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ANEMIA ON CHRONIC DISEASE IN LEPROSY BEFORE AND AFTER COMPLETING MULTI DRUG THERAPY

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ABSTRACT

Leprosy infection can cause anemia due to chronic disease (ACD). Multidrug therapy (MDT) for leprosy patients can overcome the infection, thus, erythropoiesis process returns to normal. This study aims to determine the comparison in the incidence of ACD before and three months after MDT to leprosy patients at Prof. Dr. I G.N.G. Ngoerah Central General Hospital. Method: A cross-sectional analytical observational study was conducted using secondary data from medical records of leprosy patients at Prof. Ngoerah General Hospital. A total of 142 samples were taken through total sampling. Data taken included gender, domicile, type of leprosy suffered, incidence of ACD, hemoglobin levels, and erythrocyte index before and three months after completing MDT leprosy therapy. Data analysis was carried out with SPSS version 21 using chi-square and paired t tests (dependent t-test), p value <0.05 means significant. Results: The incidence of ACD was significantly higher before leprosy MDT therapy compared to 3 months after completing leprosy MDT therapy (49.3% vs. 16.2%; p value <0.001) with a prevalence ratio of 3.043 (2.021-4.584) CI95%. The mean hemoglobin levels, MCV, MCH, and MCHC levels 3 months after MDT leprosy therapy were significantly higher than before receiving MDT therapy (13.73 ± 1.47 vs. 12.40 ± 2.06 g/dL; p value <0.001), (88.18±7.22 vs. 84.07±9.55 fl; p value<0.001), (28.32±2.76 vs. 26.72±3.17 pg/cell; p value <0.001), (32.03±1.30 vs. 31.69±1.47%; p value<0.001). Conclusion: The incidence of ACD was significantly higher before MDT compared to 3 months after MDT. Mean hemoglobin, MCV, MCH, and MCHC levels were found to be significantly higher 3 months after MDT compared to before receiving MDT.

KEYWORDS *Anemia On Chronic Disease, Erythrocyte Index, Leprosy, Multidrug Therapy.*

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INTRODUCTION

Leprosy remains a health problem in Indonesia due to several provinces not having fully eliminated the disease. Leprosy imposes a burden on sufferers both physically and mentally due to the stigma that affects the psychological condition of patients. Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae (M. leprae) (Cruz et al., 2017). In 2019, 202.256 new cases of leprosy were detected in 118 countries, with Indonesia being one of the largest contributors. Data shows that 79% of cases come from India, Brazil, and Indonesia (Riccò et al., 2019).

Chronic diseases, whether from bacterial infection or other causes, can lead to anemia. Anemia is characterized by a decrease in red blood cells or hemoglobin concentration below the normal range (Suega, n.d.). According to Sadeli, anemia has a positive correlation with leprosy, indicating that anemia can occur in leprosy patients even before therapy, with normal erythrocyte index pointing to anemia of chronic disease (ACD) (Sadeli, 2022). Anemia of chronic disease shows low reticulocytes, indicating a failure in reticulocyte production to compensate for the decreased red blood cells. Leukocyte and platelet counts follow the course of the underlying disease. Additionally, M. leprae require iron for increased pathogenicity, and the increased uptake and retention of iron due to the infection process reduce its availability for erythroid progenitor cell proliferation, disrupting red blood cell lifespan and leading to anemia (Lubis, 2022).

The ideal management for ACD involves treating the underlying disease, in this case, leprosy, with MDT. One study by Amalia et al., involving 37 leprosy patients, found lower mean hemoglobin levels (131 vs. 142 g/dL) and higher serum ferritin levels (2369 vs. 1329) in leprosy patients before MDT compared to the control group. It has been reported that anemia in leprosy patients is due to the chronic infection itself, and leprosy therapy can improve anemia caused by the chronic bacterial infection of M. leprae. This study aims to compare the incidence of ACD, hemoglobin levels, and erythrocyte indexes before and after completing MDT (Amalia et al., 2017).

