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Risk Factor Analysis of Adverse Effects of Kanamycin and Capreomycin on Kidney Function in Multidrug-Resistant TB Patients

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Abstract

***Background**: Multidrug-Resistant TB treatment's high side effects and long duration are barriers to successful TB therapy. Various side effects such as age, gender, body weight, comorbidities, and drug dose can cause severe side effects, including impaired renal function (nephrotoxic).* ***Objectives**: This study aimed to analyze the risk factors of side effects of the failure of kanamycin and capreomycin therapy that can cause impaired renal function in Multidrug-Resistant TB patients.* ***Methods**: Data were collected retrospectively by searching and recording the medical records of Multidrug-Resistant TB patients at the Multidrug-Resistant TB Polyclinic. There were 183 patients at Dr Soetomo Hospital who met the inclusion criteria.* ***Results**: There was a significant relationship between gender in the kanamycin group and the appearance of side effects of renal impairment (p= 0.035). There was no effect of age, comorbid diseases, body weight, and dose of drug administration on the side effects of kanamycin and capreomycin in treating Multidrug-Resistant TB on impaired renal function (nephrotoxic). However, nephrotoxic side effects in elderly patients were more common in the kanamycin group (p=0.001).* ***Conclusion**: Gender affects the side effects of kanamycin and capreomycin in treating Multidrug-Resistant TB in nephrotoxic patients. In addition, stricter supervision of the use of kanamycin in elderly patients (>40 years) to minimize the incidence of side effects of impaired renal function in the treatment of Multidrug-Resistant TB.*

***Keywords**: capreomycin, kanamycin, multidrug-resistant TB, nephrotoxic*

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INTRODUCTION

The high incidence of tuberculosis (TB) and multidrug-resistant Tuberculosis (MDR-TB) in Indonesia deserves special attention. The high incidence of side effects and long duration of Multidrug-Resistant TB treatment are significant obstacles to successful Multidrug-Resistant TB therapy. Drug side effects are among the leading causes of treatment failure; therefore, special attention must be paid to the occurrence of side effects in TB treatment. The World Health Organization (WHO) recommends second-line injectable drugs for the management of Multidrug-Resistant TB cases, including the aminoglycoside class consisting of streptomycin, kanamycin, amikacin, and capreomycin polypeptide class (Ratnawati *et al*., 2018). However, some drugs can cause severe side effects such as ototoxicity, electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), and impaired renal function (nephrotoxicity) (Heysell *et al*., 2018). Some problems associated with the high incidence of adverse drug events can be influenced by factors such as age, sex, weight, comorbidities, and the dose of drugs administered (Tamirat *et al*., 2020).

Drug-resistant TB continues to be a public health concern. Globally, Multidrug-Resistant or Rifampicin Resistant TB (MDR/RR TB) accounts for 3.4% of new TB cases and 18% of previously treated cases, with the highest proportion (>50% of previously treated TB cases) in the Soviet Union (WHO, 2019). In Indonesia, in 2018, there were an estimated 845,000 total TB cases with MDR/RR TB cases in Indonesia, totalling 24,000 cases. An estimated 2.4% of resistant TB cases were new cases, and as many as 13% were previously treated resistant TB cases (WHO, 2019). Several researchers have reported a success rate of Multidrug-Resistant TB treatment of only 52%, consisting of 37.2% cured and 14.5% complete treatment. This can lead to high treatment failure rates. Data from the East Java Provincial Health Office in 2018 showed that the number of TB cases reached 229,961. While the data on the most TB cases in East Java Province is Surabaya City, which is 3990 cases, and the TB mortality rate in Surabaya City is estimated to reach 10,108 BTA-positive patients, namely 3990 cases (Dinkes Jatim, 2018).

