

Comparison of the Effect of Giving Amlodipine in the Morning and Nighttime Effect on Patient Blood Pressure Decrease Profile Hypertension with Comorbid Type 2 Diabetes Mellitus

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Abstract

Someone who has blood pressure $>140/90$ mmHg is also called hypertension. Therapy for hypertensive patients is carried out for life. Amlodipine is a CCB class which is the first line therapy for elderly hypertensive patients which is consumed once a day and can be given in the morning or evening. This study aims to determine whether there is a difference in the blood pressure decrease values of patients who take amlodipine in the morning and evening with comorbid type 2 diabetes mellitus. This research uses a descriptive observational method with a cross-sectional approach. The sample in this study consisted of 80 patients who were divided into two groups, each group consisting of 40 patients. In the first group, patients took amlodipine in the morning and in the second group, patients took amlodipine in the evening. The results of the statistical test using Wilcoxon have a value for the difference between the reduction in systolic blood pressure in the morning and evening, $p=0.184$ and for the difference in the reduction in diastolic blood pressure in the morning and evening, $p=0.420$, so there is no significant comparison between the reduction in systolic and diastolic blood pressure in the morning and evening.

[Keywords: Amlodipine, Diabetes, Hypertension, Blood pressure]

Introduction

Hypertension or the silent killer has symptoms that vary from person to person. The symptoms are almost the same as those of other diseases. Hypertension is a lifelong disease with no permanent cure (Halvorsen et al., 2022). According to the JNC VIII (2014) guidelines, the target blood pressure for individuals under 60 years of age is <150/90 mmHg. Meanwhile, for all ages with diabetes mellitus, the target blood pressure is <140/90 mmHg. To determine the results of antihypertensive therapy, blood pressure should be evaluated within 2-4 weeks after therapy is started.

Age, gender, obesity and medication use are some of the characteristics and comorbidities that influence the development of hypertension. Hypertension management is important to reduce the risk of increased blood pressure. Lowering systolic blood pressure has been shown to reduce the risk of cardiovascular disease, coronary heart disease, stroke, diabetes, heart failure, and chronic kidney disease. The goal of blood pressure monitoring is to monitor blood pressure. Therefore, hypertension management is crucial for controlling blood pressure, thus achieving controlled hypertension.

Hypertension can lead to other diseases or comorbidities. Diabetes is a common comorbidity. This is because people with diabetes experience disruptions in the insulin production system, which in turn affects blood pressure. Individuals with hypertension who also have diabetes may experience these problems due to low physical activity and poor diet (Alfian Riza et al., 2017). Hypertension can be treated through pharmacological and non-pharmacological approaches. Pharmacological therapy involves the use of medications to lower blood pressure, such as diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers. Meanwhile, non-pharmacological therapy includes lifestyle changes such as diet, healthy, regular exercise, stress reduction, and avoidance of alcohol consumption and smoking. Pharmacological therapy .

Amlodipine is an effective first-line high blood pressure medication for hypertension in patients of all ages, including those with comorbidities such as diabetes. Its long half-life provides a 24-hour blood pressure-lowering effect and contributes to a reduction in cardiovascular events and mortality. Other studies have shown that amlodipine is more effective in lowering systolic and diastolic blood pressure, and amlodipine is also safer for use in hypertensive patients with other comorbidities (Hastuti, 2022).

Numerous studies have evaluated how the timing of amlodipine intake affects blood pressure reduction. Most studies indicate that the effectiveness of amlodipine in lowering blood pressure can be influenced by the timing of administration. In many studies, taking amlodipine at night resulted in better blood pressure control throughout the day and a reduced risk of morning hypertension, compared to taking amlodipine in the morning. One such study was conducted by Khalisah et al. (2022) said that amlodipine, a single antihypertensive drug given once a day, either in the evening or in the morning, had a significant effect in lowering systolic and diastolic blood pressure. Research from (Admaja et al, 2020) states that the majority of hypertension patients experience sleep disorders. poor sleep also affects the reduction of antibodies with indications of fatigue weakness And which converts the sympathetic nervous system which causes an increase in blood pressure.

