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Original Research Article

Effect of clofazimine on nerve function impairment in pauci-bacillary leprosy patients

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ABSTRACT

Background: Clofazimine is a riminophenazine derivative which is useful both for treating the leprosy and managing reactive episodes. Previous studies demonstrated that clofazimine may have a useful prophylactic role against neuritis/type 1 reaction and nerve damage. The WHO Technical Advisory Group (TAG), in its Third meeting in 2002, proposed that uniform MDT regimen (U-MDT) of 6 months duration should be considered to treat all types of leprosy. This study was aimed to determine any additional beneficial effects of clofazimine as part of UMDT in the prevention of nerve function impairment (NFI) in paucibacillary (PB) leprosy patients.
Methods: Sixty paucibacillary leprosy patients were randomized into two groups, A and B consisting of 30 patients each. Group A received U-MDT for 6 months and group B received MDT-PB for 6 months. Nerve function assessment (NFA) using various modalities was done at the beginning (0 month) and at the completion of MDT (6 months) and results were compared.
Results: No statistically significant difference in improvement or deterioration of NFI was found in two groups.
Conclusions: On the basis of present study, we found that addition of clofazimine in standard dose as part of U-MDT has no beneficial role in prevention or improvement of NFI in PB leprosy patients. However, a larger longitudinal study taking substantial number of population in both groups might be helpful to derive any conclusion.

Keywords: Clofazimine, Uniform-MDT, Paucibacillary, Nerve function impairment

INTRODUCTION

Nerve function impairment (NFI) denotes the sensory, motor and autonomic nerve function deficit occurring singly or in combination of these. Episodes of type 1 and type 2 reactions in leprosy (delayed hypersensitivity and immune complex mediated reactions respectively) can cause neuritis, leading to further deterioration of the primary nerve function impairment. NFI varies from 6–56% in newly diagnosed patients with leprosy and can even deteriorate during and after treatment as a result of leprosy reactions.[1]

Early detection of nerve involvement at the time of diagnosis or during a leprosy reaction is important so that adequate treatment can be started to prevent further nerve function impairment. Regular nerve function assessment is essential for detection of silent neuritis at an early stage and prevention of permanent nerve function impairment.[2] The utility of nerve conduction studies (NCS) in the detection and monitoring of nerve function impairment in leprosy and other neuropathies have been well established.[3] we have compared different modalities of nerve function assessment (NFA) to identify patient at risk of deterioration of nerve function.

Clofazimine is a riminophenazine derivative that is bacteriostatic and anti- inflammatory; thus it is useful both for treating the disease and managing reactive episodes. The anti-inflammatory effect of clofazimine first suggested by Browne has proved to be effective in controlling erythema nodosum leprosum (ENL).[4] It has also limited use in type 1 reaction, as it took 3-4 months to act and by then irreversible nerve damage had occurred.[5] Earlier study by Arunthati et al demonstrated that clofazimine may have a useful prophylactic role against neuritis / type 1 reaction and nerve damage.[6] But this study used a modified regimen, consisting of initial high doses of clofazimine for 3 months followed by regular multibacillary multidrug therapy (MB-MDT) in high risk borderline leprosy patients.

The WHO Technical Advisory Group (TAG), in its third meeting in 2002, proposed that uniform MDT regimen (U-MDT) of 6 months duration should be considered to treat all types of leprosy.[7] As WHO has advised U-MDT in all leprosy cases, we hereby attempted to study any additional beneficial effects of clofazimine as part of U-MDT in the prevention of nerve function impairment in paucibacillary leprosy patients.

METHODS

Sixty consecutive patients of leprosy classified as paucibacillary (PB) type according to present WHO classification attending the Urban Leprosy Centre (ULC) of Post Graduate Institute of Medical Education and Research (PGIMER) and Dr. Ram Manohar Lohia Hospital, New Delhi from September 2011 to February 2013, were included in the study. All paucibacillary leprosy patients were randomised in two groups A and B each containing 30 patients. Patients presented with type 1 reaction, hypersensitivity to any of the drug used in MDT and patients who already receiving or have received specific treatment for leprosy in past were excluded.