Kanamycin is an aminoglycoside antibiotic with side effects on the kidneys because it contains a cationic group (Mamlouk *et al*., 2019). Capreomycin is a polypeptide antibiotic with a structure similar to that of the aminoglycoside group; therefore, it can be used as a second choice if the patient experiences adverse drug effects on the use of kanamycin or if there are contraindications to kanamycin. Both drugs are second-line or group B injectable drugs for the classification of Multidrug-resistant TB drugs (WHO, 2016). Neither drug can be absorbed orally, making it injectable. Side effects of kanamycin are common. The occurrence of nephrotoxicity is an effect of the administration of kanamycin caused by toxicity to the renal tubules, decreased glomerular filtration, and decreased blood flow to the kidneys, leading to impairment of renal function characterized by non-oliguria, hypoosmotic polyuria, increased serum urea and creatinine, and as many as 13% of cases of resistant TB that have been treated before (Kwiatkowska *et al*., 2021).

Previous studies have shown that kanamycin and capreomycin have side effects on kidney function and electrolytes. Research conducted by Arto *et al* (2017) through collecting patient medical record data from 2012-2017 revealed that after the first month of Multidrug-Resistant TB treatment, there was a significant decrease in mean serum potassium (4.0 + 0.4 mEq/L to 3.7 + 0.5 mEq/L) in patients using kanamycin and (4.1 + 0.5 mEq/L to 3.2 + 0.6 mEq/L) in patients receiving capreomycin therapy (Soeroto *et al*., 2019). Based on research by Ratnawati *et al.* (2018), using kanamycin in patients with MDR-TB caused functional disorders in 147 patients (61.8%). In addition, nephrotoxicity also occurred in 9.8% of patients at 4.8 months of MDR-TB treatment (Mwansasu *et al*., 2017). Kanamycin and capreomycin are used in Multidrug-Resistant TB treatment at Dr. Soetomo Hospital. The long-term use of these drugs requires regular monitoring of renal function and serum electrolyte levels. The number of possible risk factors that can affect kidney function during treatment will also be a separate consideration. Therefore, researchers are interested in examining the risk factors for the side effects of kanamycin and capreomycin on kidney function in patients with multidrug resistance at Dr. Soetomo Hospital.

MATERIALS AND METHODS

Study design

This was a retrospective observational research, specifically tracking and recording data on patients with Multidrug-Resistant Tuberculosis who received treatment at Dr. Soetomo Hospital between January 2018 and June 2020. The inclusion criteria in this study were adult Multidrug-Resistant TB patients (aged >18 years), including those who were pregnant, dropped out of treatment, died, transferred treatment to Public

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Health, received short-term and individualized regimens, and had complete laboratory examination data. The exclusion criteria included patients with a history of kidney disease and thyroid disorders, undergoing hemodialysis, NSAIDs, ACEIs, and ARBs, and interactions with other drugs that affected serum electrolytes.

Method of collecting data

Data were collected by searching and recording the medical records of Multidrug-Resistant TB patients at the Multidrug-Resistant TB Polyclinic Dr. Soetomo Hospital from January 2018 to June 2018, who met the inclusion criteria for data analysis. The instruments used in this study included patient medical records containing patient observational record sheets that recorded the patient's clinical condition, laboratory examination result sheets, and data collection sheets. Data recorded in the data collection sheet included medical record number, demographic data, doctor's diagnosis, disease history and drug history, laboratory data, and supporting clinical data such as regimens obtained, gene expert results, and side effects of drugs.

Data analysis

Analysis of the influence of risk factors of sex, age, weight, presence or absence of comorbidities (Diabetes Mellitus, Hypertension, and Hepatitis B), and drug dose on the adverse effects of renal impairment was performed using binary logistic regression statistical test. If the data were normally distributed, the chi-square statistical test was used to compare the effects of kanamycin and capreomycin on adverse effects, such as impaired renal function and electrolyte disturbances. If the data were not normally distributed, an independent t-test was used.

Ethical approval

This study was approved by the Health Research Ethics Committee of Dr. Soetomo Hospital (number 0105/LOE/301.4.2/VIII/2020).

