The Effectiveness of Rifampicin, Ofloxacin, and Clarithromycin Combination Therapy in Multibacillary Leprosy Patients

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Abstract: *The aim of this* research is to evaluate the effectiveness of rifampicin, ofloxacin, and clarithromycin (ROC) combination therapy in the treatment of multibacillary leprosy by comparing it with the multi drug therapy (MDT) for multibacillary leprosy (MB) recommended by WHO. This double-blinded RCT was done in 26 previously-untreated MB leprosy patients who were given 600 mg rifampicin, 400 mg ofloxacin, and 500 mg clarithromycin combination therapy for 12 weeks (n=13) and MDT regimen (n=13). Clinical improvement, acid fast bacilli examination, and histopathological examination were assessed before and after the 12-week treatment period. This study showed that the group treated with ROC combination therapy showed superior bacteriological and histopathological improvement compared to the MDT group. The ROC regimen is a potential alternative regimen for MB leprosy patients, especially those who experienced relapse or are uncompliant.

1 INTRODUCTION

Leprosy is a chronic granulomatous bacterial inflammatory disease that develops slowly and is caused by Mycobacterium leprae which may result in significant comorbidities and disfigurement. The current approved regimen is the combination of Rifampicin, Clofazimine, and Dapsone, also known as the multidrug therapy (MDT). However, the lack of adherence, long duration of treatment, pigmentation induced by clofazimine, and episodes of dapsone hypersensitivity have been reported and are important issues that need to be addressed. (*Prasad, 2010) (Kumar, 2015)*

The combination of rifamipicin, ofloxacin, and minocycline (ROM) been considered as an alternative treatment for leprosy patients. However, WHO only recommends this regimen in paucibacillary (PB) patients with single lesion and studies have shown lower efficacy compared with MDT treatment.(*Setia, 2011*) *(Manickam, 20141)* Although a study suggested that ROM might be as effective as MDT in MB patients, the long treatment duration (24 months). Together, these findings prompt the search of a more effective alternative treatment and shorter therapy duration to improve clinical outcome and patient compliance. *(Kumar, 2015)*

Clarithromycin has been shown to exhibit potent bactericidal activity as shown by >99% M.leprae reduction as well as satisfactory clinical improvement.(*Ji, 1993*) However, data on the use of clarithromycin is very limited. A study showed that short term combination therapy of rifampicin and clarithromycin for 3 months successfully decreased IgM titers in subclinical leprosy. (*Tanasal, 2005*) A trial by Hubaya et al showed a significant bacteriologic improvement in 337 patients following 600 mg rifampicin once a month and 250 mg clarithromycin given twice daily for 3 months.(*Hubayal, 2017*) They showed a significant improvement in both clinical and bacteriologic examinations. Thus, it is necessary to investigate the efficacy of a combination of rifampicin 600 mg and ofloxacin 400 mg (weekly) plus clarithromycin 500 mg / day for 12 weeks in MB leprosy patients by assessing clinical improvement, bacteriological and histopathologic profiles before and after treatment and compare it to the MDT standard regiment.

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2 METHODS

2.1 Study Design

This study was a double-blind randomized clinical trial where 26 previously untreated MB leprosy patients were divided into two groups. The first group received WHO multidrug therapy (MDT) and the second group was treated with 600 mg rifampicin, 400 mg ofloxacin (both given three times a week) and 500 mg clarithromycin (taken every day). Clinical improvement, acid fast bacilli examination, and histopathological examination using hematoxylin eosin (HE) and Fite Faraco staining were carried out before and after the 12-week treatment and the results were compared between the two treatment groups.

2.2 Subjects

Eligible subjects were 18-60-years-old previously untreated MB patients who came for treatment to Wahidin Sudirohusodo hospital with a minimum bacteriological index of +2 and were willing to give their consent. Subjects who were pregnant, experiencing leprosy reactions, had history of hypersensitivity to one or more of the above agents, or having abnormal liver function tests were excluded from this study. Consecutive sampling method was used where all eligible patients coming to the Dermatovenereology department were included and randomly assigned into each group.

2.3 Assessment

The primary objective was to evaluate the effectiveness of rifampicin, ofloxacin, and clarithromycin combination therapy in treating MB leprosy and comparing it to the standard WHO MDT regimen. This was achieved by evaluating the clinical condition, microscopic bacteriologic examination, and histopathological examination using HE staining before and after the 12-weeks treatment period.

The clinical condition was graded as improved, not improved, and worsened and was assessed through the improvement in erythema, infiltrates, size, and morphology. Bacteriological examination was calculated semi-quantitatively based on Ridley classification and was compared between both groups before and after treatment.

Histopathological examination using HE staining was graded as excellent (LL becomes BT or TT, BL becomes TT), good (LL becomes BB, BL becomes BT, BB, and TT), moderate (LL becomes BL, BL becomes BB and BB becomes BT) dan no improvement (no type changes).

