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COMPARISON OF THE EFFICACY OF INTRALESIONAL INJECTIONS OF MEGLUMINE ANTIMONIATE VERSUS METRONIDAZOLE IN PATIENTS PRESENTING WITH CUTANEOUS LEISHMANIASIS AT TERTIARY CARE HOSPITAL, KARACHI

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Abstract

Introduction: Cutaneous leishmaniasis (CL) is one of the common parasite disease that affects people. Sand fly bites are the primary mode of transmission for leishmaniasis, which is often identified by a microscope-assisted smear examination of the afflicted region. Pentavalent antimony compounds like sodium stibogluconate and meglumine antimoniate are the preferred therapies for leishmaniasis. Ongoing research is being done to find effective, less hazardous therapies for leishmaniasis, however alternative drugs have been suggested for the disease.

Objective: To compare the efficacy of "intralesional meglumine antimoniate (MA) versus metronidazole" in patients presenting with CL.

Study Design: "Randomized control trial".

Subjects and methods: All the 60 patients presenting with Cutaneous Leishmaniasis (CL) at the Outpatient Department of Dermatology, JPMC, Karachi during **29-04-21** till **29-10-21** meeting the selection criteria were enrolled. Disease history, demographic information and written informed consent was obtained from study participants. Patients were divided into two groups at random; (A) Intralesional injections of meglumine antimoniate group and (B) Intralesional injections of metronidazole. The procedure was done weekly for a maximum of 8 weeks' duration and during each visit the lesions was measured in size and photographed again and documented. Efficacy was labeled if patients with Cutaneous Leishmaniasis lesion in either group showed complete response. All the data collected and entered in the pre-designed Performa.

Results: Mean age and duration of CL in the meglumine antimoniate group was 48.21±6.24 years and 1.54±0.78 weeks. Mean age and duration of cutaneous leishmaniasis in the metronidazole group was 49.48±8.41 years and 1.97±0.56 weeks. Efficacy in meglumine antimoniate and metronidazole group was 24 (80%) and 12 (36.7%) respectively.

Conclusion: Meglumine antimoniate injections intralesionally have demonstrated an improved degree of cure in terms of the lesions' decreased size and induration. Treatment for cutaneous leishmaniasis with this approach is painless, simple to use, effective, and has few adverse effects.

Keywords: Cutaneous leishmaniasis, meglumine antimoniate, glucantim and metronidazole, efficacy

INTRODUCTION

Cutaneous leishmaniasis (CL) is caused by an "intracellular parasite" that is transferred to humans by a sand fly bite. It is endemic throughout Asia, Africa, Mediterranean region and Amrecia.[1] In Pakistan, this endemic parasitic disease poses a significant threat to public health.[2] Typically, this condition is benign and self-limiting, affecting just the skin. But with lingering disfiguring scars, it typically takes many months for complete healing to occur.[3] Every year, over 1 million CL cases are reported. CL is a globally dispersed illness, with the Asia, Middle East, America, and the Mediterranean basin accounting for around one-third of cases worldwide.[4]

Clinical observations of the disease may reveal both dry and wet forms. Lactobacillus tropicalis has a common association with the late ulcerative or dry urban type. All that is present is a single, <4 cm ulcer that goes completely after a year. The L. major causes the "wet, rural, or early" ulcerative type, which is characterised by many, often healing ulcers within a year.[5, 6] Mucocutaneous leishmaniasis, leishmaniasis recidivans, and diffuse cutaneous leishmaniasis are the rarest types of the disease.[7]

The preventative approach for leishmaniasis is to avoid being bitten by sand flies, as there is currently no authorised vaccination for the disease. Currently, roughly 25 medications have been shown to be clinically effective against leishmaniasis, although only a handful of them have been shown to be effective.[8, 9] For leishmaniasis, pentavalent antimonials are the 1st line of treatment. The illness is a therapeutic obstacle, and CL treatment remains difficult.[10] Additional adverse effects that might arise, particularly with intravenous or intramuscular injections, include arthralgia, soreness, weariness, upset stomach, elevated levels of liver, lipase, and amylase, anaemia, leukopenia, and abnormalities on the electrocardiogram.[4, 11] Furthermore, recent inferential data showed that a growing proportion of patients are not responding to conventional therapies.[12, 13] Aside from this, the total dose of medicine administered intralesionally may equal that of intramuscular or intravenous injections. Thus, the systemic adverse effects associated with any injection technique can be identical.[14, 15] Unfortunately, intralesional injection of metronidazole causes excruciating discomfort, which discourages compliance. 26.7% of intralesional metronidazole group patients showed efficacy compared to 73.3% of intralesional glucantime group patients (p=0.000).[16] Another study by Mapar et al. compared the rates of success for metronidazole and intra-lesion(IL) injections of meglumine antimoniate (MA) vs CL therapy, and found that the rates were 16.6% and 81%, respectively.[17]

