



ORIGINAL RESEARCH PAPER

Dermatology

MDT THERAPY IN PAUCIBACILLARY LEPROSY: A CLINICOPATHOLOGICAL ASSESSMENT.

KEY WORDS: Histopathology, Leprosy, Skin Biopsy, MDT

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ABSTRACT

Background: Leprosy, is a chronic infectious disease affecting mainly the skin and nerves. Use of MDT improved the compliance of patients. However, persisting activity, reactions and relapses have been observed in a section of these patients, and above all classification itself poses problems in the field setup at times. To overcome this, and to benefit the field staff, Uniform MDT (UMDT) has been advocated.

Objectives: This study was conducted to evaluate the clinical and histological advantages of adding clofazimine in PB patients.

Material and Methods: All new patients who were diagnosed to have PB leprosy attending the outpatient department of Skin and VD at CCM Medical College, Durg (CG), between January 2016 to June 2017 were included in the study. The number and morphology of lesions and anaesthesia were recorded. The site and thickening of the nerve trunk was noted. Slit-skin smear was done from all patients and only smear-negative patients were included. Skin biopsy was done after obtaining a written consent from the margin of the lesion. After confirming the diagnosis alternate patients were started on PB and MB regimens. Patients were followed up every month when changes in the skin and nerve trunk lesions were recorded.

Results: Forty four patients completed the study including one year of follow-up. There were 32 males and 12 females. The age group ranged from 10 to 72 years with a mean age of 25.8 years. Clinical improvement, revealed that out of 26 patients with Grade-IV resolution, 20 patients received MB regimen. Improvement in nerve thickening, revealed 70% improvement with the MB regimen. We did not encounter side effects of antileprosy drugs in the study group.

Conclusion: To conclude, the addition of clofazimine in the PB regimen is fully justified adding strength to the concept of Uniform MDT (U-MDT).

Introduction:

Leprosy is a chronic infectious disease caused by *M. leprae*. It affects mainly the peripheral nerves. It also affects the skin, muscles, eyes, bones, testes and internal organs.¹ The South East Asian region accounts for about 66.21% of the global prevalence and 71% of all new detected cases at the end of first quarter of 2013.² The National Leprosy Control Programme was launched in 1954 in India and converted to National Leprosy Elimination Programme (NLEP) in 1983 with the objective to eliminate leprosy.¹ With the introduction of MDT (Multi Drug Treatment) since 1983 as recommended by the WHO study group, India has achieved the goal of elimination of leprosy in December 2005.³ A total of 0.92 lakh cases are on record as on 1st April 2013, giving a Prevalence rate (PR) of 0.73 per 10,000 population.⁴

Leprosy, is a chronic infectious disease affecting mainly the skin and nerves.⁵ The World Health Organization (WHO) classified leprosy into paucibacillary (PB) and multibacillary (MB) on the basis of the number of patches on the skin and number of nerves involved. PB patients are those who have five or less than five patches and up to one nerve trunk involvement. WHO recommended Multi Drug Therapy (MDT) for the treatment of leprosy in the year 1981. MDT improved the compliance of patients. However, persisting activity, reactions and relapses have been observed in a section of these patients, and above all classification itself poses problems in the field setup at times.⁶ To overcome this, and to benefit the field staff, Uniform MDT (UMDT) has been advocated. Clofazimine-containing regimen have an added advantage that the same drugs may be given for varying durations depending upon the clinical classification.^{7,8}

Aims and objectives:

This study was conducted to evaluate the clinical and histological advantages of adding clofazimine in PB patients.

Material and methods:

All new patients who were diagnosed to have PB leprosy attending the outpatient department of Skin and VD at CCM Medical College, Durg (CG) and Pt. JNM Medical College, Raipur (CG) between January 2016 to June 2017 were included in the study. The patients were classified according to the WHO guidelines. The

number and morphology of lesions and anaesthesia were recorded. The site and thickening of the nerve trunk was noted. Slit-skin smear was done from all patients and only smear-negative patients were included. Skin biopsy was done after obtaining a written consent from the margin of the lesion. Histology of PB leprosy was considered when there was a granuloma composed of epithelioid cells with a rim of lymphocytes along with dermal Langhan's giant cells and cutaneous nerves showing granulomatous destruction with intact perineurium. After confirming the diagnosis alternate patients were started on PB and MB regimens. Patients were followed up every month when changes in the skin and nerve trunk lesions were recorded. A complete evaluation was done at the end of six months. Criteria for clinical resolution in the skin and nerve lesions, histological resolution in the dermal infiltrate and in the nerves are shown in Table 1. The results were analyzed by Fisher's exact test and by Cramer's V test.

