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Comparative Effect of Topical Trichloroacetic Acid and Intralesional Meglumine Antimoniate in the Treatment of Acute Cutaneous Leishmaniasis

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Abstract: Cutaneous Leishmaniasis (CL) is a prevalent parasitic disease throughout the world. Pentavalent antimonials, including Meglumine Antimoniate (MA) are the first line treatment of CL, yet treatment failures are increasingly common in many endemic areas and new treatment modalities are sought. Trichloroacetic Acid (TCA) peeling has been effective for the treatment of some cutaneous problems including photodamaged skin with potential induction of collagen synthesis. This study was designed to evaluate the effect of topical TCA in the treatment of CL compared to intralesional MA. Eighty patients between 5-75 years were recruited with 7 patients dropping during the treatment course. In TCA group, 38 patients were treated three times (every 2 weeks) using TCA 50% and 35 patients received intralesional MA, weekly up to healing/or maximum 6 weeks. After six weeks, 26 patients (68%) in TCA group and 23 (65.7%) patients in MA group had complete clinical cure. There were 8 patients (21%) with partial cure in TCA group and 7 (20%) in the MA group; and 4 versus 5 patients showed no response after six-week treatment in each group, respectively. There was not any significant difference in clinical efficacy between TCA and MA groups. The same efficacy of TCA peeling, as a topical approach with the effect of intralesional MA shown during this pilot study, could potentially be promising in the treatment plan of CL.

Key words: Cutaneous leishmaniasis, Trichloroacetic acid, intralesional Meglumine Antimoniate

INTRODUCTION

Old world Cutaneous Leishmaniasis (CL) is a parasitic infection caused by leishmania species. Every year, an estimated 1.5-2 million children and adults develop symptomatic disease (cutaneous 1-1.5 million; visceral 0.5 million) and the incidence of infection is substantial when subclinical infections are included. Leishmaniasis is associated with about 2.4 million disability-adjusted life years and around 70 000 deaths per year. Ninety percent of cutaneous leishmaniasis infections develop in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil and Peru; Ninety percent of visceral leishmaniasis occurs in India, Bangladesh, Nepal, Sudan and Brazil (Murray *et al.*, 2005).

Not all CL lesions require treatment. It is a self-healing disease and systemic treatment seldom is used. Cosmetically unacceptable lesions, chronic lesions, large lesions, lesions in immunosuppressed patients,

lesions over joints and mucosal disease, multiple lesions, nodular lymphangitis and worsening lesions are some frequent reasons for the treatment of CL (Markle and Makhoul, 2004). Because of long duration of healing and scar formation, optimum treatment of this disease is desirable. Antimonial compounds are the most commonly used and the treatment of choice, particularly in the treatment of CL due to *L. tropica*. Intralesional injection of Meglumine Antimoniate (MA) has also been used. Although most of the side effects associated with systemic administration of antimonial compounds can be prevented by intralesional administration (Mujtaba and Khalid, 1999), still it is a painful modality. Also antimonial compounds are expensive and parasite resistance has been reported in different areas (Soto *et al.*, 2005; Arevalo *et al.*, 2001).

Local treatment modalities including topical paromomycin, cryotherapy, localized controlled heat and Carbon dioxide laser therapy also can be effective

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against *Leishmania major* or *Leishmania tropica* (Minodier *et al.*, 2005; Asilian *et al.*, 2004).

Trichloroacetic acid (TCA) above peeling has been used for the treatment of several skin lesions including actinic degeneration and acne scarring. The resultant good efficacy of TCA in the treatment of the above conditions in part could be due to epidermal regeneration, as well as the regenerating of new collagen in the dermis (Coleman, 2001; Al-Waiz and Al-Shariqi, 2002; Rubin, 1992; Glogau and Matarasso, 1995; Lehoj, 1998). Based on these effects TCA could potentially be considered useful in the treatment of CL. This study was designed to test the potential advantage of TCA in collagen synthesis for the treatment and re-epithelization of the lesions in CL. The effect of topical TCA peeling (as an alternative method) in the treatment of CL was compared with intralesional MA (as a standard approach).

MATERIALS AND METHODS

A randomized clinical trial was designed to compare the efficacy of intralesional MA with TCA peeling for the treatment of CL.

A total number of 80 patients (5-75 year) referred to Skin Disease and Leishmaniasis Research Center (SDLRC), Isfahan, Iran were recruited in this study. The diagnosis was confirmed by positive direct smear. Subjects were excluded from this study if they were pregnant or nursing mothers, were treated previously for CL, had any known intercurrent illness or a history of allergy to MA, patients with palpebral lesions, having more than 5 lesions or a lesion > 3 cm, or if the duration of lesions was >12 weeks. All selected patients or their parents were given complete information about the trial and signed a written consent form before recruitment.

Patients were randomly divided into two groups of 40 patients that were treated with either TCA 50% or intralesional MA. MA was injected into the lesions from the intact margin in amount enough to bleach the lesion and 1 mm of its surrounding normal skin. After cleansing with alcohol TCA 50% (wt/vol) (Bridenstine and Dolezal, 1994) was applied on the lesions using cotton swab and after frosting the lesion was covered with Vaseline (Peikert *et al.*, 1994a, b). There was no need to wash off TCA from the lesion. TCA was applied every two weeks until complete re-epithelization or up to 3 times.

MA was injected weekly until complete re-epithelization of the lesions or up to 6 weeks.

