**EXTRA MURAL RESEARCH**

**A Randomized Double Blind Clinical Trial of A Homoeopathic Medicine In The Treatment Of Trophic Ulcer And Neuropathy In Leprosy**

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**Introduction:** Leprosy is a disease of global concern not only because of its potential to affect large number of people and its continued transmission but also because of the occurrence of deformities in a great proportion of patients. It is also a fact that multi-drug regimen has been effective in killing *Mycobacterium leprae* but it has no impact on associated disability due to nerve function impairment and trophic ulcer in leprosy. To explore the other means of treatment to save the leprosy patient from disability, a randomised double blind clinical trial was undertaken.

**Methodology:** 160 leprosy patients who were released from treatment (RFT) and were suffering from either trophic ulcer and peripheral anaesthesia were randomly selected. All the patients in study groups were given *Mercurius solubilis* orally for a period of two years or till recovery, whichever was earlier, while control group received placebo.

**Results:** Statistically significant improvement was observed in the healing of ulcers and regaining of nerve sensation. The biopsy from the treated cases showed almost normal dermis containing new nerve twigs and sweat glands and blood vessels with no evidence of perivascular or perineural inflammatory reaction. Radiographs of the patients with ulcer showed absence of osteomyelitic changes of phalanges with bony remodeling of metatarsal bone.

**Conclusion:** This treatment was found to be most suitable for cure of neuropathy and trophic ulcer in multi drug treated leprosy patients.

**Keywords:** leprosy, *mycobacterium leprae*, trophic ulcer, *mercurius solubilis*, anaesthesia, homoeopathy

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**INTRODUCTION**

Leprosy still continues to be of global concern, not only because of its potential to affect large number of people and its continued transmission, but also because of the occurrence of deformities in a great proportion of patients. Widespread application of Multi Drug Therapy (MDT) over the past decade has resulted in significant reduction in the prevalence of the disease leading to the achievement of the target of its elimination in the whole world. Although MDT regimen has been effective in killing *Mycobacterium leprae* resulting in cure of leprosy patient from infection, it has no impact on the occurrence of neuropathy and trophic ulcers.

Development of trophic ulcer is the most serious complication in leprosy, resulting from impaired nerve function. This ulcer, recognised as Grade II disability, if remains untreated, generally leads to deformity. In leprosy, affliction of peripheral nerve leads to sensory, motor and trophic changes in extremities and predisposes the skin to ulceration. Among all disabilities, leprosy contributes 15 –20% disables. Thus leprosy is a disease not only of public health importance but has got tremendous socio economic implication.

There is some degree of nerve damage caused by *Mycobacterium leprae* throughout the whole spectrum of the disease, the pathogenesis of which is not properly understood. So, to prevent the disability, early detection of nerve damage is very essential. It is a fact that inspite of best efforts early detection of this...
disease could not be made possible in most of the cases.

In WHO recommended Multi Drug Therapy (MDT) regime, patients are treated on detection of leprosy. The aim of this treatment, however, confines to kill the pathogens and to check the infection. The patients are declared cured on the basis of absence of pathogens in the host and absence of granuloma in tissue. However, even after released from treatment (RFT), the patients suffer from neuropathy, loss of pigmentation, ulcer and other secondary complications for rest of their life. In many cases after completion of MDT, the patients become AFB negative, but the bacteria remain in dormant stage in skin, nerve and in certain other locations like dartos muscle which can cause relapse of the disease.

Available literature cited no treatment for regaining of sensation and recover lost hair or pigmentation in leprosy. For treatment of ulcer, only bed rest is advised which is not practical and pragmatic. In view to save patients from trophic ulcer and neuropathy, the grave outcome of leprosy, there is a need to find out some means of treatment for which this trial was undertaken.

Materials and Methods

The present study included, 160 randomly selected patients with the complaint of loss of sensation and trophic ulcers were included. All of these patients were selected from two different geo-climatic zone, during the period from November 2004 to June 2005. All the patients were subjected to a detailed clinical study. The history of all the patients revealed that they have had leprosy and all of them were treated with Multi Drug Therapy. According to Ridlay and Jopling, all the patients were classified as the patients of Lepromatous Leprosy (LL).

