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Relationship Between Cephalosporin Use and Increased APTT and PT in Cardiovascular Patients at Government Hospital Bengkulu

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ABSTRACT: The interaction that occurs between warfarin and antibiotics is a pharmacokinetic interaction which cause bleeding. This study aims to determine whether there is a relationship between the use of cephalosporins and an increase in APTT and PT in cardiovascular patients. This retrospective observational study employs case-control analysis to examine APTT and PT features in cardiovascular patients receiving single anticoagulant or anticoagulant + cephalosporin therapy for the period July-December 2020. The sampling method used in this study is a convenient sampling method that meets the inclusion and exclusion criteria. Analysis of the data used is Logistic Regression. The study found among 65 male and 15 female, 40 patients used anticoagulant, and another 40 patients used anticoagulant and cephalosporine. Among 40 patients who used combination anticoagulant and cephalosporin, 22 of them had experienced of increasing APTT and PT. Cephalosporins showed a significant correlation with APTT and PT, with a P-value of 0.015. From this study, it can be concluded that the use of cephalosporins increases in APTT and PT values in cardiovascular patients who are given anticoagulant drugs and cephalosporins.

Keywords: **anticoagulants; APTT and PT; cephalosporins.**

Introduction

Cardiovascular disease is one of the main causes of death in the world. Cardiovascular disease is non-contagious and accounts for 17.9 million deaths globally, approximately 31% of all deaths worldwide. It is the second leading cause of death after cancer. The prevalence of factors causing cardiovascular disease is due to cardiometabolic risks, such as diabetes and obesity [1].

Cardiovascular disease is claimed to be the number one cause of death in women over the age of 65 on the European continent. In Indonesia, the mortality rate due to CVD across all age groups has more than doubled, increasing from 292,000 in 1990 to 659,000 in 2019. [2] The hormone estrogen plays a role in protecting women from CHD, therefore acute myocardial infarction occurs at an older age than men. They are also at an increased risk of death and greater comorbid coronary heart disease (CHD) risk factors. Estrogen plays a role in regulating metabolic factors, such as lipids, inflammatory markers, thrombotic systems, vasodilation receptors [3]. Therefore, the occurrence of menopause influences the incidence of CHD. Although in general the risk of CHD is not different between the two sexes, there are several factors that tend to be greater. Under age 50, smoking is worse than for men; Women who smoke experience menopause 2 years earlier. Obesity is more common during menopause, and is often accompanied by metabolic syndrome. As menopause begins, dyslipidemia increases; However, the risk of hypercholesterolemia in women under 65 years of age is lower than in men. Women with diabetes mellitus also have a higher risk of cardiovascular complications than men [3].

One of the drugs used

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to treat cardiovascular disease is an anticoagulant, an anticoagulant is a type of drug used to reduce the risk of blood clots. Anticoagulants prevent and destroy clots present in the blood vessels. Based on several journals that the authors obtained, patients with cardiovascular disease will receive warfarin anticoagulant therapy [4]. Patients with cardiovascular emergencies are treated in a unit that is currently called an intensive cardiovascular care unit or better known as an Intensive Cardiac Care Unit (ICCU). The patient's weak condition will make the patient susceptible to infectious endocarditis (EI) [4].

The patient's weak condition will make the patient susceptible to infectious endocarditis (IE). The cause of endocarditis is caused by a complex interaction between the host (valve endothelium, immune system, hemostatic mechanisms, cardiac anatomy), infecting microorganisms (both producing toxins and enzymes), and events that can cause bacteremia [5]. CHD patients with infectious endocarditis (IE) are given antibiotics according to blood culture results, cephalosporin antibiotics are given if microorganisms in the Viridan Streptococci and D Streptococci groups are found which are sensitive to penicillin [6].

