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Research Article

## N-Acetylcystein has Potential Effect to Reduce Haematological Abnormalities in HIV/AIDS Patients Undergoing ARV Treatment

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### ABSTRACT

**Aims:** to determine the effect of NAC administration on hematological abnormalities in HIV/AIDS patients who are undergoing ARV treatment.**Method:** This was a pilot study using a double blind randomized clinical trial. A total of 32 subjects who met the inclusion and exclusion criteria were divided into 2 groups, namely placebo and NAC. Subjects in the NAC group were given NAC at a dose of 3x200 mg/day, while the placebo group was given lactose at a dose of 3x200 mg/day. Each group was given treatment for 12 weeks. Before and after treatment, subjects were examined for hematologic parameters.**Results:** Most of subjects had normal hematological features. NAC administration did not have a significant effect on the mean levels of Hb, Ht, number of erythrocytes, leukocytes and platelets ( $p > 0.05$ ). However, NAC administration can reduce the degree of anemia and improve the condition of thrombocytopenia, leukopenia and lymphopenia.**Conclusion:** NAC administration can reduce hematological abnormalities HIV/AIDS patients undergoing ARV treatment.**Keywords:** ARV, Hematological abnormalities, HIV/AIDS, NAC.**Article Info:** Received 21 June 2020; Review Completed 26 July 2020; Accepted 08 August 2020; Available online 20 August 2020

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### INTRODUCTION

HIV infection is known to cause various disorders in the hematopoietic system.<sup>1</sup> This condition is caused by various factors, including the direct effect of HIV infection. HIV infection causes disruption of cytokine balance and suppresses the hematopoiesis system, resulting in hematological abnormalities of the sufferer.<sup>2</sup> The presence of secondary infections that accompany HIV infection, such as tuberculosis or side effects of antiretroviral drugs such as zidovudine (AZT) given, can also cause hematological abnormalities.<sup>3</sup>

Hematologic abnormalities are one of the important prognostic markers for people with HIV/AIDS.<sup>4</sup> Hematological abnormalities, associated with an increased risk of morbidity and mortality in HIV patients.<sup>5</sup> Anemia, thrombocytopenia or leukopenia, is the most common hematological abnormality in HIV patients.

Antiretroviral (ARV) treatment is standard therapy for people with HIV. ARV have been shown to successfully reduce viral replication, thereby increasing CD4 cell counts

and inhibiting disease progression.<sup>5</sup> However, several studies have shown that ARV use causes haematological abnormalities.<sup>6-8</sup> In addition, the use of ARV is also known to increase oxidative stress in people with HIV.<sup>9</sup> N-acetylcystein (NAC) is one of the antioxidant compounds that has been widely used as medicine. This compound can increase glutathione levels which play a major role in maintaining redox conditions in cells. Until now, there is only a few research discusses uses of NAC as an additional supplement for HIV patients undergoing ARV treatment. This study aims to determine the effect of NAC on hematological abnormalities that occur in HIV patients who are undergoing ARV treatment.

### MATERIAL AND METHOD

#### Study Design

This study was a pilot study that uses a double blind randomized clinical trial design. The study was conducted in July 2019 - February 2020 at the Dr. Mohammad Hoesin Hospital, Palembang.

## Subject

The research subjects were HIV/AIDS sufferers who were treated at the Dr. Mohammad Hoesin Hospital Palembang during Juli until Agustus met the inclusion criteria, i.e.: all patients who had been diagnosed with HIV/AIDS, aged 20-60 years, received anti-retroviral (ARV) drugs, and were willing to take part in the study by signing an informed consent form. Subjects were excluded from the study if they had a history of allergy to NAC, and took antioxidant drugs other than NAC during the study. Subjects were discontinued in the study if the subject dropped out of the NAC drug, died, side effects arose so that the giving of the NAC drug had to be stopped, and stopped participation before the study was completed. Based on these criteria, there were 32 HIV sufferers who were the subjects of this study. Subjects were divided randomly into 2 groups, namely the placebo and NAC group. Each group is 16 people. Subjects in the NAC group were given capsules containing NAC at a dose of 3x200 mg / day for 12 weeks. Subjects in the placebo group were given capsules containing lactose at a dose of 3x200 mg / day for 12 weeks. This study was approved by the ethics committee of the Faculty of Medicine, Sriwijaya University and Dr. Mohammad Hoesin Hospital, Palembang (No. 552/kepkrsmhfkunsri/2019).

