

Unveiling the Past: Retrospective Exploration of Multidrug Therapy (MDT) Efficacy in Multibacillary Leprosy Patients

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Abstract

Background: The bacterial index (BI) and morphological index (MI) values on slit skin smear (SSS) examination are supporting examinations that can be used to evaluate the treatment of multibacillary (MB) leprosy patients.

Method: This study was a retrospective study, by measuring SSS examination before and after treatment, from January 2018-December 2020 patients' medical records at Tertiary Hospital, Surabaya, Indonesia. In this study, 49 MB patients with a positive SSS examination and had completed multidrug therapy (MDT).

Results: After completing MDT, the BI score was 0 at 71.4% ($p < 0.05$) and the MI score was 0% at 100% ($p < 0.05$).

Conclusion: MDT therapy was shown to have significant results, but there was still a positive BI value of 28.6% and an increase in BI of 2% in patients. The current 12-dose MDT-MB therapy is still an option for patients with MB leprosy, particularly in endemic areas such as Indonesia.

Keywords: leprosy, multidrug therapy, bacterial index, morphological index.

Introduction

The World Health Organization (WHO) at the end of 2020 recorded 127,396 new leprosy cases, or 16.4 per 1,000,000 populations. Indonesia ranks third as the country with the highest leprosy cases after Brazil and India (WHO, 2023). Multibacillary (MB) leprosy is the most common type of leprosy in Indonesia (Indonesia, 2018). In 2016, East Java recorded 3,952 (93.92%) cases of multibacillary (MB) leprosy and 256 (6.08%) cases of paucibacillary (PB) leprosy. A study conducted by Aisyah in 2018 recorded 640 (89.8%) patients with MB leprosy (Aisyah & Agusni, 2018). Another study also noted that the number of MB leprosy cases was higher than PB, with 93.9% of MB leprosy cases and 6.1% of PB leprosy cases (Desrina et al., 2020). The large number of new MB leprosy

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cases is an indicator of potential sources of transmission and the risk of complications that can cause disability if not treated adequately.

Kaur, et al., reported the results of examinations in 136 patients with MB leprosy before MDT treatment for 12 months, found that the average initial bacterial index (BI) 3.6, became 0 in 39.7% of patients, and 84.8% of patients with BI $\leq 3+$ became 0 in the second year after therapy (Kaur et al., 2002). Another study reported a total of 34 MB leprosy patients, and found BI 0 in 97.1% of patients examined 5 years after therapy (Shen et al., 2012). The study conducted by Soneja, et al., stated that there was a significant decrease in morphological index (MI) after patients received MDT therapy for 12 months (Soneja et al., 2021). Desrina, et al., also found that MI was 0 in all leprosy patients who had completed MDT therapy (Desrina et al., 2020). Tiwow, et al., also reported the same thing, namely MI 0 was found in all patients at the end of MDT therapy (Tiwow et al., 2014).

In 1991, WHO recommended MDT therapy in leprosy patients. Several studies were subsequently conducted and reported similar findings between the 12-dose and 24-dose regimens, resulting in MDT-MB therapy being shortened from 24 months to 12 months (Smith et al., 2017). Shortening the duration of treatment is an important factor in achieving elimination targets. The WHO Congress in 2014 reported preliminary multicentric results as equivocal, leading to the simplification of leprosy therapy to 6 months for all types of leprosy (Rao et al., 2015). Various studies found a decrease in BI and MI after MDT therapy, but the decrease was not uniform. Based on previous studies, we aimed to evaluate the efficacy of MDT therapy in leprosy patients at the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia.

Materials and Methods

Study design

This study was a quasi-experimental study or a single group without control pretest-posttest design, by measuring before and after treatment, based on the medical records of leprosy patients who received MDT therapy at the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia in 2018-2020.

Study population and samples

The study population was patients diagnosed with MB leprosy who received MDT at the Outpatient Clinic of a Tertiary Hospital, Surabaya, Indonesia. The study sample was all patient populations who met the sample acceptance criteria.

The inclusion criteria for this study included patients over 14 years of age who were recorded in the medical records, both electronic medical records (EMR) and special outpatient notebooks, with a diagnosis of MB leprosy who received complete MDT-MB of 12 blisters with a duration of treatment of 12-18 months, positive SSS results, and SSS testing at the beginning and end of MDT, at the Tertiary Hospital Outpatient Clinic, Surabaya, Indonesia, from January 1, 2018 to December 31, 2020. Exclusion criteria in this study were patients under 14 years of age, not fully recorded in medical records, either EMR or special outpatient record books, did not receive complete MDT-MB of 12 blisters with a duration of treatment of 12-18 months, negative SSS test results, and did not have a history of SSS testing before and after therapy.