In order to establish the local viewpoint, this study aims determine the effectiveness of IL injections of meglumine antimoniate(MA) with metronidazole in patients presenting with CL. This is because insufficient local data are available. Leishmania is the cause of cutaneous leishmaniasis, which is usually challenging to treat. It has been treated with a variety of therapy techniques, although not always with effectiveness. Information from this study might assist position it as the preferred course of therapy, which would lower costs and benefit the patient on both a financial and psychological level.

METHODS AND MATERIALS

This "Randomized Controlled Trial (RCT)" study was conducted during April to Oct, 2021 after obtaining the ethical approval from the institutional ethical review committee and College of Physicians and Surgeons Pakistan.

Sample Size Estimation: Using the "WHO sample size calculator", the following parameters used; significance level=5%, Power=90%, and Metronidazole (16.6%) and Meglumine Antimoniate (81%), intralesional injections, as treatments for Cutaneous Leishmaniasis.[15] The sample size of n=**60** patients with **30** in each group.

All the 60 patients presenting with Cutaneous Leishmaniasis (CL) at the Outpatient Department of Dermatology, JPMC, Karachi meeting the following selection criteria were enrolled using "Non-probability consecutive sampling technique" in the study. Patients who presented with CL were labeled on the basis of the following criteria: (1) Patients having a typical, non-healing, painless, indurated papule, nodule, or plaque with or without crust on clinical assessment was labeled as having cutaneous leishmaniasis. (2) CL was confirmed by a direct smear taken from the lesions, which will then be stained with Giemsa stain showing Leishman bodies (amastigotes) on microscopic examination. Patients of age between 20-60 years, either gender were included and those who were non-consenting, with longer and severe disease duration(>12 weeks) and surface area > $10cm^2$, lesions around the eyes, history of receiving local or systemic anti-leishmanial treatment during the last 6 weeks, peripheral neuropathy, prolonged corticosteroid therapy, melanoma, Chronic diseases (i.e. cardiac disease, liver disease, COPD, stroke) and those who were pregnant were excluded to control the bias. Detail disease history of demographics and written informed consent were obtained. Patients were examined. Then the lesions length and width was measured by a ruler and documented and photographed by the camera of the researcher. Patients were assigned at random using opaque, sealed envelopes bearing (A) Intralesional injections of meglumine antimoniate group and (B) Intralesional injections of metronidazole. Both the injections in each group A and B will be identified using red and green tape attached to the syringe respectively. During each visit for a total of eight visits, the lesion and perilesional area of the lesion was sterilized by povidone iodine 10%. In group A, weekly intralesional injections of meglumine antimoniate 150—600 mg = 0.5—2 ml of meglumine antimoniate ampoule. In group B, weekly intralesional injections of metronidazole 2.5—10 mg = 0.5—2 ml. This procedure was done weekly for a maximum of 8 weeks' duration and during each visit the lesions was measured in size and photographed again and documented. Efficacy was labeled if patients with CL lesion in either group showed complete response; complete re-epithelialization, disappearance of edema, induration, lesions becoming flatter and turning from erythematous to blue or dark gray in color assessed on photograph and clinical examination. Patients not achieving complete response in each group were switched to Intralesional injections of 0.2 mL of sodium stibogluconate. All the data collected and entered in the pre-designed Performa.

SPSS Version 20 was used for data analysis. For the quantitative variables, mean and standard deviations were computed, while frequencies and %es were computed for the qualitative variables. The efficacy of two groups was compared using chi-square. The effect modifiers were controlled by the method of stratification. A chi square test was used post stratification, and a p-value < 0.05 considered significant.

