

THE USE OF ANTITUBERCULOSIS THERAPY CAUSES AN INCREASE OF URIC ACID LEVELS IN PATIENTS WITH TB-MDR (TUBERCULOSIS MULTI DRUG RESISTANT)

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ABSTRACT

Background ; TB-MDR (Tuberculosis multi-drug resistant) is TB caused by TB bacteria who had been resistant for 2 types of antituberculosis drug, they are INH and Rifampicin. long term medication of Tuberculosis that use a Multidrug principle often caused various side effect, one of them is an increased uric acid level. The purpose of this study was to determine the correlation of using antituberculosis drugs on the changing of uric acid level on TB-MDR patients at Undata Hospital Central Sulawesi Province.

Objectives ; TB-MDR patients at Undata Hospital Central Sulawesi Province with normal uric acid level.

Methods ; This research is a cohort retrospective study with purposive sampling technique of patients who fulfill the inclusion and exclusion criteria and data analysis is using paired samples t-test.

Result ; The results of the study on MDR-TB patients before using antituberculosis therapy obtained 30 patients (100%) with normal uric acid levels, after using OAT obtained 8 patients (27%) normal uric acid levels and 22 patients (73%) are above normal condition. The statistical test is using paired samples t-test, it obtained Sig. (2-tailed) is 0,000 ($p < 0.05$)

Conclusion ; Based on this research it can be concluded that there is a significant correlation or difference between before using antituberculosis therapy and after using it.

Keywords: Tuberculosis Multi-Drug Resistant, Tuberculosis Therapy, Hyperuricemia.

INTRODUCTION

Tuberculosis disease or often called pulmonary TB is a direct infectious disease caused by Mycobacterium tuberculosis. This bacterium most often attacks the pulmonary organ with transmission source are TB-patients with positive acid-resistant bacteria. Mycobacterium tuberculosis bacteria can enter through various tracts, such as the respiratory tract, digestive tract and burns to the skin, and until now TB is still a major health problem in various countries in the world (1). One type of resistance is TB Multidrug Resistant. TB-MDR is TB caused by resistant TB bacteria to 2 types of anti-tuberculosis drugs namely INH and Rifampicin. The resistance of TB bacteria to anti-tuberculosis drugs has been emerged for a long time. Drug resistance in patients who have a history of previous treatment is 4 times, whereas in TB-MDR is 10 times or more compared to patients who have never treated (2).

Tuberculosis treatment using multidrug principle with long treatment often causes various side effects. One side effect is an increase in uric acid levels. Actually, uric acid is a natural substance in the body but becomes unnatural in the body when uric acid rises and exceeds normal limits. Excessive

uric acid will not be accommodated and fully metabolized by the body, so there will be an increase in uric acid levels in the blood called hyperuricemia. Uric acid disorders are characterized by a sudden attack in the joint area, pain appears suddenly. Hyperuricemia is a state of uric acid concentration of more than 7 mg/dL in men and above 6 mg/dL in women (4).

A research by (3), related with the description of uric acid levels in patients with pulmonary tuberculosis who received anti-tuberculosis drug therapy, hyperuricemia occurred in 60% of TB patients undergoing anti-tuberculosis drugs therapy, an increase mainly occurred in patients using a combination of pyrazinamide and ethambutol. As mentioned above, the researcher conducts a research on the relationship of the use of anti-tuberculosis drugs to changes in uric acid levels in patient with TB-MDR (Tuberculosis Multidrug Resistant) at Regional Hospital of Undata, Central Sulawesi Province.

METHODS

This research is a retrospective cohort with a one group before and after intervention design approach. Population is diagnosed-patient with TB-

MDR. The sample were all TB-MDR patients undergoing outpatient treatment that met the inclusion criteria, namely adult patients aged ≥ 18 years, patients diagnosed with TB-MDR for the first time, patients receiving anti-tuberculosis drugs. Exclusion criteria patients have a history of gout (uric acid), patients consume drugs that can increase and decreases uric acid levels, and patient dies. It was conducted at the pulmonary clinic of Regional Hospital of Undata, Central Sulawesi Province started on April-June 2018. Data was collected by looking at the medical record of patient including medical record number, age, sex, education, occupation and laboratory examination results such as uric acid levels of the patient before given anti-tuberculosis drugs therapy and after anti-tuberculosis drugs therapy for more than a month. The data are presented descriptively to see the percentage of each variable and the data analysis uses paired samples t-test to see the relationship between two variables

RESULTS AND DISCUSSION

Sample Characteristic

Based on the samples obtained from the medical records of TB-MDR patients who underwent outpatient treatment at the pulmonary clinic of the Regional Hospital of UNDATA, Central Sulawesi Province, as many as 91 patients diagnosed with TB-MDR positively while they met the inclusion criteria were 30 patients.

