Research Article

Intralesional Metronidazole (5%) VS Intralesional Meglumine Antimonate in Cutaneous Leishmaniasis

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Abstract

Background: Leishmaniasis is a vector-borne disease that causes skin infections around the world through the bite of sand fly. This leads to the formation of cutaneous leishmaniasis and scars on the area that a cosmetically significant.

Objective: Our study aimed to evaluate the efficacy of intralesional metronidazole (5%) in comparison with intralesional-meglumineantimonate in the treatment of cutaneous leishmaniasis.

Methods: In the current study 40 patients with cutaneous leishmaniasis having upto 3 lesions on either upper limb, lower limb or trunk with a maximum diameter of 3cm in the longest dimension were included in the study and were randomly allocated to either group A (intralesional meglumineantimonate) or group B (intralesional metronidazole). Both treatments were given as intralesional injections on weekly basis, for 12 weeks. Patients were assessed and clinical photographs of the site of treatment were taken on every visit. The response was recorded according to the reduction in the size of the lesion, flattening of the lesion, change in colour, re-epithelialization and disappearance of signs of inflammation. More than 80% improvement to complete resolution of the lesion was considered as a cure.

Results: At the end of 12 weeks of treatment 18 out of 20 (90%) patients in treatment group A (intralesional meglumine antimonite) were cured (mean 1.10, SD 0.308), while15 out of 20 (75%) patients responded to the treatment with intralesional metronidazole (mean 1.25, SD 0.444). Although, group A patients had a better cure rate than group B patients but the response to both treatments was found statistically significant and the p-value was 0.0001.

Conclusion: This study denoted that cutaneous leishmaniasis best responds to intralesional meglumineantimonate butintralesional metronidazole is found to be a safe and effective alternative treatment for this chronic ailment.

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Introduction:

Leishmaniasis is a vector-borne disease caused by unicellular, flagellated, intracellular protozoan of the genus *Leishmania*[1]. It is a group of diseases that clinically presents in three forms (cutaneous, mucocutaneous and visceral leishmaniasis) caused by more than twenty well-known species of genus Leishmania. The human being is infected through a bite of the female sand fly that belongs to genera *Phlebotomus*or *Lutzomyia*, mainly during the night and at outdoor places[2].

Cutaneous leishmaniasis (CL) is the ninth most prevalent skin infection around the world, with an estimated annual incidence of 0.6–1.0 million new cases[3]. CL is an endemic parasitic skin disease with the majority of cases (76%) occurring in seven countries: Afghanistan, Pakistan, Syria, Iran, Iraq, Algeria and Brazil[4]. In 2018, more than 19,000 cases were reported in Pakistan. However, it is estimated that in Pakistan true CL incidence might range between 50,000 and 100,000 casesannually[4]. Leishmania Tropica and Leishmania Major are the main endemic species in all provinces of

Pakistan as well as Azad Jammu Kashmir[5,6]. At the site of sandfly bite, after an incubation period ranging from weeks to months, lesion of CL usually appears as painless, erythematous papule or nodule which may chronically enlarge to form plaques or ulcerating lesions depending upon the immune response of the host and Leishmania species causing the disease. The lesions may heal spontaneously, but they may persist for several months oreven years before complete resolution occurs. Without treatment these sores can develop into chronic disfiguring lesions or swelling of the affected area even the whole limb, causing disability, disfigurement and restriction in daily activities[7]. The sand flies bite mostly on the uncovered body parts and lead to the formation of CL lesions and scars on the areas that are of cosmetic significance, which often causes many psycho-social issues including psychological disturbance, stigmatization, discrimination in family, friends and community for the affected person especially if the person is female or if the lesions are present on the face. So, the lesions on cosmetically and functionally important sites should be treated[6,8,9]. For decades, pentavalent antimonials including meglumineantimonate and sodium stibogluconate both intralesional and intramuscular are the mainstay of treatment for CL[10].

Metronidazole, a drug which was previously known as one ß-hydroxyethyl, 2 methyl and 5 nitroimidazoleis a drug of choice for the treatment of trichomoniasis[11] and also have proven efficacy in giardiasis and amoebiasis. Many studies suggested that Metronidazole (intravenous infusion) hasantileishmanial activity because of the nitro group of nitroimidazoles, which in leishmania got activated by novel nitroreductase and results in the production of reactive nitrogen species, including nitric oxides which have direct lethal effects on the parasite leading to their death[12]. Moreover, it is also postulated that metronidazole may locally interfere with the osmotic pressure and harms the microorganism[13]. Previously, intralesional Metronidazole efficacy in CL has been assessed by many studies but the results are conflicting[5,13-17].