Cephalosporins are the largest group of beta-lactam antibiotics. The mechanism of action of cephalosporins is by inhibiting the synthesis of microbial cell walls, what is inhibited is the third step transpeptidase reaction in a series of cell wall formation reactions Cephalosporins are characterized by the presence of an N-methyl-thiotetrazole (NMTT) side chain [7]. One of the interactions of warfarin is with antibiotics, cephalosporin antibiotics have the potential to increase bleeding when given concurrently with warfarin The interactions that occur between warfarin and antibiotics are pharmacokinetic interactions that occur in the metabolic phase, because antibiotics inhibit the effects of CYP2C9, which is one of the enzymes that metabolize warfarin. When warfarin metabolism is reduced there is an increased risk of bleeding [8]. The interaction between cephalosporins and warfarin anticoagulants can cause the concentration of warfarin anticoagulants to increase, causing an increase in the side effect of warfarin, namely bleeding [9]. To assess the interaction or not, routine examinations to assess coagulation activation are Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and fibrinogen levels, while routine hemostasis tests to assess fibrinolysis activation are D-dimer examination [9].

Limited study on relationship between the use of cephalosporins and an increase in APTT and PT in cardiovascular patients has made this study important to be conducted.

Methods

This study was a retrospective observational study with a case-control analysis to analyze the features of APTT and PT in cardiovascular patients who were given single anticoagulant and anticoagulant + cephalosporin therapy for the period July-December 2020. Ethical approval was sourced from the Health Research Ethics Committee from the Poltekkes Kemenkes Bengkulu, and an approval letter, NO.KEPK/004/03/2021, was given before data collection. The population of this study were all patients with cardiovascular diagnosis who were given anticoagulant therapy in the internal medicine ward of Government Hospital Bengkulu. The data collected in the study will be processed and displayed in the form of a frequency table. The inclusion criteria included cardiovascular disease patients treated in the ICCU at Government Hospital Bengkulu who received anticoagulants and cephalosporins during the study period. The exclusion criteria were cardiovascular disease patients with cancer, HIV/AIDS and autoimmune disease. In this study, the authors will count cardiovascular patients using a single anticoagulant and anticoagulant + cephalosporin who are in the ICCU room of Government Hospital Bengkulu. In addition, data collection by recording patient medical record data and the results of measuring the patient's APTT value. identification of data on the patient (name, age, weight, gender, main disease), drug data (name of drug, route of administration, dose, frequency of administration, duration of administration) and recorded in the Data Collection Sheet. Subsequently, the data was processed using SPSS 24, employing Chi-Square, Fisher's Exact Test, and independent sample T-tests.

Result and Discussion

During the research period, namely the July-December 2020 period, there were 139 cardiovascular disease patients who were treated in the ICCU Room of Dr. Hospital Dr. M. Yunus Bengkulu. Of the patients treated in the ICCU at Dr. M. Yunus Bengkulu, 80 had traceable medical records.

In Table 1, it can be seen that the characteristics and the number of research subjects in July-December 2021 used in this study were 80 patients where there were 2 therapy groups, namely cardiovascular patients who were given single anticoagulant therapy as many as 40 patients (50%) and cardiovascular patients who received

Table 1. Number of patients and type of therapy.

No	Type of Therapy	Number of Patients
1	Single Anticoagulant	40
2	Anticoagulant cephalosporin	40
	Total	80 patients

Table 2. Distributions of research variable.

Variables	Total (%)	P value
Gender		
Male	65 (81,2 %)	
Single Anticoagulant	32 patients	
Anticoagulant+Cephalosporin	33 patients	0,271 *
Female	15 (18,8%)	
Single Anticoagulant	8 patients	
Anticoagulant+Cephalosporin	7 patients	
Age (years)		
<15	0 (0,0)	
15-24	0 (0,0)	
25-34	0 (0,0)	
35-44	5 (6,25%)	0,299 *
45-54	15 (18,75%)	
55-64	39 (48,75%)	
65-74	16 (20%)	
>75	5 (6,25%)	
Comorbidities(DM)		
Single Anticoagulant	7 patients	0,005 *
Anticoagulant + Cephalosporin	10 patients	
Improved APTT & PT	43 (53,8)	
Single Anticoagulant	16 patients	0,015*
Anticoagulant Cephalosporin	27 patients	
Bleeding	0 patients	
Single Anticoagulant	3 patients	0,998**
Anticoagulant+Cephalosporin		
Death		
Single Anticoagulant	0 patients	
Anticoagulant+Cephalosporin	0 patients	

*Chi-square
*Fisher's Exact

anticoagulant therapy. 40 patients were given anticoagulant + cephalosporin therapy (50%).

