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Original Articles

A COMPARATIVE TRIAL OF SINGLE DOSE CHEMOTHERAPY IN PAUCIBACILLARY LEPROSY PATIENTS WITH TWO TO THREE SKIN LESIONS

2-3 Lesion Multicentre Trial Group*

A multicentric, double-blind, controlled, clinical trial was carried out to compare the efficacy of a combination of rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg (ROM) administered as single dose with that of standard WHO/MDT/PB six months regimen. The study subjects were 236 previously untreated, smear-negative patients, without nerve trunk involvement and having only two or three skin lesions. Randomization was done on individual patient basis. Results were analyzed for mean clincal score for improvement, marked clinical improvement and complete clinical cure at the time of release from treatment and at 12 months and 18 months of follow-up.

Clinical improvement was seen in most patients in both regimens. Marked improvement (i.e., more than 90% reduction in clinical score) at 18 months was seen in 46.2% and 53.4% of the patients treated with ROM and standard regimens, respectively. But, significant difference in favour of standard PB regimen was seen in patients with three skin lesions and in patients in whom more than one body part was affected. Reversal reaction and adverse drug reactions were minimal in both groups.

INTRODUCTION

An international study group convened in October 1981 by World Health Organization (WHO) made a significant recommendation that patients with paucibacillary (PB) leprosy should be treated for six months with a combination of two drugs, dapsone (daily) and rifampicin (monthly). With the introduction of multidrug therapy (MDT) since then, prevalence of leprosy has dramatically declined. With this regimen, the relapse rate among patients with PB leprosy

*The details of the composition of this group is given at the end of this paper.

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is only around 1% over nine years of suryeillance (WHO 1995). Attention was still focussed on two issues, drug compliance among patients with PB leprosy and further shortening the duration of chemotherapy for PB leprosy, especially for cases with a single lesion. The search for newer drugs and shorter regimens therefore, continued. During the last decade, a large number of bactericidal drugs have been tested for anti *M. leprae* activity and their potential for clinical use (Gelber 1987, Grosset et al 1988, Franzblau & White 1990). It has been shown that monthly dose of rifampicin, 600 mg, is almost as effective as daily rifampicin (Ji et al 1996). It has been established that a single dose of rifampicin (600 mg) exerts a very strong bactericidal effect on *M. leprae* (Levy et a1 1976, Ji et al 1992). Addition of ofloxacin 400 mg and minocycline 100mg, has the potential to prevent the selection of rifampicin-resistant mutants, if any, in skin-smear negative PB leprosy where the bacterial population is expected to be well below one million (WHO 1982). It has been shown in a multicentric double-blind controlled clinical trial that a combination of rifampicin, ofloxacin and minocycline (ROM), administered as a single dose, was almost as effective as the standard six-month PB/MDT regimen in the treatment of single-lesion PB leprosy, and the frequency of occurrence of mild side-effects and leprosy reactions was less than 1% with the single dose ROM regimen (Single Lesion Multicentre Trial Group 1997). Since PB leprosy constitutes the major part of the case load in endemic regions, it was considered to extend this regimen to cover patients with two to three skin lesions in whom also the number of leprosy bacilli is expected to be well below one million and a single dose ROM might be sufficient to treat these patients.

A multicentric double-blind randomized controlled clinical trial was undertaken with the objective to compare the efficacy of ROM, administered as a single dose, with that of the standard six-months WHO PB/MDT regimen in the treatment of PB leprosy patients with 2-3 skin lesions.

MATERIAL AND METHOD

PATIENTS

Based on clinical and bacteriological examination, PB leprosy patients with two or three skin lesions, who were skin-smear negative, and were previously untreated and having no evidence of any peripheral nerve trunk involvement (no nerve trunk thickened/tender), were included in the trial.

Children below five years of age, pregnant women, patients known to be allergic to any of the proposed drugs or their derivatives, and those who were HIV positive (if tested), were excluded from the trial.