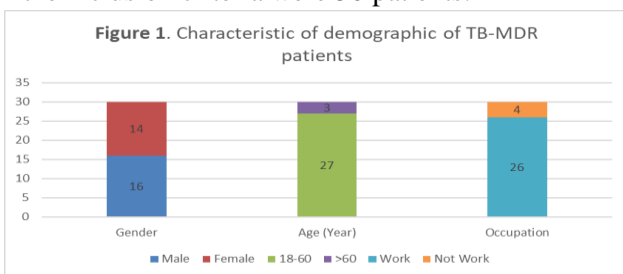


Figure 1. Characteristic of demographic of TB-MDR patients at Regional Hospital of Undata, Central Sulawesi Province.

Table 2. Profile of drug use of TB-MDR patients at Regional Hospital of Central Sulawesi Province

Administering route	Group	Type of drugs	n	%
Oral	First-line anti-tuberculosis drugs	Pirazinamid (Z) Ethambutol (E)		
	Second-line bacteriostatic anti-tuberculosis drugs	Etonamid (Eto) Cycloserin (Cs)		
	Fluoroquinolones anti-tuberculosis drugs	Levofloxacin (Lfx)	30	100
Injection	Second-line injection anti-tuberculosis drugs	Kanamycin (Km)		

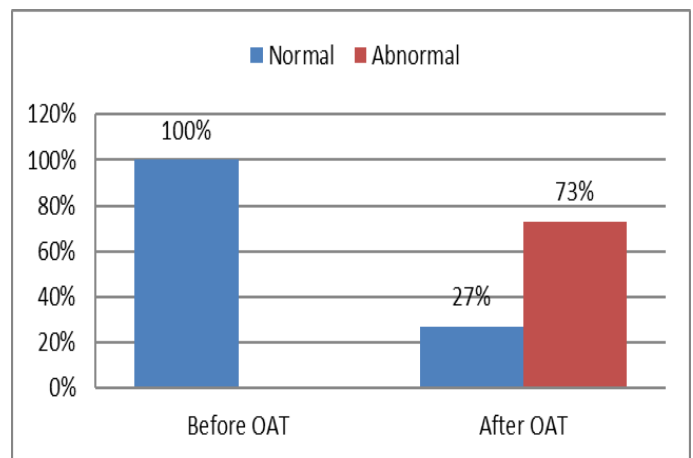


Figure 2. Profile of uric acid levels of MDR-TB patients at Regional Hospital of Undata, Central Sulawesi Province.

Table 2. Results of Paired samples t-test analysis

	Paired Differences					T	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Before anti-tuberculosis drugs - After tuberculosis drugs	-4.19000	1.45871	.26632	-4.73469	-3.64531	-15.733	29	.000

As result of the research obtained as many as 53% patients were male. This is in accordance with research conducted by (5), who found that the gender proportion of TB-MDR of Persahabatan Hospital is 53 people (52.5%) male and 48 people (47.5%) female, where there is a relationship between gender and TB-MDR, probably because of the prevalence of TB is more for male. This is due to several factors including that most male have a habit of smoking, drinking alcohol and taking illegal drugs, as well as differences in activities outside the house, especially for work, social and community relations between men and women are also different. The most common age group in TB-MDR patients is 18-40 years (49%). This can be caused because TB mostly affects adult at the most productive age. This happens because in the productive age group everyone will tend to be high in activity, so the possibility of exposure to *Mycobacterium tuberculosis* is greater, but all age groups remain at risk. According to (6) argues that about 75% of TB patients are the most productive age group. Many activities can also be a cause of negligence in undergoing treatment so that it becomes TB-MDR.

As many as 67% of patients with low education, that education is related to the patient knowledge. Low education of patient results in low knowledge, it allowing patients to drop out of treatment due to lack of knowledge and lack of understanding about treatment. It results in patient not being able to regularly in the treatment program. Education will describe a person's behavior in health, the lower of education, the less of knowledge in the field of health, both related to food intake, handling sick families (7).

The highest number of patients who work as laborers (37%) and the second highest of patients as housewife, this can be triggered because daily activities in dusty environments and particle exposure in exposed areas will affect the occurrence of problems in respiratory tract. Chronic exposure to polluted air will increase morbidity, especially the occurrence of respiratory diseases and most pulmonary TB. Housewives whose daily activities in the home environment, when feeling cough for a

long time tend to let and feel just a normal cough and not feeling severe. They does not go directly to the health service center and is likely to be associated with shame and often experiences fears of being ostracized from the family and the environment due to illness (8).