Table 1 describes the characteristics of research subjects by sex who used a single anticoagulant and anticoagulant + cephalosporin. In this study, from 80 research subjects, 65 men (81.25%) and 15 women (18.75%).

In this study, from 80 subjects, it was known that the characteristics of cardiovascular patients according to gender were found to be the most male with 65 subjects (81.2%) and p value = 0.271 which means that gender has no effect on increasing APTT and PT. This result is slightly different from a study conducted by Mariana Garcia *et al* which stated that the highest gender prevalence of cardiovascular disease occurred in women [10]. In accordance with studies from several other countries, it is more commonly found

Table 3. Type of anticoagulant research subject.

Types of Anticoagulants	Total (%)	Duration	
		Stemi/Nstemi	COPD
Fondaparinux	4 (5%)		
UFH/ Heparin	76 (95)	5 days	3 days
Total	80 (100%)		

in women than men. Sex has a relationship with coagulation activation because female subjects were influenced by the estrogen hormone which stimulates the immune response, while men are influenced by testosterone which suppresses the immune response [11].

Table 1 also outlines the research subjects' characteristics, including comorbidities. Among patients on single anticoagulant therapy, seven had comorbid conditions. In contrast, in patients receiving both anticoagulant therapy and cephalosporins, there were ten instances of comorbidities, all of which were DM. The p-value obtained is 0.005 <0.05, which means that a family history of disease affects the increase in APTT and PT. Increase in APTT and PT was observed in Table 1, which describes that 16 patients on single anticoagulant therapy showed elevated APTT and PT values. In contrast, among patients receiving both anticoagulant therapy and cephalosporins, 27 patients experienced an increase in these values. The data processing results indicated a p-value of 0.015 ($p < 0.05$), demonstrating that the combination of cephalosporins with anticoagulants significantly affects APTT and PT levels.

Table 1 also describes the characteristics of the study subjects based on the incidence of bleeding, namely in patients on single anticoagulant therapy there was no bleeding incident in the patient and patients whereas in patients with anticoagulant therapy + cephalosporins there were 3 patients with bleeding.

The results of data processing for patients with bleeding, obtained a value of $p = 0.998$, which means that the administration of cephalosporins and anticoagulants has no effect on the incidence of bleeding.

Coagulopathy or bleeding is said to be positive (+) if at least 2 of the following signs are present:

1. Prothrombin Time (PT) > 18 seconds
2. Activated Partial Thromboplastin Time (APTT) > 36 seconds
3. INR > 1.6

In Table 2, it is also explained based on the incidence of death, namely in patients on single anticoagulant therapy or anticoagulant + cephalosporins, no deaths were found in patients.

There were 5 people aged 25 - 45 years (6.25%), 15 people aged 46 - 55 years (18.75%), 39 people aged 56 - 65 years (48.75%), 16 people aged 66-75 aged (20%), and 5 people aged >75 (6.25%). Based on the results of data processing using SPSS, obtained p value = 0.299 > 0.05, which means that age has no effect on increasing APTT and PT.

According to age characteristics, data on cardiovascular patients who used anticoagulants were found to be the most at the age of 55-65 years. This is in accordance with a study by Righini, et al which stated that patients who used the most anticoagulants were patients aged >60 years [12]. But with p value 0.299 > 0.05 which means that age has no effect on increasing APTT and PT. According to the characteristics of the history of comorbidities and based on data

Table 4. Type of cephalosporins used.

Typesof Cephalosporins	Total (%)	Duration
Inj. Ceftriaxone	28 (70%)	
Cefixime	12 (30%)	5 days
Total	40 (100%)	

Table 5. Type of antiplatelets used.esearch subjects.

