Comparison of Meglumine Antimoniate and Miltefosine in Cutaneous Leishmaniasis

Atiya Rahman[1], Moizza Tahir[2], Tehseen Naveed[3], Mohammad Abdullah[4], Nida Qayyum[5], Danish Hafeez Malik[6] and Bushra Amin[7]

[1]*Department of Dermatology, PNS Shifa Hospital and Bahria University, Karachi, Pakistan*
[2]*Department of Dermatology, Combined Military Hospital, Gujranwala, Pakistan*
[3]*Department of Dermatology, Combined Military Hospital, Peshawar, Pakistan*
[4]*Department of Stroke Medicine, Russells Hall Hospital, Dudley, UK*
[5]*Department of Dermatology, Combined Military Hospital, Multan, Pakistan*
[6]*Department of Dermatology, Combined Military Hospital, Lahore, Pakistan*
[7]*Department of Community Medicine, Combined Military Hospital Lahore Medical College, Lahore, Pakistan*

ABSTRACT

Objective: To compare the efficacy and safety of meglumine antimoniate and miltefosine in the treatment of cutaneous leishmaniasis in Pakistan.

Study Design: Randomised-controlled trial.

Place and Duration of the Study: Department of Dermatology, Combined Military Hospital, Lahore and Peshawar, from January to December 2021.

Methodology: Smear positive and/or skin biopsy-confirmed cases of cutaneous leishmaniasis in adult males aged between 18-60 years were enrolled after receiving informed consent. Patients were randomly divided into Group A and Group B by lottery method. Group A received intramuscular meglumine antimoniate 15-20mg/kg/day, and Group B received oral miltefosine 50 mg thrice a day for a duration of 28 days. Data were analysed by SPSS 22. Effectiveness and safety of therapeutic agents were calculated by Independent t-test and p-value of 0.05 or less was taken as significant.

Results: Sixty-six patients, 33 in each group, participated in the study. Total number of cutaneous leishmaniasis lesions were 77 in Group A and 76 in Group B. The duration of lesions was 3.5 months in Group A and 3.2 months in Group B. Treatment response, in terms of complete or near complete resolution of lesions, was significantly higher in Group A as compared to Group B ($p = 0.011$). Both therapeutic agents had considerable side-effects with more patients withdrawn from Group A as compared to Group B ($p = 0.010$).

Conclusion: Intra-muscular meglumine antimoniate was more effective in comparison to oral miltefosine in the treatment of cutaneous leishmaniasis. However, efficacy of meglumine antimoniate is mired by its side-effect profile.

Key Words: *Cutaneous leishmaniasis, Meglumine antimoniate, Miltefosine, Efficacy, Side-effects, Adverse effects, Safety, Treatment, Old world cutaneous leishmaniasis.*

How to cite this article: Rahman A, Tahir M, Naveed T, Abdullah M, Qayyum N, Malik DH, *et al.* Comparison of Meglumine Antimoniate and Miltefosine in Cutaneous Leishmaniasis. *J Coll Physicians Surg Pak* 2023; **33(12)**:1367-1371.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a common parasitic infestation of the tropics and subtropics, caused by the bite of sandfly which transmits the *Leishmania* species to human skin. About twenty *Leishmania* species have been identified.[1] CL is an important cause of disability in 98 endemic countries.

Correspondence to: Dr. Atiya Rahman, Department of Dermatology, PNS Shifa Hospital and Bahria University, Karachi, Pakistan
E-mail: atiya_rahman7@yahoo.com
Received: April 06, 2023; Revised: October 21, 2023; Accepted: November 13, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.12.1367

It is estimated that there are between 0.7 to 1.2 million new cases of CL per year worldwide.[1] It is a neglected third commonest vector borne disease in the world.[2] It is widely spread in different parts of the world including South and Central America, Mediterranean Basin, Middle East, and Central Asia.[3] In Pakistan, CL reported prevalence varies from 1.6 to 2.7%, in the north-western land with incidence of 4.6 cases/1000 persons/year in the last ten years.[2] *L. major* (97.9%) is reported mostly in lowland and *L. tropica* (76.2%) in highland areas.[4] However, widespread and frequent travelling makes this demarcation arbitrary.

