The Relation of Drug Amount, Comorbidity, Blood Pressure, and Residential Area to Drug-Related-Problems of Hypertension Patients

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Article Info	Abstract
	Hypertension is a direct cause of various cardiovascular diseases that can cause complications if not controlled. Drug Related Problems (DRPs) are treatment-related problems that can intervene in therapeutic outcomes, one of which is blood pressure. This study analyzed the relationship of factors that influence the case of DRPs in hypertensive patients. This research was an observational quantitative study with a cross-sectional study design conducted by direct interview method to 141 hypertensive prolanis patients in Semarang City Health Center. The instrument used was a questionnaire. The results showed there was a relationship between the number of drugs (p = 0.038), comorbidity (p = 0,000), and blood pressure (p = 0,000) with the case of DRPs. There was no relationship between the area of residence and the case of DRPs (p = 0.569). Multivariate models showed the most influential factors were comorbidity (p = 0,000, OR: 21,689) and blood pressure (p = 0,000, OR: 13,277). The conclusion of this study is comorbidity and blood pressure are the predictors that most influence the case of DRPs in hypertensive patients.

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INTRODUCTION

Hypertension is defined as a condition of arterial blood pressure that exceeds the normal level of persistence. Hypertension is a direct cause of various cardiovascular diseases, so it can increase mortality and morbidity (Dipiro et al., 2017). Hypertension occurs in 1.13 billion people worldwide in 2015 and will be projected to increase to 1.56 in the next 10 years (WHO, 2019). The high prevalence of hypertension in the world is also consistent with what is in Indonesia that in the population> 18 years, this case increased from 25.8% in 2013 to 34.1% in 2018 (Ministry of Health RI, 2013; Ministry of Health RI, 2018).

Hypertension has a variety of complications, such as increased aortic stiffness, kidney disorders, and the case of cardiovascular events (Tientcheu et al., 2015). This condition will occur if there is no effort to stabilize blood pressure with a healthy lifestyle and consumption of drugs. The most familiar non-pharmacological therapy is DASH (Dietary Approaches to Stop Hypertension) related to the dose of sodium, the amount of alcohol, and the pattern of physical activity. Pharmacological therapy uses a variety of antihypertensive agents by selecting them according to clinical conditions (Dipiro et al., 2017). The use of pharmacological therapy has the risk of drug related problems.

Drug related problems are treatment-related problems that are able to intervene in targeted therapeutic outcomes (Mil & Westerlund, 2017). DRPs can cause patients to experience worsening of the disease which results in increased mortality and morbidity (Bhagavathula et al., 2017). The DRPs domain is divided into 5 based on the point at which a person experiences therapeutic problems, namely drug of choice, drug use process, drug interaction, adverse drug reaction, and compliance (Mil & Westerlund, 2017). Based on research by Supraptia (2014), DRPs that occur in hypertensive patients both actual and potential are able to cause 2/3 of the total 350 respondents to not reach blood pressure according to the outcome of

the therapeutic algorithm by the American Heart Association.

Drug related problems can be influenced by several factors, such as the number of drugs, comorbid conditions, blood pressure, and area of residence. The amount of drugs that are too much to consume can lead to the condition of DRPs (Niriayo et al., 2018). Comorbid conditions that occur together with hypertension or called multidiagnosis, are also able to cause DRPs (Arini et al., 2016). Blood pressure which is the main indicator of therapeutic outcome is also able to influence DRPs (Farha et al., 2016). Then the geographical location of a group of people with hypertension will affect DRPs because it is related to various social aspects and facilities, such as lifestyle and access to health services (Magnabosco et al., 2015).

Based on the background above, it is necessary to know how the relationship between the amount of drugs, comorbidities, blood pressure, and the area of residence to the case of drug related problems in hypertensive patients. This study analyzed the factors that influence the case of drug related problems.

METHODS

This study is an observational quantitative study with a cross-sectional study design. The population of this study were all hypertensive Prolanis (Chronic Disease Management Program) patients in Semarang City Health Center. The total sample in this study was 141 patients. Patients included in this study were (1) who had hypertension, whether with comorbidities or not, (2) came to a city health center when the study was conducted, (3) did not use the other therapy except from city health centre, (4) was able to communicate. Sample was collected by accidentally sampling.