RESULTS

Mean age and duration of Cutaneous leishmaniasis(CL) in Maglumine Antimoniate (MA) group was 48.21±6.24 years and 1.54±0.78 weeks. Similarly, in the metronidazole group mean age and duration was 49.48±8.41 years and 1.97±0.56 weeks. in MA group 14 (46.7%) and 16 (53.3%) patients were in age group 20-40 years and 41-60 years respectively. Whereas, in the metronidazole group, 15 (50%) and 15 (50%) were in age group 20-40 years and 41-60 years respectively. In the MA group, 19 (63.3%) and 11 (36.7%) were male and female and in the metronidazole group, 17 (56.7%) and 13

(43.3%) were male and female. 16 (53.3%) patients had duration ≤ 2 weeks and 14 (46.7%) had duration > 2 weeks of disease in the MA group and in the metronidazole group, 14 (46.7%) and 16 (53.3%) patients had duration ≤ 2 weeks and > 2 weeks respectively. Patients in the meglumine antimoniate group, 16 (53.3%) patients were from urban and 14 (46.7%) were from rural residence, in the metronidazole group 18 (60%) and 12 (40%) patients were from urban and rural residence respectively. Frequency distribution of size of lesion showed that out of 30 patients in the meglumine antimoniate group, 14 (46.7%) and 16 (53.3%) had lesion ≤ 2 and > 2 cm lesion size in the MA group and in the metronidazole group, 08 (26.7%) and 22 (73.3%) had lesion ≤ 2 and > 2 cm respectively. In the MA group, 09 (30%), 09 (30%), 07 (23.3%) and 05 (16.7%) had lesion on the face, neck, upper limb and lower limb respectively. Whereas in the metronidazole group, 06 (20%), 14 (46.7%), 03 (23.3%) and 07 (23.3%) had lesion on the face, neck, upper limb and lower limb respectively. In the MA group, 08 (26.7%) and in the metronidazole group, 06 (20%) had family history of CL. In the MA group, 02 (6.7%), 06 (20%), 15 (50%), 05 (16.7%) and 02 (6.7%) and in the metronidazole group, 04 (13.3%), 03 (10%), 14 (46.7%), 06 (20%) and 03 (10%) patients belonged to lower, lower middle, middle, upper middle and upper income groups respectively. In the MA group, 12 (40%) patients and in the metronidazole group 16 (53.3%) were unemployed. (Table1)
Comparison of efficacy between MA and metronidazole groups showed that, 24(80%) vs. 11(36.7%) efficacy in both groups respectively (P: 0.01). (Figure 1)

Stratification analyses for all the associated factors like age, gender, disease duration, size, site etc. younger age, Male gender, less than 2 week of disease duration, urban residence, more than 2 cm lesion, except lower limb all the site, family history, socioeconomic status and occupational status showed significant association (P<0.05)

Table 1: Descriptive Statistics of Patients Characteristics

Study Variable	Meglumine Antimoniate Group (n=30)	Metronidazole Group (n=30)
Age (in years)	48.21+/-6.24(20-60)	49.48+/-8.41(20-60)
Duration Of CL (in weeks)	1.54+/-0.78(1-3)	1.97+/-0.56(1-3)
Age Groups		
20-40 Years	14 (46.7%)	15 (50%)
41-60 Years	16 (53.3%)	15 (50%)
Gender		
Male	19 (63.3%)	17 (56.7%)
Female	11 (36.7%)	13 (43.3%)
Duration Of CL		
≤ 2 Week	16 (53.3%)	14 (46.7%)
> 2 Week	14 (46.7%)	16 (53.3%)
Residence		
Urban	16 (53.3%)	18 (60%)
Rural	14 (46.7%)	12 (40%)
Lesion Size		
≤ 2cm	14 (46.7%)	08 (26.7%)
> 2 Cm	16 (53.3%)	22 (73.3%)
Lesion Site		
Face	09 (30%)	06 (20%)
Neck	09 (30%)	14 (46.7%)
Upper Limb	07 (23.3%)	03 (10%)
Lower Limb	05 (16.7%)	07 (23.3%)
Family Hx Of CL		

Yes	08 (26.7%)	06 (20%)
No	22 (73.3%)	24 (80%)
Socioeconomic Status		
Lower	02 (6.7%)	04 (13.3%)
Lower Middle	06 (20%)	03 (10%)
Middle	15 (50%)	14 (46.7%)
Upper Middle	05 (16.7%)	06 (20%)
Upper	02 (6.7%)	03 (10%)
Occupational Status		
Employed	18 (60%)	14 (46.7%)
Unemployed	12 (40%)	16 (53.3%)

