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Abstract

Background: Cutaneous leishmaniasis is one of the endemic and neglected diseases known to exist in Ethiopian highlands. However, a neglected tropical disease overshadowed by lack of effective anti-leishmaniasis agent in Ethiopia. Thus, high number of population is faced for various degree of socio-economical and psychosocial morbidity. Hence, this study was initiated and conducted from July-February, 2017/18 to assess the patterns and effectiveness of different types of anti-leishmaniasis agents in Boru Meda Hospital, Dessie District.

Methods: A cohort study design was employed in six treatment categories via randomly allocated cutaneous patients from three clinical types at Boru Meda hospital Dermatology department. Detailed clinical assessment, biopsy/fine needle aspiration cytology, and skin slit smear leishmania parasite detection were done to confirm clinical suspension. Then, the intended treatment types were administered for three cycles. Finally the data were analyzed using Epi-Info, SPSS and the results presented using graphs and tables.

Results: Among patients with mucocutaneous leishmaniasis who has took Systemic Sodium Stibogluconate (SSG) with Intra-Lesional SSG (IL SSG) the cure rate was 85.7%, systemic SSG with allopurinol was as effective as 78.6%. Patients with diffused cutaneous leishmaniasis who took both systemic SSG with allopurinol had an 80% cure rate and systemic SSG and local therapy both cryotherapy and IL SSG had a clinical cure rate of 85.7%. In addition, patients who diagnosed as localized cutaneous leishmaniasis and took only cryotherapy had 92.3% cure rate while as those patients who had a combined local therapy of both cryotherapy and IL SSG therapy showed clinical cure rate of 96.1%.

Conclusion: As our study showed for any clinical type of cutaneous leishmaniasis, administering combined forms (Pentavalent antimonial with local therapies i.e. cryotherapy or/and IL SSG) of anti-leishmaniasis agents had a better cure rate than single therapies.

Keywords: Cutaneous leishmaniasis; Pattern of treatments; Effectiveness; Ethiopia;

Author Summary

Most cases of cutaneous leishmaniasis in Ethiopia are caused by *L. aethiopica*. Among these nearly 100% are localized cutaneous leishmaniasis, more than 80% mucocutaneous leishmaniasis and more than 75% diffused cutaneous leishmaniasis treated with pentavalent antimonials (SSG) having a great cure rate when it was in a combined form with local therapies than a single pattern.

Introduction

Cutaneous Leishmaniasis (CL) is a chronic, neglected tropical infectious disease caused by a group of protozoan parasites of the Leishmania genus. The parasites are transmitted to humans via the bite of phlebotomine sand flies and predominantly target reticulo-endothelial cells [1-3].

Cutaneous leishmaniasis was first described in Ethiopia by an Italian epidemiologist Martogilo in 1913. CL is known by different vernacular name in different localities of Ethiopia such as: “Volbo” in Ocholo, “Finchoftu” in central Shoa, “Kunchir” in Gojam, Gonder and parts of Wollo, “Giziwa” in Tigray, “Chewie” in Sodo, “Simbirahalkani” in Wollega and “Shahegne” in north Shewa [3].

Cutaneous leishmaniasis can present with a spectrum of clinical manifestations. Ulcerative skin lesions occurring at the site of the bite of the sand fly is the most common cutaneous manifestation (localized CL—LCL). While usually healing spontaneously after several months, it remains disfiguring and stigmatizing and often heals with scarring. There are several more rare forms like diffuse CL (DCL), and muco-cutaneous leishmaniasis which is often difficult to treat [1,4,5].
Most cutaneous leishmaniasis lesions are self-limiting and may heal in 1–5 years. In spite of this, treatment is justified in a variety of cases, namely early lesions, multiple lesions, lesions involving cosmetically sensitive sites, mucosal lesions, disseminated lesions and patients with significant immunosuppression [2,6].

The disease still presents a therapeutic problem in several parts of the world. To-date, there is no safe, simple, cheap and effective amebicidal treatment for cutaneous leishmaniasis except melphalan though not available in Ethiopia. Pentavalent antimony compounds, “the best drug of a bad bunch” still remain the mainstay of treatment in the majority of cases. Antimony compounds have the disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions where they have been in use for a long time [6,7,8].

Cutaneous leishmaniasis in the Old World is predominantly caused by *L.tropica* and *L.major*, it is still estimated that several tens of thousands of cases are due to *L.aethiopica*. These predominantly occur in Ethiopia, and more exceptionally in Kenya. Within Ethiopia, the annual cutaneous leishmaniasis burden is estimated at around 20,000 to 40,000 cases per year, of which 99% is thought to be due to *L.aethiopica* [9,10]. A recent study estimated almost 30 million of Ethiopians to be at risk for CL. CL in Ethiopia is a zoonotic disease, mainly occurring in the highland regions, involving rocky environments [11].