All patients underwent complete history, physical examination including clinical palpation of peripheral nerves for nerve thickness, tenderness and consistency. Slit skin smears (SSS) with Ziehl Neelsen staining were done in all patients. At least 100 oil-immersion fields of the smears were examined for the presence of acid fast bacilli (AFB) and any patient with slit skin smear positivity excluded from study. Skin biopsy from the inner margin of the largest skin lesion was stained by haematoxylin and eosin (H&E). The tissue sections were examined for diagnostic histopathological changes. Group A received Uniform MDT (U-MDT) regimen for 6 months and group B received MDT-PB regimen for 6 months. In both groups nerve function assessment (NFA) was done at the beginning (0 month) and at the completion of MDT (6 months) and results were compared. Sensory nerve function assessment was carried out using Semmes Weinstein monofilaments (MF) and sensory nerve conduction study (SNCS). Motor nerve function assessment was carried out using voluntary muscle testing (VMT) using medical research council (MRC) grading for muscle strength and motor nerve conduction study (MNCS). The data was collected after treatment and number of patients showing improvement, deterioration and no change on nerve function assessment in both groups were compared. Nerve function assessment was done by following methods

A) Nerve palpation (NP)

All patients in both groups were thoroughly examined for any peripheral and cutaneous nerve thickening, nodularity, abscess formation, and tenderness. Nerve thickening was graded in to four groups (0, 1, 2, and 3) according to WHO grading as shown in Table 1. Criteria for improvement and deterioration mentioned as below.

Improvement – Reduced score from 3+ or 2+ to 1+/0,
Deterioration– Increased score to 3+ or 2+ or 1+.

Table 1: WHO grading of nerve thickness.

Grade	Degree	Description
0	Not thickened	Nerve not thickened and feels normal
1	Mild thickened	Thickened compared to contra lateral side
2	Moderate	Thickening is rope like
3	Severe	Nerve thickened and also nodular or beaded

B) Touch sensibility testing using monofilaments (MF)

Touch sensibility was tested with a standard set of five colored Semmes–Weinstein monofilaments (MF) as described by Krotoski.[8] Patients were tested according to site of skin lesions as mentioned below.

Upper limbs: Ulnar, median, radial nerves were tested using monofilaments

Lower limbs: Deep peroneal, posterior tibial nerves were tested using monofilaments.

Patients who had leprosy lesion on face were excluded from MF testing as well as sensory nerve conduction studies of upper and lower limbs. So 3 patients in group A and 4 patients in group B were excluded hence 27 patients in group A and 26 patients in group B were tested for MF and sensory nerve conduction study.

The monofilaments used were 0.05 g (green), 0.2 g (blue), 2 g (purple), 4 g (red), 10g (orange) and 300 g (light red). Normal reference values were up to 200 mg for hands and 2 g for the foot. Test sites used are shown in Figure 1. Sensory impairment was diagnosed in the following situations: a) The monofilament threshold increased by 3 or more levels in one site or, b) By 2

levels in one site and 1 level in another site or, c) By 1 level in all 3 sites for a nerve tested.

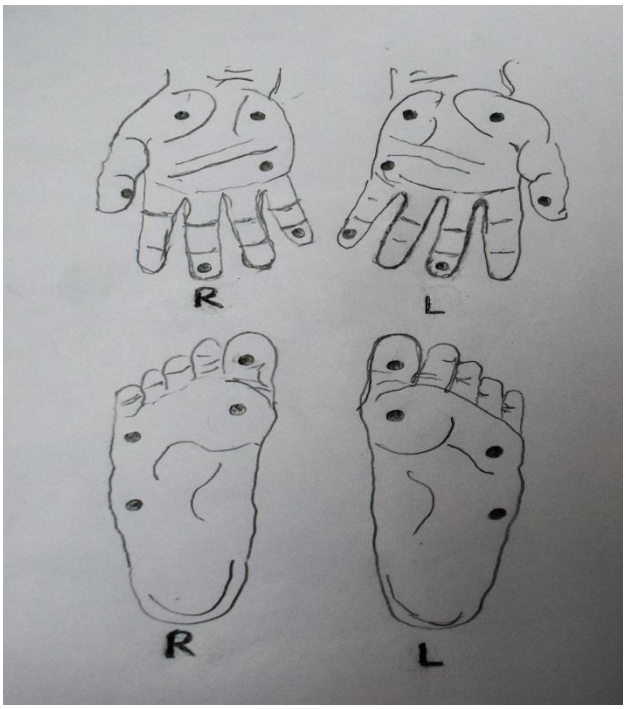

Figure 1: Test sites for clinical sensory testing using SW monofilaments.

