Pharmaciana
Vol.12, No.2, July 2022, Page. 218-226
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v12i2.21491

The comparison between combination of candesartan-amlodipine and candesartan-furosemide on blood pressure in hypertensive patients with chronic kidney disease

Dian Ayu Juwita*, Fitri Rachmaini, Almahdy, Rahmad Abdillah, Yolanda Mayestika Wati
Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Andalas University, Padang, West Sumatera, Indonesia

Submitted: 28-10-2021 ***Reviewed: 08-03-2022*** ***Accepted: 23-04-2022***

ABSTRACT

Chronic renal disease is significantly increased by hypertension. Controlling blood pressure is critical in hypertensive individuals. Patients who have good blood pressure (BP) control can reduce morbidity and mortality. This study aimed to compare blood pressure reduction of candesartan-amlodipine with the candesartan-furosemide combination in hypertensive patients with chronic renal disease. The study was conducted by a cohort study design. Retrieval of medical record data was carried out prospectively during the period February-April 2019. The blood pressure reduction was assessed by changes in mean systolic and mean diastolic blood pressure and mean diastolic blood pressure and was analyzed statistically with the SPSS program. A total of 54 patients met the inclusion criteria, consisting of 27 patients receiving candesartan-amlodipine combination and 27 patients receiving candesartan-furosemide combination therapy. The results of the sociodemographic characteristics patients were male 30 patients (55.6%), age 56-65 years 24 patients (44.4%), senior high school education level 31 patients (57.4%). Candesartan-amlodipine and candesartan-furosemide combinations both decreased blood pressure in patients. However, the result of the statistical analysis revealed that there was no significant difference in blood pressure decline. ($p > 0.05$) between the two combinations.

Keywords: blood pressure, candesartan, amlodipine, furosemide, hypertension, CKD

Corresponding author:
Dian Ayu Juwita
Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Andalas University
Padang, West Sumatera, Indonesia
Email: dianayujuwita@phar.unand.ac.id

INTRODUCTION

Blood pressure (BP) control is crucial in the treatment of hypertensive patients with Chronic Kidney Disease (CKD) at all stages (National Heart Foundation Australia, 2016). Increased blood pressure is a factor that can initiate kidney damage and accelerate the decline in kidney function. The volume of blood flowing through the kidneys decreases, and blood pressure in the kidney glomerulus decreases due to narrowing the local arteries (Dipiro et al., 2020). Effective reduction in blood pressure can prevent blood vessel damage and has been shown can reduce morbidity and mortality. The effectiveness of hypertension treatment is based on blood pressure measurements. Hypertensive therapy is effective when it reaches target blood pressure of <140/90 mmHg in general patients without complications, <130/80 mm Hg in patients with diabetes, <130/80 mm Hg in patients with chronic kidney disease (National Heart Foundation of Australia, 2016).

It is difficult to maintain BP with a single drug (Chazova et al., 2011; Lee et al., 2012; Parati et al., 2016). Several studies have confirmed that using two or more drugs to regulate blood pressure in hypertensive individuals with CKD delivers better results. Combining two antihypertensive drugs can increase blood pressure reduction rather than increase one antihypertensive drug (Gradman et al., 2011; Haller, 2008). Combination therapy outcomes in a rapidly therapeutic response in many patients (potentially beneficial in high-risk patients), a higher probability of reaching blood pressure goals in patients with higher blood pressure levels, and a lower chance of decreasing patient compliance with more treatment modifications.

There are physiological and pharmacological interactions between multiple types of medications that lead to fewer adverse effects and greater benefits than a single drug (Mancia et al., 2013). Calcium channel blockers and angiotensin receptor blockers are the most widely used of two combinations of oral hypertension drugs (Fares et al., 2016; Gradman et al., 2011; Parati et al., 2016). Based on the background above, the researchers were interested in studying the comparison of blood pressure reduction on the combination of candesartan-amlodipine with candesartan-furosemide in hypertensive patients with CKD.

MATERIALS AND METHODS

Study Design

This study is a comparative analytical study with a cohort study design. Data retrieval was carried out prospectively using medical record data from February-April 2019. The Health Research Ethics Committee of Dr M. Djamil Hospital Padang have accepted this study protocol, with number 70/KEPK/2019.1137/UN6.KEP/EC/2018. Informed consent has been obtained from all patients who participated in this study.

Sample

This study's inclusion criteria were patients with HT and CKD stages 3, 4 and 5, check-ups at Dr M. Djamil Hospital Padang from March-May 2019, aged 17-65 years, blood pressure ≥160 mmHg, received a combination of candesartan-amlodipine or candesartan-furosemide therapy. Passed away patients and incomplete medical record data were excluded from the study.