Meglumine antimoniate is the first line of treatment for CL but studies have reported its low efficacy and myriad of side-effects. Meglumine antimoniate is administered parentally in a dose of 10 - 20 mg/kg/day for 3 – 4 weeks.[5] Treatment can be

repeated if warranted. This therapeutic agent is associated with a variety of side-effects in considerable proportion of patients. They include cardiotoxicity, derangement in liver and renal function tests, anorexia, nausea, vomiting, injection site pain, myalgia, and arthralgia.[6] It is difficult to administer daily as it requires expertise of health professionals. In addition, it is costly and difficult to acquire, and reports are emerging of its resistance.

Rifampicin, itraconazole, allopurinol, and paromomycin have been used as combination therapy with meglumine antimoniate.[7,8] Such combinations increase the efficacy of management plans while reducing the incidence of adverse effects.[7] Despite different available options, there is no universal cure for all types of CL. In cases of antimony resistance, miltefosine has been considered as second-line therapy with 80 - 90% parasitological improvement in diffuse CL.[9]

There is limited data to compare the two medicines locally. With potential serious adverse effects of meglumine antimoniate, search for an affordable, safe and competitive option continues for this neglected disease. The aim of this study was to compare the efficacy and safety of meglumine antimoniate and miltefosine in the treatment of cutaneous leishmaniasis in Pakistan.

METHODOLOGY

A multicentre, randomised-controlled trial was conducted in the Departments of Dermatology, Combined Military Hospital, Lahore and Combined Military Hospital, Peshawar, from January to December 2021. Respective ethical approval was sought from both hospitals before the commencement of the study (264/2020 dated 4/1/2021 and 67/2021 dated 12/2/2021). The sample size of the study was calculated by WHO sample size calculator. The estimated sample size was calculated to be a minimum of 26 in each group, assuming a 95% confidence interval with a margin of error of 5%; keeping 1.6% as the prevalence of CL.[7] After written informed consent, sixty-six patients were enrolled in the study, employing non-probability consecutive sampling technique. Thirty-three patients were assigned to two groups (A and B) randomly by lottery method.

Adult males with age range of 18-60 years and weight between 60-85 kg were included in the study. CL diagnosis in each case was confirmed either by slit skin smear for Leishmania donovanii body, or with skin biopsy for histopathology, or both. All study patients had CL lesions for the last 1-12 months. Patients with cardiac, liver, renal disease, diabetes mellitus, hypertension, and those who received treatment for CL in the last 3 months or had hypersensitivity to meglumine antimoniate or miltefosine, and patients who had more than seven CL lesions were excluded.

CL lesions were defined as nodule for solid, palpable, round or ellipsoidal lesion, diameter >0.5cm; plaque as solid plateau like elevation that occupied a relatively large surface in comparison with its height above the normal skin level and diameter larger than 1.0 cm and ulcer as defect of skin in which the epidermis and at least the upper dermis had been removed with raised edges and surrounding red skin. CL lesions were assessed for their morphology, number, size, site, and spread along the lymphatics, (sporotrichoid spread), prior to the initiation of treatment as baseline reading and subsequently reassessed on Day 14 and 28 for efficacy of treatment. Patients had following laboratory investigations done: complete blood count, serum for liver function test, urea, creatinine, electrolytes, amylase, and ECG. The tests were done at baseline and then repeated weekly. Additional tests like ultrasound abdomen or of the site of injection, CT scan abdomen and other laboratory tests were done as per individual patient management plan while undergoing therapy. The final response, at 28th day, was graded as excellent for 91-100% reepithelisation of skin ulceration and/or flattening of the skin along with disappearance of induration, good for 75-90% reepithelisation of skin ulceration and/or flattening of the skin along with reduction of induration, fair for 50-74% reepithelisation of skin ulceration and/or flattening of the skin along with reduction of induration and poor response for less than 50% of re-epithelisation of skin ulceration and/or flattening of the skin along with reduction of induration.

Both groups' study participants received treatment for 28 days. Group A participants received intramuscular (deep intragluteal) meglumine antimoniate 15-20mg/kg/day after intra--dermal skin test dose. Group B study participants received oral miltefosine 50 mg twice a day in the first week and then thrice daily for the next 3 weeks.