SAMPLES

In all, 236 patients were included in the study, 118 each to the study group (ROM single dose) and the control group (WHO/PB regimen) by random allocation. It was necessary to have a sample size of atleast 100 patients in each arm for equivalence study for 50% efficacy in terms of complete clearance of lesions with 80% of power and 20% permissible difference (μ =0.05).

REGIMEN

ROM (Study) Regimen: rifampicin (600 mg), ofloxacin (400 mg) and minocycline (100 mg), administered as a single dose (Children were given half the dose).

Standard (Control) Regimen: six-months WHO PB/MDT, i.e. rifampicin (600 mg) monthly and dapsone (100 mg) daily for six months (children were given appropriate dose).

PARTICIPATING CENTRES

Five centres participated in the study, namely, CJIL Field Unit (now part of NIE, ICMR), Avadi, District Leprosy Officer, Chennai city, The Leprosy Mission Hospitals at Barabanki and Naini and Tuberculosis Research Centre (ICMR), Chennai.

TRIAL PROCEDURE

Intake of patients was spread over seven months, from October 1995 to April 1996. Information on patient identification particulars and medical history was collected and informed consent obtained. In all, 236 patients (163 adults and 73 children), from the five centres were allocated randomly to either of the two regimens following random permutation of two digits (0,1) by using Statistical Tables for Biological and Medical Research by Fisher & Yates. All patients, in both the regimens, were "treated" for six months, with appropriate drugs and identical looking placebo preparations. The administration of drugs (including placebo) at the monthly visits was fully

supervised in blinded fashion, in both regimens. Patients completing six months treatment within nine months were considered "regular".

CLINICAL SCORING

Each patient was assessed at four points of time, at admission, at six months (release from treatment or RFT), at 12 months and at 18 months. For each lesion, the maximum possible score at intake was 18 and the minimum score at follow-up was 0. Each patient was clinically assessed and scores were given as shown in table I.

Table I. Details of clinical scoring followed in the study

Clinical feature	Score awarded in			
	Marked	Moderate	Mild	Nil
1. Hypopigmentation	3	2	1	0
2. Erythema	3	2	1	0
3. Infiltration	3	2	1	0
4. Appearance of lesion	3 (Clearly visible)	2 (Faintly visible)	1 (Doubtful)	0 Nil
5. Anaesthesia	3 (Complete loss)	2 (Definite impairment)	1 (Doubtful impairment)	0 (No loss)

6. Size (Area of lesion » Length x Breadth): Initial score: 3. For every upto 20% increase or decrease, add or subtract 0.5; lesion disappeared: 0.

The above scoring system is somewhat different from the one previously used in the single lesion study (Single Lesion Multicentre Trial Group 1997). In the single lesion trial, for the parameter hypopigmentation - erythema - infiltration, the highest possible score assigned at intake was 3. Thus at follow up deterioration in terms of clinical scores on each component could not be assessed. To overcome this problem separate grading was given at intake itself for each of the above parameters.

OUTCOME MEASURES

Following outcome measures were considered for assessing the efficacy of the regimens: (1) improvement in terms of reduced clinical score, (2) complete disappearance of all lesions and (3) treatment failure (i.e. smear positivity or appearance of new lesion/lesions at any point of time during follow-up, or no improvement or worsening in disease status at the end of study).

Patients confirmed as treatment failures were put on the appropriate standard WHO MDT regimen.

IMPLEMENTATION AND DATA ANALYSIS

The multicentre trial had an overall trial coordinator to ensure that the trial protocol was followed uniformly in all the centres. Reporting forms were collected, monitored and compiled at the then CJIL Field Unit, Avadi (now part of National Institute of Epidemiology (ICMR), Chennai). Fisher's exact test or Chi-square test was employed for comparing proportions. Student's t-test (if permissible) or Mann-Whitney U test was used to test significance of difference between two means.

