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RESEARCH ARTICLE

Effectivity Evaluation of Bisoprolol as Additional Hypertension Therapy in Geriatrics with Type 2 Diabetes Mellitus while ongoing with Dual Oral Anti-Hypertension Agent: A Cohort Study

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ABSTRACT:
Background: Bisoprolol is a beta-blocker agent that is widely used as an antihypertensive agent, cardiac rate control, and agent to improve the cardiac ejection fraction. Bisoprolol is commonly added to hypertension therapy in patients with a high risk of heart disease such as hypertension with diabetes. The effectiveness of beta-blocker agents in the treatment of hypertension in geriatrics with diabetes without a history of CVD who are currently using dual therapy is still minimal. Evaluation of this matter needs to be done to complement scientific evidence in the use of bisoprolol in the treatment of hypertension in geriatrics with type 2 diabetes mellitus. Objective: This study aims to compare the effectiveness of bisoprolol as additional therapy in geriatric patients who have diabetes hypertension without CVD history while they are ongoing dual oral antihypertension therapy. Method: A cohort study involving 82 geriatrics was prospectively observed for four weeks. The exposure in this study was the bisoprolol agent. Subjects were divided into two groups, where all patients would undergo dual antihypertensive agents, namely Angiotensin-Receptor-Blocker (ARB) and Calcium-Channel-Blocker (CCB). Reductions in systolic and diastolic blood pressure were observed as primary outcomes, and success in achieving blood pressure goals was observed as a secondary outcome in the study. Result: There was no difference in the decrease in systolic and diastolic blood pressure in the exposure and non-exposure groups (p> 0.05). Judging from the large number of patients who successfully achieved the therapeutic target also showed no significant difference between the exposure and non-exposure groups with systolic and diastolic risk difference (RD) values of 1,091 (CI95%: 0.545-2.184) and 1,222 (CI95%: 0.781-1.913). Conclusion: The addition of bisoprolol agents in geriatric patients with hypertension and diabetes without a history of CVD is not required.

KEYWORDS: Bisoprolol, Oral Antihypertensive, Type 2 Diabetes Mellitus, Geriatrics, Combination Therapy.

INTRODUCTION:

Hypertension is a metabolic syndrome that often appears as a concomitant disease in people with diabetes, heart disease, and kidney disease. People can categorize to be hypertensive if they have a blood pressure >130/80 mmHg[1]. People with blood pressure above 140/90 needs to be watched because the risk of heart and blood vessel diseases increases two times greater[2–4].

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Diabetes Mellitus is a disease that has a correlation with hypertension. Patients with diabetes mellitus with uncontrolled blood sugar levels have a risk of experiencing secondary hypertension 1.7 times greater than non-diabetes patients[1–3].

Geriatrics is one of the populations that needs attention on this issue. Elderly patients who have diabetes with hypertension must be treated seriously[7–11]. Besides controlling blood glucose levels, controlling blood pressure has been shown to reduce the risk of cardiovascular disease by 20%-25% for myocardial infarction, 35%-40% for stroke, and by 50% for heart failure[1,4]. Geriatric populations tend to have difficulty

controlling blood pressure due to decreased physiological function of related organs and decreased vascular flexibility[13–17]. This condition requires the right combination of oral antihypertension (OAH) to be able to maintain the blood pressure within safe limits[5].

Bisoprolol is an interesting drug to discuss in the treatment of hypertension with accompanying diabetes mellitus. Bisoprolol tends to exhibit lower blood pressure reduction outcomes when given monotherapy but has an excellent effect when given in combination with Angiotensin-Converting-Enzyme-Inhibitor (ACEI), Angiotensin-Receptor-Blocker (ARB), Calcium-Channel-Blocker (CCB), and diuretic drugs[9–11]. Patients with a history of cardiovascular disease also show improvement in blood pressure control and prevent recurrent cardiovascular disease (CVD) when there is the addition of bisoprolol in hypertension therapy[6,7].