RESEARCH METHOD

Study Design

This study used an analytical design with a cross-sectional approach using secondary data. Hemoglobin levels, erythrocyte index (MCV, MCH, MCHC), and the presence of anemia before and three months after completing MDT were recorded.

Samples of The Study

Medical records of outpatient leprosy patients who received MDT Prof. Dr. I G.N.G. Ngoerah Hospital from January 2019 to December 2022 that met inclusion and exclusion criteria through consecutive sampling until the minimum required sample was reached.

Research Variables

The independent variable in this study was MDT leprosy therapy, while the dependent variables were the incidence of ACD, hemoglobin levels, and erythrocyte index in leprosy patients. Confounding variables included pregnancy, hemolytic anemia, chronic kidney failure, G6PD enzyme deficiency, rheumatoid arthritis, systemic lupus erythematosus, malignancy or neoplasia, hepatic cirrhosis, blood disorders (sickle cell anemia, thalassemia), bone marrow disorders, chronic bleeding due to gastrointestinal disorders, and deficiencies in vitamin B12 and/or folic acid.

Research Procedures

The accessible population of this study included all leprosy patients who received MDT therapy at the Dermatology and Venereology Clinic of Prof. Ngoerah General Hospital from January 2019 to December 2022 listed in medical records. Eligible samples were tested for hemoglobin, anemia, and erythrocyte index before and three months after completing MDT therapy.

Data Analysis

All data obtained was entered into Microsoft Excel and transferred to the Statistical Package for The Social Sciences (SPSS) version 21 for Windows for analysis. Descriptive analysis was performed on the subject characteristics. Chi-square analysis was conducted to determine differences in ACD incidence before and three months after MDT therapy. Paired t-tests (dependent t-tests) were conducted to compare mean hemoglobin levels, MCV, MCH, and MCHC before and three months after completing MDT therapy.

RESULT AND DISCUSSION

Characteristics of Research Subjects

The study involved 142 leprosy patients, both multibacillary and paucibacillary, who received Multi Drug Therapy (MDT). The characteristics of the research subjects can be seen in Table 1. The mean age of the subjects was 35.00±15.33 years, with the largest distribution in the adult age group (26-45 years) comprising 68 people (47.9%). The gender distribution was predominantly male with 95 patients (66.9%) and female with 47 patients (33.1%). Most of the research subjects resided in Denpasar (43%) and Badung Regency (35.9%), with 4 patients (2.8%) from outside Bali.

The majority of subjects in this study were diagnosed with multibacillary (MB) leprosy, with 127 patients (89.4%). Based on the presence of ACD before MDT therapy, 70 patients (49.3%) experienced ACD with 39 patients (55.7%) having mild anemia, 29 patients (41.4%) having moderate anemia, and 2 patients (2.9%) having severe anemia.

Laboratory data before MDT therapy showed a mean hemoglobin level of 12.40±2.06 g/dL. The mean MCV was 84.07±9.55 fl, the mean MCH was 26.72±3.17 pg/cell, and the mean MCHC was 31.69±1.47 g/dL.

The incidence of ACD three months after patients completed MDT for leprosy was found in 23 patients (16.2%). Among them, 9 patients (39.1%) experienced mild anemia, while 14 patients (60.9%) had moderate anemia. None of the patients experienced severe anemia. The mean hemoglobin level was 13.73±1.74 g/dL, mean MCV (Mean Corpuscular Volume) was 88.18±7.22 fl, mean MCH (Mean

Corpuscular Hemoglobin) was 28.32±2.76 pg/cell, and mean MCHC (Mean Corpuscular Hemoglobin Concentration) was 32.03±1.30 g/dL.