Table 1: Grading response to therapy

| Grades | Description |
|--|---|
| Clinical features – Skin lesions | |
| I | Increase in the activity of the lesion in either size, shape, erythema or appearance of new lesion. |
| II | No change in the existing lesion. |
| III | Regression, which means reduction of less than 1 cm in the size of the lesion and decrease in erythema. |
| IV | Marked improvement, which means a reduction of more than 1 cm in the size of the lesion, disappearance of erythema and satellite lesion if any. |
| Clinical features – Nerve lesions | |
| I | Increase in activity, which means increase in the thickness of the nerve or tenderness or new nerve involvement. |
| II | No change. |
| III | Decrease in thickening of the nerve and tenderness. |
| Histopathology – Skin lesions | |
| I | Active: dermal infiltration by epithelioid granulomas. |
| II | Resolution: organized epithelioid granulomas were not seen but lympho-histiocytic infiltrate in < 10% of the initial lesion. |

Results:

The number of new leprosy patients during the study period comprised 0.35% of all new dermatology outpatients. 50 patients were enrolled in the study. One patient who was clinically diagnosed as PB leprosy showed many macrophages in the biopsy and hence was not included in the analysis. Another 5 patients dropped out of the study for various reasons. 44 patients completed the study including one year of follow-up. There were 32 males and 12 females with a ratio of 4:1.5. The age group ranged from 10 to 72 years with a mean age of 25.8 years. Twenty-eight patients (63.7%) were in the age group of 11-30 years. Twenty-six patients (89%) had single ill-defined plaque with satellite lesions. Six patients had two lesions and 12 patients had three lesions. Nerve trunk was thickened in 36 patients (81.8%) only. The two groups receiving PB and MB leprosy are compared as shown in **Table 2**. Clinical improvement shown in **Table 3**, revealed that out of 26 patients with Grade-IV resolution, 20 patients received MB regimen. Improvement in nerve thickening as shown in Table 3, revealed 70% improvement with the MB regimen. Histological changes at the end of therapy between the two groups were compared and are shown in **Table 3**. Features of inactivity were seen in 12 out of 22 PB patients and in 16 out of 22 MB patients. We did not encounter side effects of antileprosy drugs in the study group. One patient on MB regimen developed reversal reaction, during the last month of treatment, which resolved with a short course of corticosteroids. The clinical and histological parameters for patients followed up for one year are shown in **Table 4**.

Table 2: Comparison of Pauci Bacillary and Multi Bacillary Group

| Characteristics | PB Group | MB Group |
|----------------------------|----------|----------|
| Mean age | 28.2 | 22.6 |
| Male | 14 | 18 |
| Female | 7 | 5 |
| Single ill defined lesions | 12 | 14 |
| Nerve involvement | 16 | 20 |

P value for above parameters didn't showed any difference

| Clinical features | | |
|-----------------------------|---------------|---------------|
| Grade | PB Group | MB Group |
| I | 0 | 0 |
| II (no change) | 16/22 (72.7%) | 2/22 (9.1%) |
| III | 0 | 0 |
| IV (marked improvement) | 6/22 (27.3%) | 20/22 (90.9%) |
| p<0.05 | | |
| Nerve lesions | | |
| Grade | PB Group | MB Group |
| I | 0 | 0 |
| II (no change) | 10/16 (62.5%) | 6/20 (30%) |
| III (decrease in thickness) | 6/16 (37.5%) | 14/20 (70%) |
| P value<0.05 | | |
| Histopathological features | | |
| Grade | PB Group | MB Group |
| I (active) | 8/22 (36.4%) | - |
| II (resolution) | 2/22 (9.1%) | 6/22 (27.8%) |
| III(inactive) | 12/22(54.5%) | 16/22 (72.8%) |
| Cramers V test p < 0.07 | | |