Sampling was carried out using a total sampling system, which was obtained from secondary data of medical records of patients diagnosed with MB type leprosy with MDT therapy at the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia, from 1 January, 2018 to 31 December, 2020.

Study procedure

Patient data such as MB leprosy, patient distribution, BI and MI values during treatment (before and after), were taken from the EMR and outpatient medical record status of patients who received MDT-MB at the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia. The data and results obtained were then entered into a data collection sheet for analysis. The BI and MI examinations were performed by the same examiner, who had received training, and wrote down the area the sampling was taken.

Data analysis

All data were entered into a computer using Microsoft Excel, and the distribution and frequency of the data were analyzed using SPSS software. Analysis of differences in BI and MI values before and after MDT treatment in MB leprosy patients was done using paired t-tests if the data was normally distributed or using Wilcoxon signed rank test if the data was not normally distributed. Analysis of changes in BI and MI values of MDT treatment in MB leprosy patients used the two independent samples t-test if the data was normally distributed or used the Mann-Whitney test if the data was not normally distributed.

Results

New patients with MB leprosy who came to the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia, for the period 2018-2020 who met the inclusion criteria were 49 patients, which was 17.4% of the total number of new patients in the Outpatient Clinic of the Tertiary Hospital, Surabaya, Indonesia. The results showed that the number of patients in 2018, 2019 and 2020 was 49 patients. The distribution of male patients was more than female with 41 (83.7%) patients. Most patients were in the age range of 20-44 years with 33 (67.3%) patients (Table 1).

Table 1 Distribution of MB leprosy patients

Variable	Total (n=49)
Gender, n (%)	
Male	41 (83,7)
Female	8 (16,3)
Age, n (%)	
14-19 years	4 (8,2)
20-44 years	33 (67,3)
45-59 years	9 (18,4)
60 years and over	3 (6,1)
Initial Bacterial Index, n (%)	
1+	23 (46,9)
2+	5 (10,2)
3+	18 (36,7)
4+	3 (6,1)
Final Bacterial Index, n (%)	
0	35 (71,4)
2+	14 (28,6)

Initial Morphological Index, n (%)	
<1%	5 (10,2)
1%-20%	44 (89,8)
Final Morphological Index, n (%)	
0	49 (100)

Bacterial index and morphological index

The distribution of the initial BI of leprosy patients was mostly BI 1+ with 23 (46.9%), while the final BI was mostly BI 0 with 35 (71.4%) patients (Table 1). The initial MI distribution of leprosy patients was patients with MI 1%-20% with 44 (89.8%), while the final MI was that all patients had MI 0 (100%) (Table 1).

Statistical analysis

Analysis of differences in BI values before and after MDT using the Wilcoxon statistical test found significant changes with $p < 0.05$ (Table 2). Meanwhile, analysis of differences in MI values before and after MDT therapy using the Wilcoxon statistical test also found significant changes with $p < 0.05$ (Table 3).

Table 2. Analysis data of BI before and after MDT

Initial BI	Final BI, n (%)		Total (n=49)	p value*
	0	2+		
1+	22 (44,8)	1 (2,2)	23 (47)	p=0.000**
2+	4 (8)	1 (2,2)	5 (10,2)	
3+	9 (18,4)	9 (18,4)	18 (36,8)	
4+	0 (0)	3 (6)	3 (6)	

* Wilcoxon test

** Significant p value < 0.05

Tabel 3. Analysis data of MI before and after MDT

Initial MI	Final MI, n (%)		Total (n=49)	p value*
	0			
<1%	5 (10,2)		5 (10,2)	p=0,000**
1-20%	44 (89,8)		44 (89,8)	

* Wilcoxon test

** Significant p value < 0.05

Discussion

The most common type of leprosy according to the WHO classification found in the Outpatient Clinic of Surabaya Tertiary Hospital, Indonesia, in 2018-2020 was MB leprosy. There were 258 (92%) patients with MB leprosy and 11 (4%) patients with PB leprosy. In this study, there were 49 patients with MB leprosy or 19% who met the inclusion and exclusion criteria of the study from all visiting leprosy patients. This is similar to Nabila, et al.'s study, which reported that MB type leprosy was the most common type of leprosy compared to PB type leprosy with a ratio of 110 (91.67%) patients to 10 (8.33%) (Nabila et al., 2012). Aisyah and Agusni's study showed that MB

leprosy was the most common type of leprosy (89.8%) (Aisyah & Agusni, 2018). Another study also reported the same thing, namely that MB leprosy was more common than PB leprosy (93.9% to 6.1%) (Desrina et al., 2020).