RESULTS

DISTRIBUTION OF PATIENTS IN THE TWO GROUPS

Of the 236 patients admitted into the study, 118 each were (randomly) allocated to the control standard regimen and study (ROM regimen) groups. The distribution of patients in the two groups by various factors at admission is shown in table II. It can be seen that the two groups of patients were similar with respect to age, sex, number of lesions and mean total clinical score at intake.

Table II. Comparison of patients in the two groups at the time of admission

Variable	Control group		Study group		P value
Age					
Adult	82	(69.5%)	81	(68.4%)	1.000
Child	36	(30.5%)	37	(31.6%)	
Sex					
Males	60	(50.8%)	49	(41.0%)	0.192
Females	58	(49.3%)	69	(59.0%)	
No. of lesions					
Two	82	(69.5%)	87	(73.7%)	0.564
Three	36	(30.5%)	31	(26.3%)	
Clinical score					
Mean of total score	26.74		26.65		0.895
SD	7.75		7.05		

COVERAGE

Two hundred seventeen of the 236 patients admitted (92%), 209 (89%) and 207 (88%) were followed up at six, 12 and 18 months respectively (table III). Losses were more at the two urban centres from Chennai.

Table III. In-take and foIlowed-up according to participating centre

Participating centre	Intake	Follow-up period		
		6 mo	12 mo	18 mo
Barabanki	23	22	22	22
Chennai	54	50	44	42
CJIL	62	59	59	59
Naini	51	48	46	47
TRC	46	38	38	37
All centres	236	217	209	207
	(100.0)	(91.9)	(88.6)	(87.7)

Numbers indicate the number of patients; figures in brackets give percentages.

Out of the 29 the patients lost to follow-up (15 from the control and 14 from the study groups), five refused treatment after initiation of therapy, 16 left the area and three patients were absent during follow-up. Among the five refusals, four belong to the study group (ROM regimen) and one to the control group (WHO regimen). The exact reason for refusal could not be ascertained. However, to the best of our knowledge none of these patients had discontinued because of side effects. In three patients, treatment was discontinued because of cancer, jaundice and anaemia respectively. In two patients, treatment was discontinued because of side effects (rashes, "flu" syndrome).

CLINICAL RESPONSE

Table IV gives separately the mean total clinical scores at intake, six, 12 and 18 months follow-up for the patients under the two regimens. In both the regimens, the mean clinical score decreased substantially over the 18 months: from 26.74 to 4.76 and from 26.65 to 5.52 in the control and study group respectively. The difference between the mean values of the two groups at each of the four rounds was not statistically significant.

It is also seen that the decrease in the mean values were similar, at each of the three follow-ups, in the two groups of patients under the two treatment regimens. The distribution of patients by the difference in total score at intake

Table VI. Mean total score at each assessmnt

Assessment done		Control group (Standard regimen)	Study group (ROM regimen)	P value
At intake	n	118	118	
	Mean score	26.74	26.65	0.895
	(S.D.)	(7.75)	(7.05)	
At 6 months	n	108	109	
	Mean score	10.51	10.30	0.802
	(S.D.)	(7.78)	(7.91)	
At 12 months	n	102	107	
	Mean score	6.81	6.95	0.691
	(S.D.)	(7.59)	(7.16)	
At 18 months	n	103	104	
	Mean score	4.76	5.52	0.295
	(S.D.)	(6.45)	(6.60)	

and at 18 months separately for patients under the two regimens is shown in Fig. 1. The two curves are quite similar, more or less coinciding with each other, showing that the overall evolution of clinical score, over 18 months, among patients under the two regimen was similar.