As we know, CL is endemic in many areas of Pakistan including Multan. So, the ideal treatment for this chronic disfiguring ailment must be cheap, non-toxic,easily available, effective and must be able to result in a better cosmetic appearance as compared to natural healing. Pentavalent antimonials which are the mainstay of treatment are expensive, toxic, at risk of resistance with their use in an endemic area and sometimes unavailable. In search of such treatment options for the betterment of mankind and inspired by the work of Vijani N. Somaratne *et al*[15]. We conducted a study in Multan to know the effectiveness of intralesional metronidazole in CL.

Methods:

After taking approval from the Hospital's Ethical Review Board, this single-blinded randomized clinical trial was done in the Dermatology department of Nishtar Hospital, Multan. The study was conducted fora duration of 8 months (August 2020 to April 2021). Informed written consent was taken from all the participants before enrolling them into the study.

Forty patients of which 23 (57.5%) were male and 17 (42.5%) female, aged 15 to 65 years with lesions of CL on the upper limb, lower limb and trunk were enrolled in the study. Only those patients who were newly diagnosed having 1 to 3 lesions with a maximum size of 3cm in the longest dimension were recruited for the study. The patients who were having lesions on the face, joint areas, already taking some other treatment for these lesions, pregnant ladies, breastfeeding mothers as well as those patients who were having concomitant liver or renal impairment, or congestive cardiac failure were not included in the study. Patients with known sensitivity to metronidazole or meglumineantimonate were also excluded.

Diagnosis of CL was made mainly by the history (patients coming from an endemic area, exposure to insect bite, presence of similar lesions in other family members and/or in people living in the surrounding area) and clinical examination (presence of erythematous to violaceous, indurated, crusted, nodular or ulcerated plaques present on exposed body parts). Only in clinically suspected lesions, the LD smear and/ or skin biopsy was taken to confirm the diagnosis. All the information was recorded in a structured proforma designed for this study.

Patients were randomly allocated into two groups regardless of gender and age according to the serial

number. Group A was given intralesionalmeglumineantimonate (inj. Glucantime), while group B was given intralesional metronidazole 5% (the solution wasmade by dissolving 5g powder of metronidazole in 100ml reverse osmosis deionized water, which was then sterilized in the autoclave at 121°C for 20 minutes in screw-capped bottles with rubber caps to allow for sterile injection). Intralesional injections were given weekly upto 12 weeks, by disposable insulin syringes after securing sterility (by cleaning the site of treatment with spirit swab, by using sterile gloves, sterile syringes and needles) in each patient. The lesions were infiltrated with the drug solution until complete blanching of the base of the lesion was reached. About 1ml to 4ml solution depending upon the size of the lesions with no added anesthetic agent was injected into the lesions. The lesions were infiltrated weekly until it cured and/or 12 weeks of treatment completed.

On each visit, clinical photographs were taken. The clinical response was assessed and graded by an investigator who did not give the injections by comparing serial photographs of the lesions with the pretreatment photographs. The response was recorded by subjective improvement in the size of the lesion, flattening of the lesion, change in colour, re-epithelialization and disappearance of signs of inflammation. More than 80% improvement to complete resolution of the lesions was considered asa cure. Side-effects were also recorded for each group. The data collected from the patients were analyzed through SPSS version 21. The frequencies, percentages, mean and standard deviation were used to describe the data. A t-test was used to check the effectiveness of treatments given to both groups at a 5% level of significance.

Results:

The results are summarized in table 1 and table 2.

