

# Comparison of Injection Meglumine Antimoniate with a Combination of Injection Meglumine Antimoniate and Carbon Dioxide Fractional Ablative Laser in Treatment of Cutaneous Leishmaniasis

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## ABSTRACT

**Aim:** To see the efficacy of meglumine antimoniate alone in comparison with combination of meglumine antimoniate and CO<sub>2</sub> ablative laser among patients with cutaneous leishmaniasis.

**Study design:** Quasi-experimental study.

**Place and duration of study:** Department of Dermatology, Pakistan Emirates Military Hospital, Rawalpindi from 9<sup>th</sup> July 2020 to 8<sup>th</sup> January 2021.

**Methodology:** Sixty patients (30 in each group) diagnosed cases of cutaneous leishmaniasis by skin biopsy or slit skin smear were enrolled. In group A; intramuscular injection of meglumine antimoniate (dose 20 mg/kg daily) was administered for 28 days and group B was treated with intramuscular meglumine antimoniate injection along with fractional CO<sub>2</sub> ablative laser. Standard digital photography was done before start of treatment and then every 2 weeks.

**Results:** Efficacy of meglumine antimoniate alone was observed in 60% of patients while it was 86.7% when combined with fractional CO<sub>2</sub> ablative laser. Better outcome was observed when such patients were treated with both meglumine antimoniate and fractional CO<sub>2</sub> laser. Efficacy was measured after 6 x weeks in all patients of both groups.

**Clinical Implication:** Hence CO<sub>2</sub> lasers are latest modality of treatment with minimal side effects and can be used in treatment of patients with cutaneous leishmaniasis.

**Conclusion:** Efficacy of meglumine antimoniate plus fractional CO<sub>2</sub> laser found to be higher as compared to meglumine antimoniate alone in treating cutaneous leishmaniasis.

**Keywords:** Cutaneous leishmaniasis, CO<sub>2</sub> fractional ablative laser, Meglumine antimoniate, Slit skin smear

## INTRODUCTION

Cutaneous leishmaniasis is a protozoal skin disease, caused on by bite of an infected female sand fly of genera phlebotomus, which usually results in a long-lasting skin ulcer and sometimes to erosive mucosal and visceral disease. Skin lesions appear on visible parts of the body few weeks to quite a few months of the sand fly bite and present as erythematous papule that enlarges to become a nodule. The lesions which may be multiple are crusted with raised margins showing induration. Self-resolution may occur within months to unspecified years leaving unsightly atrophic scars<sup>1</sup>.

Severity of disease depends on species of parasite, host immune status, area of endemicity, socioeconomic status of patient and accessibility to health care facilities<sup>2</sup>. The disease is a rising epidemic in certain areas of Pakistan like Balochistan and Khyber Pakhtunkhwa. The frequency has been estimated at 2.7% in the northern western part of Pakistan with occurrence of 4.6 cases/1000 persons/year over the previous 10 years<sup>3</sup>.

Diagnosis is made clinically most of the times in endemic areas but other diagnostic tools like slit skin smear, tissue biopsy for histology and culture are in practice as well.<sup>4</sup> A high index of suspicion for this disease should be considered especially in a newly endemic area. All above mentioned diagnostic tests become helpful to differentiate it from clinical and histological look-alikes.<sup>5</sup>

Many treatments have been suggested but pentavalent antimony compounds are the first line therapy for cutaneous leishmaniasis for quite a few years. Their results are still not promising with treatment failure rate of 10-15%<sup>6</sup>.

In Pakistan the main drug used in cutaneous leishmaniasis management is meglumine antimoniate which is a pentavalent antimony compound. Exact mechanism of action is still not known

but it is thought to encompass inhibition of parasites glycolytic and fatty acid oxidative activity resulting in decreased antioxidant defense and synthesis of adenosine triphosphate which is the main source of energy to be used for the survival of parasite. Diminished energy production eventually leads to the death of the protozoa. Duration of treatment with meglumine antimoniate is 28 days on average given as intramuscular injection in a dose of 10-20 mg/kg body weight. This treatment may be continued till clinical cure. Extensive range of monitoring is required with this drug for cardiac, liver and renal complications. Main side effects are arthralgias, vomiting, fever, fatigue, arrhythmias due to QT prolongation, anemia, thrombocytopenia, pancreatitis and deranged hepatic and renal profile<sup>7</sup>.

