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Comparing the Efficacy of Monotherapy with Intralesional Meglumine Antimoniate and Combination Therapy with Trichloroacetic Acid 50% and Intralesional Meglumine Antimoniate for the Treatment of Acute Cutaneous Leishmaniasis

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Abstract… Objective: to compare the efficacy of monotherapy with intralesional meglumine antimoniate and combination therapy with trichloroacetic acid 50% and intralesional meglumine antimoniate for treating acute cutaneous Leishmaniasis. Study Design: A randomized control trial. Place and Duration of Study: Dermatology department of DHQ hospital, Faisalabad from July 5, 2017 to July 5, 2018. **Methodology:** We divided 222 patients Group MA with 104 patients who were to be given intralesional MA and Group TCA+MA with 118 patients who were to be given TCA 50% and intralesional MA. Age, number of lesions, gender distribution, response to treatment in the form of complete, partial and no cure were compared between the groups. Independent t-test and chi-square tests were applied. The data was put in SPSS version 23 computer software and analyzed. P value of more than 0.05 was considered clinically insignificant. **Results:** There was no significant difference between the two groups in terms of age, average number of lesions and male percentage (p>0.05). Complete and partial cure of papule and nodule was seen in more patients of the Group TCA+MA while the cure rates of plaque were more in the group MA (p-value 0.014, 0.019 and 0.009, respectively). There was no statistically significant difference in the cure rates of ulcerative lesions between the groups (p=0.312). **Conclusion:** There was significantly better cure rate in the patients who were given combination therapy of intralesional meglumine antimoniate with topical Trichloroacetic acid 50%.

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INTRODUCTION

Leishmaniases is a complex of diseases which is instigated by Leishmania which is an intracellular protozoan. It is spread by a vector called sand-fly [1]. Its disease burden is very high considering almost a population of 350million at risk of leishmaniasis. Cutaneous leishmaniasis causes ulcerative skin lesions on exposed body surfaces which result in lifetime scarring and severe disability. It is the most common form of leishmaniasis. More than 95% of the cases occur in the Mediterranean basin, the Middle East, the Americas and Central Asia. According to a report, 1.5 million cases of cutaneous leishmaniasis occur every year around the world, majority of which happen to be in Iran, Afghanistan, Brazil, Columbia, Algeria and Syria [2-4]. Significant progress has been made in the past twenty years for the development of safe, effective and easily applicable diagnostic and treatment strategies [5]. Still there is a large portion of population which is deprived of access to basic treatment of leishmaniasis. Majority of the countries with endemic leishmaniasis are poor and leishmaniasis is not considered as significant health issue and functioning control programs are not maintained.

The most important hurdle in the control of leishmaniasis is poor access to basic care and lack of international funding in this respect. According to an estimate, more than 50% of the affected population is deprived of basic treatment facilities of leishmaniasis. In private sector, treatment of leishmaniasis is too costly due to which patients have to sell their valuables, thus increasing level of poverty in the already poor population [7].

Many types of treatments have been devised for cutaneous leishmaniasis including topical, systemic and intralesional, but standard treatment is still intra-lesional or systemic antimonial compounds [8-14]. For the purpose of skin rejuvenation, Trichloroacetic acid is used for chemical peeling. Trichloroacetic acid peeling is very prevalent in dermatology field as well as cosmetic surgery, and has been used for a long period; and very few side effects along with quick recovery has been observed [15]. Trichloroacetic acid is a treatment option in various skin conditions including external genital warts, photoaged skin, acne scars, molluscum contagiosum and actinic keratoses [16-18].