No	Antiplatelet used
1	Clopidogrel 75 mg/tab
2	Aspilet 80 mg/tab
3	Miniaspi (acetyl salicylic acid) 80 mg/tab

processing using SPSS, the value of p <0.05, which means that a family history of disease affects the increase in APTT and PT Based on the results of the data on patients who were given single anticoagulant therapy and anticoagulant + cephalosporin showed that of 80 patients, there were 37 people (46.2%) who had no increase in APTT and PT and 43 people (53.8%) who had an increase in APTT and PT with p value = 0.015 < 0.05. This means that the administration of single anticoagulant therapy or the administration of anticoagulant therapy with a combination of cephalosporins to patients with difficult cardiovascular disease has been shown to increase the APTT and PT values. Based on the results table of SPSS data processing for antiplatelet, p value = 0.998 < 0.05, which means that antiplatelet in the cephalosporin + anticoagulant therapy group has not significant effect on increasing APTT and PT. But based on the literature, the risk factors that can cause onset of APCD include drugs that interfere with vitamin K metabolism, one of which is antibiotics (cephalosporins) [13]. Administration of antibiotics the old one causes a decrease in production of vitamin K by inhibiting the synthesis of vitamin K2 by bacteria or it can also be directly affect the carboxylase reaction [14].

Based on the table of results of data processing using SPSS 24, other risk factors that cause an increase in APTT and PT are family history of disease, it is shown that all variables p value > 0.05, except for p value for cephalosporin results and family history of diseases. Based on the table of results of data processing using SPSS, obtained p value = 0.998> 0.05, which means that the administration of cephalosporins and anticoagulants has no effect on the incidence of bleeding. Based on the results in table 2 above, it shows that of 80 (100%) patients, all (100%) did not cause death. The data collected showed that 80 subjects (100%) 4 subjects used heparin (5%), and 76 subjects used fondaparinux (95%) as the main anticoagulants or as a combination of anticoagulants used.

This is slightly different from the results of studies outside Asia which mostly use warfarin as the main choice of anticoagulant [15]. Asian patients find it more difficult to maintain an INR within the therapeutic range (2.0 – 3.0). This is due to dietary intake and prolonged use of herbal medicines. In addition, Asian patients have higher bleeding rates when taking warfarin. Therefore, the use of other oral anticoagulants is recommended because they are better in efficacy and safety [15].

Table 3 explained about the type of anticoagulant used by research subjects consisting of 4 people using UFH/Heparin (5%), and 76 people using Fondaparinux (95%).

Based on the data that has been collected, the average dose of heparin use is 1310 IU/hour with the lowest dose of 700 IU/hour and the highest dose of 1,920 IU/hour. Furthermore, for fondaparinux the average dose of use is 2.5 mg/day. This is in accordance with the dose of anticoagulant used by the American College of Cardiology (ACC) or guidelines issued by the American College of Chest Physicians (ACCP) [16]. Macrolide antibiotics, quinolones penicillin and cephalosporins as well as azole antifungal derivatives have the potential to

Table 6. Cephalosporin group taking antiplatelet.

No	Cephalosporin anticoagulant group	Amount
1	Cephalosporin that do not increase APTT, PT and without antiplatelet	13 patients
2	Cephalosporin that have increased APTT, PT with antiplatelet	22 patients
3	Cephalosporin with increased APTT, PT without antiplatelet	5 patients
	Total	**40**

Table 7. Difference in mean APTT.

No	Difference in mean	
1	Single Anticoagulant	sig 2-tailed = 0,000 < 0,05
2	Anticoagulant+Cephalosporin	

*Independent Sample T Test

increase bleeding when given concurrently with warfarin. This is because the antibiotic inhibits the effect of CYP2C9, which is one of the enzymes that metabolize warfarin. When warfarin metabolism is reduced, it causes an increased risk of bleeding [17].

Table 4 describes the types of cephalosporins used by research subjects, consisting of 28 people using ceftriaxone (70%), and 12 people using cefixime (30%). Table 5 describes the types of antiplatelet used by research subjects in the cephalosporin + anticoagulant therapy group.

