Comparison of Intralesional Meglumine Antimonite along with oral Itraconazole to Intralesional Meglumine Antimonite in the treatment of Cutaneous Leishmaniasis

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ABSTRACT
Background & Objective: Cutaneous leishmaniasis (CL) is endemic in developing countries like Pakistan. Pentavalent antimonials are still drug of choice, despite being toxic and intolerable for patients. Second line treatments have been extensively studied but the results of their efficacy are conflicting. This, to our knowledge, will be the first study in this regard. Our objective was to determine if combination of oral itraconazole with intralesional (IL) meglumine antimoniate (MA) reduces the duration of treatment for cutaneous leishmaniasis, as compared to intralesional MA alone.

Methods: A randomized controlled trial (single blinded) was carried out from August 2017 till December 2017 on 69 patients who fulfilled inclusion criteria. They were assigned to Group-A or B by lottery method. Group-A patients received IL MA once a week while Group-B received oral itraconazole 200mg, once daily, for six weeks along with similar regimen of IL MA as Group-A. The patients were assessed every three weeks by the blinded assessor till clinical cure was achieved. A follow up visit, two months after clinical cure was done to look for relapse of the disease.

Results: Thirty patients in Group-A and 35 patients in Group-B completed the study. At 3, 6, 9 and 12 weeks the patients were assessed for: no, partial or complete response and results of the two groups were compared for statistical significance. The p-values of 0.20, 0.57 and 0.11 at 3, 6 and 9 weeks, respectively, depict that there was no significant difference at any step of assessment between the two groups in terms of healing. The p values of each t test was >0.05 refuting the hypothesis.

Conclusion: Combination of oral itraconazole with intralesional MA offered no benefit over intralesional MA alone in the management of cutaneous leishmaniasis in terms of duration of therapy.

KEYWORDS: Cutaneous leishmaniasis, Itraconazole, Intralesional meglumine antimoniate.

Abbreviations Used: IL = Intralesional, MA = Meglumine Antimoniate, LD = Leishmania Donovan, CL = Cutaneous leishmaniasis, CMH = Combined Military Hospital.

doi: https://doi.org/10.12669/pjms.35.6.363
How to cite this:
Bashir U, Tahir M, Anwar MI, Manzoor F. Comparison of Intralesional Meglumine Antimonite along with oral Itraconazole to Intralesional Meglumine Antimonite in the treatment of Cutaneous Leishmaniasis. Pak J Med Sci. 2019;35(6):1669-1673.
doi: https://doi.org/10.12669/pjms.35.6.363

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INTRODUCTION

Cutaneous Leishmaniasis (CL) is a neglected protozoal disease with a worldwide incidence of around 1.5 million cases per year according to World Health Organization.¹ It is currently a serious public health problem in developing countries like Pakistan where the incidence is on the rise due to immigrants across the country,² military deployments, humanitarian aid workers and
expanding infrastructure in the endemic areas.\textsuperscript{2,3} It is caused by more than 20 species of Leishmania, the vector in old world being Phlebotomus sand fly. Humans are accidental hosts and can act as reservoir of infection. It is recommended that all patients infected with CL should be treated to reduce the prolonged course of disease, to reduce scar formation and to eliminate the reservoir of infection.\textsuperscript{4} Management of CL is still being done with pentavalent antimonials despite being toxic and intolerable for most patients. The search for safer oral alternatives that would lead to an early cure of the disease and elimination of amastigotes in human reservoirs has led to a range of second line treatments includingazole antifungals, miltefosine, dapsone, imiquimod, azithromycin etc.

The role of itraconazole has been specifically proven of benefit, as a second line treatment, in CL in old world.\textsuperscript{4} For lesions that do not qualify of cure of the disease and elimination of amastigotes in human reservoirs has led to a range of second line treatments includingazole antifungals, miltefosine, dapsone, imiquimod, azithromycin etc.

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The decision to shift a patient, if any, to systemic antimonials also lied with the assessor. The patients were reviewed for follow up by the assessor two months after treatment ended to rule out relapse, defined by recurrence of induration/erythema in the scar.