Some studies have shown almost equal efficacy of Trichloroacetic acid and intralesional injection of meglumine antimoniate for the treatment of papules in cutaneous leishmaniasis [8, 19]. In spite of advancements in the treatment of cutaneous leishmaniasis, first line drugs still comprise of pentavalent antimonial compounds and they are administered only as intravenous, intramuscular or intralesional injections. Significant discomfort and severe side effects can be associated with the injection of antimonial compounds [13]. So far no vaccine has been developed for the prevention of cutaneous leishmaniasis in humans [20]. Some systemic reviews have been published showing that there is no safe, effective and inexpensive treatment for cutaneous leishmaniasis has been developed so far [13, 21]. Majority of the studies have ignored the concept of wound management and have focused on the efficacy of drugs in the elimination of causative agents in the treatment of cutaneous leishmaniasis [22]. According to Sadeghian et al. [23], there has been a decrease in the efficacy of intralesional MA injections because of secondary bacterial infections. The use of polyurethane containing moisturizing dressings has been suggested for the treatment of cutaneous leishmaniasis. Almost all chronic wounds are colonized with variety of microorganisms which worsens the pain as well as inflammation of the wounds and interferes with the normal mechanism of wound healing, thus resulting in the much more complex mechanism of the disease [22, 23]. Appropriate use of antimicrobial dressings can reduce the microorganism burden and aid in the treatment of ulcerative lesions of cutaneous leishmaniasis. Silver dressings help in infection control by exerting its antimicrobial effect via multiple mechanisms including the interference with DNA and preventing cell division and reproduction; and interaction with bacterial enzymes and proteins resulting in bacterial cell wall disruption. All silver dressings release Ag+ and achieve their antimicrobial effect [24-27]. In a study by Navarro et al. [28], it was seen that promastigote form of the L. mexicana was effectively killed by the interaction of silver complexes.

Methodology

This is a double blinded randomized controlled trial for which we selected 222 patients by nonprobability consecutive sampling technique. The study conducted by Nilforoushzadeh MA et al. [29] was taken as reference and sample size was calculated. The study was performed in dermatology department of DHQ hospital, Faisalabad. The duration of study was from July 5, 2017 to July 5, 2018 and proper approval was obtained from the hospital ethics committee prior to the commencement of this study. All the patients had a confirm diagnosis of cutaneous leishmaniasis and had never received any type of treatment for cutaneous leishmaniasis in the past. All the patients who had other concomitant skin condition like psoriasis, lichen sclerosis and lichen planus; and pregnant as well as lactating mothers were excluded from our study.

Proper written consent was taken from all the patients at the start of study after explaining the whole procedure to every patient. Two hundred and twenty two patients were divided into two groups. Group MA included 104 patients who were to be given intralesional meglumine antimoniate and Group TCA+MA included 118 patients who were to be given Trichloroacetic acid 50% along with intralesional meglumine antimoniate. The lesions in which drugs were injected were less than 3cm in size and were not more than twelve weeks old. The lesions present within 4cm of the palpebral fissure were excluded. Meglumine antimoniate was injected into the lesion, twice weekly, in all the patient of both the groups until the lesions resolved completely or up to 8 weeks. Intact margin of the lesion was the site of choice for the injection of the drug and the amount of drug injected was enough to blanch the whole lesion and at least 1mm rim of normal skin all around the lesion. In TCA+MA group, Trichloroacetic acid 50% was applied to the surface of the lesions using a cotton swab until complete frosting of the lesion. The application of Trichloroacetic acid was performed fortnightly. Photographs of the lesions were taken before the start as well as after the completion of treatment. Two largest perpendicular diameters were used to measure the areas of lesions, erythema and induration. The investigators who were unaware of the type of treatment took all these measurements before the start of the treatment as well as at the end of eighth week. The signs of clinical healing included complete re-epitheliazation of the lesions and disappearance of induration. The response to treatment was measured at the end of the treatment course as complete cure (clinical healing as well as negative smear), partial cure (decrease in lesion size, erythema and induration along with partial clinical improvement) and no cure (worsening of the lesion or no clinical change at all) [10].

Age and average number of lesions was compared between the two groups by applying independent t-test and gender distribution was compared by applying Pearson chi-square test. The response to treatment regimens was compared in the form of complete cure, partial cure and no cure by applying Pearson chi-square test. All the data was put in SPSS version 23 computer software and analyzed. P value of more than 0.05 was considered clinically insignificant.