Dermatotropic leishmania species replication is decreased at high temperatures so hyperthermia can be used to enhance effectiveness of drugs used when combined with it.<sup>8</sup>

Lasers were used for treatment of several skin diseases since 1970 and ablative CO<sub>2</sub> lasers are now being used for treatment of cutaneous leishmaniasis. Mentioned treatment has shown negligible side effects with better cure rate<sup>9</sup>.

In a study, efficacy of injection meglumine antimoniate with CO<sub>2</sub> ablative laser was found to be 87.0% and injection meglumine antimoniate alone as 38.5% in patients of cutaneous leishmaniasis<sup>10</sup>. With the addition of fractional CO<sub>2</sub> ablative lasers the duration of treatment can be shortened with meglumine antimoniate and degree of scar formation can be decreased.<sup>11-13</sup>

In a study by IMJ, comparison was done between fractional CO<sub>2</sub> (group A) and Er: YAG (group B) for treatment of cutaneous leishmaniasis and cure rates were 95.5% and 93.2% respectively<sup>14</sup>. In another study by Irai et al, CO<sub>2</sub> laser was combined with topical 50% TCA has been found more effective in treatment of the cutaneous leishmaniasis and results in shorter recovery time<sup>15</sup>.

The focus of study is to observe the cumulative effects of CO<sub>2</sub> lasers with meglumine antimoniate in cutaneous leishmaniasis

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and to devise a new treatment strategy. The data showing comparative studies between injection meglumine antimoniate with fractional CO<sub>2</sub> ablative laser and injection meglumine antimoniate alone are lacking in this part of the world where the disease is endemic.

## MATERIALS AND METHODS

This quasi-experimental study was conducted at department of dermatology, Pakistan Emirates Military Hospital Rawalpindi from 9<sup>th</sup> June 2020 till 8<sup>th</sup> January 2021. Sample size was calculated by the following formula using WHO calculator: A sample size of sixty cases (30 in each group) was calculated with 80% power of test, 5% level of implication and probable percentage of success (P1) 87.0% and (P2 38.5%).<sup>6</sup> Sampling technique was Non-probability, Consecutive sampling. The diagnosed cases of cutaneous leishmaniasis clinically by presence of erythematous papules, nodules, or plaques with or without central crust/ ulcer and histologically by the presence of amastigotes in slit skin smears and skin biopsy taken from skin lesions were included. Patients with age ranging from 15 to 40 years of both genders, duration of lesions for less than 3 months and size of lesion  $\leq$  3cm and number of lesions  $\leq$  3 were included. Pregnant females, lactating mothers and patients on immunosuppressive therapy and history of use of some other medication for leishmaniasis were excluded. Individuals found allergic to pentavalent antimony compounds after test dose of intradermal injection meglumine antimonate or developed serious side effects like cardiac arrhythmias during treatment with injection meglumine antimonate were excluded from study.

After authorization from institutional ethical review committee, 60 patients, fulfilling the inclusion standards were selected. Informed consent was taken from every patient and demographic details were recorded. ECG, blood complete picture, liver function test and renal function test were carried out before start of treatment then every week for four weeks. In Group A, intramuscular injection meglumine antimoniate (meglumine antimoniate; Specia, France) was given in a dose of 20mg/kg daily for 28 days after test dose. While in Group B intramuscular injection of meglumine antimoniate was combined with fractional CO<sub>2</sub> ablative laser (Qray FRX, DOSIS M&M, South Korea) with all-out power and constant wave mode after giving local anesthesia with injection 2% lignocaine. The lesion was ablated with CO<sub>2</sub> laser including 2-3mm of surrounding normal skin. After the first ablation, the surface of the lesion cleansed with normal saline soaked gauze and then second ablation was done. Ulcer was ultimately covered with fusidic acid ointment dressing after the procedure. single laser treatment session was given to patients along with intramuscular injection meglumine antimoniate daily for 28 days.