**Statistical analysis:** The results were analyzed by SPSS version 23.

**RESULTS**

Between 1st August till 30th December, 2017, 114 patients were screened positive for cutaneous leishmaniasis. Of these, 69 (95% confidence level and 7.4% confidence interval) patients who filled our inclusion criteria were included in the study. However, within the first two weeks three patients were shifted to systemic antimonial treatment due to development of newer lesions or sporotrichoid spread and one patient withdrew from the study due to his deployment in another city. Among the 65 patients, 30(46.2%) completed the trial in Group-A and 35 patients (53.8%) in Group-B. 64 (98.5%) were males and one (1.5%) was female. All the males (64) were soldiers deployed in various regions of Balochistan while the female was a resident of Quetta. There was no statistically significant difference in demographic characteristics and lesion features (location and mean size of lesions) between the two groups at the start of treatment. The lesions on lower limb were most common (47.7%) in both the groups while those on trunk were least (7.7%). The mean duration of lesions in Group-A was 4.46 weeks (SD ± 1.16) while in Group-B it was 4.65 weeks (SD ± 1.10). The mean size of lesions in Group-A was 3.87 cm ± 1.2 SD, while in Group-B it was 3.71 cm ± 1.02 SD.

On assessment of treatment response for both the groups at 3, 6 and 9 weeks the p-values of 0.20, 0.57 and 0.11 respectively, depict that there was no significance difference at any step of assessment between the two groups in terms of healing. The lesions showed complete clinical cure on 12th week assessment in both groups, it reached 100% by once a week regimen, hence no ‘t scores’ could be obtained for that assessment. All the patients completed the duration of treatment till cure in both the groups and came for follow up around two months after being declared cured. No patient in either group had to stop treatment because of any side effects. Minimal to no derangement in S. LFTs was observed in Group-B and their treatment was not withhold. There was no difference in the

| Table-I: Group comparison on treatment response at three weeks’ assessments. 1= No response, 2=Partial response, 3= Complete response. | Treatment group | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Response at 3 wks. | A | 30 | 1.07 | 0.254 | 0.046 |
| Response at 3 wks. | B | 35 | 1.17 | 0.382 | 0.065 |
| Response at 6 wks. | A | 28 | 1.93 | 0.262 | 0.050 |
| Response at 6 wks. | B | 35 | 1.89 | 0.323 | 0.055 |
| Response at 9 wks. | A | 30 | 2.07 | 0.254 | 0.046 |
| Response at 9 wks. | B | 34 | 2.21 | 0.410 | 0.070 |
| Response at 12 wks. | A | 28 | 3.00 | 0.000a | 0.000 |
| Response at 12 wks. | B | 34 | 3.00 | 0.000a | 0.000 |

a. t cannot be computed because the standard deviations of both groups are 0.

| Table-II: Independent sample t-test scores for both groups at 3-weekly assessment. | Levene’s Test for Equality of Variances | t-test for Equality of Means |
|---|---|---|---|---|---|
| | F | Sig. | t | df | Sig. (2-tailed) | 95% Confidence Interval of the Difference |
| | | | | | Lower | Upper |
| Response at 3 wks. | Equal variances assumed | 7.308 | 0.009 | -1.278 | 63 | 0.206 | -0.269 | 0.059 |
| Response at 6 wks. | Equal variances not assumed | -1.317 | 59.494 | 0.193 | -0.264 | 0.054 |
| Response at 9 wks. | Equal variances assumed | 1.331 | 0.253 | 0.568 | 61 | 0.572 | -0.108 | 0.194 |
| Response at 12 wks. | Equal variances not assumed | 12.190 | 0.001 | -1.606 | 62 | 0.113 | -0.313 | 0.034 |

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characteristics of scar formation, as observed by the assessor, between the two groups. There was no recurrence of lesions on 18th week follow up in both the groups, hence there was no edge of one treatment over another in this regard.