Criteria for improvement and deterioration on MF testing: Improvement/Deterioration-increment/ decrement in score by ≥1 point (mild), ≥2 points (moderate), ≥3 (severe).

C) Voluntary muscle testing (VMT)

This was done using the modified Medical Research Council (MRC) scale.[9] Patients were tested for respective nerves on VMT according to site of skin lesions as mentioned below.

Head and neck: facial nerve trunk: ulnar and common peroneal nerve upper limbs: ulnar, median, radial nerve lower limbs: common peroneal nerve.

Patient who had muscle scoring less than grade 5 considered as motor impairment.

Criteria for improvement and deterioration on VMT testing:

Improvement/Deterioration-increment/decrement in score by ≥1 point (mild), ≥2 points (moderate), ≥3 (severe).

Nerve conduction study

Electrophysiological studies were done using a Sierra Wave 4 channel combined electromyography, Nerve conduction/evoked potential machine (cadwell, USA). The testing room temperature was maintained at around 26°C (confirmed using ambient thermometers). Patients were allowed to acclimatise for 15 minutes before testing.

Sensory nerve conduction study

Sensory nerve conduction study (SNCS) parameters were measured on three nerves (ulnar, median and sural). The sensory conduction velocities were recorded from the wrist after index finger and fifth finger stimulation for the median and the ulnar nerve, respectively. The recordings from the lateral malleolus after stimulation of the leg's midline were used for the sural nerve. The amplitudes, distal and peak latencies and sensory nerve conduction velocities were studied.

Sensory nerve conduction study (SNCS) parameters were measured in nerves corresponding to site of skin lesions.

- Upper limb: Ulnar and median nerve
- Lower limb: Sural nerve
- Trunk: Ulnar nerve
- Head and neck: No SNCS parameters were measured.

Motor nerve conduction study (MNCS)

Monopolar surface recording electrodes were used to obtain the compound muscle action potentials (CMAP). Motor nerve conduction (MNCS) parameters were measured in nerves corresponding to site of skin lesions.

- Head: Facial nerve
- Trunk: ulnar and common peroneal nerve
- Upper limb: Ulnar and median nerve
- Lower limb: Tibial and common peroneal nerve

Criterion for nerve function impairment by sensory and motor nerve conduction studies (NCS)

Patient showing deterioration in any parameter of NCS of any nerve was counted as deteriorated. If any nerve tested for SNCS and/or MNCS found abnormal by any one parameter (latency, amplitude, velocity), it considered as abnormal.

Criteria for improvement and deterioration on SNCS/MNCS testing:

Improvement/Deterioration-increment/decrement of abnormal baseline values by 15% or attainment of normal values for the parameters of latency/conduction velocity and/or amplitude.

The data thus obtained was pooled and analyzed with Statistical Package for Social Sciences (SPSS 17) and significance of associations were tested using Chi-square and Fisher's exact tests.

RESULTS

Baseline demographic and clinical characteristic of both groups are shown in Table 2. Both groups were comparable in terms of demography, clinical features, disability grading, histopathology and type 1 reaction.

Table 2: Baseline demographic and clinical characteristics of study population.

	Group A	Group B
Mean age (range)	24.3 (10-52) years	29.7 (8-60) years
Sex ratio (M:F)	5:1	4:1
Family history positive	6.6%	3.3%
Distribution according to no. of skin lesions (0,1,2,3,4,5)	(1,11,11,5,1,1)	(3,6,10,7,3,1)
Patients with WHO disability grading (0,1,2)	(25,4,1)	(24,5,1)
Histopathology (I:TT:BT)	(3,3,23)	(1,1,25)
Type 1 reaction in both group	6.6%	3.3%

Table 3 shows number of patients showing improvement and deterioration of nerve function at the end of 6 months by different modalities.