Effectiveness assessment

The collected data consisted of patient were sociodemographic data and blood pressure data. Systolic and diastolic Blood pressure (BP) were measured once a month when the patient was check-up at the hospital. After receiving antihypertensive therapy for one month, the patient's blood pressure measurements were carried out again. Furthermore, the difference in blood pressure between the current month and the previous month is calculated to get the percentage of blood pressure reduction. BP observation was carried out for two months. The effectiveness was evaluated by the change in mean systolic and diastolic blood pressure from the first to the second check-up, and then from the second to the third check-up (London et al., 2006).

Data Analysis

Sociodemographic data (age, sex, level of education, and stage of CKD) were presented as percentages. Blood pressure data were presented as Mean ± SD. All data were transcribed into the SPSS software version 22 and analyzed using the Mann-Whitney test. P-values ≤ 0.05 were considered statistically significant.

RESULT AND DISCUSSION

The inclusion criteria were fulfilled by a total of 54 patients, consisting of 27 patients receiving candesartan-amlodipine combination and 27 patients receiving candesartan-furosemide combination therapy. The results of the demographic characteristics of most patients were male 30 patients (55.6%), age range 56-65 years 24 patients (44.4%) and senior high school education level 31 patients (57.4%), hypertensive patients with CKD stage V 36 patients (66.7%) (Table 1).

Table 1. Patient Sociodemographic Characteristics (N=54)

Characteristic	N (%)
Gender	
Male	30 (55.6)
Female	24 (44.4)
Age	
17 – 25	1 (1.8)
26 – 35	3 (5.6)
36 – 45	13 (24.1)
46 – 55	13 (24.1)
56 – 65	24 (44.4)
Level of education	
Uneducated	1 (1.8)
primary school grade	8 (14.8)
Junior high school grade	7 (13.0)
Senior high school grade	31 (57.4)
bachelor's degree	7 (13.0)
Stage of CKD	
III	11 (20.4)
IV	7 (12.9)
V	36 (66.7)

Male suffer from hypertension more than females (Lee et al., 2012). This is due to the presence of the hormone estrogen in the female body, which is a protective factor of cardiovascular disease. The hormone estrogen also acts as an antioxidant and widens the heart's blood vessels, so the blood flow becomes fluent, and oxygen supply is fulfilled (Katzung et al., 2012). Mann-Whitney analysis revealed that there is no significant association between gender and combination therapy given to reduction of blood pressure as seen in Table 2 ($p>0.05$). Similar results were also found in Lee et al., where gender did not significantly correlate with the type of drug combination therapy given to patients (Lee et al., 2012). Patients > 55 years old will be more at risk of developing hypertensive complications (Haller, 2008; Weber et al., 2014). Increasing age will reduce the elasticity of blood vessels so that blood vessels become narrower and stiffer (Dipiro et al., 2020; Mancia et al., 2013).

Kruskal-Wallis analysis results obtained (p>0.05), it is mean that there is no significant relationship between age and combination therapy given to reduction of blood pressure. All age groups have the same respond to combinations of therapies. Similar results were also found in Lee et al., there is no significant relationship between age and combination therapy given to the patients' blood pressure (Lee et al., 2012).

Statistical analysis also shows no significant relationship between the level of education and combination therapy given to reduction of blood pressure (p> 0.05). It means that respondents from all levels of education have the same outcome despite receiving different combinations of therapies. Differences do not solely influence hypertension in education levels, but the level of education influences a healthy lifestyle such as not smoking, not drinking alcohol, and exercising more often (Chiara et al., 2015; Haendra et al., 2013). Low educated people have a high risk of hypertension because of a lack of knowledge related to health. It is difficult to receive health information so that it impacts healthy behavior/ lifestyle (Chiara et al., 2015).

Most hypertensive patients with CKD stage V were found during the study; 36 people (66.7%). According to the literature, hypertension is common in CKD patients, with an incidence of 60% to 90% depending on the etiology and CKD stage (Parati et al., 2016). Hypertension is very common in CKD, especially in patients with end-stage CKD who receive hemodialysis (Ku et al., 2019; Parati et al., 2016). The stages of CKD are classified depending on the level of renal function or glomerular filtration rate (GFR); lower GFR indicates higher CKD stages (Dipiro et al., 2020). The incidence of high blood pressure is associated to GFR (Katzung et al., 2012). Patients with CKD have a high blood pressure prevalence, even when the GFR is only slightly reduced (Ku et al., 2019). The bivariate analysis shows no significant relationship between CKD stage and combination therapy (p > 0.05). It means that respondents from stage III, IV and V have the same opportunity to receive both combinations of therapies. The CKD stage did not have a significant relationship with the combination therapy to patients. The drug combination in this study was amlodipine-benazepril valsartan-HCT (Lee et al., 2012).