Table 1. Characteristics of Research Subjects

Variable	n=142 (%)
Age (average±SD)	35,00±15,33 tahun
• 18-25 years old (teenage)	32 (22,50)
• 26-45 years old (adult)	68 (47,90)
• 46 - <60 tahun (late adult)	27 (19,00)
• ≥60 tahun (elderly)	15 (10,5)
Gender	
• Male	95 (66,90)
• Female	47 (33,10)
Domicile	
• Denpasar	61 (43,00)
• Badung	51 (35,90)
• Tabanan	1 (0,70)
• Gianyar	6 (4,20)
• Klungkung	2 (1,40)
• Bangli	4 (2,80)
• Karangasem	0 (0,00)
• Buleleng	4 (2,80)
• Jembrana	7 (4,90)
• Outside Bali	6 (4,20)
	4 (2,8)
Leprosy Type	
• Paucibaciler	15 (10,60)
• Multibaciler	127 (89,40)
Data before MDT	
• Hemoglobin rate (g/dL) (Average±SD)	12,40±2,06
• MCV rate (fl) (Average±SD)	84,07±9,55
• MCH rate (pg/cell) (Average ±SD)	26,72±3,17
• MCHC rate (%) (Average ±SD)	31,69±1,47
ACD before MDT	
• Yes	70 (49,30)
• No	72 (50,70)
ACD category before MDT	
• Mild	39 (55,70)
• Moderate	29 (41,40)
• Severe	2 (2,90)
Data 3 months after completing MDT	
• Hemoglobin rate (g/dL) (Average±SD)	13,73±1,74
• MCV rate (fl) (Average±SD)	88,18±7,22
• MCH rate (pg/cell) (Average ±SD)	28,32±2,76
	32,03±1,30

• MCHC rate (%) (Average ±SD)	
ACD 3 months after completing MDT	
• Yes	23 (16,20)
• No	119 (83,80)
ACD category 3 months after completing MDT	
• Mild	9 (39,10)
• Moderate	14 (60,90)
• Severe	0 (0,00)

Difference in the Incidence of Anemia on Chronic Disease (ACD) Before and 3 Months After Completing Multidrug Therapy (MDT) for Leprosy

From the analysis, it was found that the percentage of significant incidence of ACD was higher before compared to 3 months after completing MDT (49.3% vs. 16.2%) with a p-value <0.001 and a prevalence ratio of 3.043 (2.021-4.584) with a 95% confidence interval (CI) as shown in Table 2. The PR value of 3.043 indicates that the prevalence ratio is greater than 1.

Table 2. Difference in the Incidence of ACD Before and 3 Months After Completing MDT for Leprosy

Onset	**Anemia n (%)**	**Non anemia n (%)**	**P Value**	***Prevalence Ratio* (CI95%)**
Before MDT	70 (49,30)	72 (50,70)	<0,001*	3,043 (2,021-4,584)
3 months after MDT	23 (16,20)	119 (83,80)		

* The results are considered significant if p < 0.05. The bivariate analysis was conducted using the chi-square test with a 95% confidence interval.

Difference in hemoglobin levels before and 3 months after MDT for leprosy

Based on the difference in hemoglobin levels, the mean Hb (hemoglobin) 3 months after multidrug therapy (MDT) for leprosy was 13.73±1.47 g/dL. This result is significantly higher compared to the Hb levels before MDT therapy, which were 12.40±2.06 g/dL, with a p-value of <0.001 as shown in Table 3.

Table 3. Difference in hemoglobin levels before and 3 months after MDT for leprosy

Variable	**Before MDT (Average±SD)**	**3 months after MDT (Average±SD)**	**P Value**
Hemoglobin rate (g/dL)	12,40±2,06	13,73±1,47	<0,001*

* The results are considered significant if p < 0.05, using dependent t-test.