**DISCUSSION**

Cutaneous leishmaniasis of old world is endemic in Pakistan. The areas especially affected are Balochistan, Khyber Pakhtunkhwa and Waziristan, however, incidences occur in interior Sindh, Kashmir and urban cities like Multan.\(^3\)\(^-\)\(^8\) Parenteral antimonials, mostly meglumine antimoniate, remain the cornerstone of treatment. The MA injections are toxic and intolerant for most patients due to pain at injection site, fever and arthralgias. There is a need for more effective, less time consuming and tolerable treatment modality for this disease.\(^9\)

Alternatives have been extensively studied and reported but the results are conflicting for some modes of treatment.\(^10\)\(^-\)\(^11\) The studies on efficacy of intralesional MA as compared to IM injections of MA, established that both are equally effective in achieving cure\(^10\) while MA is more effective (82%) than Sodium stibogluconate (67%) when given IL.\(^12\)

Cryotherapy, carbon dioxide laser, thermotherapy, paromomycin cream, zinc sulphate as intralesional injections have been used with variable success rates.\(^9\)\(^-\)\(^13\)\(^-\)\(^15\) The role of oral azole therapy, specifically itraconazole, in systemic treatment is also very well established.\(^16\)\(^-\)\(^18\) Despite being effective, there is not enough evidence to support the exclusive use of azoles as a single treatment mode in leishmaniasis.\(^19\)

The outcome of interest in these studies, like in our study, was an early clinical cure, defined as complete re-epithelialization of all lesions. In Balochistan leishmaniasis season is late September through October when bulk of patients report. Of the 114 patients who reported to our hospital, 69 fulfilled the criteria for topical treatment as per the WHO guidelines.\(^5\) Keeping the extensive data on efficacy of itraconazole use in clearing CL lesions, we hypothesized that combined therapy of intralesional MA with oral itraconazole would reduce the duration of therapy for intralesional MA towards clinical cure. The cure rate with IL MA had been estimated at about 80% after one month of twice a week regimen (8 injections).\(^12\) In our study, partial cure was achieved in 94.2% patients by 9th injection. In another study the duration to cure for once a week regimen of IL MA was 6.2±0.7 weeks,\(^13\) which is in contrast to our study that showed a cure at 10±1.2 weeks. The duration of treatment till cure with itraconazole 200mg for six weeks was 75% in another study,\(^4\) while in a meta-analysis the efficacy rate was 65% for itraconazole in old world CL.\(^19\) Since we did not examine the efficacy of itraconazole alone but the response rate at six weeks in Group-B was partial (100% patients) in our study. Another study comparing the cure rate of combination of itraconazole with dapsone, imiquimod or cryotherapy to monotherapy with these agents showed that monotherapy gave an overall success rate of 56.41%, whereas combination therapy was successful in 69.56% of patients.\(^18\) We achieved an equal success rate in both groups on the contrary because our monotherapy included IL MA.

The time to healing in each patient was noted separately by the assessor every three weeks. The p-value of test scores in both groups at each three weekly visit was > 0.05, which refuted our hypothesis that the combination treatment would reduce the duration of treatment. Since the patients were all soldiers except one, their follow up visit two months after cure could easily be arranged. None of the patients showed recurrence after two months,
which proved that there was no advantage of the combination therapy in this aspect too. Another variable we, unintentionally, noted in our study was the rate of conversion to systemic antimonials while on IL MA treatment, which was 3/69 patients (4.3%).

**Limitation of study:** Leishmania species identification was not done in this study which can alter the treatment response. The study is not adequately powered.

**CONCLUSION**

Combination of oral itraconazole along with intralesional injection of MA offered no benefit over intralesional Glucantime alone in the management of cutaneous leishmaniasis.

**Future recommendation:** Comparative analysis of other second line treatments in combination with intralesional pentavalent antimonials to either treatment alone can be conducted.

**Conflict of interest:** None.

**Grant support & Financial Disclosures:** None.

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**Authors’ Contribution:** UB conceived, designed, did statistical analysis and editing of the manuscript. MD did data collection, record of lesions and editing of manuscript. MIA did statistical analysis and review of literature. FM did data collection and review of literature and article.