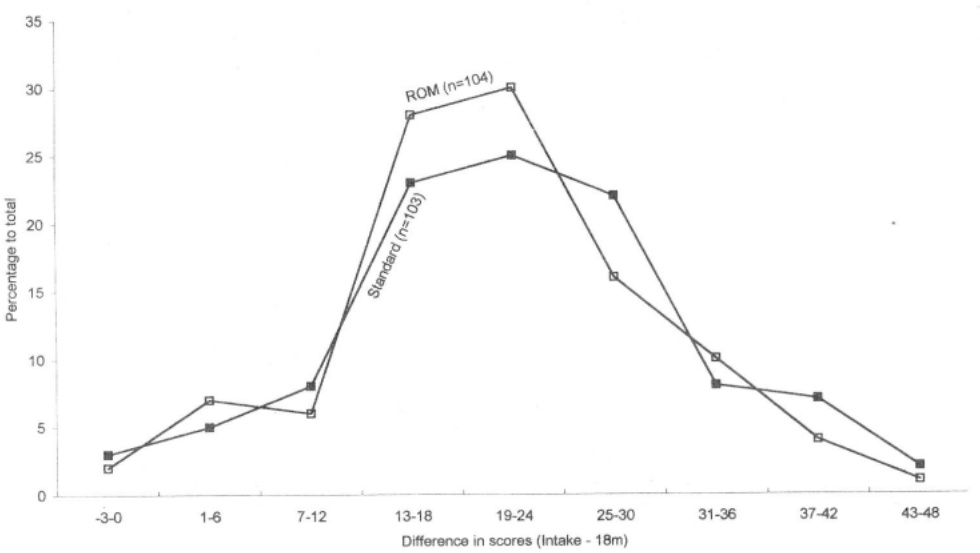

Fig. 1. Distribution of patients by difference in total score at intake and at 18 months.

Marked improvement: A patient was considered to have "markedly" improved at 18 months if there was more than 90% reduction in the initial total clinical score. It can be seen that there was marked improvement in the

disease status at 18 months (table V) in 55 of the 103 patients (53.4%) in the control group getting standard regimen, compared with 48 of the 104 patients (46.2%) in the study group getting the ROM regimen (single dose). This difference is not statistically significant (P=0.3).

Table V. Distribution of ''marked improvement" in the two groups

Improvement status	Control group (Standard regimen)		Study group (ROM regimen)	
	No.	%	No.	%
Marked improvement*	55	(53.4)	48	(46.2)
No "marked improvement"	48	(46.6)	56	(53.8)
Total	103	(100.0)	104	(100.0)

* "Marked improvement" defined as more than 90% reduction in the initial score at 18 months.

Complete cure: Complete cure was defined as "total disappearance of all lesions (i.e. total clinical score of zero) at 18 months". For patients in the control group under standard PB regimen, the proportions with complete cure were 12% at six months, increasing to 31% at 12 months and 46% at 18 months. For patients in the study group under ROM regimen, the corresponding figures were 10%, 25% and 38% at six, 12 and 18 months respectively (Fig. 2). Table VI gives the percentage of patients completely cured in the two