Data were analysed through statistical programme of social sciences 22.0 (SPSS 22.0). Descriptive statistics were calculated for age, duration, number of lesion, site of lesion and its morphology. Frequencies and percentages were calculated for type of lesions and common side effects. Chi-square test was applied to ascertain statistical significance between morphology and site of lesions between the two groups. Efficacy of treatment between meglumine antimoniate and miltefosine was compared by Chi-square test and p-value <0.05 was considered as statistically significant.

RESULTS

A total of 66 adult male patients participated in the study. Age of patients ranged from 22-55 years, mean 30.45 ± 6.5; with mean age of 28.82 ± 5.33 in Group A and 32.09 ± 7.20 in Group B. Duration of lesion ranged from 1-12 months, with mean duration of 3.5 ± 1.71 in Group A and 3.2 ± 1.9 months in Group B. There were 77 CL lesions in Group A and 76 in Group B. Mean number of CL lesions were 2.33 ± 1.68 in Group A and 2.27 ± 1.64 in Group B.

Diagnosis of CL was confirmed on skin biopsy in 35 (53.03%), slit skin smear in 26 (39.39%) and by both in 5 (7.58%) patients. Maximum size of lesion was 10.5 cm in Group A and 7.0 cm in Group B. Sporotrichoid spread was seen in 14 (21.2%) patients,

with 5 (15.15%) in Group A and 9 (27.27%) in Group B. Seventeen (51.5%) patients had lesions over joints in Group A and 12 (36.4%) in Group B. Morphology and site of lesion in both groups are shown in Table I.

Excellent response in Group A was found to be higher than in Group B (p = 0.01), as shown in Table I. Miltefosine was also an effective medicine with more than fifty percent of the patients exhibiting 75% improvement or more with 28 days' treatment.

The list of side-effects experienced by study participants is shown in Table II. Treatment breaks were seen in both groups. Injection site pain and abscess were the most common reason in Group A, where three patients' treatments were halted for 3-7 days. Other causes were more than 3-fold increase in serum ALT, high-grade fever and ECG changes. T- wave inversion were seen in 5 (15.15%), bradycardia in 2 (6.06%) and QT interval prolongation in 1 (3.03%) patient. In Group B, one patient had temporary treatment break due to high-grade fever and another due to nausea, vomiting and pain in abdomen. In Group A, nine patients (27.27%), with 19 lesions withdrew from the study; whereas in Group B, four patients (12.12%), with 12 lesions withdrew (p = 0.01), due to bothersome side-effects.

Table I: Characteristic of lesions, sites and treatment response in the two groups of cutaneous leishmaniasis.

Lesion characteristics	Group A Meglumine Antimoniate n = 77	Group B Miltifosine n = 76	p-value
Morphology			
Ulcer	24 (31.17%)	31 (40.79%)	0.291
Plaque	42 (54.55%)	39 (51.32%)	
Nodule	11 (14.29%)	6 (7.89%)	
Site			
Head and neck	11 (14.29%)	11 (14.7%)	0.086
Trunk	8 (10.39%)	2 (2.63%)	
Upper limb	34 (44.16%)	46 (60.53%)	
Lower limb	24 (31.17%)	17 (22.37%)	
Treatment response			
Excellent	11 (33.3%)	4 (12.1%)	0.011
Good	11 (33.3%)	13 (39.4%)	
Fair	2 (6.1%)	8 (24.2%)	
Poor	0	4 (12.1%)	
Discontinued	9 (27.3%)	4 (12.1%)	0.010

**p-value determined by Chi-square test and considered significant if <0.05.*

Table II: Side-effect profile in Group A and B.