The independent variables examined in this study were the number of drugs, comorbidity, blood pressure and area of residence. The study was conducted by conducting direct interviews using a

validated questionnaire. Data were analyzed by descriptive univariate analysis, bivariate using chi-square, and multivariate using logistic regression.

RESULTS AND DISCUSSION

Based on the frequency distribution in Table 1 respondents were dominated by female with a total of 107 (75.9%), while male 34 (24.1%). Respondents were mostly> 50 years old at 126 (89.4%) compared to <50 years at 15 (10.6%). The level of education of the majority of respondents was low at 116 (82.3%) with a high education of 25 (17.7%). The results showed that respondents who took one antihypertensive drug were 116 respondents (82.3%), while those who consumed more than one were 25 respondents (17.7%). The frequency distribution of respondents based on the presence or absence of disease comobidity is dominated by respondents with comobid disease that is equal to 84 respondents (59.6%), while with a single hypertension of 57 (40.4%). Blood pressure as one of the factors was dominated by respondents with uncontrolled blood pressure of 76 (53.9%), while those who controlled were 65 respondents (46.1). The majority of respondents live in city areas as many as 83 respondents (58.39%) and in village areas as many as 53 respondents (41.1%). Drug related problems were identified in 93 respondents (80.9%) and 22 respondents did not experience DRPs (19.1%).

Table 1. Frequency Distribution of Factors Affecting Drug Related Problems in Prolanis Patients at Semarang City Health Center

Demography	F	%
Gender		
Male	34	24.1
Female	107	75.9
Age		
≥50 year	126	89.4
<50 year	15	10.6
Education		
Low (SD, SMP, SMA)	116	82.3
High (D3, S1)	25	17.7
Drug Amount		
>1	25	17.7
1	116	82.3
Comorbidity		
Has	84	59.6
Doesn't have	57	40.4
Blood Pressure		
Controlled	65	46.1
Uncontrolled	76	53.9
Residential Area		
City	83	58.9
Village	53	41.1
DRPs		
There is	93	80.9
There isn't	22	19.1
Total	141	100.0

Based on table 2, the number of drugs 1 and more than one had a significant difference for experiencing DRPs ($p = 0.038$, OR: 0.370). The more drugs consumed, the more likely the patient will experience DRPs. Previous research states that the amount of therapeutic drug use tends to increase with an increase in comorbid conditions, while this is in line with this study that respondents with higher comorbidity compared with single hypertension (Tasaka et al., 2018). The use of drugs in greater amounts can be an independent risk factor in the occurrence of DRP, thus requiring strict control and monitoring (Greeshma et al., 2018).

Table 2. Bivariate Relationship of Factors Affecting Drug Related Problems in Prolanis Patients at Semarang City Health Center

Factor	DRPs				Total		* P value	OR
	Absence		Presence					
	F	%	F	%	F	%		
Drug Amount							0,038	0.370
>1	9	6.4	16	11.3	25	17.7		
1	20	14.1	96	68.2	116	82.1		
Comorbidity							0,000	11.491
Has	5	3.6	79	56	84	59.6		
Doesn't have	24	17	33	23.4	57	40.4		
Blood Pressure							0,000	6.389
Uncontrolled	6	4.3	70	49.7	76	54		
Controlled	23	16.2	42	29.8	65	46		
Residential Area							0.569	0.987
City	17	12.1	66	46.8	83	58.9		
Village	12	8.5	46	32.6	58	41.1		
Total					141	100.0		

