Journal of Pakistan Association of Dermatologists. 2022;**32(3)**:502-509.

Original Article

Triple therapy for acute and chronic cutaneous leishmaniasis using oral zinc sulfate, oral ketoconazole and topical podophyllin

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Abstract

Objective To determine the efficacy of triple therapy using oral ketoconazole and oral zinc sulfate plus topical podophyllin in the management of cutaneous leishmaniasis.

Methods This is a prospective, therapeutic study that was performed during the period, March 2019 to December 2021 where 230 patients with acute and chronic cutaneous leishmaniasis were recruited in this work. Smear and histopathology were used to confirm the diagnosis. All cases were treated by oral zinc sulfate (5-10 mg/kg/day in divided doses) while oral ketoconazole was given 200mg twice a day for adults and 100mg for young children and 50-75 mg a day for infants according to the body weight (3.3-6.6 mg/kg/day). Topical 25% podophyllin solution was applied once a week. The duration of therapy was continued up to 6 weeks to be seen every two weeks until complete cure, then followed every month for the next three months .To assess response to treatment, Sharquie's modified Leishmania scoring was applied.

Results The analysis of 230 patients with cutaneous leishmaniasis showed the age of presenting patients ranged from 6months-60years. The mean of age was 27 years with 120 (52.17%) males and110 (47.82 %) females. All patients mentioned that response was started after a week but on examination, was obvious after two weeks and complete clearance after 6 weeks. After completion of the treatment, the cure rate was 99%. No important adverse effects were noticed in any patients but gastric irritation was seen in some patients receiving zinc sulfate and skin burning in some patients using podophyllin.

Conclusion Triple therapy of cutaneous leishmaniasis using oral ketoconazole, oral zinc sulfate plus topical podophyllin was effective in treatment of acute and chronic leishmaniasis although every single therapy is effective but aiming to increase the effectiveness especially in chronic cases and to avoid failure of treatment. No important systemic and local adverse reactions were recorded.

Key words
Cutaneous leishmaniasis, zinc sulfate, ketoconazole, podophyllin.

Introduction

Cutaneous leishmaniasis (CL) is a neglected infectious disease caused by species of leishmania. In Iraq and different Middle Eastern countries, it is an endemic disease with varied incidence and prevalence.[1-3] In Iraq, two leishmania (L) species are present: L. major and L. tropica, both were recorded as causative agents of CL in this country[4] and several studies have been carried out to diagnose leishmania parasites from cutaneous leishmania lesions by using different methods such as histopathological studies, direct smears examinations, cultures, serological tests[5,6] and polymerase chain reaction (PCR).[7-10]

From 2003-2014, four previously published articles using PCR technique for identification of the leishmania species in various areas of Iraq, in two cities from the center of Iraq, Baghdad[7] and Najaf,[8] two studies were carried out and L. major and L. tropica were the major identified species: in Baghdad, L. major and L. tropica were detected in 60% and 40% respectively of the studied cases which is comparable to what previously recorded by Al-Hucheimi *et al.*[8] in al- Najaf city where L major, and L tropica were identified in 56.7% and 43.3% respectively during the period 2003–2005. While in northern Iraq, Tikrit city, L. tropica were the main recognized species in 80.24% of studied cases followed by L. major in 19.74%.[9] This in contrast to a study in Kut city (eastern Iraq), where L. major and L. tropica were identified in 70% and 18.3% of patients respectively but in 11.7% patients no organism had been detected.[10]

Many topical and systemic medications have been used for the treatment of CL and found to be effective such as intralesional injection of sodium stibogluconate (SSG),[11] 2% zinc sulfate solution,[12,13] and 7% hypertonic sodium chloride,[14,15] topical paromomycin,[16] topical 25% podophyllin solution,[17] cryotherapy,[18] oral ketoconazole and oral zinc sulfate singly and in combination,[19] systemic SSG,[20] oral allopurinol,[21] oral rifampicin,[22] oral dapsone[23] and oral fluconazole.[24]

Limited published articles on oral ketoconazole have shown some safety precautions for its use but by a new extensive research over long period of time with a huge number of cases proved its safety in the management of diverse cutaneous diseases mostly CL and dermatophytosis.[25]

Hence, this work was attempted to determine the efficacy of triple therapy using oral ketoconazole, oral zinc sulfate plus topical podophyllin in the management of CL.