The MB leprosy is the most common type of leprosy because Indonesia is an endemic area of leprosy. Leprosy patients with MB leprosy have a large number of bacilli. The MB leprosy patients are the source of leprosy infection. The high incidence of MB leprosy in new cases is an indicator of the potential for leprosy transmission.

Male participants in this study were more prevalent in 41 (83.7%) patients compared to female patients, i.e. 8 (16.3%) patients. Aisyah and Agusni's study also found that men outnumbered women, 67.7% compared to 32.3% (Aisyah & Agusni, 2018). Other studies also reported the same thing that men outnumbered women (70.4% to 29.6%). This is also in accordance with WHO data which showed that the number of male cases was greater than female, with the number of male cases 10,740 (61.59%) and female cases 6,698 (38.41%) (WHO, 2023).

Leprosy patients are more likely to be male than female because men are known to have higher mobility and are often outdoors, increasing the chance of contact with patients who are the source of infection. Women rarely leave the house, so there are fewer opportunities for contact with leprosy patients and lower chances of receiving treatment.

The age distribution in this study is divided based on the Regulation of the Minister of Health of the Republic of Indonesia Number 25 Year 2016 on Indonesian Health, namely neonatal and infants (0-1 year), toddlers (1-5 years), preschoolers (5-6 years), children (6-10 years), adolescents (10-19 years), adults (15-49 years), pre elderly (45-49 years), and elderly (60 years and over). In this study, the highest number was found in the adult age range, namely 20-44 years. Similarly, another study reported the highest number of leprosy cases in the age range of 25-44 years (Desrina et al., 2020). Another study also reported that the highest age group of leprosy patients was 25-44 years (Tiwow et al., 2014).

The incidence of leprosy patients was highest in the productive age, indicating that productive age people have high activity levels, which increases the risk of exposure to leprosy patients. The risk of leprosy in young people was lower because the incubation period varied from 2 to 20 years. The long incubation period of leprosy causes people to be infected at a young age and then symptoms will appear at an older age. This is consistent with this study where the incidence of leprosy was highest in the adult age range.

In this study, the highest final BI was found to be BI 0 in 35 (71.4%) patients. A decrease in IB score was found in 96%, i.e. 22 out of 23 patients with initial BI 1+ to 0, 4 out of 5 patients with initial BI 2+ to 0, 9 out of 18 patients with initial BI 3+ to 0, 9 out of 18 patients with initial BI 3+ to 2+, and 3 out of 3 patients with initial BI 4+ to 2+. The result of BI remained at 2%, i.e. 1 patient with initial IB 2+ remained 2+ at the end of therapy, and BI increased at 2%, i.e. 1 patient with initial BI 1+ became 2+. In all patients with initial BI 4+, there was no decrease to 0 at the end of treatment. This study is similar to the study of Soneja et al., who found that patients with initial BI 5+ became BI 3+ at the end of treatment (Soneja et al., 2021).

Kaur, et al., reported that 136 MB leprosy patients with an average initial BI of 3.6 became 0 in 39.7% of patients after 2 years, and 84.8% of patients with BI \leq 3+ became 0 after 2 years (Kaur et al., 2002). Another study also reported that of 68 patients with initial BI $<$ 3+, became 0 after 2 years of MDT therapy (Shen et al., 2012).

A statistically significant decrease between initial BI and final BI on MDT treatment was found in this study ($p < 0.05$). This indicates that the MDT regimen was strongly bactericidal. This regimen shows a decrease in the bacteriological index that kills *M. leprae* germs. The BI values indicate cellular immune function (CMI) where the bacilli

will be eliminated by the body as seen in skin smears. Poor CMI will show a high BI. A decrease in BI was seen after one year of MDT therapy, and continued even after stopping treatment. The decrease in BI varied from individual to individual, presumably due to the different immune capabilities of each individual in eliminating the bacilli.

The Th2 lymphocytes induce the production of cytokines IL-4, IL-10, and TGF- β that inhibit the microbicidal response of macrophages, allowing bacilli to survive. In addition, IL-10 also has immunosuppressive properties that suppress the destruction of intracellular pathogens by macrophages, resulting in an increase in the number of bacteria. Therefore, the bacterial index was found to be high in lepromatous leprosy patients, which was 5+ or 6+ (Griffiths et al., 2016).