* Chi-square test

Comorbidity is one factor that has a significance value of p = 0,000 with OR: 11,491. These results indicate that comorbidity can be a very significant factor in predicting the occurrence of DRPs. The risk of patients experiencing DRP is 11,491 times greater if they have comorbidities. In line with the study of Greeshma et al. (2018) that patients with comorbid conditions will have a greater chance of experiencing DRPs. The most common comorbidities are diabetes mellitus. The prevalence of this comorbidity is in accordance with the research of Rajati et al. (2019), that the most common cases in hypertensive patients are diabetes and dyslipidemia with OR values of 2.4 and 1.4, respectively. Comorbid chronic diseases cause patients to undergo therapy with a long period of time simultaneously for more than 1 disease. The combination of hypertension and diabetes therapy can cause drug interactions that cause unwanted effects and interfere with therapeutic goals. This condition is in line with the study of Kumar & Nagaruju (2018), that the use of insulin secretagogs such as sulfunilurea and biguanid when used in conjunction with Angiotension Converter Enzyme inhibitors (ACEi) can increase insulin sensitivity, so as to provide an excessive hypoglycemia effect. Patients with amlodipine as an antihypertensive therapy can also experience side effects in the form of lactic acidosis that causes myalgia and respiratory distress (Kumar & Nagaruju 2018)

Uncontrolled blood pressure has a significant relationship with the case of DRPs (p = 0,000, OR: 6,389). The more uncontrolled blood pressure, the more likely the DRP event to occur, and vice versa. Uncontrolled blood pressure can be caused by comorbidities, such as diabetes. This finding is in accordance with Song et al. (2016) research that patients with diabetes are more difficult to achieve systolic blood pressure in accordance with therapeutic goals because there are disturbances in the endocrine system (Song et al., 2016). In this study, it was found that high blood pressure tends to affect the case of DRPs in the form of subtherapeutics due to the use of antihypertensive doses that are too low or an indication of combination therapy that is not met. This condition can cause therapeutic resistance. These results are in line with research by Faselis & Papademetriou (2011), that the use of suboptimal antihypertension is able to cause resistance to treatment so that blood pressure becomes uncontrolled. The study also states, resistance therapy can be handled easily, such as increasing the dose or the use of combination therapy (Faselis & Papademetriou, 2011).

In addition, in our study also found that there was no change in treatment even though the patient had abnormal blood pressure in the last few months. This condition is called therapeutic inertia, where there is no therapeutic adjustment despite abnormal blood pressure values during the three-month treatment. Therapeutic inertia becomes the risk of uncontrolled blood pressure of 18.2 times (Essayagh et al., 2019).

Some patients in this study felt no need to take the drug because there were no symptoms of hypertension, whereas in previous studies showed that someone with high blood pressure was persistently able to disguise the symptoms that arise

due to the resetting baroreceptors (Lohmeier & Iliescu, 2015). This condition is related to the occurrence of DRPs in the form of adherence, where adherence is indispensable for the success of hypertension therapy (Rasajati et al., 2015). Although it does not cause symptoms, continuously high blood pressure can increase the risk of coronary heart disease by 5.091 times greater (Farahdika & Azam, 2015).

Based on the data obtained, the area of residence does not have a significant relationship to the case of DRPs (p = 0.569, OR: 0.987). Patients from city and village areas have an equal risk of experiencing DRPs. These results are in line with research by Rama et al. (2020), that city and village communities have behaviors in the practice of equal use of drugs, both in terms of adherence, self-medication, and understanding the treatment they get from clinicians. In addition, this research was conducted at the Public Health Center, where the Public Health Center is responsible for Public Health Efforts (UKM) and Public Health Efforts (UKM) in its working area. The size of the work area has been adjusted to the accessibility of the community to the puskesmas and the ability of the puskesmas to manage the area. Supporting Puskesmas will be created if the primary health center requires an increase in the range and quality of health services for the community in its working area (Ministry of Health RI, 2016; Ministry of Health RI, 2019). Therefore, both in village and city areas, patients have the same opportunity in accessing health care facilities.

The occurrence of drug related problems (Table 3) that were identified in 141 respondents included 43 drug selection (31.5%), 41 drug use (29.1%), 69 drug interactions (49%), unwanted drug reaction (5%), and compliance 38 (27%). Drug interactions are the most common DRPs, because they are related to the use of other drugs, especially for comorbid conditions such as diabetes, heart failure, and post-stroke events. Interaction between metformin and amlodipine, causing most patients to experience DRPs (Kumar & Nagaruju, 2018). So far, there are no specific guidelines to handle the condition of diabetes with hypertension, because

during this time the selection of antihypertension adjusts the basic management guidelines for hypertension. However, with hypoglycemic effects and difficulty reaching systolic blood pressure on target due to interactions, this has encouraged clinicians and pharmacists to adjust dosages or use other therapeutic lines in patients with these conditions so that the conditions of both diseases can be stable (Song et al., 2016).

