Clinical Pilot Study: Clarithromycin Efficacy in Multibacillary Leprosy Therapy

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Abstract

Background: Rifampicin is one of the important components in the multidrug therapy (MDT)-World Health Organization regimen for leprosy. Clarithromycin is one of the alternative therapies of rifampicin. Methods: This clinical pilot study was to compare the efficacy of 2,000 mg clarithromycin to 600 mg rifampicin in combination with dapsone and clofazimine for 3 months in multibacillary (MB) leprosy patients. They were divided into an MDT-MB regimen group that consists of rifampicin-dapsone-clofazimine and clarithromycin-dapsone-clofazimine (CDC) regimen group, each group consisted of seven patients. Results: The morphological index (MI) was reduced insignificantly after 3 months therapy in MDT-MB group (P = 0.248). While in the CDC group, the MI decrement showed a significant result (P = 0.004). The comparison of MI reduction in MDT-MB and CDC groups showed an insignificant difference (P = 0.130). Skin discoloration was occurred in both groups, whereas mild-nausea was presented in the CDC group, in addition, red-colored urine was developed in the MDT-MB group. Conclusion: We concluded that 2,000 mg clarithromycin is as effective as 600 mg rifampicin in combination with dapsone and clofazimine regimen in MB leprosy patients. Hence, clarithromycin can be considered as an alternative therapy for leprosy patients who resistance and/or allergy to rifampicin.

Keywords: Clarithromycin, leprosy, rifampicin

INTRODUCTION

The World Health Organization (WHO) recommends multidrug therapy (MDT) for leprosy therapy, which includes rifampicin as one of the potent and most important drugs. Problems regarding rifampicin have increased recently including resistance and allergy to rifampicin. Thus, clarithromycin is one of the alternative treatments of rifampicin in leprosy.

Clarithromycin is a semisynthetic macrolide which has activity against Mycobacterium leprae (M. lepra) in both in vitro and in vivo that approximates with rifampicin. It also exerts powerful bactericidal activity against M. lepra in mice and lepromatous leprosy (LL) patients.

In this clinical pilot study, we aimed to compare the efficacy of 2,000 mg clarithromycin against 600 mg rifampicin in a regimen combined with dapsone and clofazimine for 3 months in multibacillary (MB) leprosy patients.

METHODS

Subjects

Ethical approval was obtained from the local Health Research and Ethics Committee. A total of 14 newly diagnosed MB leprosy patients from Leprosy Clinic, Hasan Sadikin Hospital, were recruited into the study. These MB and paucibacillary (PB) leprosy types are the classification from the WHO. In 1981, the WHO study group on chemotherapy of leprosy for control programs classified leprosy as MB and PB according to the degree of skin-smear positivity. This was an essentially operational classification intended to serve as the basis for chemotherapy. The MB leprosy included polar lepromatous (LL), borderline lepromatous (BL), and...
mid-borderline cases in the Ridley–Jopling classification, with a bacteriological index of 2 + or more at any site in the initial skin smears. The PB leprosy included indeterminate (I), polar tuberculoid (TT), and borderline tuberculoid (BT) cases in the Ridley–Jopling classification, with a bacteriological index of <2 at all sites in the initial skin smears.\textsuperscript{[7]}

The patients were randomly allocated into two groups, with seven patients in each group [Figure 1]. There were six males and one female in the MDT-MB group, with a mean age of 45.14 ± 15.07 years old. While in the clarithromycin-dapsone-clofazimine (CDC) group, five patients were male and two patients were female, with a mean age of 38.28 ± 10.0 years old.

The patients were excluded from the study if they were a pregnant or lactating woman, have a history of hypersensitivity to one or more drugs which used in this study, abnormal results of routine hematologic, and liver and kidney function test.

This study was a clinical experimental, analytical pilot study with a pre-post design. Before the treatment, the patient underwent history taking, physical examination, bacterial index (BI), and morphological index (MI) analysis in skin smears. Then, the patients were evaluated for side effects every month until 3 months. After 3 months therapy, MI was reexamined, and the decrement of MI value was analyzed to evaluate the effectiveness of the treatment. Furthermore, the patients still received the therapy regimen until 12 months.

**Therapy regimen**
In day 1, the CDC group was given 2000 mg of clarithromycin plus 300 mg of clofazimine, whereas the MDT-MB group was administered with a single dose of 600 mg rifampicin and 300 mg of clofazimine; then, both groups were given 100 mg dapsone and 50 mg clofazimine daily for 30 days. These therapy regimens were given and analyzed for 3 months for this clinical pilot study.

**Statistical analysis**
Results were analyzed and compared using independent t-test and Fisher’s exact probability calculation. The results were considered statistically significant if \( P < 0.05 \).