2.4 Statistical Analysis

Statistical analysis was done using Mann-Whitney U and Wilcoxon Signed Ranks Test with p-value <0.05 considered as being statistically significant

3 RESULTS

Table 1 - Characteristics of MB leprosy patients who received MDT – WHO and ROC combination therapy.

Variable		MDT- WHO group (n)	%	ROC group (n)	%
Sex	Male	10	76,9	9	69,2
	Female	3	23,1	4	30,8
	Total	13	100,0	13	100,0
Age	34.5 ± 11.56 years				
Leprosy type	BB	5	38,5	6	46,1
	BL	6	46,1	4	30,8
	LL	2	15,4	3	23,1
	Total	13	100,0	13	100,0

Table 2- Comparison of clinical improvement of MB leprosy patients before and after MDT treatment WHO and ROC combination.

Treatment	Clinical improvement	n	%
MDT WHO	Improved	8	61,5
	No improvement	5	38,5
	Worsened	0	0
TOTAL		**13**	**100,0**
ROC	Improved	13	100,0
	No improvement		
	Worsened	0	0
		0	0
TOTAL		**13**	**100,0**
Statistic test*,p		*P*=0,10	

**Mann Whitney U Test*

Table 3 - *Comparison of bacteriological index (BI) and morphological index (MI) of MB leprosy patients before and after treatment in each WHO MDT treatment group and ROC Combination.*

Treatment		BI		P-value*	MI		P-value
		Before	After		Before	After	
MDT WHO	**Range**	3-5	2-4		2-8	0-4	
	Mean	3,69	2,85	*P*= 0,002	4,62	1,85	*P*= 0,001
	SD	0,63	0,55		2,50	1,77	
ROC	**Range**	3-5	0-4		2-9	0-2	
	Mean	3,84	1,23	*P*= 0,001	4,08	0,46	*P*= 0,001
	SD	0,80	1,48		2,75	0,88	
P-value**		0,68	0,006		0,51	0,005	

**Wilcoxon Signed Ranks test ** Mann whitney U test*

Table 4 - Comparison of histopathologic improvement with HE stain in patients MB leprosy before and after WHO MDT and ROC Combination Therapy.

Treatment	Type		Improvement			P-value*
Group	Before	After	Good	Moderate	None	
WHO MDT	BB,BL,LL	TT,BB,BL	0 (0%)	5 (38.5%)	8 (61.5%)	*P*= 0,65
ROC	BB,BL,LL	TT,BB,BL	7 (53.8%)	3 (23.1%)	3 (23.1%)	*P*= 0,004
P-value**	*P*=0,48	*P*=0,12	*P*=0,009			

*Wilcoxon Signed Ranks Test ** Mann Whitney U Test

Table 1 shows the demographic data of the study population where 76.9% and 69.2% in the WHO MDT regimen and ROC combination group were male. Approximately 70% of subjects in both groups were between 18 and 37 years old. In the MDT group, most patients were in the BL type (46.1%) followed by BB type (38.5%); while in the ROC combination therapy group, BB was the most common type seen (46.1%) followed by BL type (30.8%). In both groups, LL was the least type (15.4% and 23.1% in the MDT and ROC groups, respectively).

Clinical improvement was seen in 61.5% of the WHO-MDT group, with 38.5% showed no improvement and no subject suffered worsening condition. On the other hand, all subjects (100%) in the ROC combination therapy experienced clinical improvement. The clinical improvement in both groups, however, did not significantly differ (p = 0, 10) (Table 2).

Bacteriological examination, shown by bacterial and morphological index (BI and MI), showed significant decrease in both WHO-MDT and ROC combination groups before and after treatment (Table 2). However, the BI and MI after treatment in the ROC combination group showed superior result compared to the WHO MDT group (1.23 compared to 2.85 and 0.46 compared to 1.85, respectively) and was statistically significant ($p \leq 0.01$). Table 3 shows the change in leprosy type before and after treatment based on HE staining. The result suggested that there

was a significant improvement in bacteriologic examination in the ROC group after treatment (p=0.004). In addition, there were 7 subjects with 'good' improvement in the ROC group compared to none the WHO-MDT group. The improvement seen in ROC group was also significantly higher compared to the WHO-MDT group (p=0.009)

The side effects reported in the ROC group was one reversal reaction while two patients and one patient in the MDT group experienced erythema nodusum leprosum (ENL) and reversal reaction, respectively.

4 DISCUSSION

Despite the success of MDT regimen in treating MB leprosy patients, issues such as long treatment duration, the weak bactericidal effect exhibited by dapsone and clofazimine, and incidence of relapse cases, are emerging and thus required a new therapeutic approach, with at least the same efficacy as MDT.(*Prasad, 2010*) The objective of this study was to examine clarithromycin as an alternative treatment for MB leprosy patients.

Our study population consisted of 2 groups each treated with MDT and ROC, respectively. From table 1 we can see that the type of leprosy in both groups was similar between both groups. Similar result was also exhibited in table 3 and 4, where the BI, MI, and leprosy type based on histopathological examination in both groups before treatment were not significantly different, showing that the randomization process was successful.