RESULTS AND DISCUSSION

Demographic data

Many factors can influence adverse drug events, including patient-derived factors, such as sex, age, comorbidities, race, and genetic polymorphism (Tamirat *et al*., 2020). Clinical examination data and supporting examinations written in the patients' medical records were used to determine drug side effects. The only drug side effect observed was renal function (nephrotoxicity). The term nephrotoxic refers to a condition in which serum creatinine levels rise by more than 0.3 mg/dL (1.5-2 times) from baseline (Kemenkes RI, 2019).

The number of patients obtained in the medical record was 183 and included as many as 112 patients in the study inclusion criteria: 63 received kanamycin, and 43 received capreomycin in their therapy regimen. The results of the demographic status assessment are presented in Table 1. Most patients were male (56.25%, n=63), while 43.75% (n=49) were female. Males are more susceptible to Multidrug-Resistant TB due to their heavy workload, irregular rest, and unhealthy lifestyles, such as smoking and drinking alcohol (Nugroho *et al*., 2018). Most patients were 41-60 years old, which is included in the elderly age category. In this age range, a person tends to have high mobility, so the risk of exposure to TB germs is high. The high comorbidity of diabetes mellitus in patients with Multidrug-Resistant TB is because diabetes mellitus is a risk factor for tuberculosis. Patients with diabetes mellitus have impaired immune responses that facilitate the multiplication of Mycobacterium tuberculosis and cause pulmonary tuberculosis (TB). Patients with diabetes mellitus have a 2-3 times risk of developing pulmonary TB disease than people without diabetes mellitus and are mostly found at the age of over 40 years (Wijaya, 2015). Most patients received short-term regimens based on therapy regimens. Regarding the initial status of patients, most Multidrug-Resistant TB patients are new relapse patients; this occurs due to non-compliance with treatment.

Adverse Effects of Kanamycin and Capreomycin in Multidrug-Resistant TB

Kanamycin causes the loss of potassium and magnesium by a mechanism similar to that of diuretic drugs, blocking the chloride pathway associated with sodium reabsorption and inhibiting transport in protein membranes. This increases the sodium in the collecting tubules, which is exchanged for potassium (Suparyatmo *et al*., 2014). Capreomycin causes hypokalemia through a mechanism similar to that of kanamycin. Kanamycin and capreomycin can induce electrolyte balance through the stimulation of calcium-sensing receptors (CaSR) on the thick ascending branch of the arch of Henle (Penn-Nicholson *et al*., 2022).

Kanamycin is an aminoglycoside antibiotic with nephrotoxic side effects of which is nephrotoxic (Penn-Nicholson *et al*., 2022). This antibiotic causes nephrotoxicity because it has a cationic amino group, which causes the drug to accumulate in the proximal tubules (Purnasari *et al*., 2019). Nephrotoxic side effects were defined as elevated creatinine levels, classified as grade 1 if an increase of >0.3 mg/ml or 1.5-2x above baseline (Kemenkes RI, 2019). Capreomycin has a

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longer t1/2 than kanamycin, and the interval of drug administration in patients with both drugs was the same; therefore, the blood levels of capreomycin were higher than the blood levels of kanamycin. This leads to saturation of drug levels in the proximal tubules, which is an important factor in nephrotoxicity. The nephrotoxic properties of aminoglycosides are determined by the number of amine groups in their structure. Kanamycin has 4 amine groups, while capreomycin has five protonated amine groups and nine unprotonated amine groups; therefore, there are differences in the affinity of kanamycin and capreomycin to cell membrane phospholipids (Molitoris, 2017).

Table 1. Demographic data of multidrug-resistant TB patients at Dr Soetomo Hospital.

Patient Characteristics	Frequency	Percentage
Gender		
Male	63	56.25
Female	49	43.75
Aged		
< 20 years	9	8.04
21-40 years	38	33.93
41-60 years	56	50
> 60 years	9	8.04
Comorbid		
DM	42	37.5
DM + HT	6	5.36
HT	4	3.57
Hepatitis B chronic	1	0.89
No comorbid	59	52.68
Smoking and alcoholic status		
Smoking	40	35.71
alcoholic	6	5.36
Characteristic Patient		
Regimen obtained		
Short term regimen	82	73.21
Regimen Individual	10	8.93
STR moved to individual	20	17.86
Reasons for switching regimens		
Resistant	7	
Drug Adverse Effects	10	
No conversion after three months	1	
Unknown	2	
Gene Expert results		
Very Low	4	3.6
Low	20	17.86
Medium	60	53.57
High	28	25
Initial State		
New	31	27.68
Relapsed	39	34.82
Drop Out / neglect	9	8.04
Fail Category 1	31	27.68
Failed long regimen	2	1.79
Drugs used		
Kanamycin	69	61.61
Capreomycin	43	38.39
Adverse Effects of Nephrotoxic Drugs		
Kanamycin	14	20.29
Capreomycin	13	30.23

