Original article

Intralesional injections of metronidazole versus meglumine antimoniate for the treatment of cutaneous leishmaniasis

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Abstract

Introduction and objective: Oral metronidazole is reported before as effective treatment of cutaneous leishmaniasis. The aim of the present study was to evaluate the efficacy of intralesional metronidazole injection versus intralesional meglumine antimoniate (Glucantim®) in the treatment of cutaneous leishmaniasis.

Materials and methods: The 36 patients with clinical and parasitologic diagnosis of cutaneous leishmaniasis participated in this study. The patients were randomly divided into two groups. Group one, 18 patients were treated with weekly intralesional of Glucantim injections, and group two, 18 patients were treated with weekly intralesional injections of metronidazole. Intralesional injections was administered enough to blanch the lesions surfaces (0.5-2ml for each lesion in both groups).

Results: Twenty eight patients completed the study. Sixteen patients in group one and 12 patients in group two. In group one, 13 patients recovered with eight injections (81%). and of group two, only three patients recovered with eight injections (16.6%). The pain of intralesional injections of metronidazole was much more than the Glucantim injections.

Conclusions: Intralesional metronidazole injections have little effect for the treatment of cutaneous leishmaniasis.

Key words: Cutaneous leishmaniasis, Meglumine antimoniate, Glucantim, Metronidazole

Introduction

Cutaneous leishmaniasis is a common and endemic parasitic skin disease in many countries including Iran. The disease is endemic in 82 countries, and 10 million people suffer cutaneous leishmaniasis today [1]. There are about 1.5 million new cases of cutaneous leishmaniasis each year, of which over 90% occur in seven countries, namely: Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria [2]. It causes disfiguring and permanent scars. There are some reports about successful treatment of cutaneous leishmaniasis with orally administrated metronidazole [3-5], but subsequent reports did not confirm this effect [6-8]. In these reports, metronidazole was administered orally. So we decided to

evaluate the efficacy of intralesional injection method just like intralesional injection of Glucantim.

Materials and methods

This study was conducted in a private dermatology clinic in Ahvaz city south of Iran, in 2002. Pre-enrollment procedures to verify inclusion criteria included a complete blood count, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, because Glucantim is nephro and hepatotoxic.

Thirty six clinically (Fig. 1) and parasitologically positive (Leishman bodies in Giemsa-stained direct smear of the lesion scrapings) cases were recruited in the study using inclusion criteria as: duration of lesions less than three months, age between 15-40 year, no evidence of secondary bacterial infections, no mucosal involvement; negative history of underlying disease (such as cardiac, renal, or pulmonary), or pregnancy, and breast feeding. No history of previous treatment of cutaneous leishmaniasis, or of allergic reactions to Glucantim or metronidazole. Patients with cutaneous leishmaniasis localized on or near the joints were excluded.

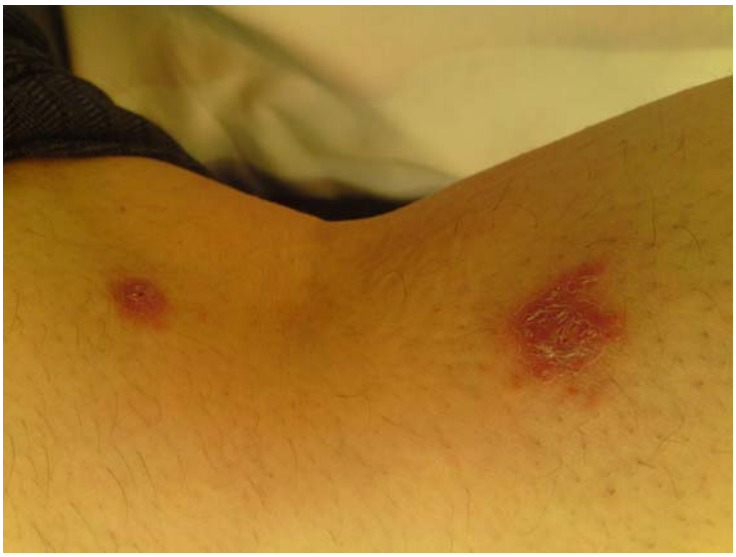

Fig. 1: Leishmaniasis lesions on popliteal area

After giving enough information to the patients, written informed consent was obtained from all participants. The patients were randomly divided into two groups. The method of randomization was selecting a card among 36 cards with odd or even numbers. In group one, 18 patients of group one had a total of 29 lesions all clinically were of dry types (without any discharge), the longest diameters of the lesions were 0.5-2.5cm. All were treated with weekly Glucantim intralesional injections (150-600mg = 0.5-2ml of Glucantim ampoule for each skin lesion), and group two, 18 patients of group two had a total of 27 clinically dry type skin lesions. The longest diameters of the lesions were 0.5-2.5cm.