The classic therapy for all forms of leishmaniasis uses pentavalent antimonials as Sodium Stibogluconate (SSG) and Meglumine Antimoniate (MA) administered intravenously or intramuscularly. Other systemic treatments used are Amphotericin B deoxycholate (AB) and Liposomal Amphotericin (LAB), both intravenously, and intramuscular paromomycin and pentamidin. Local treatments based on intralesional pentavalent antimonials, topical paromomycin, cryotherapy, or cryotherapy is used for certain cases of cutaneous leishmaniasis. But as few studies in the New World cutaneous leishmaniasis revealed that the combined therapies between systemic Sodium Stibogluconate (SSG) with allopurinol, letoconazol, cryotherapy and intra-lesional SSG showed promising effects for patients with cutaneous leishmaniasis [12-14]. Thus, this study was aims to assess three patterns of treatment and its effectiveness among patients with six categories of cutaneous leishmaniasis for treatment type under study.

**Methods**

This research was conducted from July-February, 2017/18 in Boru Meda hospital, 10 km away from Dessie district located in eastern zone of Amhara National Regional State at the north eastern edge of the Ethiopian highlands 411km from the region capital city and 470km north of Addis Ababa (capital of the country) situated between 11007’21.33’’N, 39038’05.87’’E with an elevation of 2,706 meters (8,878 ft) above sea level.

Boru Meda hospital was established by Sudan Interior Mission (SIM) in 1955. The hospital is landed in a field bounded by mountain especially in the west and north direction in addition to the mountain. The primary objective at time of establishment of the hospital was focusing to give care on ophthalmology and dermatology services. Thus, it serves on both service areas for more than 40 years but now the hospital gives a comprehensive service, i.e., emergency, outpatient service and gynecology and obstetrics and inpatient service with 140 beds among these 45 beds was assigned for dermatology ward. Regarding human resource, there are 9 specialists among these, 2 of them are dermatologists and an adequate number of all the other health professionals constitute the health care team.

The hospital provides serves for a total of 2.5 million catchment population of south Wollo, North Wollo, Oromia special zone, South Tigray and Afar region. In addition to the dermatologic cases diagnosis and treatment the hospital is used as a training center for health professionals in the surrounding health facilities and used as internship and attachment site for Wollo university medical department student.

This research was conducted on the treatment patterns, outcomes and effectiveness for intervention of various forms of cutaneous leishmaniasis. A total of 97 cutaneous leishmaniasis (MCL 28, LCL 52 and DCL 17) patients in Boru Meda hospital, dermatology department in three outpatients departments between July-February, 2017/18 one who come for the seek of curative, preventive and rehabilitation services to the hospital.

During this eight months study period, 97 patients were included in the study. 82 patients enrolled in the study whose skin slrit smear was positive, 9 patients had negative skin slit smear and suggestive Fine Needle Aspiration Cytology (FNAC) result and the rest 6 patients were included after clinically diagnosed. One patient was excluded from the study at the beginning of the study due to deviated renal and liver function test.

Though Sodium Stibogluconate is recommended for first cycle (28 days) up to five to seven repeated cycle of the treatment cycle specially patients with MCL and DCL. Thus, patients were categorized in six different treatment patterns. Then, these patients were categorized randomly based on their clinical category and drugs took as: LCL, (26 only Cryotherapy, 26 combined intra-lesional SSG with Cryotherapy), MCL, (14 allopurinol with SSG intra muscular (IM) or intravenous (IV), 14 combined SSG/IV with intralesional SSG) and DCL; (10 allopurinol with SSG IM or IV, 7 combined SSG IV/IM, Cryotherapy and intralesional SSG). Then, the patients were assessed for the clinical improvement or cure after providing respective treatment options for three cycles (of SSG therapy) or 90 days while admitting them in Boru Meda Hospital.

Meantime, those patients who took systemic SSG were had regular base line (CBC, SGOT, SGPT, ALP, BUN, Creatinine, electrolyte and ECG for children who are less than ten years) at the beginning and every a couple of weeks with daily vital sign and conducting a grand round every week with ward nurses, seniors and daily by assigned nurses who follow those cases on treatments which were available in the hospital.

Besides, all findings laboratory findings, deviated vital signs, clinical improvements, patients complain and drug took were...
recorded in the data sheets for respective clinical groups every week after grand round.

Finally, the clinical variables, drug took, socio-demographic data and outcomes were entered in to Epi-inf o and then for the seek of analysis it was export in to SPSS. Then the SPSS data will be analyzed to show the difference and similarity via ANOVA. Then, the outcome variables were presented through tables and charts.

**Definition**

"Clinical cure" was defined as complete epithelialization or visually healed at 2±1 month after completion of therapy.

"Clinical response": The response of the leishmanial skin lesions was determined at the end of therapy and at the follow up every month, 2nd and 3rd month.

"Clinical improvement" was defined as 75%–99% re-epithelialization (for non ulcerative lesions or/and 75%–99% decrease in the size of the initial lesion).

"Clinical failure" was characterized as less than complete epithelialization or visually not healed at 2±1 month after treatment completion.

**Table 1:** Characteristics of cutaneous leishmaniasis cases who received treatment in Boru Meda Hospital, Dessie, Northeast Ethiopia, 2017.