Patients who received a combination of candesartan-amlodipine had a mean initial systolic blood pressure (systolic BP) of 170.56 ± 9.68 mmHg, mean initial diastolic blood pressure (diastolic BP) of 87.81 ± 10.80 mmHg. In patients with a combination of candesartan-furosemide obtained a mean initial systolic BP of 166.19 ± 11.13 mmHg, the mean initial diastolic BP was 89.37 ± 10.49 mmHg (Table 2). The statistical analysis shows that the initial systolic and diastolic values in the two groups did not significantly different (p>0.05). This finding was supported by Utami et al., where the patient's initial blood pressure in both the systolic and diastolic groups did not differ significantly (Utami et al., 2014).

The mechanism for hypertension in CKD includes excess fluid volume, endothelial dysfunction, salt retention, and changes in the hormonal system that regulates blood pressure (Ku et al., 2019). Several variables, including genetics, impact blood pressure. Several variables affect blood pressure, including genetics, stress, anxiety, and psychological factors, as well as environmental, lifestyle, and health problems (Dipiro et al., 2020). According to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), most people with systolic blood pressure of 160 mmHg or diastolic blood pressure of 100 mmHg (hypertension stage 2) should be treated with two combinations of antihypertensive drugs. According to the literature, the combination of CCB with ARB (amlodipine-candesartan) and a combination of ARB with diuretics (candesartan-furosemide) is a combination of antihypertensive agents that allows use in these patients (Mancia et al., 2013). Using two antihypertensives agents with a low dose effectively reduces side effects than a high dose with monotherapy (Dipiro et al., 2020). In hypertensive patients with CKD, especially those with albuminuria, ACE inhibitors and ARBs are used as first-line treatment (Ku et al., 2019). ARBs and ACE inhibitors generate vasodilation in efferent arterioles, causing a reduction in intraglomerular pressure, suppressing proteinuria (Ku et al., 2019; Weber et al., 2014). However, the combination of ACE inhibitors with ARB has not been shown to effectively slow CKD progression or reduce cardiovascular events in patients with CKD (Ku et al., 2019).

Table 2. Associations of patients' sociodemographic with blood pressure reduction

Characteristic	Blood Pressure	Mean BP Reduction±SD		p
		Candesartan-Amlodipine	Candesartan-Furosemide	
Gender				
Male	Systolic (mmHg)	20.65±12,02	19.81±11.83	0.164
	Diastolic (mmHg)	11.58±11.55	11.27±6.90	
Female	Systolic (mmHg)	18,34±8,74	18,41±7,20	
	Diastolic (mmHg)	8,22±6,00	9,66±11,02	
Age				
17-25	Systolic (mmHg)	14.73±10,00	15.14±11.32	0.391
	Diastolic (mmHg)	9.92±6.40	8.48±5.11	
26-35	Systolic (mmHg)	15.44±10.11	14.88±12.82	
	Diastolic (mmHg)	8.89±7.87	7.64±4.87	
36-45	Systolic (mmHg)	16.44±12.02	15.67±11.44	
	Diastolic (mmHg)	7.44±4.31	9.27±6.76	
46-55	Systolic (mmHg)	15.88±10.57	14.67±8.83	
	Diastolic (mmHg)	10.55±5.34	9.78±6.64	
56-65	Systolic (mmHg)	24.14±14.77	23.33±13.43	
	Diastolic (mmHg)	9.56±4.43	8.96±3.88	
Education				
Uneducated	Systolic (mmHg)	10.30±8.08	11.02±7.88	0.564
	Diastolic (mmHg)	7.02±6.41	8.02±5.80	
Primary School	Systolic (mmHg)	10.24±9.11	9.82±10.02	
	Diastolic (mmHg)	6.43±7.87	7.74±4.49	
Junior High	Systolic (mmHg)	14.09±9.62	12.07±8.32	
	Diastolic (mmHg)	8.12±5.19	8.72±7.06	
Senior High	Systolic (mmHg)	15.34±9.29	14.90±7.13	
	Diastolic (mmHg)	9.21±4.44	9.68±7.14	
Bachelor	Systolic (mmHg)	22.33±8.77	19.03±9.38	
	Diastolic (mmHg)	10.16±5.01	9.52±4.49	
Stage of CKD				0.411
III	Systolic (mmHg)	12.00±8.12	12.18±8.12	
	Diastolic (mmHg)	8.19±4.91	8.56±5.77	
IV	Systolic (mmHg)	10.42±6.37	9.93±6.13	
	Diastolic (mmHg)	5.04±5.33	5.08±5.31	
V	Systolic (mmHg)	9.49±6.94	10.33±7.31	
	Diastolic (mmHg)	4.28±6.33	4.56±3.52	