There is not much evidence to explain the effectiveness of bisoprolol in geriatric patients with hypertension and diabetes without a history of CVD who are currently on dual OAH therapy. This study aims to compare the effectiveness of bisoprolol as additional therapy in geriatric patients who have diabetes hypertension without CVD history. The results of this study are expected to provide evidence related to “needed” or “not needed” for the addition of bisoprolol in geriatric patients with diabetes hypertension, non-CVD history.

METHODS:

Study Design and Sample Size:

The design of this study was a prospective cohort study. This study design was done by observed the research subjects who get exposure and non-exposure to then looking for the resulting outcomes in the future. This research was conducted at one of the hospitals owned by the Indonesian National Police, which is located in the West Java Province of Indonesia in the period December 2018 to June 2019. This study has been approved by the ethics commission with approval number B/2121/VIII/2019/KEPK. All patients included in this study were understand the aims and the objectives of the study and agreed to be involved after completing and signing informed consent. Subjects who had met the inclusion and exclusion criteria were then sampled using a non-probability technique, namely consecutive sampling. Subjects who received additional bisoprolol therapy were allocated to the exposure group and without bisoprolol to the non-exposure group. The minimum sample size that must be met based on a cohort formula in this study was 60 subjects, which were divided into two groups. This minimum number of samples had an analytical confidence level of 5% and a power of statistics of 80%.

2. Study Population and Procedures:

The population in this study was elderly (>60 years old) who were undergoing hypertension therapy and had type 2 diabetes mellitus. The study population was undergoing outpatient treatment at the Indonesian National Police Hospital in the designated time period. This study sample was a part of the population that meets the study inclusion criteria. Inclusion criteria set in the study include a subject having a minimum age of 60 years or ove have a history of at least stage I hypertension with type 2 diabetes me us; currently undergoing mono hypertension therapy with uncontrolled blood pressure; and observed on the addition of second or third hypertension therapy with ACEI, ARB, CCB, diuretic or beta-blocker (bisoprolol) according to the hospital's prescribing pattern. Patients who were not willing to be part of the study; had a history of CVD; suffered from "emergency hypertension," as well as "urgency hypertension" were excluded from this study. All patients who were included in the study criteria, but during the follow-up period, they were lost of contact, they would be categorized as dropout criteria.

In this observational study, researchers did not intervene in therapies that have been chosen by doctors. However, patients will be grouped based on the therapy obtained. Subjects who received dual hypertension therapy with the addition of bisoprolol were included in the exposure group, while subjects who received dual hypertension therapy without the addition of bisoprolol were included in the non-exposure group. All subjects in each group will be followed for four weeks. Four weeks is the subject's routine control time to the hospital. After four weeks, the outcomes that arise from exposure can be observed for analysis.

3. Data Collection:

All data were obtained through direct observation of the study subjects when the subjects exercised control at the hospital polyclinic. Supporting data was also obtained from the patient's medical record. In this study, data will be collected into several categories consisting of baseline demographic characteristics (age, gender, blood sugar profile, BMI, and duration of diabetes); oral antihypertensive drug profiles (classes, dosage, and frequency of administration); and systolic-diastolic blood pressure (before getting exposure and after getting exposure).

4. Clinical Outcome:

The outcome of this study was a decrease in systolic and diastolic blood pressure measured by mercury sphygmomanometer. The measurement of blood pressure was repeated three times. The patient's baseline blood pressure was determined by averaging the actual

measurements and the previous month's blood pressure history. Blood pressure after an observation was determined through the measurement of the average blood pressure of the patient for three consecutive days. The exposure in this study was the addition of the bisoprolol agent at a dose of 5 mg once a daily to the study subjects.

5. Statistical Analysis:

The data obtained were analyzed by IBM SPSS version 21. he primary outcome evaluation was performed using a combination of dependent t-test, independent t-test, and risk difference (RD). The t-test was used to analyze independent data that were normally distributed, such as sociodemographic parameters, comparison of systolic, and diastolic blood pressure. Chi-square was used for categorical data analysis on demographic characteristics. The risk difference was used to see the risk ratio for bisoprolol as an agent to assess the patient's blood pressure achievement (secondary outcome). All statistical analyzes were two-tailed, and p-values <0.05 were considered as statistically significant. Data on oral antihypertensive drug, dosage, and frequency of administration profile were presented descriptively.