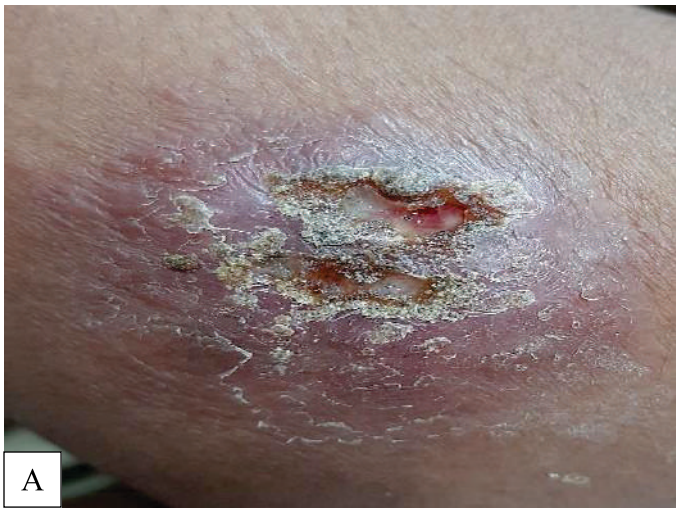
About seventy patients came to the outpatient department with CL, of which sixty-five gave consent. Twenty-five were excluded depending upon exclusion criteria. The current study included forty patients which include 27 (57.5%) males and 17 (42.5%) females, aged between 15 to 65 years with a mean of 34.35 and S.D 17.06. All the enrolled participants have successfully completed the study and not a single participants dropped out during study. Most of the patients (97.5%) were residents of Multan and were predominantly living in areas of Dolat Gate (9, 22.55%), Double Phatak (5, 12.5%), Timber market (5, 12.5%), Haram gate (3, 7.5%) and ShahiQila (3, 7.5%).87.5% of patients had a history of similar lesions either in members of the family and/ or in persons living in the same locality.

The characteristics of the lesions are described in table 1.

In group A,18 (90%) out of 20 patients with CL responded to the treatment with intralesional meglumineantimonate. Lesions in 6 (30%) cases responded to treatment and healed in 6 weeks, lesions in 8 (40%) patients responded to the treatment in 10 weeks, while it took 12 weeks for 4(20%) cases to cure (Table 2). The mean and S.D of treatment response in Group A is 1.10±0.308.

For those who were treated with intralesional metronidazole 5% solution, the response rate was 75% (15 out of 20 patients). In a duration of 6 weeks, one (5%) patient responded to the treatment, the lesion was completely healed and in 6 (35%) patients lesions responded to the treatment in 10 weeks. 40% (8 out of 20) cases responded and were cured in 12 weeks with group B treatment (table 2). The mean and S.D of treatment response in Group A is 1.25±0.444.

Patients of both groups experienced pain and post-inflammatory hyperpigmentation equally, a single patient in group A had a local inflammatory reaction in the form of redness and swelling which settled over 7 to 8 days. No systemic side effects were reported with either treatment. We applied-test to check the efficacy of treatments given to Group A and Group B and obtained a p-value of 0.0001. It denotes the fact that although int-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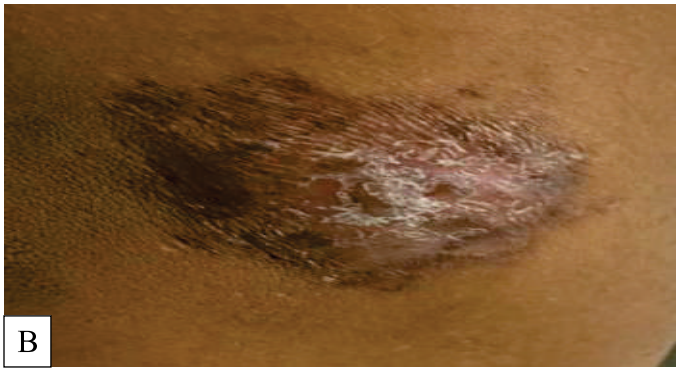

Fig. 1: *A 28- year-old male patient with CL at forearm for six monthstreated with intralesionalmeglumine antimonite (Group A) A: Before treatment, B: 12 weeks after treatment*

