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Hemolytic anemia incident in leprosy patients receiving multi-drug therapy at Haji Adam Malik Central Hospital, Medan-Indonesia

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ABSTRACT

Introduction: Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*, which is an obligate intracellular bacteria. The therapy of leprosy involves a combination of drugs called multi-drug therapy which one of the drugs included in this therapy is dapsone. Dapsone has a hematotoxic effect because of its toxic metabolite called hydroxylamine. The most common side effect of this drug is hemolytic anemia. Hemolytic anemia occurs when the production of erythrocytes is not balanced with their destruction, causing the lifespan of erythrocyte to become shorter and the bone marrow fails to compensate for this.

Methods: This research is a pre-experimental study with a pre-post design, involving 15 new leprosy patients that were diagnosed by clinical and laboratory examination. We conducted measurements of hemoglobin, MCV, MCHC, and reticulocyte count before and after the MDT therapy for 3 months.

Results: In this study, the incidence of hemolytic anemia after 3 months receiving MDT was 66.7%. There was decreased hemoglobin level (mean 11.320 g/dl), increased reticulocyte count (mean 2.341%), normal level of MCV (mean 88.807 fL), and decreased level of MCHC (mean 31.920 g%). There were significant differences in hemoglobin level, MCHC level, and reticulocyte count before and after 3 months of MDT.

Conclusion: There was a significant difference in the number of hemolytic anemia before and after MDT with a p-value < 0.05.

Keywords: *leprosy, hemolytic anemia, dapsone*

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INTRODUCTION

Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae, which is an obligate intracellular bacteria.[1-3] The program to eradicate leprosy is done by breaking the chain of transmission to reduce the disease incidence, treating and curing patients, and preventing disability. The World Health Organization (WHO) Chemotherapy Study Group in 1981 established a treatment regimen with MDT or multidrug therapy, which is a combination of two or more anti-leprosy drugs. It is known as MDT-WHO, which includes rifampicin, clofazimine, and dapsone in the treatment of leprosy.

One of the drugs included in MDT is dapsone, a sulfonamide that has a bacteriostatic effect by inhibiting the dihydrofolate synthetase enzyme.[3-5] Oral dapsone is absorbed through the gastrointestinal tract and will then be transported to the liver, undergoing different metabolic transformations. There are two main metabolic pathways, which are N-acetylation and N-hydroxylation. Acetylation is a fast acetylator in dapsone metabolism.[6,7] Deacetylation occurs spontaneously and has a stable equilibrium between monoacetyl dapsone and diacetyl dapsone, which can be achieved within hours of oral administration. It appears that acetylation levels are unrelated to the drug's half-lives in the body and do not affect drug efficacy.[8] The second pathway in dapsone metabolism is N-hydroxylation. N-hydroxylation produces hydroxylamine, which is a toxic metabolite produced by the cytochrome P-450 enzyme. The main pathway of this hydroxylation is responsible for the occurrence of hematologic disorders such as hemolysis, methemoglobinemia, and Heinz-body formation.[6,8] However, the exact mechanism of how hydroxylamine can cause this side effect is not fully understood.[6,7,9]

Hemolytic anemia is an abnormal breakdown of red blood cells. This abnormality happens when there is increased destruction of erythrocytes and insufficiency of bone marrow to compensate for this. As a result, there is a reduced erythrocytes lifespan, which is normally 120 days.[10] For detecting hemolytic anemia due to prolonged use of dapsone, complete blood examination is required every 3-4 months. A blood laboratory examination that can be assessed is a complete blood count and reticulocyte count.[7,11] The management in case of MDT side-effects, one of which hemolytic anemia, is to stop the medication temporarily and observe the patient for a period of time. If the side effects cannot be resolved, the drug administration should be discontinued.[12]

Research on leprosy drugs and side effects are still very limited in Indonesia. Therefore, this study

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aims to investigate hemolytic anemia in leprosy patients who received MDT at Haji Adam Malik Medan General Hospital (RSUP).

METHOD

This research is a pre-experimental study with a pre-post design. This research was conducted from April to December 2016 at Leprosy Polyclinic at Department of Dermatology and Venereology, Haji Adam Malik Hospital, Medan. The target population of this study was leprosy patients at RSUP Haji Adam Malik Medan. The accessible population was new leprosy patients who went to Leprosy Polyclinic at Department of Dermatology and Venereology, Haji Adam Malik Hospital, Medan during April 2016 to December 2016. The sample of the study was taken by consecutive sampling method.