The SSS examination is necessary for the evaluation of patients with high initial BI results (BI >4+) because these patients have a high initial bacterial load, which can lead to persistence of the source of infection and transmission. In addition, there is poor CMI and poor macrophage function to fight bacilli.

This study found that most of the highest initial MI found was MI 1-20% in 44 (90%) patients, followed by MI <1% in 5 (10%) patients, and no MI was found above 20%. Another study mentioned that the initial IM before treatment was found to vary from 17% to 100% (Soneja et al., 2021).

The final MI reduction was found to be significant, namely MI 0 in all patients. This study is similar to Desrina, et al.'s study, which reported that all leprosy patients who had completed MDT obtained MI 0. Another study also reported a similar thing, namely MI 0 in all patients at the end of MDT (Tiwow et al., 2014). This study is slightly different from the study conducted by Soneja, et al., which reported MI 0 in 95.9% of patients at the end of therapy (Soneja et al., 2021). Another study found that out of 35 patients, 19 patients were found with a fixed MI value, 9 patients increased, and 7 patients decreased but did not reach 0 (Narang et al., 2019).

The MI value is the percentage of intact bacilli (living bacilli) among the total bacilli that are red on ZN staining. The MI value indicates patients with active or inactive leprosy. A total of 200 single bacterial elements were counted with respect to regular staining and were intact, fragmented or granular. The MI value reflects chemotherapy. A decrease in MI indicates improvement and effective treatment, while an increase in MI indicates worsening. The MDT can generally reduce MI by 25%-75% at the beginning of therapy and to 0 within 5 to 6 months. The MI values are also a parameter of treatment failure, non-compliance, drug resistance, or relapse (Gautam & Jaiswal, 2019; Soneja et al., 2021). The MI values are standardized to evaluate the number of viable bacilli, and show a rapid decrease (much faster than BI) after MDT (Narang et al., 2019).

The decrease in MI was found to be statistically significant between initial MI and final MI in MDT treatment ($p < 0.05$). The MDT regimen is a very strong bactericidal regimen in treating leprosy patients. The MI decreases when the regimen kills the *M. leprae* germs living in the patient's body. Germs are found dead or degenerated and appear irregular and fragmented on staining.

The BI and MI calculations may differ if sampling is increased or different locations are taken. These errors can be minimized by specific reporting and re-sampling. Soneja, et al. reported skin tissue scrapings in one or two areas with very high positive results, while other smears had very few or no bacilli. This makes the BI and MI values decrease due to the average calculation of the decreased values (Soneja et al., 2021). The average BI and MI values of all areas taken will show lower results so that the severity of the disease will decrease. This shows that all smears must be reported for each area in order to know the highest index value so that special attention can be paid. In SSS assessment, it is also important to remember that a negative smear does not rule out leprosy, as *Mycobacterium*

leprae can be seen in large numbers in the dermis of MB leprosy patients with a minimum of 10,000 bacilli/gram of tissue to detect visible bacilli (Griffiths et al., 2016).

This study showed that there was a significant decrease in the bacterial index and morphological index, but in the bacterial index there were still values that did not reach 0 and there were patients who experienced an increase in the bacterial index. This needs to be highlighted and become an important note in MDT-MB. Studies related to MDT-MB treatment are still ongoing. A study in Bangladesh stated that MDT-MB treatment from 12 months to 6 months did not increase the relapse rate (Cruz et al., 2017). The WHO Congress in 2014 reported preliminary results of a multicentric study on the administration of a 6-month MDT regimen or U-MDT leading to simplification of leprosy treatment, but interim reports of U-MDT trial results stated vaguely for all types of leprosy. There were six relapses in the study, four in the MB group and two in the PB group, but bacteriologic results (skin tissue scrapings) were not mentioned (Rao et al., 2015).

Conclusion

MDT-MB has been shown to significantly reduce BI and MI in patients with MB leprosy, but BI examination is still positive and there is an increase in BI in patients. The 12-dose MDT-MB therapy is still the treatment of choice for patients with MB leprosy, especially in endemic areas such as Indonesia. Further study evidence, both in terms of clinical and bacteriological aspects, and not just relapse rates, is needed as it has a long-term impact on leprosy treatment program strategies, particularly in endemic areas such as Indonesia and worldwide.

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Authors' Contributions

All authors contributed to data analysis, article preparation, and paper revision and have collectively assumed responsibility for all aspects of this work.

Disclosure

The authors have stated their absence of any conflicts of interest regarding this study.

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Ethical Consideration

Ethical committee approval for this study was obtained from the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; the approval certificate number is 0551/KEPK/XII/2022.

Data Availability

The article contains all the necessary data to support the results; no supplementary source data is needed.

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