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Table 2. Risk factors that influence drug side effects for hypokalemia in multidrug-resistant TB patients in Dr. Soetomo Hospital

No	Risk factor	P value		OR (odds ratio)	
		Kanamycin	Capreomycin	Kanamycin	Capreomycin
1	Aged	0.792	0.770	1.239	1.010
2	Gender	0.443	0.075	0.680	0.221
3	Weight	0.524	0.101	0.987	0.951
4	Yes/no Comorbid	0.790	0.428	1.143	0.586
5	Dosage/Kg BW	0.157	0.108	5.348	1.229

Table 3. Risk factors that influence drug side effects on kidney function in Multidrug-Resistant TB patients in Dr. Soetomo Hospital

No	Risk factor	P value		OR (odds ratio)	
		Kanamycin	Capreomycin	Kanamycin	Capreomycin
1	Aged	0.571	0.905	0.090	1.187
2	Gender	0.035	0.581	1.016	1.039
3	Weight	0.420	0.788	0.537	0.934
4	Yes/no Comorbid	0.468	0.170	0.992	0.085
5	Dosage/Kg BW	0.373	0.220	1.959	1.466

This was based on the results of the study of the risk factors that affect the side effects of drugs on kidney function (Table 2). Table 3 shows that only the risk factor of gender in the kanamycin patient group had a statistically significant effect on the occurrence of nephrotoxic side effects because the variable had a significant value smaller than 5% (p=0.035).

Sex influences the appearance of side effects in kidney disorders. Men generally have a heavier workload and often have more contact with a larger environment outside the home than women, in addition to lifestyle factors such as smoking habits in men (Longe & Bindukkinasih, 2022; Nugroho *et al*., 2018). Results of the research conducted by (Reviono *et al*., 2014). We found that male patients had more impaired renal function than female patients did. Based on the data obtained from the patients' medical records in this study, 40 patients had a smoking history, of which 39 (97.5%) were male, and only one (2.5%) was female.

In this study, there was no effect between body weight and the incidence of side effects on the kidneys and hypokalemia, which was indicated by the results of p-value> 0.05, namely the value of p = 0.420 in the kanamycin group and p = 788 in the capreomycin group. Differences in outcomes can be attributed to differences in the definition of impaired renal function, different populations, and the use of various drugs (Ratnawati *et al*., 2018).

This study found no influence of comorbid factors on impaired renal function. However, most MDR-TB patients in this study had comorbid diabetes mellitus. Diabetes mellitus can increase the risk of side effects and serum creatinine with an RR value of 2.049 (95% CI:1.242–3.379) (Soedarsono *et al*., 2021). Unregulated DM is correlated with acute ketoacidosis and chronic complications, including diabetic nephropathy (Onuka *et al*., 2017). Diabetes causes glomerular hyperfiltration, which is hypothesized to predispose patients to irreversible nephron damage, thus contributing to the initiation and progression of renal disease in diabetes (Tonneijck *et al*., 2017). A study in Mexico showed that patients with diabetes mellitus had a higher risk of experiencing serious side effects of Multidrug-Resistant TB treatment, including renal impairment with an OR of 6.5 (95% CI:1.9 - 21.8) (Muñoz-Torrico *et al*., 2017).