Material and Methods

This type of research is quantitative with a descriptive observational method and uses a cross-sectional approach. because all variables are observed simultaneously. Prospective data is used, namely current data taken from the Prolanis program, which was implemented for 3 months. This research was conducted at, and has obtained research ethics approval from the Health Research Ethics Commission of Muhammadiyah University of Lamongan with No: 075/EC/KEPK-S1/04/2024. The study sample consisted of 80 patients, divided into two groups of 40. The first group took amlodipine in the morning, and the second group took amlodipine in the evening.

The sample was selected based on inclusion and exclusion criteria. The inclusion criteria were hypertensive outpatients with comorbid type 2 diabetes mellitus at the Babat Community Health Center during the 2023-2024 period who participated in the Prolanis program and received amlodipine monotherapy in the morning and evening. The exclusion criteria were patients who discontinued the Prolanis program. This research instrument used an observation sheet and a doctor's prescription. Data analysis in this study used the Wilcoxon sign test with a value of <0.05 , if the value is value $>0,05$ then there is no significant difference.

Results and Discussion

1. Characteristics Respondent

characteristics based on gender and age.

Table 1 shows the frequency of types The respondents' gender is predominantly female. Women are more likely to experience hypertension due to menopause. During menopause,

estrogen levels decrease, causing LDL levels to rise, leading to inflammation that leads to heart disease vasodilation and the appearance of atherosclerotic plaques which cause increased blood pressure. Table 2 shows that the frequency of respondents' ages is greater in the 56-65 years age group. Age is a significant factor in increasing blood pressure. This indicates that individuals aged 56-65 are particularly susceptible to hypertension.

Table 1. Distribution of Respondents by Gender Sub-chapter of Results and Discussion

No	Gender	Frequency	Percentage (%)
1	Male	21	26,3
2	Female	59	73,7
	Total	80	100

Table 2. Responden Distribution of Respondents by Age

No	Age (years old)	Frequency	Precentage (%)
1	36-45	1	1,3
2	46-55	27	33,7
3	56-65	36	45,0
4	>65	16	20,0
	TOTAL	80	100,0

Table 3 shows that taking amlodipine at night, both before (pre) and after (post) therapy, has been shown to be more effective in lowering blood pressure compared to taking amlodipine in the morning. The data indicate that taking it at night provides better blood pressure control, thus optimizing the results of hypertension therapy. This is related to the pharmacology of the circadian rhythm of blood pressure, which peaks between 6 and 10a.m. According to Nopitasari et al. (2019), amlodipine levels when taken after 6 p.m. can reduce systolic and diastolic blood pressure by 5-5.8 mg/ml compared to use in the morning. Amlodipine can significantly lower and control blood pressure well. CCBs also act as predictors of cognitive decline in elderly patients or those with diseases other comorbidities (Luo et al, 2019).

Table 4 shows a difference in systolic and diastolic blood pressure reduction between the two groups. The table shows that amlodipine taken at night showed a greater reduction. According to Yoewono et al. (2020), amlodipine taken at night can lower blood pressure more significantly, with a decrease occurring within the first hour by 22.5% compared to when taken in the morning. From table 5, it can be seen that the antidiabetic therapy most frequently received by patients is a combination therapy of Glimepiride 2mg and Metformin 500mg.

Antidiabetic therapy can be given singly or in combination. Single therapy is given if the HbA1C when examined is 7.5% (Perkeni, 2021).

Table 3. *Responden Distribution of responden by Blood Pressure Decrease Characteristics based on hypertension*

Drink	Measurement Characteristic TD (mmHg)	Systolic Blood Pressure (mmHg)	Daistolic Blood Pressure (mmHg)	F pre (%)	Percentage (%)	F Post (%)	Percentage (%)
Morning	Normal	<120	< 80	1	2,5	0	0
	Pre Hypertensi	120-139	80-89	4	10	8	20
	Stage 1	140-159	90-99	24	60	21	52,5
	Stage 2	>160	>100	11	27,5	11	27,5
				Total	40	100	40
Night	Normal	<120	< 80	3	7,5	2	5
	Pre Hypertensi	120-139	80-89	7	17,5	8	20
	Stage 1	140-159	90-99	14	35	20	50
	Stage 2	>160	>100	16	40	10	25
					40	100	40