Table 6 describes the cephalosporin + anticoagulant group with antiplatelet therapy, the data on patients who experienced an increase in APTT and PT in the anticoagulant + cephalosporin therapy group were 27 patients, of which 5 (19%) did not have antiplatelet therapy, and 22 people (81%) used antiplatelet therapy, and the data on patients who did not experience an increase in APTT and PT were 13 people. the results of SPSS data processing, obtained p value = 0.998 >0.05 which means that antiplatelet therapy in the cephalosporin + anticoagulant group has not significant effect on increasing APTT and PT

Table 7 describes the results of the different tests for the APTT values in the two treatment groups using the Independent Samples T test method. The 2-tailed sig value = 0.000 < 0.05, which means that there is a significant average difference between the Prothrombine Time (APTT) values) in the Single Anticoagulant and Anticoagulant + Cephalosporin groups

First-generation cephalosporins can be recommended as a better choice in the cephalosporin class according to regional susceptibility data. However, data found that cephalexin as a first-generation cephalosporin has a consistently increased risk of major bleeding. From the results obtained from the patient's medical record, another risk factor that affects the APTT and PT values is the patient's comorbid disease, namely DM.

Diabetes mellitus is one of the factors that can aggravate the occurrence of coronary heart disease and is the third cause of death in Indonesia. The length of time a person has diabetes is related to duration of hyperglycemia and hyperinsulinemia that affects coagulation status. In addition, it is also influenced by the treatment status of patients with diabetes [19]. between the duration of DM and APTT, the test results obtained a significant relationship ($p < 0.05$), this illustrates that there is a significant effect on the intrinsic pathway with the duration of DM.

Metabolic disorders in diabetes mellitus patients disrupt the physiological balance of coagulation and fibrinolysis, resulting in a prothrombotic state marked by platelet hypersensitivity, coagulation abnormalities, and hypofibrinolysis [20].

Diabetes that cannot be managed properly can lead to vascular complications such as CHD. From studies, it is known that diabetes mellitus is associated with a higher risk of venous thromboembolism, high atrial fibrillation, sudden cardiac death, and dyslipidemia, where these conditions can cause changes in hemostasis physiology, namely an increase in coagulation activity and a decrease in fibrinolytic activity [21].

The mechanism of interaction between the antibiotic ceftriaxone and the anticoagulant warfarin is currently not well elucidated. However, it is known that

Table 8. Difference in mean PT.

No	Difference in PT	
1	Single Anticoagulant	sig 2-tailed= 0,000
2	Anticoagulant+Cephalosporin	

*Independent Sample T-test

ceftriaxone can interfere with the normal intestinal flora that produces large amounts of vitamin K so that it will exacerbate the risk of bleeding, therefore it is necessary to add 90 mg of vitamin K for adults. Currently, there is no literature describing the degree of interaction between warfarin anticoagulants and various generations of cephalosporin antibiotics [18].

Table 8 describes the results of the different tests for PT values in the two treatment groups using the Independent Samples T test method. The 2-tailed sig value = 0.000 < 0.05, which means that there is a significant average difference between the Prothrombin Time (PT) values) in the Single Anticoagulant and Anticoagulant + Cephalosporin groups.

Aspilet works by inhibiting the cyclooxygenase enzyme, thereby inhibiting the production of thromboxane A2 (TXA2). Clopidogrel competitively and irreversibly inhibits the adenosine diphosphate (ADP) P2Y12 receptor. Adenosine diphosphate binding to the P2Y12 receptor induces changes in platelet size and temporarily attenuates platelet aggregation [22].

Conclusion

The use of cephalosporins affects the increase in APTT and PT values in cardiovascular patients who are given anticoagulant drugs and cephalosporins. Cardiovascular patients who were given anticoagulants and cephalosporins did not experience any deaths, as shown by data from 80 patients, all of whom (100%) survived after receiving the combination therapy. Bleeding is one of the side effects of some drugs, including cephalosporin antibiotics, antiplatelets, and anticoagulants. Providing drug information to patients receiving these medications or through monitoring drug therapy is an essential task for pharmacists.

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