All patients were re-examined clinically after the last treatment session, 1 and 3 months post-treatment. Patient who had not complete response were evaluated parasitologically (direct smear and culture). If the patients

were not willing to continue the study or in the case of lesion progression or worsening, they were dropped from the study and another treatment was applied by dermatologist.

Primary outcome of this study was clinical response to the treatment categorized as complete cure, partial cure and treatment failure. Complete cure was defined as complete healing and re-epithelization of the lesion (s). Partial care was defined as partial clinical improvement with reduction in erythema, induration and size of the lesions. Treatment failure was considered as the absence of any change or worsening of the lesion (s).

Statistical analysis of clinical and parasitological outcomes between two treatment groups was done using χ^2 test with the significance (α) level of 0.05.

RESULTS

From 80 patients, which participated in the study, 73 cases completed the study. Five patients did not appear for follow-up, one was not willing to continue the study and one turned sporothrichoid and systemic meglumine antimoniate was administered (Table 1). Mean age of the patients was 25.7 years (range 5-75 years). The average duration of lesions before treatment was 40 days (range 10-90 days).

The most common clinical type of the lesions in both groups was papule (44% in MA and 50% in TCA group) and nodule (24% in MA and 25% in TCA group) (Table 2).

Table 3 shows improvement of the lesions at week 4 and week 6 of the treatment period. There was not any significant difference in the rate of complete cure between MA- and TCA-treated groups ($p > 0.05$, χ^2 test). Also partial cure and failure rates were not statistically different among two treatment groups. In subgroups of patients with partial cure or treatment failure parasitologic tests were positive in 11 patients of TCA group (91.6%) and 10 patients of MA group (83.3%).

There were 4 (10.5%) cases of recurrence in MA groups and 5 (14.2%) in TCA after 3 months follow up. They were treated for another session with the same treatment, as were previously randomized for, and the response rate was 50% for both groups.

Mild erythema and itching (2 cases in MA group) were the only observed side effects.

Table 1: Description of the study population

Drugs	No. of patients	Sex Male/Female	No. of lesions (mean)
TCA	38	21/17	45(1.2)
MA	35	19/16	48(1.4)
Total	73	40/33	93

Table 2: Clinical appearance and the place of the lesions in MA and TCA treated patients. Each lesion has been considered as a case. Results have been shown as number and percent (%) of lesions

Clinical pattern of the lesions	Complete cure				Partial cure		Treatment failure		Total lesions		
	4 week		6 week		TCA	MA	TCA	MA	TCA	MA	
	TCA	MA	TCA	MA							
Papule (< 1 cm)	18 (75)	14 (70)	21 (87.5)	17 (85%)	2 (8.3)	2 (10)	1 (4.1)	1 (5)	24	20	
Nodule (1-2cm)	7 (58.3)	5 (45)	9 (75)	8 (72.7)	2 (16.2)	2 (18.2)	1 (8.3)	1 (9.1)	12	11	
Indurated plaque	<2 cm	3 (37.5)	3 (37.5)	3 (75)	6 (75)	1 (25)	1 (12.5)	0 (0)	1 (12.5)	4	8
	2-3 cm	1 (33.3)	1 (33.3)	2 (40)	2 (6.66)	1 (20)	0 (0)	2 (40)	1 (33.3)	5	3
Ulcerated plaque	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.6)	3	3	
Total	28 (58.3)	23 (51.1)	36 (75)	33 (73.3)	7 (14.58)	6 (13.3)	5 (10.4)	6 (13.3)	48	45	

TCA=Trichloroacetic acid, MA= Meglumine Antimoniate

Table 3: Clinical results of intralesional MA and TCA peeling (each patient has been considered as a case)

Clinical result	TCA group No. (%)	MA group No. (%)
Complete cure		
4 week	20(52.6)	17(48.5)
6 week	26(68)	23(65.7)
Partial cure	8(21)	7(20)
Treatment failure	4(10.5)	5(14.2)

DISCUSSION

CL is a self-healing disease but leaving scar, which could be problematic especially in open areas of the body. Secondary infection could increase the depth of necroses and affect final size of the scar. The main objective of this study was to test the clinical efficacy of topical TCA in the treatment of CL based on its reported beneficial effects on skin as increasing the amounts of collagen I and collagen III and improving the morphologic appearance of collagen and elastic fibers (El-Domyati *et al.*, 2004). To the best of our knowledge, this study is the first report of using TCA for the treatment of CL. The results of this study showed no significant difference between TCA and MA groups in terms of clinical improvement, yet could have considerable importance in the treatment of CL. Obtaining the same response from topical TCA as intralesional MA is a potential promising result in terms of outpatient treatment in endemic areas. Topical TCA is a cheaper and more convenient treatment with least adverse effect, which could be set in every outpatient clinic with simple and short term training. Induction of the skin collagen synthesis is one possible mechanism of its therapeutic effects in CL. Mechanism of action of TCA and its place in the treatment of CL are further research questions which need to be evaluated.

TCA peeling could be considered as an alternative outpatient treatment modality for intralesional MA, except for the cases where systemic MA is indicated. The effect of combined TCA and intralesional MA is currently under study and will be reported soon.

Unblindness is a limitation of this study and could affect the interpretation of the results. However, this study could be considered as a pilot study and suggests the possible effect of topical TCA in the treatment of acute CL. Further randomized controlled trials with double placebos and sufficient sample size and power are needed to support these results.

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