Both the ROC and MDT groups showed clinical improvement after completing the 12 week-period. However, the after-treatment result between both groups did not differ, suggesting that the clinical improvement of ROC was not superior to MDT. However, the ROC group showed significantly better bacteriologic and histopathological improvement. Examination under the microscope using Ridley criteria showed significantly lower BI and MI values in the ROC group (1.23 vs 2.85 and 0.46 vs 1.85, respectively). In addition, histopathologic examination using HE staining also showed that after 3 months, a significant change in leprosy type was observed in the ROC group (p=0.004) but not in the MDT group. This was an important finding as bacterial index is closely associated with immune response of an individual and determine the clinical manifestation and infectivity of the disease (*Adiga, 2016*), suggesting that clinical improvement alone is not sufficient to conclude leprosy treatment.

Other studies using clarithromycin are mostly case reports (*Hubayal*,2017) (*Gunawan, 2011*) which showed a satisfactory clinical result. However, both studies did not examine changes in the bacteriologic nor histopathological examinations. Another study evaluating the IgM titer changes in subclinical leprosy patients showed a significant titer reduction following 3 months treatment of rifampicin and clarithromycin.(*Tanasal, 2005*) Our study is thus the first randomized double blinded clinical trial assessing the effectiveness of ROC regimen and comparing it with the standard MDT regimen.

Subjects experiencing adverse events in the ROC group was also fewer (one person experiencing reversal reaction) compared to two ENL cases and one reversal case in the MDT group. However, the sample size was not sufficient to make a statistical analysis. Prospective studies with larger number of participants are needed to evaluate the safety profile of this drug.

This study showed that ROC resulted in better bacteriological and histopathological improvement compared to the MDT after 3 months of treatment with no s. As a pilot study assessing the effectivity of ROC regimen, future study with larger number of participants and longer follow-up period is needed to find the optimal protocol for Multibacillary leprosy.

5 CONCLUSIONS

Treatment using ROC therapy showed better bacteriological and histopathological improvement in MB patients. The ROC combination therapy also showed good safety profile with only one person experiencing a mild reversal reaction. This study showed that ROC therapy may serve as a potential alternative treatment for MB leprosy patients.

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REFERENCES

Adiga, D. S. A., Hippargi, S. B., Rao, G., Saha, D., Yelikar, B. R., & Karigoudar, M. (2016). Evaluation of Fluorescent Staining for Diagnosis of Leprosy and its Impact on Grading of the

Disease: Comparison with Conventional Staining. *Journal of clinical and diagnostic research: JCDR*, *10*(10), EC23.

Gunawan, D., Wijaya, L.V., Oroh, E.E., Kartini, A., 2011. Satu Kasus Kusta Multibasiler Tipe Borderline Lepromatous pada Geriatri yang Diterapi dengan Rejimen Rifampisin-Klaritromisin. *Media Dermato-Venereologica Indonesiana,* 38(2011), pp. 55-63.

Hubayal, K., & Riyanto, P., 2017. Treatment of Leprosy Patients using Combination of Rifampicin-Clarithromycin for 3 Months in Tugurejo Genera*l* Hospital Semarang. *Clinical & Experimental Dermatology and Therapies*, 09.

Ji, B., Jamet, P., Perani, E. G., Bobin, P., & Grosset, J. H., 1993. Powerful bactericidal activities of clarithromycin and minocycline against Mycobacterium leprae in lepromatous leprosy. *Journal of Infectious Diseases*, *168*(1), pp. 188-190.

Kumar, A., Girdhar, A., Chakma, J. K., & Girdhar, B. K., 2015. WHO multidrug therapy for leprosy: epidemiology of default in treatment in Agra district, Uttar Pradesh, India. *BioMed research international*, *2015*.

Manickam, P., Nagaraju, B., Selvaraj, V., Balasubramanyam, S., Mahalingam, V. N., Mehendale, S. M., ... & Team of Study Investigators., 2012. Efficacy of single-dose chemotherapy (rifampicin, ofloxacin and minocycline-ROM) in PB leprosy patients with 2 to 5 skin lesions, India: randomised double-blind trial. *Indian J Lepr*, *84*(3), pp. 195-207.

Prasad, P. V. S., & Kaviarasan, P. K., 2010. Leprosy therapy, past and present: can we hope to eliminate it?. *Indian journal of dermatology*, *55*(4), pp. 316.

Setia, M. S., Shinde, S. S., Jerajani, H. R., & Boivin, J. F., 2011. Is there a role for rifampicin, ofloxacin and minocycline (ROM) therapy in the treatment of leprosy? Systematic review and meta-analysis. *Tropical Medicine & International Health*, *16*(12), pp. 1541-1551.

Tanasal, H., 2005. *Perubahan Titer IgM pada Lepra Subklinik Paska Terapi Jangka Pendek dengn Rifampisin dan Klaritromisin*.