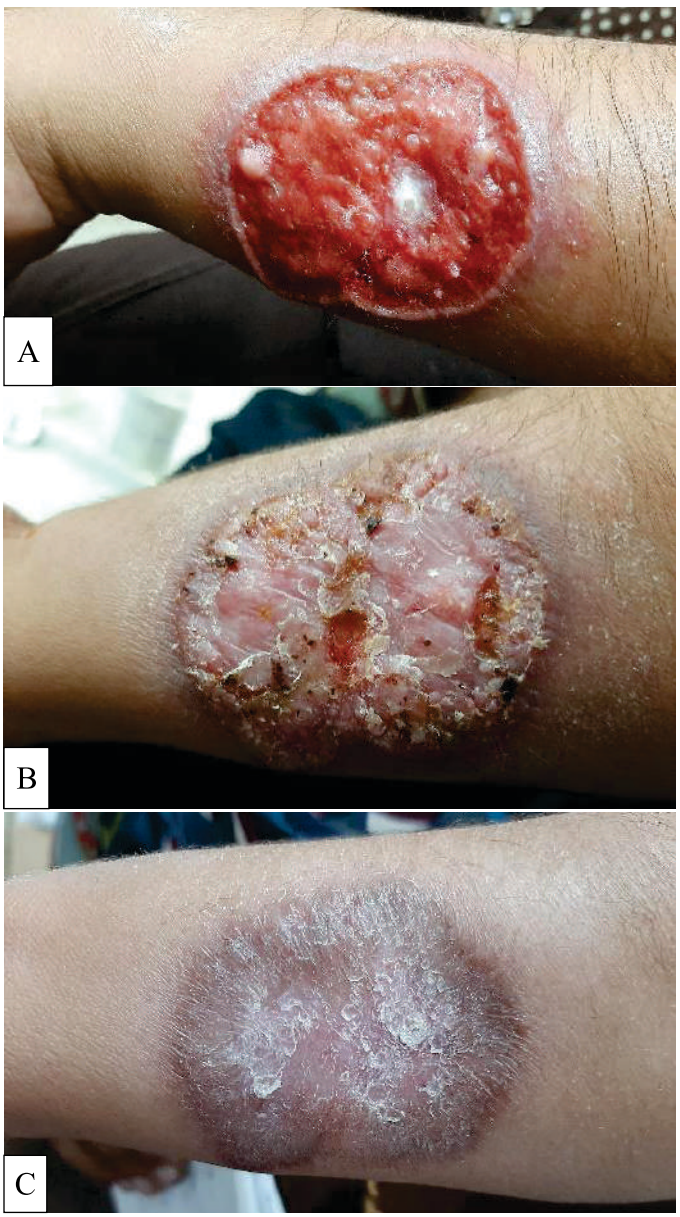

Fig. 2: *A 30- year-old female patient with CL at the forearm for six monthstreated with intralesionalmetronidazole(Group B) A: Before treatment, B: 8 weeks after treatment, C: 12 weeks after treatment.*