Drug Use Profile

Treatment of MDR-TB patients given through several stages, in the first stage patients are administered anti-tuberculosis drugs every day for 4-6 months, with 6 types of drugs. Pyrazinamide and ethambutol are administered because they are most effective and well tolerated, bactericidal canamycin injection is administered to patients until the amount of bacteria is proven to be low through negative culture results, the fluoroquinolone group is a high bactericidal drug such as levofloxacin, as well as a bacteriostatic injection of second-line etionamide and cycloserine. The injection is given for 5 days (Monday - Friday) and oral therapy is administered every day (Monday - Sunday) (1).

Treatment by injection of duration is determined by the results of culture conversion, the oral administration of drugs that are administered every day to prevent drug resistance, reduce the number of germs present in the body of patient and minimize the effect of a small portion of germs that may have been resistant since before the patient treated (2).

Uric Acid Level Profile

Based on the measurement of uric acid for TB-MDR patients before consuming anti-tuberculosis drugs obtained as many as 30 people (100%) with normal uric acid levels and the measurement of uric acid levels of TB-MDR patients after consuming anti-tuberculosis drugs obtained as many as 8 people (27%) normal uric acid levels and 22 people (73%) above normal.

Hyperuricemia can occur due to excessive uric acid production and reduced uric acid removal, as a result of taking medication, one of which is anti-TB drugs.(9) Where, the incidence of hyperuricemia is higher in combination with pyrazinamide and ethambutol compared with administration of

pyrazinamide or ethambutol alone. Pyrazinamide works bacteriostatically, pyrazinamide in the form of prodrug will be converted to pyrazinoic acid by bacterial pyrimidases, pyrazinoic acid and its analogues 5-chloro-pyrazinamide can inhibit the synthesis of fatty acids from bacteria, pyrazinamides disrupt energy traffic and transport in bacterial membrane as accumulation of pyrazinoic acid in acidic conditions will acidify the cytoplasm and damage bacterial cells. The mechanism of action of ethambutol inhibits the synthesis of important metabolites of cell metabolism and bacterial multiplication by inhibiting the formation of mycolic acids and cell walls, inhibiting cell wall synthesis is carried out by inhibiting arabinosyltransferase as involved in cell wall synthesis, this results in increased bacterial cell wall permeability.

Pirazinamide and ethambutol facilitate ion exchange in the kidney tubules which can cause excessive reabsorption of uric acid, causing hyperuricemia and if the two drugs are used together the effects will be greater. According to the results of the research (3), an increase in uric acid levels occurred in patients using a combination of pyrazinamide and ethambutol in 10 patients (66.7%), pyrazinamide in 2 patients (13.3%) and etambutol in 3 patients (20 %). In this case, the handling of hyperuricemia side effects as recommended by the hospital is by giving allopurinol 100 mg 1 x 1 tablet. The use of pyrazinamide is reduced and evaluated for three days, if the results of uric acid examination return to normal then given a dose of pyrazinamide in accordance with a predetermined dose (8).

The results of research showed that from 30 patients, obtained result after consuming anti-tuberculosis drugs as many as 8 people (27%) normal uric acid levels, the most frequent cause of low or normal cases of uric acid is actually idiopathic where medical conditions that have not been revealed clearly the cause or caused for no apparent reason, to know the cause it is necessary to do a blood test, urine test, and other supporting tests. As many as 22 people (73%) above normal. It also found the description uric acid level increased by

73%, the increasing of this uric acid level was triggered by the accumulation of purines in the blood due to purines which were not well metabolized by the Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) enzymes that play a role in converting purines into purine nucleotide, so that it can be reused as a constituent of DNA and RNA (adenosine and guanosin). If this enzyme experience purine accumulation deficiency in the blood due to the toxic effects of consuming anti-tuberculosis drugs which contains a lot of acid, the role of the enzyme is reduced and purines are increased. Purines which are not metabolized by HGPRT enzyme will be metabolized by the xanthine oxidase enzyme so that ultimately the uric acid content increases in the blood under hyperuricemia conditions.

The disadvantage of this research because it is not done prospectively and also do not see other factors causing increased uric acid other than treatment with anti-tuberculosis drugs.

Analysis of Paired samples t-test

Based on data processing using paired samples t-test, the Sig. (2-tailed) is 0.000 ($p < 0.05$), it can be concluded that there is a significant relationship between before and after consuming anti-tuberculosis drugs. Based on descriptive statistics test, uric acid levels before and after consuming anti-tuberculosis drugs were proven after consuming anti-tuberculosis drugs, the uric acid levels of TB-MDR patients were higher.

CONCLUSION

Based on the results of the study it can concluded that there is a significant relationship between before and after consuming anti-tuberculosis drugs with $p = 0.000$ ($p < 0,005$).

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