Table 4. *Respondens Distribution Of Pressure Reduction*

Time Giving	No. Patient	Earlvly TD (mmHg)	Final TD (mmHg)	Difference Sistole	Difference Diastole
MORNING	43	140/80	122/77	-18	-3
	44	133/69	128/60	-5	-9
	46	174/88	166/79	-8	-9
	50	165/86	178/65	13	-21
	51	186/99	170/89	-16	-10
	52	144/94	148/75	4	-19
	53	151/82	130/98	-21	16
	54	140/69	150/65	10	-4
	56	220/78	213/70	-7	-6
	57	140/80	147/78	7	-2
	59	161/82	144/70	-17	-12
	63	155/75	140/70	-15	-5
	69	161/81	152/78	-9	-3
	70	165/81	145/82	-20	1
	72	157/80	150/60	-7	-20
	74	152/79	127/67	-25	-12
	76	162/81	131/70	-31	-11
	79	140/87	130/76	-10	-11
80	150/93	160/60	-10	-33	
	Average decline			-11,1	-8,97

NIGHT	1	147/96	142/90	-5	-6
	3	185/111	168/95	-17	-16
	4	167/102	160/100	-7	-2
	7	177/48	149/77	-28	29
	9	170/80	129/75	-41	-5
	10	149/80	130/70	-19	-10
	14	170/108	128/84	-42	-24
	16	188/113	186/104	-2	-9
	18	188/105	177/98	-11	-7
	18	150/86	120/69	-30	-17
	19	221/61	216/55	-5	-6
	23	169/105	144/102	-25	-3
	24	161/64	136/82	-25	18
	25	169/105	158/91	-11	-14
	26	156/104	147/100	-9	-4
	30	148/69	145/59	-3	-10
	31	120/80	104/68	-16	-12
	33	119/67	166/80	-47	13
	35	168/110	135/88	-33	-22
	38	146/83	160/63	14	-20
39	130/86	120/80	-10	-6	
40	180/90	144/85	-36	-5	
	Average	Decline		-17,57	-10,37

Table 5. *Diabetes therapy* Antidiabetic therapy received by patients

No	Therapy	Frequency	Percentage (%)
Single Therapy			
1.	Glimepiride 2mg	22	27,4
2.	Glibenclamid 5mg	2	2,5
3.	Metformin 500mg	1	1,3
Combination Therapy			
1.	Glimepiride 2mg + Metformin 500mg	53	66,3
2.	Glibenclamide 5mg + Metformin 500mg	2	2,5
Total		80	100

According to (Dipiro, 2020) the first line of antidiabetic treatment is biguanide group such as metformin then from the sulfonylurea group such as glimepirid, glipizide dan glibenclamid. Administering combination therapy to patients is expected to control blood sugar levels more effectively because it utilizes two complementary drug mechanisms of action. Combination therapy has a synergistic effect due to the sulfonylurea and biguanide compounds. Sulfonylureas affect insulin receptor sensitivity by first stimulating pancreatic secretion, then

allowing the biguanide compound to work more effectively. (Putra & Permana, 2022). Amlodipine can significantly lower and control blood pressure well. CCBs also act as predictors of cognitive decline in elderly patients or those with diseases other comorbidities (Luo et al, 2019).

From table 6 it can be seen that the other therapy most frequently consumed by patients is from the statin group, namely simvastatin 20mg. Statins have beneficial effects, namely increasing bioavailability and reducing endothelin secretion and can block intracellular pathways related to the action of angiotensin II (Ruszkowski et al., 2019).. However, administering simvastatin therapy can also make it difficult to lower blood pressure.