Table 3. Patients' blood pressure at the first check-up

Blood Pressure	Combination Therapy		
	Candesartan-Amlodipine (mean±SD)	Candesartan-furosemide (mean±SD)	p
Systolic (mmHg)	170.56±9.68	166.19±11.13	0.197
Diastolic (mmHg)	87.81±10.80	89.37±10.49	0.631

After receiving antihypertensive therapy for two months, patients who were using a combination of candesartan-amlodipine reported a decrease in systolic blood pressure of 18.52 ± 12.94 mmHg or 10.86% and a reduction in diastolic blood pressure of 10.56 ± 12.18 mmHg or 12.02% of initial blood pressure (Table 3, Figure 1). Patients using a combination of candesartan-furosemide also decreased blood pressure. A decrease in systolic blood pressure was 21.52 ± 15.69 or 12.94% and diastolic blood pressure of 9.26 ± 11.63 or 10.35% of pressure initial blood (Table 4, Figure 2).

Table 4. Blood pressure reduction after one month of medication in hypertensive patients

Blood Pressure	Mean Blood Pressure Reduction		p
	Candesartan-Amlodipine (mean±SD)	Candesartan+ Furosemide (mean±SD)	
Systolic (mmHg)	18.52±12.94	21.52±15.69	0.178[a]
Diastolic (mmHg)	10.56±12.18	9.26±11.63	0.527[b]

[a]Independent Sample t test(α=0.05)
[b]Mann-Whitney test(α=0.05)

Statistical analysis showed that there was no significant effect in decreasing blood pressure in hypertensive patients receiving combination therapy of candesartan-amlodipine and candesartan-furosemide (p> 0.05). It means that both groups had no better combination effect in a decrease in blood pressure (Table 3). This finding was supported by Chazova et al. and Lee et al. (Chazova et al., 2011; Lee et al, 2012).

Antihypertensive drugs that work to inhibit Renin Angiotensin Aldosterone System (RAAS) such as ARB or ACEI have been widely studied and proven to reduce blood pressure better as a combination. The addition of one of these RAAS inhibitors significantly increases the tolerability profile of CCB. The presence of the sympathetic effects of RAAS inhibitors can minimize the increase in heart rate and neutralize peripheral oedema, which is a side effect of the use of CCB (Gradman et al., 2011). Antihypertensive combination therapy is more effective using diuretics (Saad, 2018). The combination of diuretics and RAAS inhibitors has been shown to have an additive effect of lowering blood pressure. Combining diuretics with RAAS inhibitors can reduce the intravascular volume and reduce RAAS activation, which causes vasoconstriction. The occurrence of salt and water retention and RAAS inhibitors to diuretics can also improve safety and prevent hypokalemia (Gradman, 2011).

CKD is associated with increased RAAS activity and reduced blood flow in the glomerulus. As a result, the glomerulus in this area undergoes renin hypersecretion, leading to an increase in circulating angiotensin II levels. Angiotensin II has a strong vasoconstrictor action, which elevates blood pressure and systemic vascular resistance. Because the number of functioning glomeruli is reduced in CKD, each surviving glomerulus must improve the glomerular filtration rate (GFR), which requires raising systemic arterial pressure to promote perfusion and GFR. (Dipiro et al., 2020; Ku et al., 2019).

After two months of receiving antihypertensive therapy, patients who used a combination of candesartan-amlodipine experienced a decrease in systolic blood pressure of 8.33 ± 16.53 mmHg or 5.48%, a decrease in diastolic blood pressure of 0.81 ± 11.00 mmHg or 1, 04% of the previous month's

blood pressure (Table 4, Figure 1). Patients with a combination of amlodipine-candesartan experienced a decrease in systolic blood pressure of 6.41 ± 22.06 or 4.43% and decreased diastolic blood pressure 1.67 ± 11.34 or 2.08% (Table 5, Figure 2).