RESULTS:

During the study period, 122 patients were found to be potentially part of the study. In the initial screening, 36 subjects were excluded because they did not meet the study criteria. A total of 86 subjects met the study criteria and followed the treatment for four weeks. During the follow-up process, there were four subjects dropped out because they lost contact. A total of 82 study subjects was successfully followed until the final stage. The process of determining the subjects of study in more detail is presented in Figure 1.

The demographic characteristics showed no significant difference between the two groups, except for the BMI variable. Subjects in the exposure group had a higher tendency for BMI compared to other groups. In general, subjects in this study can be stated to have uniform baseline characteristics. Detailed demographic characteristics data are shown in Table 1. From a total of 82 subjects observed, all patients went home with a dual OAH consisting of ARB and CCB. In the exposure group, additional bisoprolol therapy was observed during the study. Profile of drug types, dosages, and frequency of administration are presented in more detail in Tables 2 and 3.

The baseline of blood pressure between groups was equivalent. Its average range was 150/84mmHg to 153/87mmHg. This condition described that patient's blood pressure was still in the category of stage I hypertension based on JNC 7[1]. Before this study was conducted, the patient was still using OAH as a monotherapy. Patients with diabetic hypertension have a blood pressure target of <130/80 mmHg, so that clinicians tried to make additional dual and triple therapy.

After four weeks of prospective follow-up, the study subjects showed improvement in blood pressure. Both the non-exposure and exposure groups showed significant improvement in blood pressure compared to baseline blood pressure (p <0.05). Interesting things were found when comparing groups. The addition of the 5 mg bisoprolol agent (exposure group) to the study subjects did not show superior changes in systolic and diastolic blood pressure compared to the non-exposure group (p> 0.05). Results are shown in Tables 4 and 5.

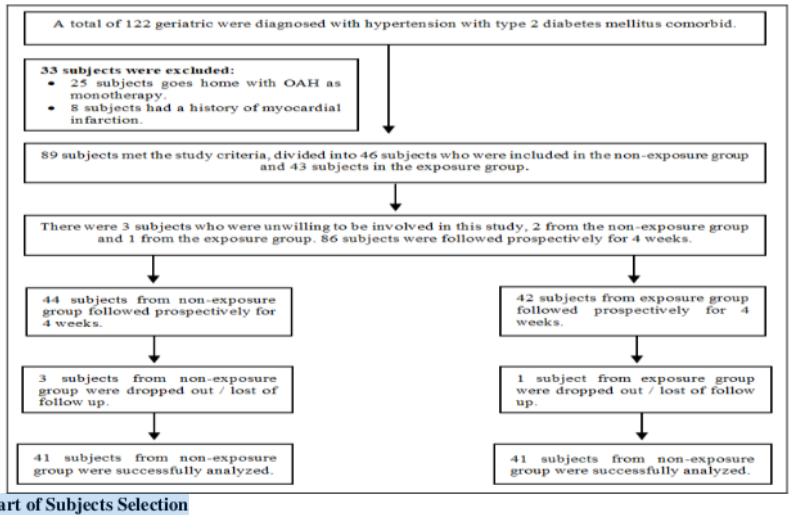

Figure 1. Flow Chart of Subjects Selection

Table 1. Subject Baseline Characteristics

S. No	Baseline Characteristics	Non-Exposure Group (n=42)	Exposure Group (n=42)	p-value	Type of Analysis
1	Age (year ± SD)	70 ± 5	71 ± 6	0.342	t-test
2	Gender [n (%)]				
	Male	17 (41.46)	16 (39.02)	0.822	Chi-S
	Female	24 (58.54)	25 (60.98)		
3	Blood Pressure (mmHg ± SD)				
	SBP	150 ± 17	153 ± 18	0.415	t-test
	DBP	84 ± 13	87 ± 16	0.349	t-test
4	**ARBG (mg/dL ± SD)**	167 ± 56	161 ± 49	0.637	t-test
5	**BMI (kg/m2 ± SD)**	24 ± 1	26 ± 2	0.003*	t-test
6	Diabetes Duration [year (%)]				
	>5 year	26 (63.41)	30 (73.17)	0.342	Chi-S
	<5 year	15 (36.59)	11 (26.83)		

Table information: n=subjects; SD=standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; ARBG=average random blood glucose; BMI=body mass index; Chi-S=chi-square test; *=statistically significant.