**Results**
The number of lesions in leprosy patients in both groups MDT-MB and CDC group was counted, for determined the therapy category based on the WHO criteria.\textsuperscript{[7]} All patients were categorized as MB patients with the number of skin lesions more than five lesions. As shown in Table 1a, each MDT-MB and CDC group showed an insignificant decreased between BI value before and after the treatment (\( P = 0.226 \) and \( P = 0.105 \), respectively). Our results also showed that the decrement of BI value after 3 months of therapy was higher in CDC group (mean = 0.92) compared to MDT-MB group (mean = 0.77). Nevertheless, there was no significant difference between the reduction of both groups, with \( P = 0.763 \).

The MI value was decreased insignificantly after 3 months of therapy in the MDT-MB group (\( P = 0.248 \)) while, in the CDC group, it showed a significant decrease (\( P < 0.05 \)) [Table 1a]. Furthermore, the reduction of MI before and after the treatment was higher in the CDC group (mean = 24.56%) compared to the MDT-MB group (mean = 10.63%). However, the statistical analysis showed an insignificant difference between both groups (\( P = 0.130 \)). The comparison of MI value after the treatment in both groups showed no significant differences [Figure 2].
In Table 1b, the most frequent events in the MDT-MB group were the coppery color of the skin that occurred in five patients (71.4%) and red-colored urine in five patients (71.4%) while, in the CDC group, there was nausea in two patients (28.5%). This nausea was highly correlated with clarithromycin although the severity was mild and lasted only for 5 h then subsides spontaneously. Hence, it can be concluded that there were no differences regarding the side effects of rifampicin and clarithromycin.

**Discussion**

The new drugs for leprosy will become very important due to the potential growth of resistance problem of the leprosy drugs or regimen. Rifampicin has strong bactericidal activities against *M. leprae*. This drug binds with a β-subunit of RNA polymerase and inhibits RNA synthesis.[8] Clarithromycin as one of the choice of the newer drugs for leprosy.[9] Clarithromycin is a member of the macrolide group of antibiotics and displays significant bactericidal effect against *M. leprae* in mice and in humans. Clarithromycin as one of the alternatives of rifampicin has a bactericidal effect to *M. leprae* although the mechanism of action is still poorly understood. It binds to 50 ribosomal subunits and will inhibit bacterial protein synthesis,[10,11] and adenosine triphosphate concentration in *M. leprae*, hence, prevented the bacterial oxidation.[12]

A previous study showed that BI reduction to 1+ commonly found after 1 year therapy, whereas in this study, BI reduction was only less than one in both groups due to the patients were being followed up for only 3 months after therapy. Furthermore, in other study showed that the reductions in serum phenolic glycolipid I levels were observed for most of the patients at 3 weeks, and the significant clinical improvement was evident after 4 weeks of treatment, which indicated that clarithromycin is rapidly bactericidal for *M. leprae* in humans.[13] Clarithromycin was proved as effective as minocycline. Of the 12 patients treated with clarithromycin alone, 42% showed definite clinical improvement and 50% showed marked clinical improvement after 1 month of treatment. It also resulted in significant reductions in BI after 3 months.[14] It is similar with the results of our study that BI reduction was found decreased after 3 months of therapy.

### Table 1a: Comparison of bacterial index and morphological index between multidrug therapy-multi bacillary group and clarithromycin-dapsone-clofazimine group

|                | BI  | MI  |  
|----------------|-----|-----|  
| **MDT-MB (n=7)** | CDC (n=7) |  
| **Before therapy** |  
| Mean±SD        | 3.18±0.78 | 3.43±0.80 | 0.571  
| Median          | 3.30   | 3.00     |  
| Range           | 1.67-4.00 | 2.67-5.00 |  
| **After therapy** |  
| Mean±SD        | 2.40±0.94 | 2.51±0.80 | 0.825  
| Median          | 2.60   | 2.30     |  
| Range           | 1.00–3 | 1.60-4.00 |  
| **Reduction**   |  
| Mean±SD        | 0.77±0.63 | 0.92±1.05 | 0.763  
| Median          | 0.67   | 0.67     |  
| Range           | 0.00-1.97 | 0.00-3.00 |  
| **MDT-MB (n=7)** | CDC (n=7) |  
| **Before therapy** |  
| Mean±SD        | 42.96±21.87 | 41.99±25.66 | 0.941  
| Median          | 40.00   | 41.57     |  
| Range           | 15.00-74.20 | 11.00-71.24 |  
| **After therapy** |  
| Mean±SD        | 32.33±20.14 | 17.34±10.49 | 0.106  
| Median          | 22.45   | 20.10     |  
| Range           | 10.00-60.20 | 1.60-33.00 |  
| **Reduction**   |  
| Mean±SD        | 10.63±7.43 | 24.56±21.65 | 0.130  
| Median          | 7.90    | 16.57     |  
| Range           | 0.78-20.07 | 4.00-59.80 |  