Table 5. Mean of blood pressure reduction in hypertensive patients after two months of therapy

Blood Pressure	Mean Blood Pressure Reduction		P
	Candesartan-Amlodipine (mean±SD)	Candesartan-Furosemide (mean±SD)	
Sistolik (mmHg)	8.33±16.53	6.41±22.06	0.959[a]
Diastolik (mmHg)	0.81±11.00	1.67±11.34	0.780[a]

[a]*Mann-Whitney test*(α=0.05)

The statistical analysis results showed that after two months of receiving antihypertensive therapy, there was no significant difference in blood pressure lowering effect between patients getting candesartan-amlodipine candesartan-furosemide medication (p> 0.05). It means that both groups had no better effect of decreasing blood pressure after undergoing therapy for two months (Table 5). This finding was supported by other research (Gradman et al., 2011). Adequate blood pressure reduction can reduce morbidity and mortality and prevent damage to blood vessels. Rational use of drugs, both single and in combination, can reduce blood pressure. Combination therapy at low doses with CCB and ARB has a better effect on blood pressure reduction than high-dose CCB monotherapy A significant blood pressure reduction in combination therapy nifedipine-candesartan compared to candesartan alone (National Heart Foundation Australia, 2016).

Antihypertensive combinations that cannot be given to CKD comorbid are ACE inhibitors and ARBs. These two hypertension drugs can raise blood creatinine levels and cause metabolic side effects such as hyperkalemia, especially in individuals with impaired renal function (James et al., 2014). One of the primary causes of inadequate blood pressure management in CKD patients is noncompliance with medication. More than 50 percent of Patients with chronic kidney disease need two or more drugs to keep their blood pressure under control. Because of the simultaneous treatment required for metabolic acidosis, hyperphosphatemia, and other CKD co-symptoms, many CKD patients are on a high dose of medication (Ku et al., 2019).

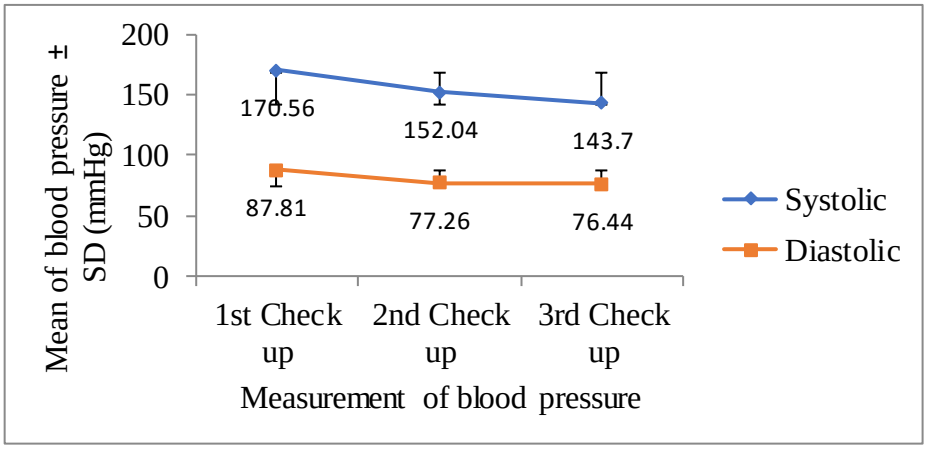

Figure 1. Mean of systolic and diastolic blood pressure in hypertensive patients with CKD who received a combination of candesartan-amlodipine

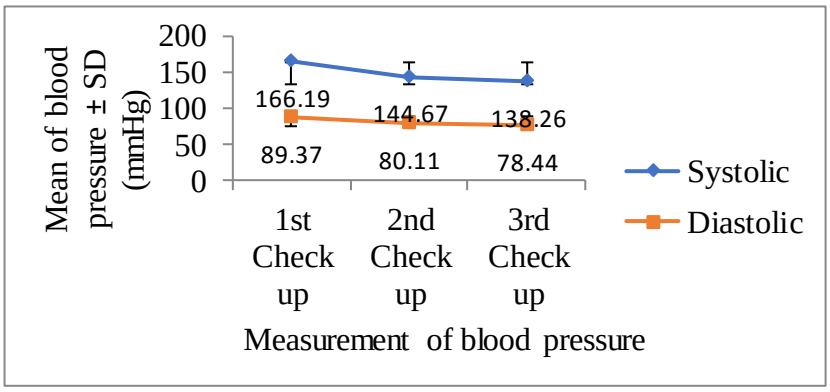

Figure 2. Mean of systolic and diastolic blood pressure in hypertensive patients with CKD who received a combination of candesartan-furosemide

CONCLUSION

Candesartan-amlodipine and candesartan-furosemide both have the ability to lower blood pressure in hypertensive patients with CKD, but no significant variations in efficacy were discovered between the two combinations ($p > 0.05$).

ACKNOWLEDGEMENT

The authors gratefully acknowledge the Faculty of Pharmacy, Universitas Andalas for the support and adequate facilities.

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