Adverse Effect	Group A Meglumine Antimoniate n = 33	Group B Miltefosine n = 33
Injection site pain	13 (39.3%)	0
Injection site abscess	7 (21.2%)	0
Nausea/vomiting	1 (3%)	21 (63.6%)
Abdominal fullness	0	11 (33.3%)
Fever	2 (6.1%)	5 (15.2%)
Myalgia/Arthralgia	13 (39.3%)	2 (6.1%)
Chest tightness	5 (15.2%)	0
ECG Changes	8 (24.2%)	0
Raised ALT	6 (18.2%)	3 (9.1%)
Raised Creatinine	0	3 (9.1%)
Raised Amylase	1 (3)	0

DISCUSSION

Cutaneous leishmaniasis is a poverty related neglected tropical disease. At present, the most effective treatment is pentavalent antimonial compound in the underdeveloped countries.[5] Resistance to therapeutic agents has mainly been documented in new world cutaneous leishmaniasis, especially in patients infected with *L. guyanensis* and *L. braziliensis* species.[5,10] Soleimanifard *et al.* collected isolates from patients of CL who had not responded to meglumine antimoniate and performed nested polymerase chain reaction to identify the species. Interestingly, they did not find any significant differences in the isolates obtained from such patients as compared to the standard *Leishmania* species strain. They concluded that resistance to meglumine antimoniate may be due to environmental and host factors rather than intrinsic resistance.[11] In addition, degree of polymerisation of the therapeutic agent, its storage conditions, and duration can potentially affect its pharmacokinetics.[5] Keeping these research findings in mind, the study was conducted to document the efficacy of this therapeutic agent in old world cutaneous leishmaniasis.

Mohammadzadeh *et al*. in Iran in a prospective study found meglumine antimoniate to be an effective medication, reporting failure rate of 22.6% in CL patients, treating with intralesional (for lesions smaller than 3 cm) or intramuscular route.[12] Soleimanifard *et al.* demonstrated that non-healing CL lesions were re-treated with meglumine antimoniate and responded satisfactorily. They emphasised its administration under supervision of skilled professionals and for adaptable policy-making.[11] In the present study, similar to earlier researchers' findings on old world CL, meglumine antimoniate was found to be a very effective medicine. Only 6 percent of the patients, who completed the four weeks' treatment plan, had 50-75% improvement. Rest of the participants' improvement was more than this. The study participants were admitted in the medical facility and the medicine was administered and monitored by trained healthcare professionals.

Miltefosine is a therapeutic alternative of meglumine antimoniate in the treatment of CL. It has been found to be effective against some but not all species of CL. It is given in a dose of 1.8 to 2.5 mg/kg/day for 28 days with a maximum dose of 150mg/day.[13] Adverse effects include vomiting and diarrohea (62%), hepatic and nephro toxicities in 10-15% cases. To reduce incidence of side-effects, the authors used 100mg/day during the first week and then increased it to 150 mg thereafter. Drug-resistance is an emerging problem of miltefosine due to long half-life.[14] In a study conducted on children at Columbia, where *L. guyanensis*, and *L. panamensis* predominate, miltefosine was found to be superior than meglumine antimoniate in efficacy (p=0.04) with mild adverse events noted for both medicines.[13] This is in contrast to the current study done on adults, having old world CL.

Preliminary studies done locally and in the same region yielded good response to miltefosine. Rahman *et al.* reported cure rate of 93% with miltefosine and 73.3% with meglumine antimo-

niate at 3 months and 86% and 66.6% at six months follow-up.[15] However, in a recent study, Ware *et al*. treated 26 patients of CL with oral miltefosine and reported it to be safe though with imperfect efficacy in treatment of *Leishmania* species; 77% (20/26) of the patients met their criteria of cure.[16] The therapeutic agent was reduced in dose or discontinued temporarily for manageable toxic adverse effects. Nausea and vomiting were reported as the most common side-effects experienced in 97% patients. In three patients, i.e. 11.5%, treatment had to be discontinued due to severe side-effects. Side-effects typically occurred within 1-2 weeks of starting the treatment. This observation is similar to the current study's findings. Adjusting the dose to 100mg during Week 1 and subsequently increasing it to 150 mg/day led to better tolerance of the medicine. Iranpour *et al*. in a meta-analysis reported no significant difference between the efficacy of miltefosine and glucantime, in treatment of CL.[17] However, excluding CL lesions caused by *L. braziliensis* indicated superiority of miltefosine.