Patients and methods

In this prospective, therapeutic study that was performed during the period, March 2019 to December 2021, 230 patients with cutaneous leishmaniasis were enrolled in this study. Acute leishmaniasis was considered when the duration of lesions was within 6 weeks while considered chronic when the duration was ranged from more than 6 weeks to months and years.[1,19] smear and histopathology were used to confirm the diagnosis. All patients were treated by systemic zinc sulfate (5-10 mg/kg/day in divided doses) while oral ketoconazole was given 200 mg twice a day for adults and 100 mg for young children and 50-75 mg a day for infants according to the body weight (3.3-6.6 mg/kg/day). 25% podophyllin solution was applied topically once a week and it was left to dry for few minutes and the patients were informed to wash it after 5 hours.[17,26]

A thorough history with appropriate examination were carried out. Name, age, gender, residence, job and past medical and drug history, and reproductive history were gathered from the patients. Type of the lesion, duration, site, size and number of the lesions were also assessed.

History of allergy to any medication used in this work, pregnancy, lactating, patients who had used any topical and systemic treatments in the last 4 weeks, unreliable patient and chronic

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diseases like diabetes mellitus were considered as exclusion criteria.

This research followed the Declaration of Helsinki Principles and the research protocol was elucidated to the patients or his/ her parents, who were provided informed consent.

Close-up photographs were taken before starting therapy and during the follow-up period and all enrolled patients agreed to share their pictures in this study. This research was approved by the Ethics Committee of Al-Anbar Health Directorate, Fallujah Teaching Hospital.

Before starting therapy and during four weeks and eight weeks therapy, laboratory investigations were carried out including blood urea, serum creatinine, serum aspartate aminotransferase. (AST), full blood count (FBC), alanine aminotransferase (ALT), total Bilirubin (TBL), prothrombin time (PT) and alkaline phosphatase (ALP).

The duration of therapy was continued for up to 6 weeks and to be seen every 2 weeks during treatment course, then followed every month for the next three months. The healing of lesions was evaluated by using Sharquie's modified Leishmania score to evaluate the objective response[19] **(Table 1)**.

Results

A total 230 patients with CL were evaluated, the age range of presenting patients were from 6months-60 years with mean age of 27 years with 120 (52.17%) males and 110 (47.82 %) females. Patients had mostly multiple lesions and the duration of lesions ranged from 4 weeks to 5 years with a mean of 6 months (70% patients within three months while 30% with duration ranged from more than three months to 5 years with a mean of 8 months). 59 (25.65%) patients had acute CL while, 171 (74.34%) patients had chronic CL. Among chronic CL cases, 18 (10.52%) cases were leishmania recidivans type.

The lower limbs in 78 (33.91%) cases were the most frequently affected site followed by upper limbs in 68 (29.56%), face in 65 (28.26%) and trunk in 19 (8.26%). The size of lesions was variable but ranged from 0.7 cm to 3.5 cm in diameter with a mean of 2 cm.

All patients mentioned that response was started after a week but on examination, was obvious after two weeks and complete after 6 weeks and using Sharquie modified scoring technique showed:

Two weeks after starting triple therapy: One hundred ninety (82.6%) of the cases displayed mild response, and 40 (17.39 %) displayed moderate response.

Table 1 Sharquie's modified Leishmania score to assess the objective response to the topical or systemic therapy.

Score	*Change in the color of lesion*	*Reduction rate in the color of lesion*	*Reduction rate in the induration of lesion*	*Reduction rate of ulcer/crust.*
4	Bright red	-	-	-
3	Red	0% - 25%	0% - 25%	0% - 25%
2	Dusky red	25% - 50%	25% - 50%	25% - 50%
1	Dark brown	50% - 75%	50% - 75%	50% - 75%
0	Light brown	>75%/clearance	>75%/clearance	>75%/clearance

Score 13-16: Mild response. Score 9-12: Moderate response. Score 5-8: Marked response. Score 0-4: Complete clearance & response. Both marked and complete responses are regarded as a cure. For dry lesions; where the fourth parameter (reduction in diameter of the ulcer) is not applicable; so grading was done as follow: score 12-9: mild response; score 9-6: moderate response; score 6-3 marked response; score: 3-0 complete response.