## Hematological Measurement

Hematologic parameters namely Hb, Ht, erythrocyte counts, leukocytes, platelets and leukocyte counts were examined using the Sysmex XN 1000i Hematology Analyzer, with DCL Cellpack reagents. The sample used was the subject's venous blood. For each study subject, blood was drawn twice, at the beginning of the study / before the treatment and after the treatment ended. Based on WHO criteria, subjects were declared to suffer from anemia if they had a Hb level of less than 13 gr/dL for men and less than 12 gr/dL for women. Subjects were declared to have thrombocytopenia if their platelet count was less

than 170.000 cells/ $\mu$ L; thrombocytosis if the platelet count is more than 396.000 cells/ $\mu$ L, leukopenia if the number of leukocytes is less than 4.730 cells/ $\text{mm}^3$  and leukocytosis if the number of leukocytes is more than 10.800 cells/ $\text{mm}^3$ .

## Statistical Analysis

The statistical analysis used mean, standard deviation, independent T test or Mann Whitney and dependent T test or Wilcoxon. The test results are statistically approved if the p value <0.05.

## RESULTS

### General Characteristics

Most research were male (81,25%) with age range of 31-40 years (50%), had secondary education (43,75%) and worked in the private sector (62,5%). The majority of subjects involved in this study were stage 1 HIV sufferers without comorbidities and had only been on ARV treatment for less than 1 year.

### Hematological Parameters

Hb levels in the placebo and NAC group before treatment were higher when compared to Hb levels after treatment, but not significantly. However, the range of minimum and maximum values in the placebo and NAC groups after treatment was higher than before treatment. In contrast to Hb, erythrocytes and leukocytes count in the placebo and NAC groups before treatment, was lower when compared to erythrocytes count after treatment. Ht levels and platelet count in the placebo group before treatment was lower than the Ht level and platelet count after treatment. The opposite was found in the NAC group, where Ht levels and platelet counts before treatment were slightly higher when compared to levels after treatment, but were not significantly different (Table 1). Furthermore Hb and Ht levels, erythrocytes and leukocytes count in the NAC group after treatment, was higher when compared to the placebo group, although it was not significantly different (Table 1).

**Table 1: Characteristics of Hematological Parameters**

Parameters	N	Mean $\pm$ SE/Median (Min-Maks)		P
		Plasebo	NAC	
<b>Hb level</b>				
- . Before	16	14,85(9,5-16,5)	15,00(8,7-16,8)	0,724 <sup>c</sup>
- . After	16	13,9(12,3-17,0)	14,9(11,7-16,9)	0,724 <sup>c</sup>
<b>p Before vs After</b>		0,518 <sup>a</sup>	0,737 <sup>a</sup>	
<b>Erythrocytes Count</b>				
- . Before	16	4,31 $\pm$ 0,19x10 <sup>6</sup>	4,66 $\pm$ 0,19x10 <sup>6</sup>	0,213 <sup>d</sup>
- . After	16	4,55 $\pm$ 0,14x10 <sup>6</sup>	4,68 $\pm$ 0,15x10 <sup>6</sup>	0,538 <sup>d</sup>
<b>p Before vs After</b>		0,140 <sup>b</sup>	0,813 <sup>b</sup>	
<b>Ht level</b>				
- . Before	16	40,68 $\pm$ 5,83	44,50(27-50)	0,184 <sup>c</sup>
- . After	16	41,62 $\pm$ 4,36	42,06 $\pm$ 1,07	0,468 <sup>d</sup>
<b>p Before vs After</b>		0,366 <sup>b</sup>	0,815 <sup>a</sup>	
<b>Platelet Count</b>				
- . Before	16	262.000 (190.000 - 419.000)	260.000 (156.000 - 367.000)	0,867 <sup>c</sup>
- . After	16	271.625 (174.000 - 445.000)	259.000 (198.000 - 487.000)	0,780 <sup>c</sup>
<b>p Before vs After</b>		0,485 <sup>a</sup>	0,127 <sup>a</sup>	
<b>Leukocyte Count</b>				
- . Before	16	6.083 $\pm$ 423	6.600 $\pm$ 468	0,419 <sup>d</sup>
- . After	16	6.710 $\pm$ 508	7.091 $\pm$ 409	0,564 <sup>d</sup>
<b>p Before vs After</b>		0,275 <sup>a</sup>	0,265 <sup>a</sup>	