At the time of registration, 16 patients in group A (53.33%) and 18 patients (60%) in group B presented with thickened peripheral nerve. In group A, improvement in nerve thickening was seen in only one patient (3.33%), deterioration in two patients (6.67%) and no change in 27 patients (90%). In group B improvement in nerve thickening was not seen in any patient (0%), deterioration in one patient (3.33%) and no change in 29 patients (96.67%). No statistically significant difference in improvement and deterioration of nerve thickening was found in both groups (p>0.05). In group A, 16 patients had nerve thickening out of which 14 patients showed NFI on clinical and nerve conduction studies. Out of 14 patients with no nerve thickening, 7 patients had NFI on clinical and nerve conduction studies. While in control group 18 patients had nerve thickening of which 16 patients showed NFI on clinical and nerve conduction studies. Out of 12 patients with no nerve thickening, 7 patients had NFI on clinical and nerve conduction studies.

In group A, 27 patients were tested for nerve function assessment by MF test of which 9 patients (33.33%) had Nerve function impairment (NFI) and 18 (66.67%) patients were normal before treatment. After completion of treatment, deterioration was seen in 6 patients (22.22%) whereas improvement was not seen in any patient. In group B, Total 26 patients were tested for nerve function assessment by MF test of which 12 patients (46.15%) had NFI and 14 patients (53.85%) were normal before treatment. After completion of treatment deterioration was seen in 10 patients (38.46%). Improvement was seen in one patient (3.85%). Most commonly affected nerve was ulnar. No statistically significant difference in improvement or deterioration of NFI by MF test was found in two groups (p>0.05).

Table 3: Number of patients showing improvement and deterioration of nerve function at the end of 6 months by different modalities.

	At 0 month	At the end of 6 months I D NC
On nerve palpation	Group A N 14	0 0 14
	EN 16	1 2 13
	Total 30	1 2 27
	Group B N 12	0 0 12
	EN 18	0 1 17
	Total 30	0 1 29
On monofilament testing	Group A N 18	0 3 15
	AB 9	0 3 6
	Total 27	0 6 21
	Group B N 14	0 5 9
	AB 12	1 5 6
	Total 26	1 10 15
On voluntary muscle testing	Group A N 25	0 2 23
	AB 5	2 0 3
	Total 30	2 2 26
	Group B N 24	0 2 22
	AB 6	1 2 3
	Total 30	1 4 25
On sensory nerve conduction study	Group A N 15	0 5 10
	AB 12	1 4 7
	Total 27	1 9 17
	Group B N 12	0 2 10
	AB 14	0 5 9
	Total 26	0 7 19
On motor nerve conduction study	Group A N 23	0 2 21
	AB 7	3 2 2
	Total 30	3 4 23
	Group B N 19	0 3 16
	AB 11	1 5 5
	Total 30	1 8 21

N=number of patients without nerve function impairment AB=number of patients with nerve function impairment, I=Improvement, D=Deterioration, NC=No change.

In group A, 30 patients were tested for motor power by VMT, 25 patients (83.33%) were normal and 5 patients (16.67%) had NFI before treatment. Improvement was seen in 2 patients (6.67%) while deterioration was seen in another 2 patients (6.67%) after treatment. In group B, 30 patients were tested for motor power by VMT, 24 patients (80%) were normal and 6 patients (20%) had NFI before treatment. Improvement was seen in 1 patient

(3.33%) while deterioration was seen in 4 patients (13.33%) after treatment. No statistically significant difference in improvement or deterioration of NFI was found in two groups (p>0.05).

In present study among group A, out of 27 patients tested on sensory nerve conduction study (SNCS), 12 patients (44.44%) had sensory NFI and 15 patients (55.56%) were normal before treatment. 9 patients (33.33%) were deteriorated while 1 patient (3.70%) was improved after treatment. In group B, out of 26 patients tested on sensory nerve conduction study 14 patients (53.85%) had sensory NFI and 12 patients (46.15%) were normal before treatment. Seven patients (26.92%) were deteriorated after treatment. Not even a single patient was improved after treatment. No statistically significant difference in improvement or deterioration of sensory NFI was found in two groups (p>0.05). In our study, SNCS detected NFI in additional 3 patients in group A and 2 patients in group B before treatment, which was not detected by MF testing. This shows higher sensitivity of nerve conduction study than MF test in detecting NFI.

In group A, Out of 30 patients tested for motor nerve conduction study (MNCS), 23 patients (76.67%) were normal and 7 patients (23.33%) had NFI, before treatment. After treatment, 4 patients (13.33%) were deteriorated while 3 patients (10%) were improved. In group B, out of 30 patients tested for motor nerve conduction study, 19 patients (83.33%) were normal and 11 patients (16.67%) had motor NFI before treatment. 8 patients (26.66%) were deteriorated while 1 patient (3.33%) was improved after treatment. No statistically significant difference in improvement or deterioration of motor NFI was found in two groups (p>0.05).