Figure 1 Ten-months old female patient showing cutaneous leishmaniasis affecting mainly the forehead and other parts of the face: (A) Before treatment, (B) 4 weeks after treatment with triple therapy and (C) 6 weeks after the same therapy.

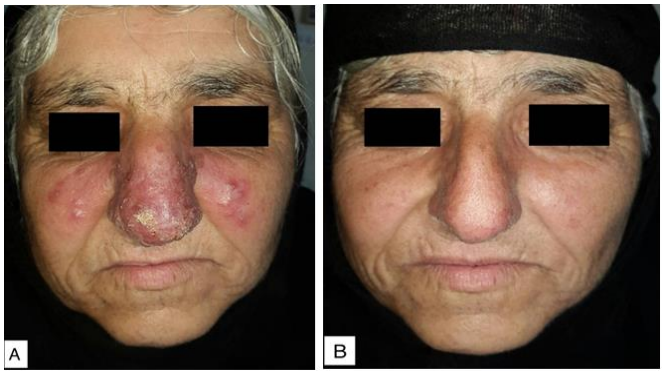

Figure 2 Sixty-five years old female patient showing cutaneous leishmaniasis affecting the nose: (A) Before treatment and (B) 4 weeks after treatment with triple therapy.

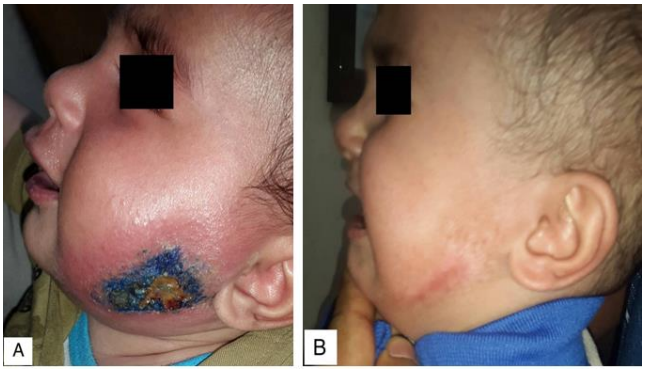

Figure 3 Nine months old male patient showing cutaneous leishmaniasis affecting the left side of the face: (A) Before treatment and (B) 4 weeks after treatment with triple therapy

Four weeks after starting treatment: twenty (8.69%) of the cases displayed moderate response, 129 (56%) displayed response and 81 (35.21%) displayed complete clearance.

Six weeks after starting treatment: Thirty (13%) cases displayed marked response, while 198 (86%) displayed complete clearance but only 2 patients showed moderate response and these together were considered a cure in 99% of cases.

No important adverse effects were noticed in any patients but mild transient increase in serum AST and ALT was seen in 12 (5.21%) of patients, gastric irritation was seen in 30 (13%) patients receiving zinc sulfate and transient skin burning in 51 (22.17%) patients using podophyllin. These adverse effects subsided with over time and all patients well tolerated this combination.

In majority of healed lesions, there was minimal or no scarring at the healed lesions sites, but post-inflammatory hyperpigmentation was noticed in all cured lesions.

Discussion

Although CL is a self-resolving infectious disease but it may last for long period, months or years before complete clearance is achieved.[1,11] Severe disfiguring scars affecting the esthetic appearance particularly when it involves the face where it may result in major psychological trauma to many patients, so its treatment is essential. So, the aim of the therapy is to shorten the duration of the disease and to limit possibility of scarring. With reviewing of published papers; many topical and systemic medications were recorded in the treatment of cutaneous leishmania lesions with variable results.[27]

Systemic treatment for CL is indicated in an immunocompromised patient, markedly enlarged regional lymph nodes, >4 lesions of substantial size or individual lesion(s) measuring ≥5 cm, ineffective topical treatment, patients who refuse local treatment, and lesions involving face, mucosa, ears, fingers, toes, genitalia and skin overlying a joint.[28–30]

This paper aimed to evaluate the efficacy and safety of triple therapy, oral zinc sulfate and oral ketoconazole and topical 25% podophyllin solution in the treatment of acute and chronic CL.