Difference in erythrocyte index (MCV, MCH, and MCHC) before and 3 months after MDT for leprosy

In terms of erythrocyte index, significant differences were found in MCV, MCH, and MCHC before and 3 months after MDT for leprosy. The mean MCV 3 months after MDT therapy was significantly higher compared to before therapy (88.18±7.22 vs. 84.07±9.55 fl) with a P-value <0.001. Significant differences were also observed in MCH, where the mean MCH 3 months after MDT therapy was significantly higher than before therapy (28.32±2.76 vs. 26.72±3.17 pg/cell, p <0.001). Similarly, the mean MCHC 3 months after therapy was significantly higher compared to before therapy (32.03±1.30 vs. 31.69±1.47 g/dL, p=0.008)

Tabel 4. Difference in Erythrocyte incides (MCV, MCH, and MCHC) before and 3 months after MDT for leprosy

Variable	Before MDT (Average±SD)	3 months after MDT (Average±SD)	P Value
MCV rate (fl)	84,07±9,55	88,18±7,22	<0,001*
MCH rate (pg/cell)	26,72±3,17	28,32±2,76	<0,001*
MCHC rate (%)	31,69±1,47	32,03±1,30	0,008*

* The results are considered significant if p < 0.05, using dependent t-test.

Discussion

Leprosy infection falls under chronic diseases. Similar to other chronic diseases, leprosy infection can lead to anemia due to chronic disease, characterized by hemoglobin levels below the normal range but with normochromic normocytic hemoglobin morphology. In leprosy infection, particularly in borderline lepromatous (BL) and lepromatous (LL) types, cytokines play a role in the pathogenesis of chronic disease anemia, namely interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-ά), which work by directly inhibiting erythropoiesis. Erythropoiesis is the process of forming erythrocytes or hemoglobin through several stages, after which the erythrocytes are released into the bloodstream.

The characteristics of anemia in chronic disease are typically found in mild to moderate anemia, with hemoglobin levels ranging from 7 to 11 g/dl and a normochromic normocytic morphology. In our study, the majority of chronic disease anemia (CDA) patients fell into the mild (55.7%) and moderate (44.1%) categories, consistent with this theory. Mycobacterium leprae infection also causes an immune response involving the release of cytokine cells and the reticuloendothelial system, which induces iron homeostasis, erythroid progenitor cell proliferation, erythropoietin production, and erythrocyte lifespan, all contributing to the occurrence of chronic disease anemia (CDA) in leprosy patients. Disruption of erythropoiesis is caused by direct infiltration into the bone marrow, as well as the production of pro-inflammatory cytokines and free radicals that can damage erythroid progenitor cells.

The administration of MDT can eradicate M. leprae, preventing the production of bacterial toxins and allowing the erythropoiesis process to proceed without hindrance (Cambau & Williams, 2019). A study by Muhaira et al. at RS

Haji Adam Malik Medan found the occurrence of hemolytic anemia in patients three months after starting MDT therapy. These study findings differ from those in our research. The hemolytic anemia observed was induced by dapsone, which was consumed for three months during blood examination (Muhaira et al., 2018).

Other studies that found different results from ours include those by Deps et al., Dupnik et al., and Gupta et al., which reported higher occurrences of anemia during MDT administration compared to before MDT. These results could be due to the timing of hemoglobin and erythrocyte index examinations while patients were undergoing MDT therapy. During MDT, the process of eradicating the leprosy infection is ongoing, so erythropoiesis has not fully normalized. Additionally, dapsone in the MDT regimen can cause side effects such as hemolytic anemia (Dupnik et al., 2013; Gupta et al., 2020).

The pathogenesis of anemia in chronic disease is not precisely known, but several theories are believed to be causes, including impaired iron release from the reticuloendothelial system such as macrophages, shortened erythrocyte lifespan, disrupted erythropoietin synthesis, and decreased bone marrow response to erythropoietin. The diagnosis of anemia in chronic disease can show symptoms such as pale face, pale conjunctiva, fatigue, weakness, and other symptoms related to anemia. However, patients may also be asymptomatic. Supporting examinations to establish anemia in chronic disease include a complete blood count, which shows mild to moderate anemia, hemoglobin levels around 7-11 g/dL, usually with normochromic or mildly microcytic morphology. A mildly microcytic picture can be found in patients with anemia in chronic disease; normal or slightly decreased MCV; decreased serum iron; decreased total iron-binding capacity; decreased transferrin saturation; and normal or increased serum ferritin (Cappellini & Motta, 2015).