In our study, MNCS detected NFI in additional 2 patients in group A and 5 patients in group B before treatment, which was not detected by VMT. It shows higher sensitivity of MNCS in detecting NFI than VMT. In present study T 1 R occurred in 2 patients in group A while in 1 patient in group B. These were mild in nature in all 3 patients and managed with oral non-steroidal anti-inflammatory drugs only. No statistically significant difference in occurrence of T 1 R was found in two groups (p>0.05).

DISCUSSION

Nerve thickening is important risk factor for development of NFI but non-thickened nerves are also at risk of NFI which can be detected on clinical tests (MF+VMT) and nerve conduction studies. Persistence of nerve thickening after treatment was observed in more than 95% of the patients in our study, which is not in concordance with study by Porichha et al.[10] This may be because of shorter time period of follow up of 6 months as compared to 5 years in study by Porichha et al.[10] The most commonly involved nerve in our study was ulnar nerve followed by common peroneal nerve. These findings are in concordance with earlier study.[11] we selected monofilament testing over ball point pen because higher sensitivity of earlier in detecting NFI which was demonstrated by Koelewin et al.[12]

Previous study recommended that all leprosy patients should have nerve function assessment at every visit to clinic to prevent deformities by early detection and treatment of NFI.[2] The interpretation of electrophysiological functions of nerve trunks is usually based on the analysis of three basic criteria - velocity, latency and amplitude of evoked response. Our study finding shows higher sensitivity of nerve conduction study than MF in detecting NFI which is in concordance with study by Khambati et al.[13] Also further improvement and deterioration in NFI was more readily seen on SNCS than MF test.

Slowing of conduction velocities in MNCS has been observed in patients without any clinical abnormality.[14] Reduced conduction velocities in clinically normal nerves probably represent the preclinical stage (without symptoms and signs) of damage which becomes manifest when certain defined quantum of nerve fibres becomes non-functional. It has been observed that even though clinically normal, 16% among ulnar and 20% among median nerves were electrically abnormal in leprosy. In our study also, even clinically normal nerves showed NFI on nerve conduction studies.

It is said that latency changes occur much earlier than amplitude or conduction velocity changes in compression neuropathies.[15] Leprosy is being a mixed neuropathy such presentations were not seen because compression occurs rather late in leprosy in comparison to inflammatory demyelination. Our study results are in concordance with earlier studies, which detected that in a significant proportion of cases, sensory velocity was at the lower limit of normal or slightly delayed while amplitude and duration of action potential is normal range. These findings suggest that leprosy results in diffuse neuropathy even at a stage where it cannot be detected by routine clinical testing.[16]

It was interesting to note that the conduction velocities never reached zero i.e., some conduction continued to occur even in cases which showed no response on clinical testing for sensory-motor functions.[17] It might be due to discharges from regenerating nerve fibres. Prasad et al reported the use of MB- MDT therapy in paucibacillary leprosy in which they concluded that addition of clofazimine helps to resolve leprosy lesion both clinically and histologically thus justifying the concept of uniform MDT regimen for all patients.[18]

Schreuder et al suggested the long term treatment with high dose of clofazimine in chronic recurrent steroid dependent ENL.[19] Earlier study by Arunthathi et al found that clofazimine has useful prophylactic role against neuritis/type 1 reaction.[6] However, no studies

investigating the possible efficacy of clofazimine as part of U-MDT in the prevention of nerve function impairment have been reported.

On the basis of our study, we found that addition of clofazimine as part of U-MDT has no beneficial role in prevention or improvement of NFI in PB leprosy patients. These findings are not in concordance with previous work by Arundhathi et al. It may be because of inclusion of only paucibacillary patients in present study while Arunthathi et al included high risk patients in their study (BL, BT-BB with three or more nerves involvement) where incidence of T 1 R was high. Another reason might be the use of low dose clofazimine in our study. It is possible that sufficient tissue level of drug might not achieved with daily 50 mg of clofazimine. However, a larger longitudinal study taking substantial number of population in both groups might be helpful to derive any conclusion.

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