55.81%)	22 (47.83%)	
Total	43 (100%)	46 (100%)	
Site of lesions			
Facial	34 (35.41%)	41 (39.04%)	0.605
Upper limbs	25 (26.04%)	26 (24.76%)	
Lower limbs	21 (21.87%)	24 (22.85%)	
Trunk	16 (16.66%)	14 (9.52%)	
Total	96 (100%)	105 (100%)	
Clinical presentation			
Plaque	58 (60.41%)	52 (49.52%)	0.291
Nodule	24 (25%)	32 (30.47%)	
Papule	14 (14.58%)	21 (20%)	
Total	96 (100%)	105 (100%)	

Where: **P.value ≤ 0.05 mean high Significant



Table 2: Percentage of response to therapy in both study groups (A and B) in 1st, 3rd and 6th week and 3rd month.

Response	Week 1		Week 3		Week 6		Month 3	
	Group A N=43	Group B N=46	Group A N=43	Group B N=46	Group A N=43	Group B N=46	Group A N=43	Group B N=46
Complete	1 (2.23%)	0 (0.0%)	27 (62.79%)	8 (17.39%)	35 (81.39%)	31 (67.39%)	40 (93.02%)	42 (91.3%)
Partial	16 (37.20%)	1 (2.17%)	12 (27.90%)	18 (39.13%)	7 (16.27%)	12 (26.08%)	2 (4.65%)	3 (6.52%)
poor	26 (60.64%)	45(97.83%)	4 (9.30%)	20(43.47%)	1(2.32%)	3(6.52%)	1 (2.32%)	1 (2.17%)
Test of sig.	FE= 19.241		Chi square =22.105		Chi square =2.460		FE= 0.148	
P. Value	0.0001**		0.0001**		0.292		0.929	



Figure 1: The findings of Combination therapy (systemic Ivermectine) plus sodium Stibogluconate with sodium Stibo-gluconate in both group A and B. Where: *P. value >0.05 non-Significant (NS)

decrement, while group B poor responses were high especially in the week 45(97.82%) and 20(43.47%) first and third week respectively. There was significant statistical difference in response rate with in the 1st and 3rd weeks of follow-up, while 6th week and 3rd months did not showing this differences (Table 2 and Figure 1).

Discussion

The pentavalent antimony is the most accepted treatment for cutaneous leishmaniasis [20], but the need for many painful injections in addition to high cost, which is problematic particularly in children which leading to large number of defaulters that increasing failure rate that leading to resistance emergence [21,22]. The seeking for combination and augmentation of treatment was necessary for decreasing the treatment sessions number with the persevering cure rate either(similar, or higher) that shortening the duration of disease, secondary bacterial infection risk and destruction of local tissue and in turn ultimately minimizing scar or preventing scar formation. The augmented treatment may be seem higher costs than monotherapy in disease of short term courses, but if appropriately used, it can causing significant savings such as lower treatment failure rate, lower case fatality ratio and fewer side effects than monotherapy, slower development of resistance and consequently, less money needed for the development of new drugs [25]. In the current study the CL patient were crossly matched well regarding their age, gender, duration of disease, site of the lesion and finally clinical presentation to avoid the role of confounding effects of some factors and also to minimize bias, response was categorized into complete (full) , partial and poor response according to the clinical criteria while the durable

classification was according to mention nominated weeks and months in the guidelines, weekly follow up the patient was evaluated(till healing) for complete, partial and poor responses to the given therapy. The present study recorded that high rate of complete response in group A in six week 35(81.39%) compared to 1st week 1(2.23%) when as compared with group B which was with very good response rate in 6th week 31(67.39%) while no response in 1st week. The complete response A and B was relatively equal 40(93.02%) and 42(91.3%) respectively in third month. The highest rate of partial response was observed in the first week 16(37.20%) and then reduced in the third week 12(27.90%) and sixth week 7(16.27%) while the percentage of reduction of group B-partial response in was higher than group A as a compared group. The group A poor responses were 26(60.46%) 4(9.30%) and 1(2.32%) in the 1st, 3rd, 6th week respectively, which showing obvious decrement, while group B -poor responses were high especially in the week 45(97.82%) and 20(43.47%) first and third week respectively. There was significant statistical difference in response rate within the 1st and 3rd weeks of follow-up, while 6th week and 3rd months which showing the differences in response rate which was higher than other studies that measuring the efficacy of single line of treatment such Navara et al. meta-analysis of systematic review [26] for IL-SSG efficacy for gathered (5679) patients, with 75% a global efficacy of (68–82% - Confidence Interval 95%), which was comparable to results of antimony parenteral treatment of New World for with [27] and also comparable Old World-systematic reviews local treatments by other strategies [28-30]. While for the single use of Ivermectin efficacy in comparison to other drugs (in-vitro & in-vivo) Ivermectine lead to viable promastigotes number reduction sharply in vitro. The Ivermectine efficacy was higher than other comparative group rather than ILSSG [31]. The results concluded that the efficacy of Ivermectine was higher than drugs in killing the parasites in vitro and by subcutaneous inoculation, in term of durable response our study was comparable to Kadir et al. study that show cure rate one month post treatment with Ivermectine were excellent (100%), followed by pentostam 70%, followed by other such berenil (60%), metronidazole 50%, and amphotericin B (50%) [31]. Mandy et al study focusing in an important thing that, in vivo & in vitro activities of Ivermectine are achievable in a concentrations of clinically reachable depend on the pharmacokinetic studies in human done in healthy and parasitized patients, that explain the durable response [32].

Strength of the Study

- 1st evaluative follow up study done for CL in Al-Nasiriyah.
- Avoidance of confusing and biased factors among the comparative group that cofounding the response result
- Studying of as a parameter for the prediction.

Limitations

Comparison with other local or systematic method of treatment.



Conclusion

Addition of Ivermectine as Combined type of treatment show early good and partial response than ILSSG alone with significant durable effect.

Recommendation

Usage of this combination can give good durable effect, if there's no contraindication for use of this augmented therapy.

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