Intralesional injection of SSG was very effective therapeutic modality for CL.[11] Resistance to this therapy or progression to chronic cutaneous type has been reported in limited number of patients in the last decades. Nowadays, upsurge of chronic CL and leishmania recidivans have been observed as a consequence of resistant cases to SSG therapy.[31]

So, the combined treatment regimen has applied novel method in management of CL. The combination of antileishmanial medications could decrease the duration of treatment and the potential toxic adverse effects while increase the cure rate and limit drug resistance. Many studies have illustrated that some medications in combination increase their antileishmanial effect.[19,31]

Although mono-therapies, using oral ketoconazole, oral zinc sulfate,[19] or topical podophyllin[17] have given a satisfactory result. In addition to the very encouraging results of this combination of triple therapy in the treatment of leishmania recidivans with 100% cure rate[31] and this finding had encouraged us to use this combination in the treatment of ordinary acute and chronic CL.

In the present study, the cure rate was 99% which is higher than Sodium stibogluconate both systemic (76.5%)[32] or intralesional (94.6%).[11] Also using systemic SSG is costly drug with several systemic side effects such as: abdominal pain, nausea, myalgia, cardiac arrhythmia, non-specific T changes on ECG, pancreatic inflammation elevated liver enzymes and nephropathy.[33] But when given intra-lesional, it is painful requiring frequent hospital visits that can result in missed doses either due to poor compliance or due to occasional interruption of supply and it can also induce leishmania recidivans.[31]

While triple therapy used in this study is economical, not painful, easy to administer, well tolerated by the patients, available at all times and has with no significant adverse effects.

Also, the cure rate in this work was higher than Sharquie *et al*. study in which oral ketoconazole and oral zinc sulfate were used alone or in combination for six weeks duration and the cure rate with oral ketoconazole, oral zinc sulfate and with the combination of both drugs was 50%, 60% and 96% respectively.[19] This increment in

the cure rate in our study could be due to synergistic effect of the combination therapy and additional to antileishmanial effect of topical 25% podophyllin.

The high cure rate (99%) recorded in our study was higher than several studies that used different medications in the treatment of CL such as oral azithromycin,[34] oral dapsone[23] and oral fluconazole[24] where the cure rate was 85%, 82% and 43.8% respectively. This superiority of cure rate in the present work could be due to the high efficacy and the synergistic effects of combination drugs used in this work with their antileishmanial activity.

The mechanism of action of triple therapy could be explained as zinc is an intracellular signal molecule that plays an essential role in enhancing the function of monocytes, macrophages, dendrocytes and cell-mediated immunity that are in turn effective in body defense mechanism against Leishmania parasite.[35] While ketoconazole is an antifungal safe drug that block ergosterol synthesis via inhibiting 4-alpha-demethylase enzyme.[36]

The therapeutic benefit of combined treatment regimen using oral ketoconazole and oral zinc sulfate give a solution for drug to drug interaction and the rapid development of resistance, they act in a synergistic process by: 1) Ketoconazole prevent ergosterol synthesis via inhibiting 4-alpha-demethylase enzyme. This process could be improved by the utilization of oral zinc sulfate.[37] 2) Zinc inhibits the enzymes that are responsible for the protozoa carbohydrate metabolism.[38,39] Regarding the probable antileishmanial action of podophyllin, it could not be well elucidated but the established actions of podophyllin on cells could be applied on leishmania parasites and these actions include: blocking oxidation enzymes in tricarboxylic acid cycle, arresting cellular mitosis in metaphase, inhibiting axonal transport, protein, DNA and RNA synthesis.[40]

From these different antileishmanial actions of the medications mentioned here, in addition to our experience with these drugs in the management of different skin disorders, we are encouraged to use this triple therapy in this study to obtain a synergistic effect, short duration of treatment and high cure rate, with minimal or no important adverse effects.

This study also documented that this combination is well tolerated by patients with no serious systemic or topical adverse effects were recorded apart from mild transient elevation in serum AST and ALT that were seen in 5.21% of patients that disappeared after discontinuation of treatment with absent clinical and laboratory features of hepatitis.

Conclusion

Triple therapy of CL using oral ketoconazole, oral zinc sulfate and topical podophyllin solution was found to be most efficacious and safe in the management of acute and chronic CL. Moreover, this combination showed 99% cure rate and it seems to have promising results in the management of CL. Although every single therapy is effective but aiming to increase the effectiveness especially in chronic cases and to decrease the possible toxic adverse effects and inhibit drug resistance in order to avoid failure of therapy. No important systemic and local adverse reactions were recorded.

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