Table 3. Frequency of Drug Related Problems

Kind of DRPs	F	%
Drug of choice	43	31.5
Drug use process	41	29.1
Drug interaction	69	49
Adverse drug reaction	7	5
Noncompliance	38	27

The second most common type of DRPs is drug selection, this is related to the choice of drugs, monotherapy and combination therapy, and dose selection. Third is the use of drugs related to the time, frequency and method of drug consumption. These results are in line with research by Zaman & Fun Wee. (2013), that drug selection, dosage and interaction are the most common DRPs. Patient non-compliance became the fourth highest DRPs. Noncompliance occurs because patients often feel no symptoms, so they can change the behavior of consumption of therapy to be irregular. These results are in accordance with previous studies, that hypertensive patients who have no symptoms or complaints will tend to be obedient in therapy. Even without symptoms, patients with this condition can eventually experience serious cardiovascular consequences (Gebreyohannes et al., 2019).

Unwanted drug reactions have the lowest frequency. Most patients get dihydropyridine calcium channel blocker (CCB) antihypertensive therapy, which is 5 mg or 10 mg amlodipine. The CCB antihypertensive has been postulated to be able to cause angioedema through the mechanism of arteriolar vasodilation, increased membrane permeability, and the role of bradykinin and nitric oxide production, although this still needs to be

proven again. However, when compared to other groups such as angiotensin converting enzyme inhibitors (ACEi), the angioedema effect of amlodipine is very rare in the field.

Multivariate analysis using logistic regression first step involved 3 variables which had a significance value <0.25, namely the number of drugs, comorbidity, and blood pressure was shown in Table 4. The second step was to exclude variables with the greatest significance value, namely the number of drugs (p 0.094). The multivariate model shows that there is no OR difference of more than 10% on the variables in the model, so that the model is declared to be appropriate. The third step, the blood pressure variable is omitted but the OR value is different by more than 10%, so the model is declared inappropriate. Thus, there are two variables that most influence the case of drug related problems. First, comorbidities (OR: 21,689) where patients with comorbid diseases have a risk of 21,689 times more likely to experience drug related problems. Second, blood pressure (OR: 13,277), where patients with uncontrolled blood pressure tend to experience DRPs that interfere with therapy.

Table 4. Logistic Regression Factors Affecting Drug Related Problems in Prolanis Patients at Semarang City Health Center

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Drug Amount	-1.124	.671	2.802	1	.094	.325
	Comorbidity	3.020	.625	23.312	1	.000	20.488
	Blood Pressure	2.596	.614	17.884	1	.000	13.412
	Constant	-8.191	1.992	16.905	1	.000	.000
Step 2[a]	Comorbidity	3.077	.621	24.535	1	.000	21.689
	Blood Pressure	2.586	.604	18.334	1	.000	13.277
	Constant	-10.295	1.711	36.191	1	.000	.000
Step 3[a]	Comorbidity	2.442	.534	20.944	1	.000	11.491
	Constant	-5.202	.961	29.326	1	.000	.006

[a] Variable (s) entered on step 1: Drug Amount, Comorbidity, Blood Pressure

CONCLUSION

Based on the results of research on factors related to drug related problems (DRPs) conducted at the Semarang City Health Center, it was concluded that most respondents were female (75.9%), aged > 50 years (89.4%), with a low level of education (82.3%), taking one hypertension drug (82.3%), having comorbidity (59.6%), having uncontrolled blood pressure (53.9%), living in an city area (58.9%), and experienced DRPs (80.9%). There is a relationship between the number of drugs, comorbidities, and blood pressure on DRPs, but there is no relationship between the area of residence and DRPs. The most influential factors on the case of DRPs are comorbidity with an OR: 21.689 and blood pressure with an OR: 13.277.

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