**Exp:** <sup>a</sup> p value uses the Wilcoxon test; <sup>b</sup> the p value uses the paired T test; <sup>c</sup> p values using the Mann Whitney test; <sup>d</sup> Value of p using the unpaired T test. All tests perform at  $\alpha$  5%.

Based on the WHO criteria above, before treatment there were 5 subjects suffering from anemia, 3 in the placebo group and 2 in the NAC group. The giving of NAC can reduce the degree of anemia from moderate to mild (Figure 1). In addition to reducing the degree of anemia, giving of NAC can also improve the condition of

thrombocytopenia, leukopenia and lymphopenia in the subject. Although in the placebo group there also appeared to be improvement, but the addition of NAC seemed to be able to increase the effectiveness of the improvement that occurred (Figure 2).

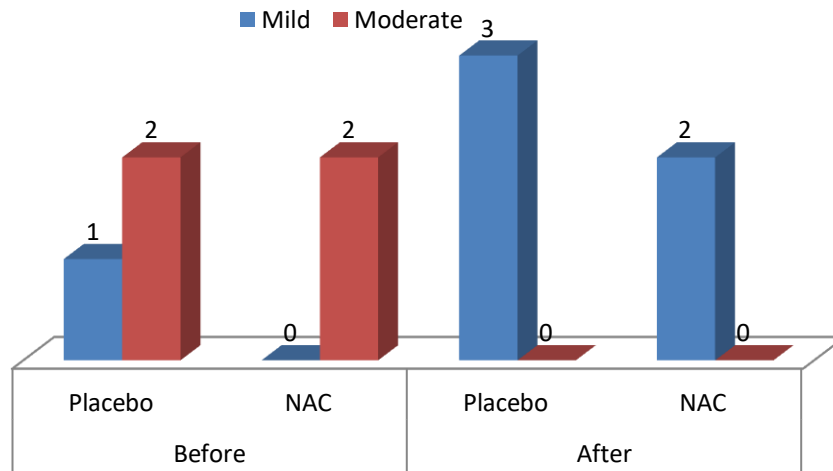


Figure 1: Anemia profile in placebo and NAC group before and after treatment.

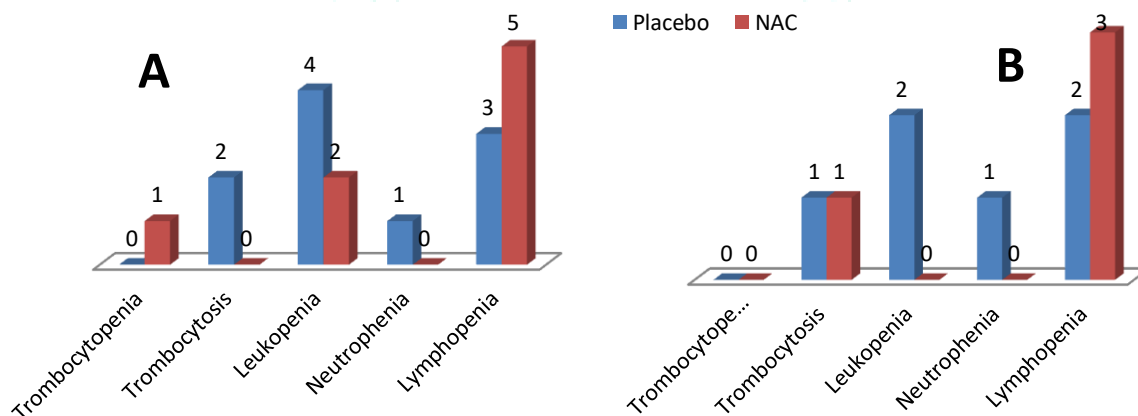


Figure 2: Hematologic abnormalities in the placebo and NAC groups

Note: (A) Before treatment; (B) After treatment.