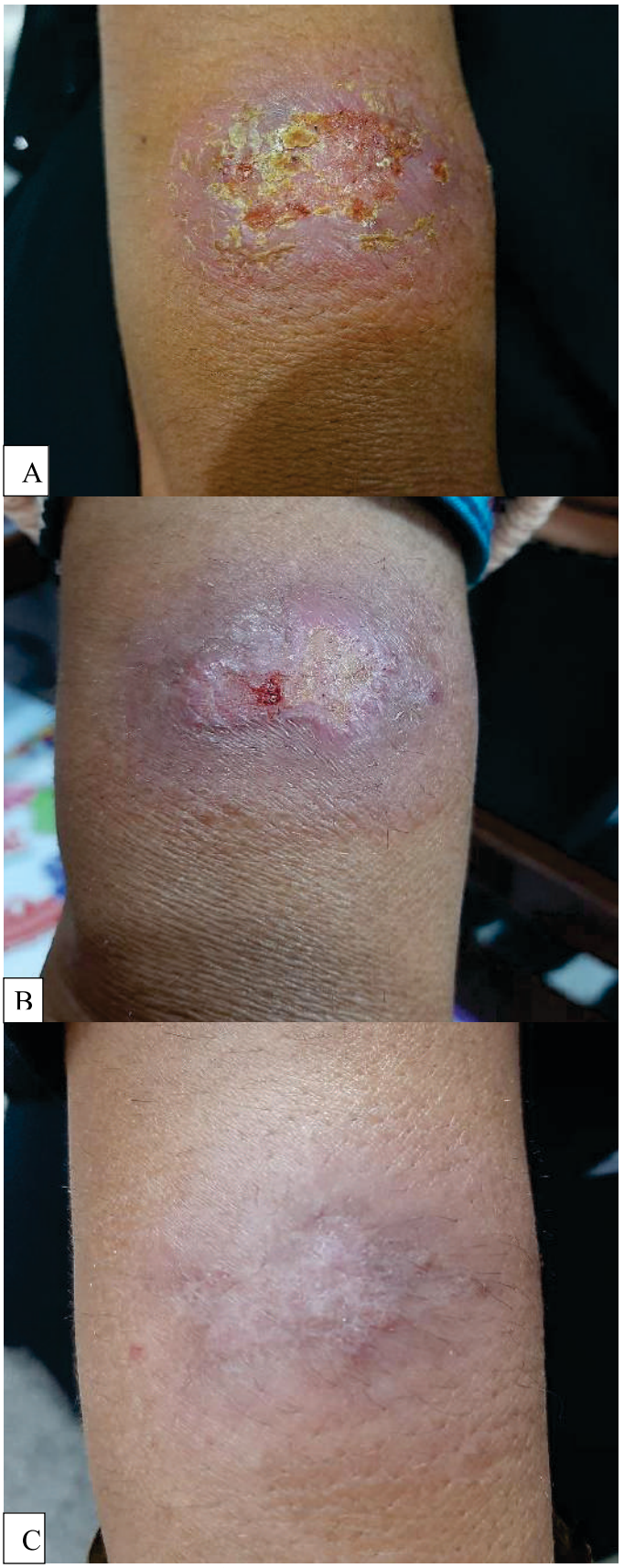

Fig. 3: *A 36-year-old female patient with CL at the forearm for six monthstreated with intralesionalmetronidazole (Group B) A: Before treatment, B: 8 weeks after treatment, C: 12 weeks after treatment.*

Table 1: *Characteristics of Lesions*

Variable		Frequency	Mean±S.D
Disease Duration	1 -5 months	22(55%)	6.13±3.16
	6-10 months	14(35%)	
	≥ 10 months	4(10%)	
Site of lesion	Trunk	4(10%)	2.1±0.56
	Upper Limb	27(67.5%)	
	Lower Limb	9(22.5%)	
Number of lesion	1	29(72.5%)	1.4±0.82
	2	3(7.5%)	
	3	8(20%)	
Type of lesion	Ulcerative type	14(35%)	2.53±0.72
	Dry-type	26(65%)	

ple factors; women have more social barriers to seeking health care, females are usually more covered with clothes than males, even indoors, males are usually more exposed to bites because of having the habit of floor bedding when they reside on workplaces, where they came from other cities to earn living. In a study of Baluchistan[17], median age of patients was 48 years while in our study median age was 34 years. Most of the patients had a single lesion (72.5%) and the most affected site was upper limbs (67.5%) which was found similar to the older studies[5,15,16]. Dry-type (65%) of lesions were the commonest presentation in our patients, similarly, a study of the same country by Suzette Kämink *et al*[17] have

Table 2: *Duration of the desired outcome versus response to treatment in Group A& Group B*

	Treatment Response	Duration of the desired outcome (weeks) 6	8	10	12	P-value
Group A	Yes	6(30%)	4(20%)	4(20%)	4(20%)	0.0001
	No	0	0	0	2(10%)	
Group B	Yes	1(5%)	1(5%)	5(25%)	8(40%)	0.0001
	No	0	0	0	5(25%)	

ralesional meglumineantimonate is more effective to cure CL, but intralesional metronidazole is also safe and effective alternative for the treatment of CL (fig: 1, fig: 2 and fig: 3).

Discussion:

Cutaneous leishmaniasis is an endemic disease in many areas of Pakistan including Multan. Ayazet al.[18] has documented that 198 diagnosed cases of cutaneous leishmaniasis were reported in Multan between June 2015 to September 2016 which was higher in number than the previous studies conducted in the same area. While in our study between August 2020 to April 2021 about seventy patients visited the tertiary care hospital of Multan. The difference between studies is due to the difference in the demographics. First, in the former study patient who came in all clinical laboratories, health care providers and union councils were included while in our study we counted only those who came to Nishtar Hospital. Second, due to the COVID-19 pandemic lesser number of patients have seen medical personal due to the ben-ign nature of the disease.

In our study population, there were more males than female patients like many other comparable studies of Pakistan[5,16,17]. This difference may be because of multi-

documented more patients with the dry type of lesions (56.6% plaque, 19.7% nodule %) than ulcerative type (23.7%). While ulcerative type was the predominant lesion type in studies of Sri Lanka.[14,15]This difference in lesion types may be due to the prevalence of different species of leishmaniain different areas.