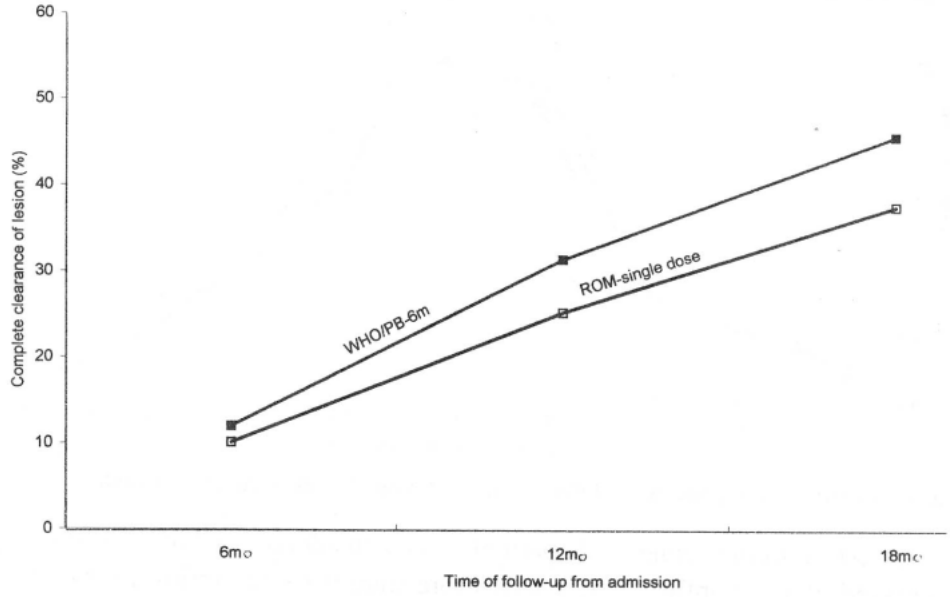

Fig. 2. Percentage of patients with complete clearance or the lesion.

groups according to age, number of lesions and number of body parts involved. Among child patients, 36.4% under standard regimen (control group) were completely cured compared with 40.0% under ROM regimen (study group) (P=0.95). However, among adult patients the corresponding figures were 50.0% for the control group and 36.2% for the study group (P=0.14).

Table VI. Percentage of patients in the two groups showing complete clearance of lesions at 18 months for the two regimens

Factor	Control group (Standard regimen)	Study group (ROM regimen)	P value
AGE			
Child	36.4 (12/33)	40.0 (14/35)	0.953
Adult	50.0 85/70)	36.2 (25/69)	0.142
All	45.6 (47/103)	37.5 (39/104)	0.296
NO. OF LESIONS			
Two	42.9 (30/70)	39.5 (30/76)	0.805
Three	51.5 (17/33)	32.1 (9/28)	0.206
NO. OF BODY PARTS INVOLVED			
One	44.2 (34/77)	44.6 (33/74)	0.912
Two	59.1 (13/22)	21.4 (6/28)	0.015
Three	(0/4)	(0/2)	—
Total	45.6 (47/103)	37.5 (39/104)	0.296

Figure in brackets gives actual number of patients / total in that set.

Considering the number of lesions, in patients with two lesions, 42.9% of those getting the standard regimen (control group) were completely cured compared with 39.5% getting the ROM regimen (study group) (P=0.8). Among patients with three lesions, the corresponding figures were 51.5% for standard regimen (control group) and 32.1% for ROM regimen (study group) (P=0.21)

Considering the number of body parts involved, among patients in whom only one body part was involved, the proportions of patients completely cured were similar in the two groups, they being 44.2% and 44.6% in the control and study groups respectivey (P=0.91). Among patients in whom two body parts were involved, the corresponding figures were 59.1% and 21.4% for the control and study groups respectively. This difference was statistically significant (P=0.015).There were only six patients in whom three body parts were involved and it was interesting to note that in none of them complete cure was seen.

Treatment failure: There were eight cases of treatment failure (3.8%) among the 210 patients who had completed the 18 months follow-up (table VII). They were equally distributed in the two groups, four (3.8%) of the 104 patients under the standard regimen and four (3.8%) of the 106 patients under the ROM regimen. Among those who had WHO/PB/MDT, three showed no clinical improvement and one patient had become smear-positive (BI 0.33). In the study group, two patients showed no clinical improvement and one had become smear-positive (BI 0.67); and new lesions had appeared in one patient (table VII). In both smear-positive patients (one each from the two groups) identified at the time of RFT, skin smear was positive only at one site and no clinical deterioration was seen during subsequent follow-up. All "treatment failure" cases were administered standard MDT.