Table 2. Oral Antihypertensive Profile in Subjects

S. No	OAH Classes	Generic Name	Non-Exposure Group [n (%)] n=42	Exposure Group [n (%)] n=42
1	ARB	Valsartan	21 (51.22)	35 (85.37)
		Telmisartan	6 (14.63)	0 (0)
		Candesartan	10 (24.39)	4 (9.76)
		Irbesartan	3 (7.32)	1 (2.44)
2	CCB	Amlodipine	33 (80.49)	39 (95.12)
		Nifedipine	8 (19.51)	2 (4.88)
3	Selective BB	Bisoprolol	0 (0)	41 (100)

Table information: OAH=oral antihypertension; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; BB=beta blocker; n=subjects.

Table 3. Oral Antihypertensive Dosage and Frequency of Administration Profile in Subjects

S. No	OAH Classes	Generic Name	Dosage	Frequency of Administration
1	ARB	Valsartan	80 and 160 mg	Once Daily
		Telmisartan	80 mg	Once Daily
		Candesartan	8 and 16 mg	Once Daily
		Irbesartan	150 and 300 mg	Once Daily
2	CCB	Amlodipine	5 and 10 mg	Once Daily
		Nifedipine	30 mg XR	Once Daily
3	Selective BB	Bisoprolol	5 mg	Once Daily

Table information: OAH=oral antihypertension; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; BB=beta blocker; XR=extended release.

Table 4. Comparative Analysis of Dependent and Independent Systolic Blood Pressure

Group	Variable	Baseline (mmHg ± SD)	Post Observation (mmHg ± SD)	Differences (mmHg ± SD)	p-value Dependent Group	p-value Independent Group
Non Exposure (n=41)	SBP ± SD	150 ± 17	141 ± 19	9 ± 1	0.004*	0.115
Exposure (n=41)	SBP ± SD	153 ± 18	142 ± 22	11 ± 4	0.009*	

Table information: n=subjects; SD=standard deviation; SBP=systolic blood pressure; *=statistically significant.

Table 5. Comparative Analysis of Dependent and Independent Diastolic Blood Pressure

Group	Variable	Baseline (mmHg ± SD)	Post Observation (mmHg ± SD)	Differences (mmHg ± SD)	p-value Dependent Group	p-value Independent Group
Non Exposure (n=41)	DBP ± SD	84 ± 13	78 ± 10	6 ± 3	0.001*	0.585
Exposure (n=41)	DBP ± SD	87 ± 16	82 ± 12	5 ± 3	0.021*	

Table information: n=subjects; SD=standard deviation; DBP=diastolic blood pressure; *=statistically significant.

Table 6. Risk Difference Analysis of Systolic Blood Pressure

Group	SBP Goal (<130mmHg)	SBP Not Achieved (>130mmHg)	RD	CI 95%	p-value
Non Exposure (n=41)	12 (29.27%)	29 (70.73%)	1.091	0.545-2.184	0.806
Exposure (n=41)	11 (26.83%)	30 (73.17%)			

Table information: n=subjects; SBP=systolic blood pressure; RD=risk difference; CI=confidence interval.

Table 7. Risk Difference Analysis of Diastolic Blood Pressure

Group	DBP Goal (<80mmHg)	DBP Not Achieved (>80mmHg)	RD	CI 95%	p-value
Non Exposure (n=41)	22 (53.66%)	19 (46.34%)	1.222	0.781-1.913	0.377
Exposure (n=41)	18 (43.90%)	23 (56.10%)			

Table information: n=subjects; DBP=diastolic blood pressure; RD=risk difference; CI=confidence interval.