Fifteen new leprosy patients were included in the study. History taking, physical examination, dermatological examination, and neurological examination were performed before the patients received multi-drug therapy (MDT). Additionally, the type of leprosy, either PB (paucibacillary) or MB (multibacillary), was also assessed the subjects receive MDT. The investigators recorded blood sampling for hemoglobin (Hb), MCV (Mean Corpuscular Volume), MCHC (Mean Corpuscular Hemoglobin Concentration), and reticulocyte count and results. Patients were given MDT according to the type of leprosy (MB or PB), then re-examined after 3 months of receiving MDT. The collected data is then processed and analyzed by the researcher.

RESULTS

There are 15 subjects included in this study, and most of the subjects are male (53.3%). The demographic data also showed that most of the subjects are in the 15-29 years and 30-44 years age group,

Table 1 The characteristics of research subjects based on gender, age, and type of leprosy

Characteristics		n (15)	%
Gender	Male	8	53.5
	Female	7	46.7
Age in years	15-29	6	40.0
	30-44	6	40.0
	45-59	2	13.3
	≥ 60	1	6.7
Type of Leprosy	PB	1	6.7
	MB	14	93.3

Table 2 Profile of hemoglobin, MCV, MCHC and reticulocyte count in leprosy patients

	Parameter				
Profile	Mean	Min	Max	SD	*p*
Hb (g/dl) before MDT	13.907	12.1	16.7	1.3656	0.000
Hb (g/dl) after MDT	11.320	8.6	14.1	1.6367	
MCV (fL) before MDT	83.460	70.2	89.5	4.9674	0.053
MCV (fL) after MDT	88.807	65.9	101.6	10.3877	
MCHC (g%) before MDT	33.213	30.5	36.7	1.6767	0.009
MCHC (g%) after MDT	31.902	28.9	34.5	1.5992	
Reticulocyte count (%)before MDT	1.218	0.8	1.7	0.2119	0.001
Reticulocyte count (%) after MDT	2.341	1.2	4.7	1.0500	

Table 3 Hemolytic anemia after receiving 3 months of MDT

	Before MDT		After MDT		
	n	%	n	%	*p*
Normal	15	100.0	5	33.3	
Hemolytic anemia	0	0	10	66.7	0.002
Total	15	100.0	15	100.0	

both accounting for 40% out of total subjects. Almost all of the subjects (93.3%) has MB type.

The average profile of hemoglobin, MCV, MCHC and reticulocyte count before receiving MDT is normal. Before the MDT, the average hemoglobin level is 13.907 g / dl, the average MCV is 83.460 fL, the average MCHC is 33.213 g%, and the average reticulocyte count is 1.218%. However, after MDT administration, there was a decrease in hemoglobin level with an average of 11.320 g / dl, normal MCV with an average value of 88.807 fL, a decrease in MCHC levels with an average value of 31.920 g% and an increase in reticulocytes count by an average of 2.341%. There were significant differences ($p < 0.05$) in hemoglobin, MCHC and reticulocyte counts in leprosy patients before and after 3 months of receiving MDT. However, there was no significant difference ($p < 0.05$) between MCV levels in leprosy patients before and after 3 months of receiving MDT. Of the 15 subjects, hemolytic anemia was found in 10 patients (66.7%) and a significant difference ($p < 0.05$) was found before and after 3 months of receiving MDT.

DISCUSSION

In this study, male leprosy patients were found more than female leprosy patients (53.5% vs. 46.7%). This number is similar to the research performed by Tosepu, *et al.,* which reported that 55.9% male and 44.1% female in Bombana, Southeast Sulawesi were affected by leprosy.[14] Leprosy is an infectious disease that can affect both men and women. Reports from most countries in the world showed that the prevalence of leprosy in men is more than women. The low incidence of leprosy in women is likely to be due to the environmental and socio-cultural factors.[4] Differences in sex ratios occurring in adults versus children also reflect the exposure to infections rather than susceptibility to disease types.[13]

The result of this study also showed that most of the subjects are aged 15 to 44 years old. This is in line with the research by Scheelbeek *et al.,* which reported that patients with leprosy in Cebu, Philippine, in 2010 were mostly found in the age group between 15-29 years. This may be associated with long periods of incubation of leprosy and related to the patients' residence in which people who live in leprosy endemic areas are more susceptible to leprosy. Additionally, there is an increased exposure risk of leprosy transmission in adult as compared to other age groups.[15]