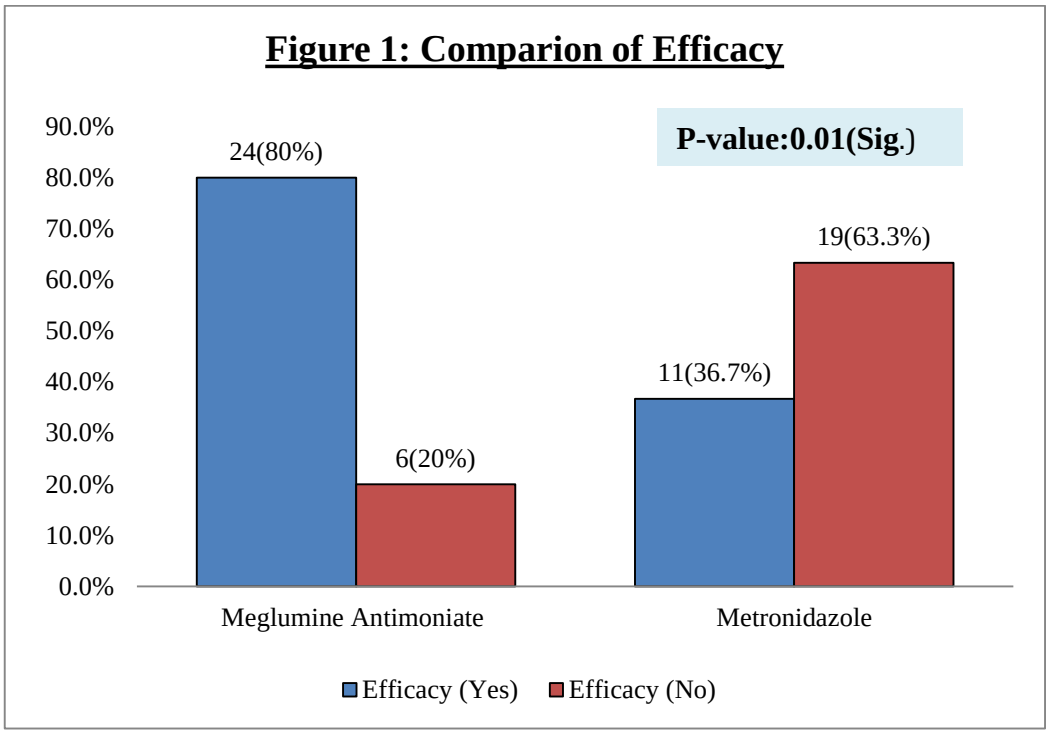

Table 2: Comparisons of efficacy between groups with respect to associated factors

Associated Factors	Meglumine Antimoniate Group		Metronidazole Group		P -value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Age					
20-40 Years	13 (92.9%)	01 (7.1%)	03 (20%)	12 (80%)	0.01
41-60 Years	11 (68.8%)	05 (31.2%)	08 (53.3%)	07 (46.7%)	0.37
Gender					
Male	17 (89.5%)	02 (10.5%)	05 (29.4%)	12 (70.6%)	0.01
Female	07 (63.6%)	04 (36.4%)	06 (46.2%)	07 (53.8%)	0.39
Duration Of Disease					
≤ 2 Week	11 (68.8%)	05 (31.2%)	02 (14.3%)	12 (85.7%)	0.01
> 2 Week	13 (92.9%)	01 (7.1%)	09 (56.2%)	07 (43.8%)	0.02
Residence					
Urban	14 (87.5%)	02 (12.5%)	06 (33.3%)	12 (66.7%)	0.01