The patients were divided into four groups. Group - I consisted of 40 patients having complicated plantar ulcer of different sizes, with loss of sensation of the hands and feet. In this study group, all the patients received homoeopathic medicine, whereas the Group – III was constituted with 10 patients having identical problem of Group I and was treated as control of Group I by giving placebo. Group – II consisted of 90 patients who were suffering from loss of sensation of the hands and feet without trophic ulcer and Group IV, the Control Group of Group II, included 20 patients having similar clinical signs of Group II which was on placebo. The grouping was done on the basis of lottery. All the patients were allotted a code number by a third agency. All the patients were subjected to sugar test. The estimation of blood glucose was carried out following the method described by Trinder. Serological test was carried out for all the patients for HIV in National Cholera and Enteric Diseases, Indian Council of Medical Research, Kolkata.

The skin biopsies were fixed in 10% formal-saline solution and processed for paraffin sectioning at 5µ thick following standard techniques and stained with routine haematoxylin and eosin. The duplicate sections were subjected to Enzyme label techniques for immunocytochemical study using Rabbit Anti- Cow S – 100 and (2) Goat Anti Rabbit Immunoglobulins HRP conjugated Polyclonal Rabbit Anti Human Factor VIII (make M/S DakoCytomation, Denmark A/S Produktionsvej 42, DK – 2600 Glostrup, Denmark) for quantative estimation of nerve cell and blood vessel.

One anti-syphilitic medicine Mercurius solubilis of 200 potency was given to all the patients of the study group once a week per os following the principle of treatment as described by Chakraborty and Adhikary for lepromatous leprosy. This principle was based on the method of generalization instead of individualization. The Methodical Pyramid (Fig - 1) in this study represented a triangular disposition. The Accumulated Similar symptoms (ASS) was the combination of symptoms derived from the disease symptoms, particular symptoms (related to a particular organ) and general symptoms. Six symptoms, like loss of sensation (anesthesia), aggravation of neuralgic pain in the extremities, mental restlessness, fear and sleeplessness at night with violent dreams, very sensitive to heat and cold, profuse thirst but moist mouth with profuse salivation and profuse sweating were considered as Accumulated Similar Symptoms and were observed in all the patients. Based on these ASS, the specific medicine was selected. This medicine was given for a period of two years or till recovery, whichever was earlier. In the case of deep and complicated ulcer, the patient showed the sign of fever and pain due to secondary infection and had swelling of the part with pus formation. In these cases, in addition to Mercurius solubilis, Kali. mur. 12x and Calc. sulph 12X were given four tabs, four times a day, till ulcer became free of discharge.
Fig. 1- Methodical Pyramid

ASS : Accumulated similar symptoms
GS : General symptoms
PS : Particular symptoms
DS : Disease symptoms

The assessment of healing of ulcer was based on the determination of the volume of the ulcer, calculated from the maximum length, breadth and depth, recorded at the time of first appearance and thereafter every three months. The assessment was done by a group consisting of a physiotherapist and a surgeon. Regarding the care of ulcer, daily dressing was done till the ulcer was dry and thereafter once a week, with dry gauge pack and bandage. Cleaning of ulcer was never done with soap and water, except on the first day of dressing. All the patients were allowed to perform normal activities and no one was advised rest because most of the patients were self dependent for their daily livelihood and were mainly from daily labour class. Throughout the treatment, no topical application was given. To monitor the medicine administration, all the medicines were given to the patients once a week on regular basis by the trained staff at their doorstep. To ensure double blind controlled study, no difference was maintained between medicine and placebo and both were supplied to the study group and control group respectively, in a similar type of phial with same instruction. To get a result free from bias, the paramedical staff, physiotherapist, clinician and surgeon were kept in dark about the placebo group and the medicine group.

Sensory nerve function testing of the palms of the hands and soles of the feet was carried out in each patient. Testing was carried out using ball-point pen, as described by Jean Watson at twelve standard points on each palm and on eleven points on the soles. On the palm, five points were taken as supplied by the ulnar nerve and seven for the median.

Touch sensation was tested using a standard set of coloured Semmes – Weinstein monofilaments. The monofilaments used were 200mg, 2g, 4g, 10g and 300g. Normal reference values were 200mg for hand and 10g for the foot. The test site and scoring methods are given as follows:

Test sites

On the ulnar side of the hand:
- a) Hypothenar eminence
- b) Fifth metacarpal head (MCP 5)
- c) Volar surface of the distal phalanx of the little finger

On the median side of the hand:
- a) Thenar eminence
- b) Volar surface of the distal phalanx of the thumb
- c) Volar surface of the distal phalanx of the index finger

For the radial cutaneous nerve:
- a) Dorsal on the thumb, at the site of the motor point