This study also found that the most common type of leprosy is MB, which accounts for 93.3% out of all subjects. One of the possible explanations for this is because the MB leprosy types are more contagious than the PB types.[17] The study by Kumar, *et al.* shows that MB type of leprosy is more common than all new leprosy patients (65.9%). It's chronic nature, various social factors such as leprosy level and low economic level, and environmental factors such as leprosy endemic areas are the possible reasons why MB leprosy is the most common type.[18]

In this study, there was a decrease in hemoglobin levels with the mean of 11,320 g / dl after 3 months of MDT. This decrease in hemoglobin level occurs probably due to hemolytic anemia, where the longer the dapsone is given, the higher the direct oxidant effect to the red blood cell membrane.[19,20] Absorption of dapsone via metabolic N-hydroxylation pathway results in a toxic metabolite called hydroxylamine. This toxic metabolite can cause abnormal destruction of red blood cells, resulting in a decrease in hemoglobin levels.[6,8,10] Al-Sieni *et al.* revealed that there was a 10-30% decrease in hemoglobin (Hb) levels in both men and women after 3 months of MDT administration.[19] The study by Singh, *et al.* found that Hb levels decreased by 17% after 90 days of receiving MDT.[21]

In this study, normal MCV was found after 3 months of MDT with the average of 88.807 fL. This is found probably because the toxic metabolite causes disruption in the production of erythrocyte or increased in cell destruction, but does not affect the volume of erythrocyte, which is represented by MCV. This is frequently seen in acute hemolytic anemia. In chronic hemolytic anemia, large erythrocyte measurements can be seen from increased MCV. However, changes in these MCV levels may be variable.[22,23] Different result was reported by Singh *et al.* who found that MCV level is elevated by 3% after 90 days of receiving MDT. Hematological profile shows abnormalities both before and after receiving MDT. They found the side effects of dapsone are very high, and therefore supportive therapy along with MDT is required.[21]

This study showed a decrease in MCHC levels with a mean of 31,920 g%. This is likely because the Hb levels per unit of erythrocyte volume are found to decrease, leading to smaller erythrocyte size. This is a form of cell compensation to be more readily attached to oxygen with limited Hb content.[22,23] A similar study was reported by Al-Sieni *et al.* which found that there was a decrease in MCHC levels after 3 months of taking MDT. They concluded that this decline was a reaction of anemia but was not related to red cell count changes.[19] A study by Singh, *et al.* reported that as many as 9 out of

73 leprosy patients who took dapsone for 90 days had a decreased level of MCHC by 1%.[21]

In this study, reticulocyte count increased after 3 months MDT with a mean of 2,341%. This is due to the presence of hemolysis resulting in increased production of red blood cells about two or three times the normal to compensate for this. In normal individual blood, reticulocyte persists in blood within 1 day. As blood cell production increases, reticulocytes are released prematurely and persist in circulation within 2 to 4 days.[23] A similar study reported by Singh, *et al.* found that 9 out of 73 leprosy patients assessed after taking dapsone within 90 days showed increased reticulocyte count by 36.5%.[21] The study by Halim, *et al.* reported an increase in reticulocyte count after receiving MDT with an average of 7.3 ± 1.0% and a p-value of <0.05. Reticulocytes increased by 4-fold during the study. This shows that dapsone may induce hemolysis.[20]

In this study, the incidence of hemolytic anemia after 3 months of taking MDT was 66.7%. Hemolytic anemia is anemia associated with a shortening lifespan of red blood cells less than 120 days, which results from the rapid destruction of red blood cells. If hemolytic anemia is suspected, it is necessary to perform a complete blood test with reticulocyte count. The increased reticulocyte count is an important sign of hemolytic anemia as it can reflect the activity of bone marrow to compensate for increased red blood cell destruction.[24] Another study by Deps, *et al.* states that hemolytic anemia was found to be in 51% patients who received dapsone in MDT after 3 months. In those patients, hemoglobin and hematocrit levels were found to be decreased. Side effects that occur due to MDT can be severe and therefore may cause temporary termination of drug administration, and supportive therapy may be given. However, if the side effects cannot be resolved, then the drug should be stopped and WHO recommends that the causative drug is replaced by alternative therapies.[25]

CONCLUSION

This study found that 66.7% of subjects have hemolytic anemia after 3 months of receiving MDT. From the results of this study, it is suggested that hemoglobin levels and reticulocyte counting can be performed in leprosy examination procedures every 3 months, as they can be used as predictors of hemolytic anemia to monitor the side effects of MDT.

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