All lesions were treated with weekly intralesional injections of metronidazole. Intralesional injections were administered intradermally enough to blanch the lesions surfaces (2.5-10mg = 0.5-2ml for each lesion). (Metronidazole 500mg/100ml vials were made by Fresenius, Bad Homburg). Clinical criteria for cure were: complete re-epithelialization, disappearance of edema,

induration, and other signs of inflammation, flattening of the lesions and change of color from erythematous to blue or dark gray. Statistical analysis was done using SPSS13 for windows and differences in proportions were compared with chi square test. P value<0.05 defined significant.

Results

The 36 patients with clinical and parasitologic diagnosis of cutaneous leishmaniasis participated in this study with a total of 56 skin lesions. The mean age of the patients was 28.8 years. Range between 15-40 years. Twenty one (58.3%) patients were male and fifteen were female, the mean duration of disease was 48 days. Twenty eight patients completed the study. Sixteen patients in group one and 12 in group two. In group one, 13 patients recovered with up to eight injections (81%). and of group two, only three patients recovered with eight injections (16.6%).

According to the patients complained the pain of intralesional injections of metronidazole was much more than the Glucantim injections. There was not any local or systemic adverse effect with metronidazole but in Glucantim group, two patients developed local inflammatory reactions with edema and induration that subsided in about 10 days. In both groups the patients complained of severe pain at the site of injections but group two had unbearable terrible pain.

Discussion

Cutaneous leishmaniasis is an endemic parasitic disease and important public-health problem in many parts of the world including in Iran [1,2,9] . It is usually a self-limiting disease, but it may cause disfiguring and permanent scars. Treatment of cutaneous leishmaniasis represents a major therapeutic challenge. Unfortunately, no ideal therapy for cutaneous leishmaniasis has yet been identified. Various systemic and topical treatments for cutaneous leishmaniasis have been proposed, the first choice of therapy in Iran is Glucantim [9].
Although the efficacy of intralesional antimonials injection for the treatment of cutaneous leishmaniasis has been confirmed [10-12], they have a high incidence of side effects including severe pain and sometimes reactions at the injection site. Other side effects that may develop specially with intravenous or intramuscular injections are, aching, arthralgia, fatigue, gastrointestinal upset, elevation of amylase, lipase, and liver enzyme levels, leukopenia, anemia, and electrocardiograph abnormalities [9,13].

Recent circumstantial evidence revealed that an increasing number of Iranian patients with cutaneous leishmaniasis are unresponsive to Glucantim [14]. Besides if multiple skin lesions occur, the total amount of intralesional drug may be as much as intramuscular or intravenous injections. Therefore the systemic side effects may be the same with each method of injections. Since, the patients in Iran and other countries, where resistance is becoming more common, do not respond to pentavalent antimonials it is necessary to develop new treatment strategy [14].

Metronidazole was discovered in France in 1957 and became the drug of choice for treatment of trichomoniasis. It was subsequently proven to be effective for both amebiasis and giardiasis [15] and for cutaneous leishmaniasis [3-5]; however, in further studies its efficacy in cutaneous leishmaniasis was not proved [6-8]. So the effectiveness of oral metronidazole for the treatment of cutaneous leishmaniasis remains controversial. Therefore we decided to evaluate intralesional injection method on some of our patients. Unfortunately intralesional metronidazole injection was very painful and all the

patients were complaining against severe pain. The six patients who dropped out of this group were perhaps due to severe pain of injections, and probably due to non satisfactory results. Only three patients of this group showed complete improvement.

In a recent clinical trial in Iraq [16], effectiveness of intralesional metronidazole injection was significant; and 85-87% of patients cure with 1-3 injection, The differences in the result of this study and ours is very much, these differences may be due to different method of drug preparation, or different criteria for determining cure, or may be due to differential sensitivities of different geographical variances of the parasite species to metronidazole. In the Iraq study**,** metronidazole solutions were prepared by dissolving metronidazole powder in 100ml of bidistilled deionized water. While in our study, the drug was standard vial for intravenous injection made by Fresenius Company, Bad Homburg. Our results are in agreement with those who showed ineffectiveness of oral metronidazole [6-8]. The major defects in our study are relatively small number of patients, lack of the culture of the sores and the unidentified species and strains of the genus leishmanias. It is recommended that, due to significant differences between the results of our study and the study in Iraq, similar studies again be done by other researchers with more patients.

Conclusion

In conclusion, although this study showed that metronidazole is ineffective, we believe that the search for a painless, easily applicable, and efficient modality with minimal side effects for the treatment of cutaneous leishmaniasis is mandatory.

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