The Correlation of Antihypertensive Therapy to Timed-Up-and-Go-Test as a Fall Risk Approach in Elderly at RSUP. Dr. Sardjito Yogyakarta

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ABSTRACT

Elderly is a group of patients with a decrease in physiological and psychosocial functions where these conditions increase the incidence of degenerative diseases such as hypertension, cardiovascular disorders, sensory and neurological disorders, so that the consumption needs of drugs increase to improve the quality of life of the elderly, especially antihypertensive use. Moreover, the Elderly is also a high potential group of falls that can increase morbidity and mortality. This study aims to analyze the correlation of antihypertensive use which represent by the amount of antihypertensive and duration of antihypertensive with timed-up-and-go-test (TUGT) as a fall risk approach in the elderly at RSUP Dr. Sardjito Yogyakarta. Data collection was carried out prospective cross-sectionally in 86 elderly patients at Geriatric Policlinic from 30th April to 20th July 2018. Analysis of the correlation between antihypertensive therapy to the TUGT with Pearson correlation analysis. A multivariate analysis was conducted to determine the correlation of independent variables (number and duration of therapy antihypertensive) to the dependent variable (TUGT) by considering confounding variables (age, gender, body mass index, history of falls, blood pressure, living alone, comorbid diseases, and use of other drug therapies). The result showed that elderly at Geriatric Policlinic have good mobility showed by the TUGT score (13.1± 5.9 seconds). Bivariate analysis tests showed that the amount of antihypertensive and duration of antihypertensive therapy did not significantly affect the risk of falls in the elderly ($p > 0,05$), and multivariate analysis between independent variables and confounding variables to the TUGT showed that age and gender did significantly affect the score of TUGT with a significance of 0,000 and 0.001. Antihypertensive therapy did not have a significant correlation to timed-up-and-go-test (TUGT) as a fall risk approach in elderly

Keywords: antihypertensives, timed-up-and-go-test (TUGT), risk of falls, elderly

1. INTRODUCTION

The Elderly is defined as someone who reaches the age of 60 years, with special needs in terms of independence, communication, transportation, supervision, and therapy. The number of elderly in the world is increasing as a result of an increase in life expectancy and a decrease in mortality. Health status in the elderly is affected by biological changes associated with increasing age. These changes can disrupt the body system and degenerative diseases. With age, physiological function decreases due to the aging process so that many non-infectious diseases appear in the elderly. In addition, degenerative problems reduce the body's resistance so that it is susceptible to infectious diseases. The results of Riskesdas in

2013, the most common diseases in the elderly are Non-Infectious Diseases including hypertension, arthritis, stroke, chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM). Hypertension ranks the first disease with the highest prevalence in the elderly, 45.9% in the age group 55-64 years, 57.6% in the age group 65-74, and 63.8% in the age group above 75 years [1].

Changes that occur in the elderly can affect the balance of the body because there is a decrease in functions in the central nervous system, sensory systems such as the visual system, vestibular and proprioception, and the musculoskeletal system [2]. Falling events as a direct impact of balance disorders can be minimalized by recognizing risk factors for balance disorders. These factors consist of internal and external factors. Internal factors related to balance disorders are age, gender, occupation, affective and psychological disorders, cardiovascular disease, metabolic disorders, musculoskeletal disorders, neurological disorders, sensory abnormalities, physical activity, the use of certain medications amounting to 4 or more such as antiarrhythmics, diuretics, digoxin, narcotics, anticonvulsants, psychotropics, and antidepressants. Also, external factors include the environment, the use of walking aids, and improper use of footwear and clothing [3], [4].

Tinetti et al showed that almost all elderly over 70 years suffered from hypertension. A study showed a decrease in the risk of cardiovascular disease in the elderly by 28% using antihypertensive therapy. Because antihypertensive can't be avoided in the elderly with hypertension or cardiovascular disorders, it is necessary to evaluate the balance disorder using timed up and go test (TUGT) as a fall risk approach, especially for elderly patients to see the effect of antihypertension on the risk of falls and as a recommendation for clinicians in prescribing antihypertensive for elderly patients so that the quality of life can improve.