Table VII. Clinical details of treatment failures

Clinical details	Control group (Standard regimen) No.	%	Study group (ROM regimen) No.	%
No improvement in clinical score at 18 mo.	3		2	
Smear positive (BI at RFT)	1		1	
New lesions (at RFT)	–		1	
Total no. of treatment failures	4	(3.8)	4	(3.8)
No. of patients improved in clinical score	100	(96.2)	102	(96.2)
Total	104	(100.0)	106	(100.0)

SIDE EFFECTS AND REVERSAL REACTIONS

Side effects and reversal reactions were very few. None of the patients in the study group under ROM regimen suffered any adverse reactions. Among patients those in the control group (under standard regimen), one case of "flu" syndrome and one case of bullous eruptions were reported. Two adult patients treated with ROM regimen reported with type-1 reaction. One patient was treated with a short course of steroid while the other did not require any anti-reaction treatment.

DISCUSSION

This study was undertaken to compare the efficacy of the single-dose ROM regimen with that of the standard six months WHO/PB/MDT regimen in the treatment of smear-negative PB leprosy patients having only two or

three skin lesions and no nerve trunk involvement. The assessment was made in terms of reduction in disease status based on clinical score according to set criteria, complete disappearance of all 1esions and treatment failure. Treatment failures were few and were equally distributed in the two groups. In assessing drug regimens in single lesion cases one would look for changes in clinical score in the lesion. In patients with two or three skin lesions one must look for clinical improvement considering. the patient as a whole. In routine smear examinations starting with a random smear field, there is a possibility of missing occasional bacilli. Therefore, standardized smear examination procedures by trained and standardized technicians were carried out and grading of the smear positivity was done according to Ridley scale. The results of the study showed that a single dose of rifampicin (600 mg), ofloxacin (400 mg) and minocycline (100 mg) was almost as effective as the standard six-months WHO-multidrug regimen for PB leprosy, in terms of mean reduction in clinical score over the 18-month study period. Some clinical improvement, in terms of reduction in clinical score, was seen in 96% of the patients in both the groups. Complete clearance of the lesions at 18 months was seen in 45.6% and 37.5% of the patients receiving the WHO/PB/MDT and the single dose ROM regimen respectively and the difference noted between the two groups in this regard was not statistically significant (P=0.30).

Next, by sub-group analysis, we looked into the influence of some variables like age, number of lesions and the number of body parts affected on the treatment outcome. In terms of complete cure, ROM single dose regimen was almost as effective as WHO/PB/MDT in child patients and in patients with only two skin lesions. However, in adult patients and in patients with three skin lesions the standard WHO regimen for PB leprosy was found to be better than ROM regimen. When the disease was confined to a single part of the body, the single dose ROM regimen was as effective as the standard regimen, but when lesions were present on two different parts of the body, the standard regimen was significantly better than the single dose therapy.

Another important factor to be monitored among these patients is the occurrence of reversal reaction and/or neurits. Ganapathy reported that during the first year of follow-up after ROM therapy the occurrence of reaction depended on the extent of the disease, viz. 1.7% in single lesion cases, 7.4%

in cases with 2-9 lesions and 14.7% in cases with more than ten lesions (Ganapathy et al 1998). We observed that only two adult patients under ROM therapy during the period of eighteen months developed reversal reaction. Also, none of the patients under ROM therapy developed any severe adverse drug reaction.

As mentioned earlier, the relapse rate in PB leprosy is very low. About 50% of the relapses among PB leprosy are expected to occur during first two years of surveillance. Moreover on clinical grounds it may be difficult in PB leprosy, to distinguish relapse from reversal reaction (WHO 1988). The present study is based on 236 patients and the follow-up period was only 18 months. With this sample size, it is not possible to look for relapse, and surveillance beyond 1 1/2 years was not carried out.

We found that single dose ROM therapy was safe and acceptable. We have attempted some sub-group analysis but it is based on small numbers. While instituting single dose ROM regimen care needs to be taken for selection of cases taking into account the age of the patient and the number of body parts affected. To understand the therapautic effect of single dose ROM therapy, over the entire spectrum of PB leprosy, possible relapse rates and its operational feasibility further field-based clinical trial under programme conditions is presently in progress.

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