Rural	10 (71.4%)	04 (28.6%)	05 (41.7%)	07 (58.3%)	0.12
Lesion Size					
≤ 2cm	10 (71.4%)	04 (28.6%)	03 (37.5%)	05 (62.5%)	0.11
> 2cm	14 (87.5%)	02 (12.5%)	08 (36.4%)	14 (63.6%)	0.01
Lesion Site					
Face	08 (88.9%)	01 (11.1%)	03 (50%)	03 (50%)	0.09
Neck	07 (77.8%)	02 (22.2%)	03 (23.1%)	10 (76.9%)	0.01
Upper Limb	07 (100%)	00 (00%)	01 (33.3%)	02 (66.7%)	0.01
Lower Limb	02 (40%)	03 (60%)	04 (36.7%)	04 (50%)	0.72
Family Hx Of CL					
Yes	08 (100%)	00 (00%)	04 (66.7%)	02 (33.3%)	0.01
No	16 (72.7%)	06 (27.3%)	07 (29.2%)	17 (70.8%)	0.01
Socioeconomic Status					
Lower	02 (100%)	00 (00%)	02 (50%)	02 (50%)	0.01
Lower Middle	04 (66.7%)	02 (33.3%)	02 (66.7%)	01 (33.3%)	0.05
Middle	12 (80%)	03 (20%)	05 (35.7%)	09 (64.3%)	0.01
Upper Middle	04 (80%)	01 (20%)	02 (33.3%)	04 (66.7%)	0.12
Upper	02 (100%)	00 (00%)	00 (00%)	03 (100%)	0.01
Occupational Status					
Employed	12 (66.7%)	06 (33.3%)	05 (35.7%)	09 (64.3%)	0.01
Unemployed	12 (100%)	00 (00%)	06 (37.5%)	10 (62.5%)	0.08

Chi-square test applied. P value <0.05 set as significant

DISCUSSION

Over a hundred nations are home to the endemic protozoan parasitic disease leishmaniasis, which is spread by phelebotomous sand flies. Due to the Leishmania parasite's growing resistance, current leishmaniasis treatment techniques are linked with limited effectiveness (particularly L. tropica). The primary cause of treatment resistance is decreased medication concentration in parasite cells as a result of either stimulating drug metabolism and inactivation or inhibiting drug activation. Better drug penetration to the stratum corneum, increased absorption, greater concentration release, and drug attachment in parasite and macrophage cells are all provided by more recent drug delivery methods, such as "noisomes, liposomes, and nanoparticles".[18, 19]

Meglumine antimoniate (MA) is typically used as the first line of therapy for CL. In endemic regions, however, resistant variants of CL to MA are becoming more widely identified.[13] Leishmaniasis is a complicated disease that is often ignored, causing poverty and increasing issues with public health and social issues. Leishmaniasis is generally a treatable illness, however in the case of CL, there is an increasing number of patients that are not responding to therapy. Poor treatment adherence is a significant and often overlooked factor in the treatment outcome of CL.[12] In this network meta analysis, various interventions including intralesional, topical, parenteral, oral, heat therapy, and laser were compared and examined in 131 randomized clinical studies for the treatment of CL. Numerous therapies may be beneficial in raising the percentage of patients who totally recover, according to the data..[20]

In numerous studies IL glucantime injections have demonstrated success in treating CL. It has several negative effects, including as immediate pain and reactivity at the injection site. Intravenous or intramuscular injections can also cause various side effects, such as arthralgia, fatigue, increased liver enzymes, decrease Hb levels, leucopenia, GI issues, lipase and amylase and irregular ECG.[16, 18, 21]

In this review research, Heras-Mosteiro J et al. investigated the issues surrounding the toxicity, cost and emergence of drug-resistance associated with the substances sodium stibogluconate (SSG) and meglumine antimoniate (MA), despite their extensive usage. Severe adverse effects, often dose-dependent, are linked to parenteral antimonial drugs. These effects include but are not limited to "nausea, vomiting, diarrhoea, skin eruptions, dizziness, cardiac arrhythmia, hypotension, arthralgia, myalgia, headache, occasional anemia, and thrombocytopaenia". When administered intralesionally as opposed to intravenously or intramuscularly, there is more pain felt at the injection site. This review article presents evidence for the effectiveness of intralesional pentavalent antimonials for OWCL, mostly in Asia and the Mediterranean basin, based on many research studies. [14]

The current study included a total of 60 patients who met the selection criteria. Mean age and duration of CL in the MA group was 48.21±6.24 years and 1.54±0.78 weeks. Mean age and duration of CL in the metronidazole group was 49.48±8.41 years and 1.97±0.56 weeks. Efficacy in MA and metronidazole group was 24 (80%) and 12 (36.7%) respectively. The efficacy found highly significant between the study groups.