This study aims to determine the effect of antihypertensive therapy on the Timed Up and Go Test as a risk fall approach in elderly patients at RSUP. Dr. Sardjito Yogyakarta

2. METHODS

The design of this study was cross-sectional. Data collection was carried out prospectively in the elderly patients at the Geriatric Polyclinic RSUP. Dr. Sardjito Yogyakarta from 30 April to 20 July 2018. Data of antihypertensive therapy were derived from the medical record, and the risk of falls was measured with TUGT. TUGT measurement started from the subject standing from an armchair then the subject was asked to walk 3 meters, turn and walk back to the chair and sit down. Subjects conducted trials first before undergoing the actual test. This study design was approved by Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Gadjah Mada University-Dr.Sardjito General Hospital (Ref: KE/FK/0393/EC/2018).

Analysis of the correlation between antihypertensive therapy (amount and duration of therapy) to the TUGT score with Pearson and multivariate analysis using multiple linear regression analysis was conducted to determine the correlation of independent variables (number and duration of antihypertensive therapy) to the dependant variable (TUGT) by considering confounding variables (age, gender, body mass index, history of falls, staying alone, comorbid diseases, and other drug therapies).

3. RESULT AND DISCUSSION

The study was conducted on 86 elderly patients with an average age of 73.7 years and the largest group aged 60-74 years (young-old). Characteristics of patients based on fall

history showed that 53.5% of the elderly had a history of falls, while 46.5% of other elderly had no history of falls. The burden of comorbid disease based on the Charlson Comorbidity Index (CCI) showed an average CCI value of 3.9 indicates that the average elderly patient had a 53% chance of surviving for the next 10 years. The pattern of therapeutic regimen in this study compared with average TUGT score showed in Table 1.

Table 1. Patterns of drug use in elderly patients and TUGT

Therapy	N (%)	Average TUGT
Antihypertensive	55 (64%)	13.79 ± 6.81
Antihypertensive + Antihyperglicemia	22 (25.6%)	11.17 ± 2.96
Antihypertensive + drugs that affect the central nervous system (CNS)	7 (8.1%)	11.21 ± 2.43
Antihypertensive + Antihyperglicemia + drugs that affect the central nervous system	2 (2.3%)	19.95 ± 4.64

Antihypertensive consumption showed 17 types of antihypertensive drugs used with the highest used was valsartan with 30 patients or 34.9%, followed by amlodipine with 28 patients or 32.6%, and bisoprolol with 23 patients or 26.7%. Antihypertensive was one of the drugs that have a risk of falling in the elderly because of its side effect in causing hypotension. Drugs that have a postural hypotensive effect need to be recognized as an important factor causing falls [5]. An observational meta-analysis showed a 24% increased risk of falling associated with antihypertensive use [6].

The description of the risk of falls in elderly patients at polyclinic indicated by the average TUGT score 13.1 ± 5.9 seconds showing the elderly in RSUP Sardjito has good mobility. Table 2 showed the average TUGT of elderly in RSUP. Sardjito

Table 2. TUGT of elderly in RSUP.Dr.Sardjito

Classification	Interpretation	N (%)
< 10	Normal	28 (32.6%)
10 – 19	Good Mobility	48 (55.8%)
20 – 29	Problems	8 (9.3%)
≥ 30	Disturbed	2 (2.3%)

A. Correlation of antihypertensive and TUGT Score

Bivariate analysis to determine the correlation between antihypertension in the form of the amount and duration of antihypertensive and TUGT score showed no significant correlation between the amount and duration of drug use.