For this cutaneous, chronic disfiguring ailment many treatment modalities are present and among these pentavalent antimonials, both intralesional and systemic are the mainstay of treatment.[10] Although the efficacy of the drug is proven, the toxic effects of its systemic use are so high that it cannot be used as a safe treatment option[21]. The same problem happens when it is given in intralesional form on larger lesions where the total amount of given drug becomes equivalent to its systemically given concentration, so the systemic side effects may be the problem. As the disease is endemic in this regionso, resistance to the drug may also occur. One other major obstacle to the treatment with the pentavalent antimonials is their availability and cost of the treatment. To overcome these problems, it is necessary to develop newer and cheaper treatment modalities.

Metronidazole is being used both in oral and intralesional form for the treatment of cutaneous leishmaniasis

but the role of Metronidazole remains controversial[13-15,18-20,22,23]. Therefore, we decided to evaluate the efficacy of intralesional metronidazole in the treatment of cutaneous leishmaniasis in our patients and we found satisfactory results as 75% of the patients were cured. The efficacy and safety of the metronidazole are found to be in concordance with multiple previous studies. A study conducted by Vijani N. Somaratne *et al*[15] has documented the effectiveness of treatment with intralesional metronidazole by healing 76% lesions of CL. Similarly, an old study in which 1% intralesional metronidazole was given in the lesions of CL has showna cure rate of 75%[13]. Al waiz *et al.*[18] have used two different concentrations of intralesional metronidazole in the treatment of CL 0.5% and 5% and both concentrations documented a role in the reduction of the sores with 85% and 87% clearance rates respectively.

Studies conducted by some authors did not support the efficacy of intralesional metronidazole. A study of Sri Lanka[14], in which 53 patients were given intralesional pentavalent antimonial and 47 were treated with intralesional metronidazole for a duration of 8 weeks and reviewed at an interval of 12 weeks for assessment of the response; 39.6% of the pentavalent antimonial group and 14.8% of metronidazole treated patients showed complete cure at 12 weeks. This cure rate further increased to 66.03% and 29.78% at 24 weeks of treatment, respectively and this difference in cure rate was significant statistically. Similarly, the studies of Iran[19] (16.6% cure rate with intralesional metronidazole treatment) and Iraq[18] have revealed that the intralesionalmetronidazole has a little effect on CL lesions which is statistically insignificant. This difference in response may be due to various reasons. First, the use of different concentrations of drugs; in the studies of Iran and Iraq a standard preparation of the metronidazole 0.5% was injected in lesions while in ours 5% metronidazole solution was prepared and injected. Second, geographical variations and the occurrence of different parasite species in different areas which may respond differently to the drug can be the reason.

All the previous studies which were conducted to know the efficacy of intralesional metronidazole in the treatment of CL have no documented side effects[13-15,18-20]. Similarly, in our study, no local or systemic side effects were noticed with its use. Injection of meglumineantimonate (inj. Glucantime 5ml) costs 1000 rupees or more depending upon its availability and sometimes it is unavailable. Comparatively, metronidazole powder is very cheap and its 5% solution (100ml) is easy to prepare and can be used for a period of 30days.

So, the current study signifies that intralesional metronizdazole can be used as a drug alternative to intralesional antimonials in the treatment of CL as the treatment with it is safe with no serious side effects, gives high cure rate that caused healing in about 75% patients, it is easily available and cost of the therapy with it is very low. From a practical point of view, it is a better treatment option for CL because of its cost effectiveness.

There are a few limitations to the study; First, we did not isolate the species of leishmania on culture. If parasite species vary the response to the given treatment may also fluctuate. Second, the majority of the patients had a single lesion on the body so, we did not have control lesions to consider the possibility of spontaneous healing which is well known in the lesions of CL. The COVID-19 pandemic effected the patients' turnover at our hospital and a lesser number of patients visited the hospital, hence a small number of patients were included in the study.

Further studies with a larger sample size should be conducted to better analyze the efficacy of metronidazole in the treatment of CL.

Conclusion:

Although, the response to treatment with intralesional metronidazole is slower and effectiveness is less than the intralesional meglumineantimonate but the cure rate is statistically significant. This study revealed that intralesional metronidazole can be used as an effective alternative for the treatment of CL.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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