Bi of MDT-MB group before versus after therapy showed *P* value 0.226, Bi of CDC group before versus after therapy showed *P* value 0.105, MI of MDT-MB group before versus after therapy showed *P* value 0.248, MI of CDC group before versus after therapy showed *P* value 0.004, *P* value calculated by independent *t*-test analysis, statistical significant was accepted at *P* < 0.05. BI: Bacterial index, MI: Morphological index, MDT-MB: Multidrug therapy-multibacillary, CDC: Clarithromycin-dapsone-clofazimine, SD: Standard deviation

### Table 1b: Major adverse events of multidrug therapy-multi bacillary and clarithromycin-dapsone-clofazimine regimen during 3 months therapy in multibacillary leprosy patients

|                | 1st month | 2nd month | 3rd month |  
|----------------|-----------|-----------|-----------|  
| **MDT-MB (n=7)** |  
| Nausea         | 0         | 0         | 0         |  
| Vomit          | 0         | 0         | 0         |  
| Diarrhea       | 0         | 0         | 0         |  
| Skin discoloration | 0 | 4         | 5         |  
| Red-colored urine | 5 | 0         | 0         |  
| **CDC (n=7)**   |  
| Nausea         | 2         | 0         | 0         | 0.286  
| Vomit          | 0         | 0         | 0         |  
| Diarrhea       | 0         | 0         | 0         |  
| Skin discoloration | 0 | 3         | 4         |  
| Red-colored urine | 0 | 0         | 0         |  

*P* value calculated by Fisher exact test analysis. MDT-MB: Multidrug therapy-multibacillary, CDC: Clarithromycin-dapsone-clofazimine
We also performed MI analysis, to evaluate the therapy efficacy.\[15\] One study showed that the patient with initial MI of 5%–20% will reduce to zero after 5 weeks therapy.\[16\] Another study also performed a study in LL patients, they were given 1500 mg clarithromycin twice a day for 7 days, continued with 1000 mg clarithromycin for 2 weeks, and 500 mg for 9 weeks. In total 12 weeks’ duration of the treatment, it revealed significant MI reduction.\[15\] In our study, MI in both groups before treatment were >40%, and MI reductions were noted in both groups after 3 months of therapy. MI value in the MDT-MB Group was decreased after 3 months therapy (mean reduction 10.63%), but this result was insignificant [Table 1a].

From another study, the default rates were observed to be high in the standard WHO-MDT treatment both for PB and MB leprosy compared with rifampicin-ofloxacin-minocycline (ROM) treatment in this study.\[17\] While in the CDC group, the MI value had a significant reduction after 3 months therapy (mean reduction 24.56%) [Table 1a]. Moreover, when we compared MI reduction between both the groups was found insignificant [Table 1a].

Then, we observed the side effects of rifampicin and clarithromycin, which used in the MDT-MB group and the CDC group, respectively [Table 1b]. They were discoloration of the skin by clofazimine was occurred in both groups, whereas red-colored urine was developed in the MDT-MB group and mild nausea was presented in the CDC group. It showed an insignificant difference of side effects between both groups. The most common side effect is gastrointestinal irritation (including nausea, vomiting, and diarrhea), which is particularly frequent when clarithromycin is given at a dose of 2,000 mg.\[7\] In lepromatous patients, a daily dose of 500 mg of clarithromycin kills 99% of viable *M. leprae* within 28 days and >99.9% in 56 days.\[10\]

Another previous study, a randomized controlled trial assessed the effect of adding clarithromycin to ROM (C-ROM) in the treatment of single-lesion PB leprosy. The study showed that the addition of clarithromycin to ROM did not significantly improve the efficacy as measured in terms of cure rates and relapse rates in leprosy patients with a single skin lesion.\[18\]

Clarithromycin has been used for *M. leprae* elimination treatment. Ji et al. showed that 25–50 mg/kg BW clarithromycin could kill 94.9% *M. leprae*, while 10 mg/kg BW rifampicin can kill 92% *M. leprae* in mice.\[10\] Another study toward 50 new LL patients have a reduction in number of viable *M. leprae* in a group that had 2000 mg clarithromycin-200 mg minocycline (97.5%), MDT-MB (97.9%), and a single-dose rifampicin (99%) after 30 days of therapy.\[6\] Chan et al.\[3\] also performed a study in LL patients, they were given 1500 mg clarithromycin twice a day for 7 days, continued with 1000 mg clarithromycin for 2 weeks and 500 mg for 9 weeks. In total 12 weeks duration of treatment, Chan’s study revealed significant MI reduction. These showed clarithromycin can kill *M. leprae* as effective as rifampicin and similar with our results in this study.

**Conclusion**

From our results, it can be concluded that 2,000 mg clarithromycin is as effective as rifampicin for MB leprosy therapy for 3 months observation. Future research with a larger number of samples and longer observation are necessary to confirm this suggestion.

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**Conflicts of interest**

There are no conflicts of interest.

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