Table 3. The description of the amount and duration of antihypertensive therapy on the TUG test in the elderly at Dr. Sardjito Yogyakarta

Amount of therapy	N (patients)	Average TUGT (s)
≤ 3	76	13.03 ± 6.08
>3	10	13.31 ± 4.68
Duration of therapy (month)		
0 – 3	3	15.15 ± 9.48
4 – 12	14	11.58 ± 3.20
13 – 24	7	13.77 ± 5.31
>24	62	13.21 ± 6.32

The p-value in the correlation test for the number of antihypertensive therapies and the TUG test score was 0.094 with r (correlation coefficient) 0.181, which means the strength of the correlation was very weak. This was not following previous studies, where Tinetti et al. showed the amount and daily dose of antihypertensive therapy showed a hazard ratio of serious fall injury (hazard ratio (HR)) of 1.4 (95% CI 1.03 – 1.9) in patients with moderate intensity antihypertensive use, and HR 1.28 (95% CI 0.91 – 1.8) in patients with high-intensity antihypertensive use compared to the group without antihypertension [7]. There was a very small difference between the TUGT score and the

amount of antihypertensive therapy, 13.03 seconds for 3 kinds of antihypertensive and 13.31 seconds for more than 3 kinds of antihypertensive. The mean value of the TUGT also showed good mobility (10.19 seconds means good mobility).

The p-value in the correlation test for the duration of therapeutic use is 0.312 with r = 0.110 which means the strength of the correlation was very weak. This was not following the research of Shimbo et al and Butt et al. The risk for serious fall injuries increased for 15 days after administration of antihypertensive drugs (Odd ratio (OR) 1.36; 95% CI 1.19 - 1.55), with the addition of new antihypertensive types (OR 1.16; 95% CI 1, 10 - 1.23), and drug dose titration (OR 1.13; 95% CI 1.08 - 1.18). This correlation is weakened after 15 days of therapy [8]. Butt et al. stated that the risk of increased bone fracture was 43% during the first 45 days (Incidence rate ratio 1.43; 95% CI 1.19 - 1.72) [9]. This was quite relevant in this study where the mean value of the TUG test in the group of patients with short-term antihypertensive duration (0-3 months) was longer than the long-term group of patients, which was 15.15± 9.48 seconds. Some potential mechanisms of increased risk of falling in short-term antihypertensive administration are the high risk of side effects of postural hypotension, which caused neurological effects and changes in balance and gait disturbances. In addition, antihypertensive therapy induces electrolyte changes that cause side effects on the nervous and physical systems of elderly patients [8].

There were 10 patients with TUGT scores above 20 seconds, which means reduced mobility so the risk of falling is quite high. The therapeutic profile of these 10 patients showed in Table 4.

Table 4. Therapeutic profile patients with high risk of fall

No.	Antihypertensive	Anti-hyperglicemia	Drug affect CNS	TUGT
14	Valsartan, Furosemid	-	-	39,93
17	Valsartan, Diltiazem, Bisoprolol	-	-	25,02
20	Valsartan, Diltiazem, Furosemid, Bisoprolol	-	-	20,68
22	Furosemid	-	-	20,31
30	Amlodipin, Furosemid Valsartan	-	-	23,77
46	Furosemid	-	-	26,06
52	Nifedipin, Valsartan	-	-	35,74
69	Valsartan, Terazosin	Metformin, Acarbose	Donepezil	23,24
72	Spironolakton, Amlodipin	-	-	27,84
80	Valsartan, Bisoprolol, Amlodipin, Furosemid	-	-	20,04

Valsartan and furosemide were the most commonly used drugs in the elderly with TUGT scores > 20. Furosemide showed a significant association with increased risk of falls in meta-analytical studies [6], [10]. The risk of falls in patients on loop diuretics is associated with the side effect of diuresis, which allows patients to rush to the bathroom. In addition, diuretics lower blood pressure caused dizziness and the risk of subsequent falls [11]. Another side effect caused by loop diuretics was causing hypokalemia. Many studies measure changes in total body potassium during diuretic therapy with losses of about 250 – 300 mEq.