In this study, a significant difference was found between the mean hemoglobin levels of patients before and three months after completing leprosy therapy, which were 12.40±2.06 g/dL and 13.73±1.47 g/dL, respectively. The increase in mean hemoglobin levels after MDT may occur because the leprosy infection and the causative microorganism, M. leprae, have been eradicated from the patient's body. The resolution of the leprosy infection causes erythropoiesis to normalize again. Moreover, the inhibition of erythropoietin does not occur, so red blood cell production returns to normal, and the patient's hemoglobin levels normalize.

Another study by Islam et al. conducted a cohort study on 85 leprosy patients receiving MDT, yielding results consistent with our study. This study evaluated hematological parameters (hemoglobin, MCH, MCHC, WBC, and platelets), renal function in leprosy patients regularly every three months for one year during MDT (months 0, 3, 6, 12) and six months after completing MDT (month 18). This study found that hemoglobin levels in leprosy patients decreased during MDT from an initial 12.3 g/dL to 10.1 g/dL and 10.8 g/dL at months three and six of therapy. However, hemoglobin levels gradually improved at month 12 to 11.8 g/dL and returned to normal, even higher than pre-therapy levels, six months after completing MDT to 12.8 g/dL (Islam & Islam, 2016).

The mean MCV and MCH in this study were also identical to the results of Singh et al., which found that erythrocyte index levels were significantly higher post-MDT therapy compared to pre-MDT in leprosy patients. The mean MCV increased by 3% post-MDT from 87.57 fL to 89.87 fL. Meanwhile, the mean MCH increased by 6% from 30.8 to 32.6 pg/cell (Singh et al., 2011). Additionally, the study by Islam et al. also found similar results; the MCH of leprosy patients at month 0 of MDT was 32.4 pg, which then decreased to 30.1 pg, 31.6 pg, and 31.8 pg at months 3, 6, and 12 of MDT. MCH returned to normal to 32.8 pg six months after completing MDT. Similarly, MCHC levels were found to be 33.6% at month 0 of therapy, then decreased to 29.9%, 32.1%, and 32.4% at months 3, 6, and 12 of MDT, and improved to 33.1% six months after completing MDT.

Few studies have investigated anemia on chronic disease in leprosy patients and the differences in hemoglobin levels and erythrocyte indexes in leprosy patients before and three months after completing MDT therapy. This study found that with MDT, leprosy infection is resolved, and anemia due to chronic disease caused by M. leprae bacterial toxins inhibiting erythropoiesis no longer occurs, as evidenced by significantly lower ACD, higher mean Hb, and higher erythrocyte index three months post-MDT. However, a limitation of this study is the use of secondary data, and many samples were excluded due to incomplete laboratory data, especially complete blood count results three months after completing MDT therapy.

CONCLUSION

The incidence of chronic disease anemia (CDA) in leprosy patients undergoing outpatient treatment at RSUP Prof. Dr. I G.N.G. Ngoerah was found to be significantly higher before MDT administration compared to three months after completing MDT therapy. The mean hemoglobin levels and erythrocyte indexes of leprosy patients were also significantly higher three months after completing therapy. This study's results demonstrate that CDA due to leprosy infection improves with MDT therapy. If in clinical practice hemoglobin levels are found to decrease or be lower at the onset three months after completing MDT, it is necessary to evaluate the patient for hemolytic anemia or other risk factors and comorbid diseases that may cause anemia. Additionally, monitoring the patient's compliance with MDT leprosy therapy is essential. Further research using a cohort design and primary data from multiple centers is recommended to obtain more reliable and varied research results.

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