In a local investigation carried out by Ghafoor Ullah et al., the effectiveness was shown to be 26.7% in patients in the intralesional metronidazole group compared to 73.3% in the intralesional glucantime group, with a statistically significant difference (P:0.001). Intralesional glucantime is more safe and effective than topical therapy for CL, according to this study's findings. It was noted that the search for a painless, easily administered, efficient treatment option with the fewest side effects for the management of CL is crucial, even if metronidazole was shown to be ineffective in this experiment.[16] Another study by Somaratne VN et al. revealed that 49% of patients of CL responded well to intralesional metronidazole treatment.[22] IL glucantime was shown to be 38.5 percent efficient in treating CL in a different study conducted by Jaffary F. et al.[23]

Patients in this analytical observational research were administered three injections of IL-metronidazole or IL-pentostam every two weeks. The size and length of the lesions have decreased in response to metronidazole and IL injection, indicating some degree of cure. IL-pentostam was more efficacious than IL-metronidazole, despite the difference being statistically not significant.[24] In the Iran-based randomized open trial study, the effectiveness of once-weekly versus twice-weekly intralesional injections of meglumine antimoniate (MA) in treating CL was found to be 88% vs. 89% in the groups that got weekly and twice weekly IL-MA injections, respectively (P:0.808). Because the medications were shown to be effective in both methods at various dosages, no difference was noted. However, patients who got IL-MA 2 times a week saw a considerably quicker time to healing than those who received IL-MA once weekly (P<0.001). Nevertheless, the group that received IL-MA weekly twice also required more injections overall. The study suggested using IL-MA weekly once because of its satisfactory compliance and negligible adverse effects.[25]

There are a number of shortcomings with our study, such as a small patient population, no sore culture, and unknown strains and species of Leishmaniasis. Given the significant differences between the results of prior studies and our own, other researchers should carry out similar examinations with a larger number of patients. In addition, IL injections of MA derivatives are less expensive, safer, and more easy for patients with higher compliance than systemic treatment with either Glucantime or Pentostam. IL treatment is particularly beneficial for patients with a small number of lesions, older age patients, and patients with chronic diseases such as abnormal liver, heart, or kidney function.

CONCLUSIONS

Meglumine antimoniate(MA) administered intralesionally(IL) is safer and more effective. The degree of cure has improved as seen by the lesions' decreased size and duration. Treatment for cutaneous

leishmaniasis with this form of treatment is painless, simple to use, effective, and has few adverse effects.

REFERENCES

1. Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmenjaud J, Arenas R. Leishmaniasis: a review. F1000Research. 2017;6:750.
2. Yousuf M, Ahmad N, Masood Z, Majeed S, Hassan HU, Ibrahim M, et al. Prevalence of cutaneous leishmaniasis in the largest populated city Karachi, Pakistan. Brazilian Journal of Biology. 2021;83.
3. Bilgic-Temel A, Murrell DF, Uzun S. Cutaneous leishmaniasis: A neglected disfiguring disease for women. International journal of women's dermatology. 2019;5(3):158-65.
4. Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert opinion on pharmacotherapy. 2015;16(2):237-52.
5. Maleki M, Yousefi M, Bazzaz SMM, Tabassi SAS, Rakhshandeh H, Hamedi SS, et al. An overview of skin lesions adapted to Cutaneous Leishmaniasis in Persian Medicine. Electronic physician. 2017;9(11):5854-62.
6. Manfredi M, Iuliano S, Bizzarri B, Fugazza A, Gismondi P. Cutaneous leishmaniasis with long duration and bleeding ulcer. Clin Microbiol. 2016;5(229):2.
7. Volpedo G, Pacheco-Fernandez T, Holcomb EA, Cipriano N, Cox B, Satoskar AR. Mechanisms of Immunopathogenesis in Cutaneous Leishmaniasis And Post Kala-azar Dermal Leishmaniasis (PKDL). Frontiers in cellular and infection microbiology. 2021;11:685296.
8. Parkash V, Kaye PM, Layton AM, Lacey CJ. Vaccines against leishmaniasis: using controlled human infection models to accelerate development. Expert review of vaccines. 2021;20(11):1407-18.
9. Reguera RM, Pérez-Pertejo Y, Gutiérrez-Corbo C, Domínguez-Asenjo B, Ordóñez C, García-Estrada C, et al. Current and promising novel drug candidates against visceral leishmaniasis. Pure and Applied Chemistry. 2019;91(8):1385-404.
10. Berbert TRN, Mello TFPd, Wolf Nassif P, Mota CA, Silveira AV, Duarte GC, et al. Pentavalent antimonials combined with other therapeutic alternatives for the treatment of cutaneous and mucocutaneous leishmaniasis: A systematic review. Dermatology research and practice. 2018;2018.
11. Garza-Tovar TF, Sacriste-Hernández MI, Juárez-Durán ER, Arenas R. An overview of the treatment of cutaneous leishmaniasis. Faculty reviews. 2020;9:28.
12. Bamorovat M, Sharifi I, Agha Kuchak Afshari S, Karamoozian A, Tahmouresi A, Heshmatkhah A, et al. Poor adherence is a major barrier to the proper treatment of cutaneous leishmaniasis: A case-control field assessment in Iran. International journal for parasitology Drugs and drug resistance. 2023;21:21-7.
13. Tayyebi M, Darchini-Maragheh E, Layegh P, Kiafar B, Goyonlo VM. The effect of oral miltefosine in treatment of antimoniate resistant anthroponotic cutaneous leishmaniasis: An uncontrolled clinical trial. PLoS neglected tropical diseases. 2021;15(3):e0009241.
14. Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Reveiz L, Garcia-Carrasco E, et al. Interventions for Old World cutaneous leishmaniasis. The Cochrane database of systematic reviews. 2017;12(12):Cd005067.
15. de Oliveira Duque MC, Silva JJQ, Soares PAO, Magalhães RS, Horta APA, Paes LRB, et al. Comparison between systemic and intralesional meglumine antimoniate therapy in a primary health care unit. Acta tropica. 2019;193:176-82.
16. Ullah G, Ali F. The efficacy of intralesional metronidazole compared to intralesional glucantime in the therapeutic therapy of cutaneous leishmaniasis. Journal of Pakistan Association of Dermatologists. 2022;32(2):348-52.