Table 3: Comparison of improvement in the two groups at 6 months

| Table 4: Comparison of 2 groups at 1 year after therapy | | | | |
|---|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Group | Clinical resolution | Nerve examination | Histological I resolution | Histological II resolution |
| | Grade IV Marked improvement | Grade III Decrease thickness | Grade II Resolution | Grade III Inactive |
| PB | 20/22 (90.1%) | 14/16 (87.5%) | 5/22 (22.7%) | 17/22 (77.3%) |

| | | | | |
|--|--------------|--------------|-------------|---------------|
| MB | 22/22 (100%) | 20/20 (100%) | 1/22 (4.5%) | 21/22 (95.5%) |
| No difference between 2 groups p = 0.85 | | | | |

Discussion:

Epidemiological parameters like age, sex and duration of the disease were comparable with other studies in the country.⁹ There was also no statistical difference among the various parameters between the PB and MB groups. The criteria for clinical and histological resolution were modified from Kar et al.¹⁰ In contrast to bacillary positive patients, the cure or end point of treatment of smear-negative patients has been more difficult to define. The PB regimen has been in use for more than 15 years. On the whole the experience of workers in several parts of the world has been quite encouraging. However, a few difficulties have been encountered. The continued visibility of a clinically active lesion in a proportion of patients at the end of 6 months' therapy has been observed in practically all studies. The proportion of cases with active disease at the end of the stipulated six months of treatment varied from 10 to 67% in various studies at the field and institutional levels. On the follow-up of these patients clinical activity gradually subsided and the disease was cured in 30 to 80%. The remaining patients continued to have the disease beyond a period of 18 months. For this reason some workers recommended continuation of dapsone or continuation of PB regimen for six more months.¹⁰ Late reversal reaction was another problem observed, which occurred after six months of stopping treatment. For this group also, extended therapy has been suggested. The same regimen for PB and MB patients is the first step in the simplification of the treatment of leprosy.

In our study, addition of clofazimine has proved its worth. Ninety-one per cent of patients have shown Grade-IV clinical improvement. Clofazimine is also a weak bactericidal drug, which has a long half-life of 70 days. It also has anti-inflammatory property. Clofazimine, which binds to mycobacterial DNA, inhibits mycobacterial growth and exerts a slow bactericidal effect on *M. leprae*. As continued inflammatory response results in persistent activity in leprosy, addition of clofazimine helps in PB patients. We have adopted a criterion, to assess the improvement in the nerve, which is similar to the clinical criterion. There are no definite parameters available to assess cure for neuritic leprosy cases.¹⁰ Criteria for assessment and cure are highly controversial. Among the 36 patients with one nerve trunk involvement, MB regimen showed 70% improvement and hence we considered it superior.

When the pathology is evident on the surface, whether it is right to call the disease as cured, has remained an issue. The basic misconception about the Fixed Duration Therapy (FDT) in PB leprosy, is the time taken for regression of granuloma. Job et al¹¹ in their study conducted in 1997 found that 11 out of 22 patients remained active after six months and only three after 18 months. He recommended anti-inflammatory drugs or chemotherapy whenever necessary. Ebenezer et al¹² followed up 24 patients and found that only eight patients remained active after six months. She stressed the need for sequential histopathological studies and longer follow-up of patients with active lesions at the time of completion of treatment. In our study we found that granulomas regressed faster if clofazimine was added to the PB regimen. All 22 patients showed resolution and 73% revealed Grade-III resolution in comparison to 55% in the PB group. After one year of follow-up, the study group revealed that all patients in the MB regimen group showed clinical resolution. This included two patients who were in Grade-II initially. In the PB group, except two patients, others showed resolution. Both those cases were males who showed three ill-defined patches and one nerve trunk involvement. Histological resolution occurred much later than clinical resolution. Five out of eight patients with PB therapy moved from Grade I to II after one year of treatment. Similarly, five out of six patients with MB therapy moved from Grade II to III. These findings are comparable with similar studies by Job.¹¹

The final outcome in both the groups is almost similar and there is no statistical difference. On the contrary, all 26 patients who initially showed erythematous ill-defined plaques responded well

to treatment and the lesions showed a Grade III response at the end of one year post-treatment. Studies at the Central Jalma Institute of Leprosy have shown that a good number of patients diagnosed as PB leprosy clinically were acid-fast bacilli positive in the skin smear indicating their chances of getting inadequate treatment under the present program. Besides these patients would be prone for relapse.¹³ Clofazimine is cost-effective, especially when compared to its advantages.

Limitations of study:

As it is a single centre study with a relatively small study population, results cannot be generalized to the entire population.

Conclusion:

To conclude, the addition of clofazimine in the PB regimen is fully justified adding strength to the concept of Uniform MDT (U-MDT).

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