Patients in both groups were followed up 2 weekly for 6 weeks. Monitoring was done by weekly blood complete picture, liver and renal profile and ECG to rule out anemia, thrombocytopenia, deranged hepatic and renal profile and arrhythmias respectively. Standard digital photographs using same camera settings, lighting and patient positioning was taken before start of treatment and then after every two weeks. Efficacy was assessed at 6 weeks duration of treatment and clinical response was labelled as complete improvement if there was resolution of erythema, induration, papules, plaques nodules and absence of amastigotes in slit skin smear. All findings were recorded on pre-designed proforma. SPSS-25 was used for data entry and analysis. Chi-square was applied to compare the efficacy between two groups. P value was considered significant if  $\leq$ 0.05.

## RESULTS

The average age of patients in Group A was 27.1 $\pm$ 5.8 while it was 28.2 $\pm$ 4.7 in group B. A total 41 patients were aged  $\leq$ 30 years while 19 patients rest were  $>$ 30 years of age. It was observed that 100% patients in both groups were males. Mean duration of disease was compared between two groups and results are shown in Figure 1. Mean size of lesion among group A was found to be 2.1 $\pm$ 0.8 cm and in group B as 1.9 $\pm$ 0.8 cm with a range of 1-3 cm. The mean number of lesions in group-A and Group B were 2.0 $\pm$ 0.6 and

1.4 $\pm$ 0.5 respectively and majority of the patients were having 2 numbers of lesions in both groups.

Efficacy of both treatment strategies were compared and shown in table 1 and end of treatment results recorded via digital photographs as shown in figures 2 and 3. Age as an affecting factor was also compared among two treatment groups as shown in table 2. Duration of disease as affecting factor is compared for both groups and results are shown in table 3. Size of lesions when compared of both groups, an insignificant difference was observed (p-value  $>$ 0.05) in patients having 1 cm size of lesion while a significantly higher treatment outcome (p-value  $<$ 0.05) in group B was observed in patients having 2-3 cm size of lesions. With respect to number of lesions, a significant difference of group B treatment was observed (p-value  $>$ 0.05) in patients having 1 lesion while insignificant differences (p-value  $>$ 0.05) were observed in patients having 2-3 lesions.

Table 1: Comparison of efficacy in both groups (n=60)

Efficacy	Group-A [n=30]	Group B [n=30]
Yes	18 (60%)	26 (86.7%)
No	12 (40%)	4 (13.3%)

Chi square = 5.455 P value = 0.020

Table 2: Stratification for age with regard to efficacy

Age (years)	Group	Efficacy		Total	P value
		Yes	No		
$\leq$ 30	Group A	13	9	22	0.029
	Group B	17	2	19	
<b>Total</b>		<b>30</b>	<b>11</b>	<b>41</b>	
31 – 40	Group A	5	3	8	0.345
	Group B	9	2	11	
<b>Total</b>		<b>14</b>	<b>5</b>	<b>19</b>	

Table 3: Stratification for duration of disease with regard to efficacy

Duration (months)	Group	Efficacy		Total	P value
		Yes	No		
1	Group A	9	3	12	0.829
	Group B	11	3	14	
<b>Total</b>		<b>20</b>	<b>6</b>	<b>26</b>	
2	Group A	9	9	18	0.005
	Group B	15	1	16	
<b>Total</b>		<b>24</b>	<b>10</b>	<b>34</b>	

Fig. 1: Distribution of patients by duration of disease

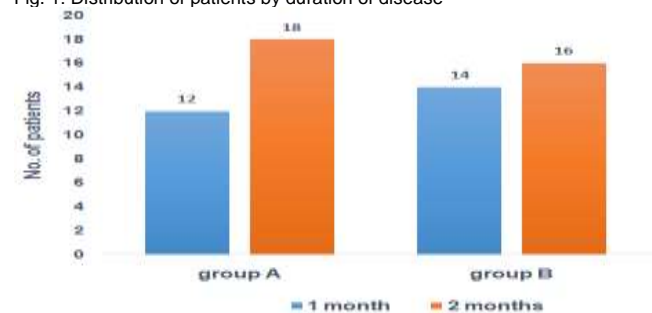


Fig. 2: Cutaneous leishmaniasis over volar aspect of wrist before (a), immediate (b) and after 4 weeks (c) of CO<sub>2</sub> ablative laser plus 4 weeks of IM inj Meglumine antimoniate treatment



## DISCUSSION

In Pakistan amongst the available therapeutic options, Antimony compounds remain the preferred treatment but extensive monitoring is required with this drug due to its adverse effects leading to cardiac, liver and renal complications. Due to side effects associated with pentavalent antimonial compounds, multiple other agents have been combined with them increasing the cure rate and minimizing the adverse events<sup>16,17</sup>.