On the foot:
- a) Plantar surface of the distal phalanx of the big toe
- b) First metatarsal head
- c) Fifth metatarsal head
- d) Plantar surface near lateral border of the foot
- e) Lateral border of the foot (just distal from the head of the first metatarsal bone)
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Scoring

<table>
<thead>
<tr>
<th>Colour of filament</th>
<th>Approx. Force</th>
<th>Score</th>
<th>Colour of Filament</th>
<th>Approx. Force</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue filament felt</td>
<td>200mg</td>
<td>0</td>
<td>Purple filament felt</td>
<td>2g</td>
<td>0</td>
</tr>
<tr>
<td>Purple filament felt</td>
<td>2g</td>
<td>1</td>
<td>Red filament felt</td>
<td>4g</td>
<td>1</td>
</tr>
<tr>
<td>Red filament felt</td>
<td>4g</td>
<td>2</td>
<td>Orange filament felt</td>
<td>10g</td>
<td>2</td>
</tr>
<tr>
<td>Orange filament felt</td>
<td>10g</td>
<td>3</td>
<td>Pink filament felt</td>
<td>300g</td>
<td>3</td>
</tr>
<tr>
<td>Pink filament felt</td>
<td>300g</td>
<td>4</td>
<td>Pink filament not felt</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Pink filament not felt</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Motor nerve function testing was also carried out by physio-technicians on every patient using modified 5 point MCR scale.

Results

Of the fifty patients included in the Group I and Group – III, one patient of the control group (Group – III) was dropped out due to irregularity. The final analysis is, therefore, based on forty patients (22 males, 18 females) of the study group and nine patients (5 males, 4 females) of the control. The mean duration of the ulcer was 8.8 years of the study group and 8.7 years of the control group. The mean volumes of ulcer in the two groups on first day of appearance, at the end of three months, six months and nine months are presented in Table - I.

Table I. MEAN VOLUME OF ULCERS IN THE CONTROL AND STUDY GROUPS ON FIRST DAY OF APPEARANCE, AT THE END OF THREE, SIX AND NINE MONTHS

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Arithmetic mean volume and range (cu.mm) of the Ulcer at three different time-points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On first day of appearance</td>
</tr>
<tr>
<td>Control group</td>
<td>9125 (3696 – 24624)</td>
</tr>
<tr>
<td>Study group</td>
<td>16028 (90 – 107328)</td>
</tr>
</tbody>
</table>

In the study group (Group – I) mean decrease in the volume of ulcer, over that at first day of appearance, was 94.79% at the end of three months and 99.63% at the end of six months. At the end of ninth month, all the ulcers were completely healed. As shown in Table – I, the mean volume in the control group was 9125 cu.mm on the first day. The mean values for this control group at the end of three and six months were quite higher than the respective means in the study group. The increase in the mean volume of ulcer over that on the first day was 10.79% at the end of three months, 32.47% at the end of six months and 50.24% at the end of nine months. The rate of decrement in the mean volume of ulcer in the first three months was lower than the next three months, which was 17.77%. Total healing of the ulcer was observed in thirty eight patients of the study group at the end of sixth month. Two patients had ulcers of 1500 cu.mm and 864 cu.mm at the end of six months, which showed complete healing at the end of nine months. The photographs of the two patients of Group I at the time of first appearance at and the end of treatment are represented in Figures 2(a), 2(b), 3(a) & 3(b). The formation of new ulcers during the treatment was observed in two patients of the control group but none in those of the study group.
To study the effectiveness of the medicine, a non-parametric statistical test, Mann Whitney test, was carried out, which revealed that the medicine had improved the condition of the patients of the study group, over the control group. There has been significant reduction (at 1% level of significance) in the size of ulcers in the Study group compared to the control group.

90 persons of the study group (Group – II) had loss of sensation but no ulcer. Out of them, 35 showed complete regain of touch and pressure sensation. 35 patients showed relief of 80% or above. 11 patients were relieved to the extent of 60% or above, 5 patients 40% or above and 1 patient showed 20% and above regain of sensation. Three patients of the study group were not available for the last assessment, so eighty seven patients were taken for statistical analysis, as shown in Table-II. To undertake the statistical analysis, it was observed that there was no change in the control group over the time period of the study and hence the standard deviation of the difference in the scores of the patients in the control group was zero. Hence, no standard statistical tests could be carried out. So the 'Randomization test' (also called permutation test) was applied, which proved that the treatment had significantly improved the conditions of the patients of the study group.