In this study, local pain at the injection site and myalgias were the commonest adverse effects with meglumine antimoniate, followed by ECG changes. The ventricular repolarisation alterations, including T wave flattening or inversion, and prolonged QT interval are serious and potentially fatal side-effects and require monitoring during the therapy.[8] These cardiac effects are dose- and time-dependent, and treatment may be resumed cautiously after a break, using smaller dose. However, the study participants were reluctant to continue the same medication and were withdrawn from the study. Tahir *et al.* reported early repolarisation defects with standard dose of 15mg/kg body weight of meglumine antimoniate in CL patients; T wave inversion occurring in 47.12% of patients and QT interval prolongation in 1.14%.[18] In another local study, conducted by Panezi *et al*. on 245 patients undergoing meglumine antimoniate at a dose of 20 mg/kg body weight, side-effects were reported as: Q wave in 67 (27.3%), prolonged QT interval in 38 (15.5%), sinus tachycardia in 37 (15.1%), sinus bradycardia in 19 (7.8%), and ST depression in 13 (5.3%) patients.[19] These high percentage of side-effects profile can be explained on the basis of the therapeutic agent's pharmacokinetics; antimony is accumulated the most in liver, followed by thyroid and heart.[8] In the current study, ECG changes were seen in 24.2% of the patients, T wave inversion was seen in 5 (15.15%), bradycardia in 2 (6.06%), and QT interval prolongation in 1 (3.03%) patient. This is comparable to the findings of Tahir *et al.*[18] but considerably less than what was observed by Panezi *et al.*[19] The difference can be due to different storage conditions and monitoring protocols in different studies. To reduce the systemic toxicity of MA, it has been used intra-lesionally and augmented with other modalities like cryotherapy and topical niosomal zinc sulphate.[20]

Meglumine antimoniate presents formidable challenges to medication adherence due to daily intramuscular injections compounded by its adverse and potentially fatal effects and emerging resistance. A newer technology of delivering meglumine antimoniate as nanocarriers to mitigate the side effect profile is still in the infancy stage.[8] Lack of availability of funds for effective management of this neglected tropical disease is a vital factor in this regard. An effective therapeutic alternative is much required.

The study limitations include lack of *Leishmania* species identification and not following up with patients at the end of the therapy. It is recommended that similar multi-centric studies, augmented by species identification, must be conducted to confirm or repudiate this study's results.

CONCLUSION

Meglumine antimoniate is more effective in comparison to miltefosine in treatment of cutaneous leishmaniasis. However, it is associated with a myriad of side-effects, marring its use in cutaneous leishmaniasis.

ETHICAL APPROVAL:

This study was performed in line with the principles of the Declaration of Helsinki. Approvals were granted by the Ethical Review Committee of Combined Military Hospital, Lahore and Combined Military Hospital, Peshawar (264/2020 dated 4.1.2021 and 67/2021 dated 12.2.2021, respectively).

PATIENTS' CONSENT:

Informed consents were obtained from patients to participate in the study and for publication of study results.

COMPETING INTEREST:

The authors had no relevant financial or non-financial interests to disclose.

AUTHORS' CONTRIBUTION:

AR: Study conception and design, data gathering and analysis and interpretation, manuscript writing and drafting of the final version.
MT: Data interpretation, manuscript-writing and drafting of the final version.
TN: Study conception and design, data-gathering, manuscript-writing.
MA: Data entry in SPSS software, analysis and interpretation, manuscript-writing.
NQ, DHM: Study conception and design, data gathering, manuscript-writing.
BA: Data analysis and interpretation, manuscript-writing, drafting the results section in the first draft version.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Sunyoto T, Verdonck K, el Safi S, Potet J, Picado A, Boelaert M. Uncharted territory of the epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa-A systematic review. *PLoS Negl Trop Dis* 2018; **12(10)**:e0006914. doi: 10.1371/journal.pntd.0006914.
2. 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 Infect Dis* 2021; **21(1)**:622. doi: 10.1186/s12879-021-06327-w.