In this study, it was found that bisoprolol did not provide better systolic and diastolic blood pressure improvements, although it was found to be a significant improvement in blood pressure when compared with baseline blood pressure. This illustrates that, if the patient has characteristics similar to the subjects in this study, the addition of bisoprolol as an additional therapy is not necessary. The analysis continued by looking at the distribution of study subjects who achieved their hypertension therapy goals in diabetes mellitus. The results of the analysis are shown in Tables 6 and 7.

The results of the number of study subjects who achieved the systolic and diastolic blood pressure goals between groups also showed results that were not significantly different (p>0.05). Risk difference (RD) values for systolic and diastolic blood pressure were 1.091 (CI95%: 0.545-2.184) and 1.222 (CI95%: 0.781-1.913), respectively, where these results describe that both the non-exposure and exposure groups have a balanced ability to improve blood pressure to achieve goals. The addition of bisoprolol agents in this study did not show better changes in systolic and diastolic blood pressure compared to other groups.

DISCUSSION:

Bisoprolol is a beta-1 selective antagonist drug, where it is widely used in CVD therapy[10]. The role of bisoprolol as an antihypertensive agent, cardiac rate control, and an agent for maintaining cardiac ejection fraction has been proven effective[8–13]. The results of this study showed that bisoprolol did not provide a better outcome in reducing systolic and diastolic blood pressure compared to the control group. Generally, based on evidence, beta-blocker agents do not show better effectiveness compared to antihypertensive agents such as ACEI, ARB, CCB, and diuretic when the patient has no history of CVD[6,14–16]. A systematic review shows that the administration of beta-blocker agents was no better in terms of total mortality and the incidence of Adverse Drug Reaction (ADR) than diuretic agents, CCB, and Renin-Angiotensin-Aldosterone System (RAAS). However, beta-blockers show better outcomes in patients with CVD[6,10,11,13,14,16].

The subjects in this study did not have a history of CVD, but they had a CVD risk. In this condition, bisoprolol as an exposure agent shows no better blood pressure reduction outcome. Bisoprolol has a selective mechanism of action to reduce cardiac output by inhibiting beta-adrenergic receptors so that blood pressure can decrease, rate control is better, and can improve the reduction in heart ejection fraction[8,9,14,15]. Hypertension in subjects without a history of CVD showed good effectiveness in reducing blood pressure when interfering with total peripheral resistance and cardiac output by RAAS, diuretic and CCB drugs therapy without beta-blocker drugs[3,4,8,13,14].

The results of this study indicate that geriatric patients who have hypertension and diabetes without a history of CVD, the selection of dual or triple therapy is recommended to choose a combination of RAAS, CCB, or diuretic agents before adding beta-blocker agents[6,11,14,15]. The addition of a beta-blocker agent cannot be stated wrong in this case, but the addition of a beta-blocker in this condition is still unnecessary in the subject's condition in this study[6,8,14,15]. This study has the limitation of not evaluating the potential side effects of bisoprolol that may occur in people with hypertension and diabetes. Some studies say that beta-blocker agents were at risk for causing dangerous ADRs such as hypoglycemia in patients with diabetes, but there was not much solid evidence to support that finding[16–19].

Recommendations that can be informed to clinicians who treat geriatric patients with hypertension and diabetes based on the results of this study are always to monitor the patient's blood pressure and blood sugar profile. Geriatrics is a population that is vulnerable to ADR, so it needs to increase vigilance during the use of polypharmacy. When geriatric blood pressure has not been controlled with monotherapy or dual therapy, consider adding other antihypertensive agents such as RAAS, CCB, or diuretics first before choosing a beta-blocker agent[7,16,18,20]. Evaluation of geriatric blood pressure should be done more frequently, like 2-3 times a month.

CONCLUSION:

The addition of bisoprolol agents in geriatric patients with hypertension and diabetes without a history of CVD showed ineffectiveness related to a reduction in systolic and diastolic blood pressure. Geriatrics with uncontrolled blood pressure without a history of CVD have not yet required bisoprolol as an additional antihypertensive agent to control the blood pressure of these geriatric patients.

CONFLICT OF INTEREST

This paper was written independently. All authors disclose no financial or personal relationships with other

people or organizations that could inappropriately influence the work.

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