Utami et al, (2020) stated that the combination of amlodipine with simvastatin causes the effect of the drug to be reduced because amlodipine can increase Simvastatin's effectiveness is enhanced by slowing the rate of simvastatin metabolism. This can increase the drug's effectiveness by increasing peak concentrations and improving the AUC value of simvastatin. At higher doses, it can potentially increase the risk of myopathy, including rhabdomyolysis. Myopathy is a condition that causes muscle weakness and pain, while rhabdomyolysis is a more severe form in which significant muscle damage occurs and harmful substances are released into the bloodstream, which can lead to serious complications such as kidney failure.

In other therapy, there is also a group of NSAIDs, namely diclofenac sodium, NSAIDs can cause increased blood pressure and reduce the effectiveness of antihypertensive medications. Even small increases in blood pressure from NSAID use can significantly increase the risk. Cardiovascular complications, especially with prolonged use. NSAIDs can reduce the vasodilatory effect due to decreased prostaglandin synthesis in the kidneys, which can affect fluid homeostasis and reduce the antihypertensive effect. Interactions should always be monitored, including the antihypertensive effect. Kidney function should be monitored regularly for signs of kidney impairment.

To prevent unwanted drug interactions, paracetamol can be substituted for a safer therapy for geriatric patients. In this study, only a few patients received paracetamol; most received diclofenac sodium, ibuprofen, and mefenamic acid. Table 7 shows that the data is not normally distributed.

Table 6. Other Therapies

N	Class	Name of Drug	Frequency	Percentage (%)
1.	Statin	Simvastatine 20 mg	51	63,6
2.	PPI	Omeprazole 20 mg	7	8,2
3.	Antihistamine	Cetirizine 10 mg	5	7,0
4.	NSAID	Ibuprofen 200 mg	4	5,0
		Asam mefenamate 500 mg	4	5,0
		Nadic 50 mg	9	11,2
5.	Antipiretik	Paracetamol 500 mg	4	5,0
6.	Decongestant	Phenylpropalamine _paracetamol+clorpheniramine maleat	2	2,5
7.	Streoid	Dexametasone 0,5 mg	2	2,5
8.	Vitamine	B Complex	5	8,2
9.	Without other therapy	-	7	8,2

Table 7. Normality Test Result Normalization Test

Test Statistic	Data Normality
Asymp. Sig. (2-tailed) 0,024	Abnormal

Table 8. Hypothesis Test Result

Wilcoxon test for systolic and diastolic blood pressure given in the morning and evening

	<i>p-value</i>	Description
Diference Sistole in Morning-Evening	0,184	Not significant
Diference Diastole in Morning-Evening	0,420	Not significant

The Wilcoxon test is used to measure the difference between the difference between morning systole and evening systole and the difference between morning diastole and evening diastole. From table 8, the difference between morning and evening systole shows a p-value of 0.184 or >0.05 , which means the hypothesis is rejected, or there is no significant comparison of the decrease in morning and evening systolic blood pressure. For the difference in morning-evening diastolic blood pressure, a p-value of 0.420 or >0.05 is seen, which indicates a rejection of the hypothesis or the absence of a significant difference in the decrease in morning-evening diastolic blood pressure.

From the hypothesis test, both for the reduction of systolic and diastolic blood pressure, It is known that there is no significant difference between patients suffering from hypertension and receiving treatment. Amlodipine in the morning compared to the evening over a 3-month period of consistent use. This aligns with research by Baiq Leny et al. (2019), which found no significant differences within 24 hours of amlodipine use. This difference

was due to several factors, including age, gender, ethnicity, comorbidities, and pharmacogenomics. Several of these factors can affect how the drug works in an individual's body, thus resulting in varying results.

Conclusion

The profile of systolic and diastolic blood pressure reduction in amlodipine therapy administered at night decreased systolic and diastolic blood pressure more than use in the morning. The comparison of the average systolic and diastolic blood pressure in hypertensive patients with morning administration experienced a decrease in systolic by 11.1 mmHg and diastolic by 8.97 mmHg, while those who took it at night experienced a decrease in systolic blood pressure. of 17.57 mmHg and diastolic of 10.37 mmHg. Amlodipine therapy given in the morning or evening often do not show significant differences in terms of lowering blood pressure systolic and diastolic with the results of the Wilcoxon sign test stating that H₀ is accepted and H₁ is rejected.

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