3. Ghatee MA, Taylor WR, Karamian M. The geographical distribution of cutaneous leishmaniasis causative agents in Iran and its neighboring countries, a review. *Front Public Health* 2020; **8**:11. doi: 10.3389/fpubh.2020.00011.
4. Afghan AK, Kassi M, Kasi PM, Ayub A, Kakar N, Marri SM. Clinical manifestations and distribution of cutaneous leishmaniasis in pakistan. *J Trop Med* 2011; **2011**:359145. doi: 10.1155/2011/359145.
5. Carvalho SH, Frézard F, Pereira NP, Moura AS, Ramos LMQC, Carvalho GB, *et al*. American tegumentary leishmaniasis in Brazil: A critical review of the current therapeutic approach with systemic meglumine antimoniate and short-term possibilities for an alternative treatment. *Trop Med Int Health* 2019; **24(4)**:380-91. doi: 10.1111/tmi.13210.
6. Garza-Tovar TF, Sacriste-Hernández MI, Juárez-Durán ER, Arenas R. An overview of the treatment of cutaneous leishmaniasis. *Fac Rev* 2020; **9**:28. doi: 10.12703/r/9-28.
7. Berbert TRN, de Mello TFP, 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. *Dermatol Res Pract* 2018; **2018**:9014726. doi: 10.1155/2018/9014726.
8. Madusanka RK, Silva H, Karunaweera ND. Treatment of cutaneous leishmaniasis and insights into species-specific responses: A narrative review. *Infect Dis Ther* 2022; **11(2)**:695-711. doi: 10.1007/s40121-022-00602-2.
9. Mohebali M, Fotouhi A, Hooshmand B, Zarei Z, Akhoundi B, Rahnema A, *et al*. Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomised clinical trial in Iran. *Acta Trop* 2007; **103(1)**:33-40. doi: 10.1016/j.actatropica.2007.05.005.
10. Salam N, Al-Shaqha WM, Azzi A. Leishmaniasis in the Middle East: Incidence and epidemiology. *PLoS Negl Trop Dis* 2014; **8(10)**:e3208. doi: 10.1371/journal.pntd.0003208.
11. Soleimanifard S, Arjmand R, Saberi S, Salehi M, Hejazi SH. Treatment Outcome of the drug-resistant zoonotic cutaneous leishmaniasis by glucantime. *Adv Biomed Res* 2017; **6**:17. doi: 10.4103/2277-9175.201329.
12. Mohammadzadeh M, Behnaz F, Golshan Z. Efficacy of glucantime for treatment of cutaneous leishmaniasis in Central Iran. *J Infect Public Health* 2013; **6(2)**:120-4. doi: 10.1016/j.jiph.2012.11.003.
13. Rubiano LC, Miranda MC, Muvdi Arenas S, Montero LM, Rodríguez-Barraquer I, Garcerant D, *et al*. Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. *J Infect Dis* 2012; **205(4)**:684-92. doi: 10.1093/infdis/jir816.
14. Chakravarty J, Sundar S. Current and emerging medications for the treatment of leishmaniasis. *Expert Opin Pharmacother* 2019; **20(10)**:1251-65. doi: 10.1080/14656566.2019.1609940.
15. Rahman SB, ul Bari A, Mumtaz N. Miltefosine in cutaneous leishmaniasis. *J Coll Physicians Surg Pak* 2007; **17(3)**:132-5.
16. Ware JM, O'Connell EM, Brown T, Wetzler L, Talaat KR, Nutman TB, *et al*. Efficacy and tolerability of miltefosine in the treatment of cutaneous leishmaniasis. *Clin Infect Dis* 2021; **73(7)**:e2457-e2562. doi: 10.1093/cid/ciaa1238.
17. Iranpour S, Hosseinzadeh A, Alipour A. Efficacy of miltefosine compared with glucantime for the treatment of cutaneous leishmaniasis: A systematic review and meta-analysis. *Epidemiol Health* 2019; **41**:e2019011. doi: 10.4178/epih.e2019011.
18. Tahir M, Bashir U, Ahmed N, Mumtaz J. Electrocardiographic changes with standard dose of meglumine antimoniate therapy in cutaneous leishmaniasis. *Pak Armed Forces Med J* 2021; **71(4)**:1235-38. doi: 10.51253/pafmj.v71i4.4048.
19. Panezai A, Inayat S, Saifullah TD, Habibullah D, Afridi M, Ghani S. ECG manifestations of meglumine antimoniate in treatment of cutaneous leishmaniasis [Internet]. *J Pak Assoc Dermatol* 2020; **30(3)**:382-7. Available from: http://www.jpad.com.pk/index.php/jpad/article/view/1568.
20. 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. *J Parasit Dis* 2018; **42(4)**:616-20. doi: 10.1007/ s12639-018-1044-5.