<table>
<thead>
<tr>
<th>Ser. No</th>
<th>Variables</th>
<th>Characteristic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>Age</td>
<td>1-15</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16-45</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Above 45</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Educational Status</td>
<td>Illiterate</td>
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<tr>
<td></td>
<td></td>
<td>Grade 1-8</td>
<td>41</td>
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<tr>
<td></td>
<td></td>
<td>Grade 9-12</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diploma and above</td>
<td>7</td>
</tr>
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<td>3</td>
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<td></td>
<td></td>
<td>Urban</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Family Income</td>
<td>Farming</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Merchants</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Civil servants</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>9</td>
</tr>
</tbody>
</table>

**Clinical Characteristics**

The patients were admitted to the hospital for a standardized period of time for up to three cycles of the standard therapy with a couple of weeks rest between the cycles. Thus, all patients were complete their respective treatment patterns except one patient whose renal and liver function tests elevated more than three times to the normal range was excluded to the study at the beginning of the study.

In addition, 33 (34%) of the patients who were included to the study had history of herbal application with significant scar around the lesions (Leishmania recidivans). But the rest 64 (66%) patients did not have history of neither any herb application nor any medicine from the health institution (See table 2) and (See table 3).
A total of 97 cutaneous leishmaniasis with three clinical types (MCL 28, LCL 52 and DCL 17), and six therapeutic categories: LCL (26 only Cryotherapy, 27 combined intralesional SSG with Cryotherapy), MCL; (14 only SSG intramuscular (IM) or IV, 14 combined SSG IV/IM with intralesional SSG) and DCL;

Table 2: Diagnostic methods used for cutaneous leishmaniasis cases detection who received treatment in Boru Meda Hospital, Dessie, Northeast Ethiopia, 2017/18.

<table>
<thead>
<tr>
<th>Ser. No</th>
<th>Investigation type</th>
<th>Result (N, %)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total tested</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>Skin slit smear</td>
<td>97 (100%)</td>
<td>82 (85%)</td>
</tr>
<tr>
<td>2</td>
<td>Biopsy/FNAC*</td>
<td>15 (15.5%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>3</td>
<td>Clinical diagnosed</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Total</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

*FNAC-Fine needle aspiration cytology

Table 3: Clinical characteristics for cutaneous leishmaniasis cases who received treatment in Boru Meda Hospital, Dessie, Northeast Ethiopia, 2017/18.

<table>
<thead>
<tr>
<th>Ser. No</th>
<th>Clinical variables</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scar lesions</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Herbal application</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>Previous Rx Hx</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Co-morbid</td>
<td>6</td>
</tr>
</tbody>
</table>

(10 only SSG IM or IV, 7 combined SSG IV/IM, Cryotherapy, and intralesional SSG).

Among those cutaneous leishmaniasis patients who were admitted and took drugs in six different clinical types had an overall clinical cure rate of 94.8% with respective improvement (See figure 1).

Those 14 patients with mucocutaneous leishmaniasis who have took systemic sodium stibogluconate with intralesional SSG 85.7% was improved, while as the clinical cure rate for those patients who took systemic SSG with allopurinol was 78.6%.

For patients who diagnosed as diffused cutaneous leishmaniasis, 10 patients were admitted and took both systemic SSG and allopurinol and the curative rate was as high as 80% where as those 7 patients who took systemic SSG and local therapy with both cryotherapy and IL SSG had a clinical cure rate of 85.7% (See table 4).

A total of 52 patients who diagnosed as localized cutaneous leishmaniasis and took local therapy provide different clinical improvements in a combined and single treatment pattern. Twenty-six 26 patients who had only cryotherapy showed clinical cure of 92.3% at the 3rd dose where as the rest the 26 patients had a combined cryotherapy and IL SSG therapy with a cure rate of 96.1%.

Discussion

Though the magnitude of cutaneous leishmaniasis is not yet precisely known in Ethiopia, it results in numerous socio-economical and psychosocial effects on the population. Moreover, all the available anti-leishmania agents are considered as ineffective for leishmania aethiopica (2, 3). But cutaneous leishmaniasis patients who are admitted and as out or inpatients for various patterns of treatment showed promising cure rate where agents are administered as a single and combined ways.

Patients with Mucocutaneous Leishmaniasis (MCL) who have took systemic sodium stibogluconate via intra muscular or/ and intravenous with weekly intralesional pattern was as effective as
Patients with Diffused Cutaneous Leishmaniasis (DCL), who have took systemic sodium stibogluconate via intra muscular or/ and intravenous with allopurinol showed the cure rate of 78.6%. This result was relatively higher with the study conducted in Saudi Arabia (71%) [13]. This difference might be because of the etiologic agents and treatment phases or cycles [3,1].

As our study showed a combined anti- leishmaniasis agents like SSG IM with IL, SSG IM with local therapies (cryotherapy + IL SSG), cryotherapy only or combined both local therapies (cryotherapy + IL SSG) results 85.7% (MCL), 85.7% (DCL)&% 92.3% (LCL)and 96.1% (LCL) effectiveness for respective clinical category, respectively.

Thus, for any clinical type of cutaneous leishmaniasis ad ministering combined forms (Pentavalent antimonial with local therapies i.e. cryotherapy or/and IL SSG) of anti-leishmaniasis agents had a better cure rate than single therapies.

References