Results

There was no significant difference between the two groups in terms of age, average number of lesions and male percentage ($p>0.05$). Table-I

No cure, partial cure and complete cure of papules was seen in 5.9%, 12.7% and 12.7% patients of the TCA+MA group as compared to 14.4%, 5.8% and 6.7% patients of the

intralesional MA group, respectively. It was significantly better in the combination group (p=0.014). No cure, partial cure and complete cure of nodules was seen in 2.5%, 4.2% and 9.3% patients of the TCA+MA group and was significantly better as compared to 8.6%, 6.7% and 2.9% patients of the intralesional MA group, respectively (p=0.019). No cure, partial cure and complete cure of plaques was seen in 9.3%, 18.6% and 5.9% patients of the TCA+MA group as compared to 3.8%, 12.5% and 16.3% patients of the intralesional MA group, respectively. This response was statistically much better in the intralesional MA group (p=0.009). The response of both the treatment regimens was not statistically different on ulcerative nodules (p=0.312). Table-II.

Table-I: Basic characteristics

Variable	MA (n=104)	TCA+MA (n=118)	p-value
Age, years	23.01±14.01	20.53±11.94	0.155
Number of lesions	2.13±5.68	2.60±6.63	0.576
Gender, male (%)	66 (63.5)	70 (59.3)	0.528

Data is put as mean± S.D unless mentioned otherwise.

Table-II: Type and clinical response of the lesions between the two groups

Lesions (N)	CURE	MA (n=104)	TCA+MA (n=118)	p-value
Papule (112)	Non cure	15 (14.4)	7 (5.9)	0.014
	Partial	6 (5.8)	15 (12.7)	
	Complete	7 (6.7)	15 (12.7)	
Nodule (113)	Non cure	9 (8.6)	3 (2.5)	0.019
	Partial	7 (6.7)	5 (4.2)	
	Complete	3 (2.9)	11 (9.3)	
Plaque (189)	Non cure	4 (3.8)	11 (9.3)	0.009
	Partial	13 (12.5)	22 (18.6)	
	Complete	17 (16.3)	7 (5.9)	
Ulcerative Nodule (75)	Non cure	4 (3.8)	7 (5.9)	0.312
	Partial	8 (7.7)	9 (7.6)	
	Complete	11 (10.6)	6 (5.1)	

Data is put as number (percentage).

Discussion

Cutaneous leishmaniasis lesions have self-healing capacity but the leave a permanent scar. The first line therapy for cutaneous leishmaniasis is still the antimonial compounds but they have side effects and resistance to these compounds have developed[8-14]. For the purpose of skin rejuvenation, trichloroacetic acid is used for chemical peeling which is very prevalent in dermatology field as well as cosmetic surgery, and has been used for a long period; and very few side effects along with quick recovery has been observed [15]. Higher success rates in the treatment of external genital warts with trichloroacetic acid 85% was observed in the study conducted by Taner ZM et al. [16]. El-Domyati M et al. [6] observed dermal and epidermal reconstruction with trichloroacetic acid treatment of photo damaged skin. This was associated with improved morphologic appearance of elastic fibers and collagen as well deposition of new collage fibers. Yug A. et al [17] topically applied six doses of trichloroacetic acid 95% at interval of six weeks and observed complete treatment of the acne scars in three patients. Increase in the collagen component and elastic fibers improved the depth of scar histologically as well as cosmetically. Sakai A. et al [31] performed skin peeling with 40% and 60% trichloroacetic acid and cryosurgery. They evaluated the changes in the Langerhans cells and observed a significant decrease in the number of Langerhans cells. They suggested that the frequent use trichloroacetic acid impairs the skin's defense mechanism and can be carcinogenic.

Conclusion

There was significantly better cure rate in the patients who were given combination therapy of intralesional meglumine antimoniate with topical Trichloroacetic acid 50%.

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