Dosing accuracy is very important for TB treatment therapy because the treatment obtained is maximized with the appropriate dose and patient therapy is guaranteed. If the dose given is lower than the standard dose, it can cause the desired therapeutic effect of the drug not to be achieved, so that the treatment objectives are effective in patients, which can prolong treatment, and patient recovery will take longer (Shibeshi *et al*., 2019). Excessive doses can also cause various side effects in patients with Multidrug-Resistant TB. Less than 1% of the gut absorbs aminoglycosides. All aminoglycosides were rapidly absorbed in injectable form. The highest concentrations were found in the renal cortex and vestibular regions. Aminoglycosides cause ototoxic, nephrotoxic, and electrolyte disturbances (hypokalemia, hypomagnesemia, and hypocalcemia) (Suparyatmo *et al*., 2014). Patients experiencing nephrotoxic side effects have a significantly longer duration of aminoglycoside treatment and a larger total dose (Shibeshi *et al*., 2019). However, in this study, no

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dose effect was observed on the occurrence of side effects in the kidneys.

The demographic characteristics of the patients using kanamycin and capreomycin in Table 4 show significant differences in age between those using kanamycin and those using capreomycin. While other characteristics, namely sex, body weight, presence or absence of comorbidities, dose per kg of body weight, and initial potassium levels of patients, showed no significant differences between the two groups of patients.

Previous studies have reported that old age is a risk factor for impaired renal function when administering aminoglycosides (Ahmad *et al*., 2018; Alene *et al*., 2019; Ratnawati *et al*., 2018). In this study, the results of statistical tests using binary logistics showed that age did not significantly affect the occurrence of the side effects of renal impairment. However, the age characteristics of the patients in the capreomycin group were significantly different from those in the kanamycin group. Nephrotoxic side effects in older adults were more common in the kanamycin group. In line with the results of research from (Ratnawati *et al*., 2018), who stated that the relationship between risk factors and side effects that occur in Multidrug-Resistant TB patients who receive kanamycin drug therapy, they found that those aged> 59 years were 3.8 times more likely to have impaired renal function than those aged < 40 years. Aged 40-59 years were 1.89 times more likely to have renal impairment than patients aged < 40 years.

This study has limitations, namely that most Multidrug-Resistant TB patients have a history of diabetes mellitus, so there is an influence of the use of insulin by patients on potassium levels, which can affect kidney function disorders. Some of these factors may have caused the bias in this study. The comparison of the number of patients in the characteristics of age and BMI in this study is less balanced and does not mention the influence of genetic factors that might have affected the investigation results.

Table 4. Baseline characteristics of patients taking kanamycin and capreomycin in multidrug-resistant TB patients in Dr. Soetomo Hospital

No	Characteristic	Statistic Test	P value	Interpretation
1	Aged	Independent t-test	0.001	Significant
2	Gender	Pearson Chi-square	0.750	Not significant
3	Weight	Independent t-test	0.561	Not significant
4	Yes/no Comorbid	Pearson Chi-square	0.262	Not significant
5	Dosage/Kg BW	Independent t-test	0.708	Not significant
6	Initial potassium levels	Independent t-test	0.700	Not significant

CONCLUSION

Male sex affects the occurrence of side effects of kanamycin and capreomycin in the treatment of Multidrug-Resistant TB with impaired renal function (nephrotoxic). Body weight in Multidrug-Resistant TB patients did not affect the occurrence of side effects of renal impairment, and there was no influence of comorbid factors or the dose administered on renal impairment. Stricter supervision of kanamycin use in elderly patients (>40 years) is needed to minimize the side effects of renal impairment in the treatment of Multidrug-Resistant TB.

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AUTHOR CONTRIBUTIONS

Conceptualization, S. N. F.; Methodology, S. N. F.; Software, S. N. F.; Validation, B. S. Z.; Formal Analysis, S. N. F., H. Y.; Investigation, B. S. Z.; Resources, H. Y.; Data Curation, B. S. Z., H. Y.; Writing - Original Draft, H. Y.; Writing - Review & Editing, H. Y.; Visualization, H. Y.; Supervision, B. S. Z.; Project Administration, S. N. F., H. Y., B. S. Z.; Funding Acquisition, S. N. F., H. Y.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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