As leishmania species are heat sensitive and are killed at higher temperatures so CO<sub>2</sub> ablative lasers are now being used for cutaneous leishmaniasis. This laser emits an energy at 10600nm, which is absorbed by water leading to tissue vaporization (>100°C) in the center and tissue coagulation in the periphery (>60°C). In a recent study by Zaib et al<sup>1</sup> reported between effectiveness of ablative CO<sub>2</sub> laser (Group A) alone versus combination of cryotherapy and intralesional meglumine antimoniate (Group B) in patients of cutaneous Leishmaniasis. Overall efficacy after 08 weeks was 79.4 % and 73.5% respectively showing more cost effectiveness and better tolerability with CO<sub>2</sub> ablative laser.

Jaffary et al<sup>3</sup> reported that patients with CL were divided into three groups. Group A was given intralesional injection meglumine antimoniate, group B was given treatment with intralesional meglumine antimoniate plus CO<sub>2</sub> ablative laser and group C was given intralesional meglumine antimoniate with topical 50% trichloroacetic acid. Complete recovery was seen in 38.5% patients in group A, 90% in group B and 87% in group C.

Combination therapy of injection meglumine antimoniate with CO<sub>2</sub> ablative laser or topical trichloroacetic acid showed better results than with injection meglumine antimoniate alone.<sup>15</sup>

Osman et al<sup>18</sup> in their study evaluated the efficacy of CO<sub>2</sub> ablative laser in the treatment of cutaneous leishmaniasis in a group of 10 Sudanese patients reported that the majority of the patients (8 out of 10) had either a complete or very good improvement by the end of follow up at 08 weeks duration. Pain occurred post-operatively in all patients, while edema, infection and hypo/ hyperpigmentation occurred in only two patients. These side effects were trivial and disappeared a few days after treatment. In the present study, efficacy of meglumine antimoniate alone was in 60% of patients while efficacy of meglumine antimoniate plus fractional CO<sub>2</sub> ablative laser was 86.7%. Recovery was more in group B patients who received CO<sub>2</sub> ablative laser along with injection meglumine antimoniate as compared to meglumine antimoniate alone. Side effects were pain at injection site which was managed by oral and topical analgesics and four patients developed mild anaemia (Hb around 10gm/dl) and decreased platelets count (around 100 x10<sup>9</sup>/L). Patients were observed clinically and by repeating blood complete picture on twice weekly basis. Side effects in group B also included pain during CO<sub>2</sub> laser and hyperpigmentation after healing.

Efficacy of treatment groups was assessed in present study with reference to age groups and recovery was found to be complete in 25 patients (p-value <0.05) in group A with age group of ≤30 years whereas it was seen in 13 patients with age group >30 years. Duration of disease was also assessed as an affecting factor and no significant difference in efficacy was noted. Complete recovery in patients was higher with 1 month's disease duration as seen in 17 patients as compared to be in 9 and 12 patients with disease duration of 2 and 3 months respectively. Similarly Size and number of lesions were also assessed as factors affecting the treatment outcomes but no significant differences were found. Overall patient's recovery was significantly higher in group B patients who received treatment with CO<sub>2</sub> ablative laser with injection meglumine antimoniate as compared to injection meglumine antimoniate alone. Hence CO<sub>2</sub> lasers are latest

modality of treatment with minimal side effects and can be used in treatment of patients with cutaneous leishmaniasis.

**Ethical consideration:** Permission was granted by ethical committee

## CONCLUSION

Efficacy of meglumine antimoniate alone was very low as compared to the efficacy of meglumine antimoniate plus fractional CO<sub>2</sub> laser. Higher age, more than one lesion in a patient and size of lesion were the factors associated with poor outcomes of meglumine antimoniate alone while addition of fractional CO<sub>2</sub> covers all the factors, affecting efficacy.

**Conflict of interest:** Nil

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