**DISCUSSION**

In patients with HIV, various hematological disorders can be found that can act as independent predictors of the mortality and morbidity of sufferers.<sup>10</sup> Some of the most common abnormalities include anemia, thrombocytopenia and leukopenia.<sup>11</sup> This is due to decreased ability of the bone marrow to produce blood cells, resulting in deficiency nutrition, and disorders of the immune system of people with HIV.<sup>12-14</sup>

In this study, it was known that most subjects had normal hematological parameters. The mean Hb, Ht, erythrocyte, leukocyte and platelet counts in this study were still within normal limits. There was no difference between the mean levels of some of these parameters, before and after treatment (Table 1). This is certainly not surprising, because all subjects have received ARV treatment. In accordance with the research of Geletaw et al.,<sup>5</sup> that the giving of antiretroviral drugs can improve hemotological abnormalities that occur in people with HIV.

The giving of NAC did not have a significant effect on Hb, Ht and erythrocyte counts (Table 1). This is because the subject is an HIV sufferer who has received ARV, so the levels of these parameters in most patients, have been in normal conditions. Interestingly, giving of NAC to subjects suffering from moderate anemia can improve their condition. After administration of NAC, the subject's condition became mildly anemic (Figure 1). This seems to be related to the role of NAC as a GSH precursor. Several previous studies have shown that GSH in HIV sufferers has decreased significantly.<sup>15-17</sup> Other studies conducted by Wagiallah et al.,<sup>18</sup> show that a reduction in GSH has a significant effect in reducing hemoglobin levels, thus causing anemia. Provision of antiretroviral drugs in people with HIV, indeed proven able to significantly increase GSH levels, but not as high as GSH levels in people who do not suffer from HIV.<sup>19</sup> Giving of NAC, is expected to help increase GSH levels in HIV patients who are given ARV, so that it can help improve the degree of anemia subject.

Like Hb levels, platelet counts are also affected by HIV infection. In this study, samples with thrombocytopenia

and thrombocytosis can be found, although the majority of samples have platelet counts that are still within normal limits. Giving of NAC can increase the platelet count in samples with thrombocytopenia, so that the platelet count is within normal limits (Figure 2). Unfortunately, there is only 1 sample of patients with this condition, so it cannot be concluded whether the effect is indeed caused by NAC or other causes. Therefore, further research is needed with a larger number of samples to find this out.

According to Katemba et al.,<sup>11</sup> leukopenia is also a disorder that is found in many people with HIV. In line with this opinion, in this study also found that there are subjects with leukopenia, amounting to 6 people. Leukopenia in people with HIV is caused by a decrease in the number of CD4 + T lymphocytes and NK cells, which are part of leukocytes, due to viral activity.<sup>11</sup> Giving of NAC, can increase the number of leukocytes in subjects with leukopenia so that the number becomes normal (Figure 2). Interestingly, NAC was also able to increase the number of lymphocyte cells in subjects with lymphopenia (Figure 2). Lymphocytes are the cells most affected by HIV infection. Therefore, these cells usually experience a very significant decrease during infection. The giving of antiretroviral drugs can reduce the amount of virus significantly, thereby reducing the rate of apoptosis in lymphocyte cells.<sup>20-22</sup> The giving of NAC as an additional supplement to HIV sufferers, seems to be able to increase the effectiveness of ARV given, especially in subjects with lymphopenia after receiving ARV. It also seems to be related to the ability of NAC as an antioxidant that can inhibit the activity of ROS molecules formed in leukocyte cells during infection, thereby increasing cell viability and decreasing apoptosis that occurs.<sup>23-24</sup>

## CONCLUSION

NAC administration can reduce hematological abnormalities in HIV patients undergoing ARV treatment, although still need to be studied further.

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