17. Mapar MA, Omidian M. Intralesional injections of metronidazole versus meglumine antimoniate for the treatment of cutaneous leishmaniasis. Jundishapur Journal of Microbiology. 2010;3(2):79-83.
18. Farajzadeh S, Ahmadi R, Mohammadi S, Pardakhty A, Khalili M, Aflatoonian M. Evaluation of the efficacy of intralesional Glucantime plus niosomal zinc sulphate in comparison with intralesional Glucantime plus cryotherapy in the treatment of acute cutaneous leishmaniasis, a randomized clinical trial. Journal of parasitic diseases : official organ of the Indian Society for Parasitology. 2018;42(4):616-20.
19. Kayani B, Sadiq S, Rashid HB, Ahmed N, Mahmood A, Khaliq MS, et al. Cutaneous Leishmaniasis in Pakistan: a neglected disease needing one health strategy. BMC Infectious Diseases. 2021;21(1):622.
20. Sridharan K, Sivaramakrishnan G. Comparative assessment of interventions for treating cutaneous leishmaniasis: A network meta-analysis of randomized clinical trials. Acta Tropica. 2021;220:105944.
21. Kashani MN, Firooz A, Eskandari SE, Ghoorchi MH, Khamesipour A, Khatami A, et al. Evaluation of meglumine antimoniate effects on liver, kidney and pancreas function tests in patients with cutaneous leishmaniasis. European Journal of Dermatology. 2007;17(6):513-5.
22. Somaratne VN, Ranawaka RR, Jayaruwan H, Wipuladasa D, de Silva SP. Randomized, double-blind study on intralesional metronidazole versus intralesional sodium stibogluconate in Leishmania donovani cutaneous leishmaniasis. Journal of Dermatological Treatment. 2019;30(1):87-91.
23. Jaffary F, Nilforoushzadeh MA, Siadat A, Haftbaradaran E, Ansari N, Ahmadi E. A comparison between the effects of glucantime, topical trichloroacetic acid 50% plus glucantime, and fractional carbon dioxide laser plus glucantime on cutaneous leishmaniasis lesions. Dermatology research and practice. 2016;2016.
24. Bahnan BA, Shabu SA, Sleman SA. Intralesional pentostam versus intralesional metronidazole in treating cutaneous leishmaniasis: A comparison study. Zanco Journal of Medical Sciences (Zanco J Med Sci). 2019;23(2):257-63.
25. Javadi A, Khamesipour A, Ghoorchi M, Bahrami M, Khatami A, Sharifi I, et al. Efficacy of intra-lesional injections of meglumine antimoniate once a week vs. twice a week in the treatment of cutaneous leishmaniasis caused by L. tropica in Iran: A randomized controlled clinical trial. PLoS neglected tropical diseases. 2022;16(7):e0010569.