Some of the serious complications of hypokalemia were arrhythmias, muscle weakness, rhabdomyolysis, sugar intolerance, and several other complications that lead to increased ammonia production, such as protein and nitrogen residues and hepatic coma. The effects of hypokalemia associated with falls include the risk of arrhythmias and muscle weakness. Potassium is a compound needed for muscles to contract. If the muscles weaken due to a lack of potassium levels, the elderly's ability to support the body is reduced, causing balance disorders [12]. A meta-analysis showed loop diuretics increasing significantly the risk of falling in

the elderly, so even though in this study furosemide was not significantly associated with the risk of falling, drug monitoring in the elderly should still be carried out.

Valsartan was an Angiotensin Receptor Blocker (ARB) drug that acts selectively on Angiotensin I receptors, thereby reducing the effects of Angiotensin II. Valsartan showed an increase of 52% in AUC (0 – 24 hours) and 70% in AUC (0 – infinity) in the elderly. For a mean patient age of 70 years, plasma clearance of valsartan was estimated to be reduced by 22% compared to a group average of 55 years [13]. Despite a decrease in plasma clearance and an increase in AUC levels, meta-analysis shows that the association between ARB therapy and the risk of falling was not significantly influenced [10]. This suggests that valsartan is quite well tolerated in elderly patients.

An interesting case was patient 69 that received 3 treatment groups that increase the risk of falling, antihypertensives (valsartan, terazosin), antihyperglycemic agents (metformin, acarbose), and drugs that affect the central nervous system (donepezil). Alpha-blockers (terazosin) were associated with an increased risk of hip and thigh fractures due to falls (aOR 1.9; 95% CI 1.1 – 3.0) [14], [15]. Thus with valsartan, the combination would increase the risk of falling. Meanwhile, the management of type 2 diabetes mellitus with metformin and acarbose. Metformin was recommended as first-line therapy in DM with its mechanism of action in increasing insulin receptor sensitivity. Metformin was not directly associated with an increased risk of falling, but the condition of vitamin B12 deficiency due to metformin consumption can cause neuropathy, indirectly increasing the risk of falling. Approximately 20% of patients treated with metformin have vitamin B12 deficiency. Administration of additional vitamin B12 can reduce the risk of falls in the patient, and in this case, the patient has received vitamin B12 therapy. As for acarbose, which is an alpha-glucosidase inhibitor, it did not show an increased risk of falling acarbose could provide a protective effect. A study showed acarbose decreased postprandial hypotension, whereas postprandial hypotension predisposes to fainting leading to falls [16], [17]. Donepezil is an AcetylCholinesterase Inhibitor (ChEIs) that works in a reversible and non-competitive inhibiting central acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine, thereby increasing the concentration of acetylcholine in synapse transmission in the CNS. Meta-analysis showed that ChEIs were associated with a greater risk of fainting (OR 1.53; 95% CI 1.02 – 2.30), but were not associated with falls, fractures, and accidental injuries [18]. Exposure related to these drugs shows that the use of drugs that have a high risk of falling can increase the risk of falling in elderly patients. Administration of 5 to more drugs was significantly associated with an increased risk of falls in elderly outpatients (OR 4.5; 95% CL 1.7 – 12.2) after adjusting for potential confounding variables. Outpatients can experience a 14% increase in the risk of falling on the addition of drugs over 4 drug regimens (OR 1.14; CI 1.02 – 1.27; p = 0.027) [19]. Although in this study, pharmacological therapy did not significantly affect the risk of falling, but individually in therapy for elderly patients there is a risk of falling that needs to be considered and monitored.

B. Correlation of Confounding Variables and TUGT score

Bivariate analysis was also conducted on confounding variables including age, gender, body mass index, blood pressure, history of falls, living alone at home, comorbid diseases, and other drug therapies. Age, gender, history of falls, and comorbid dis-

ease showed p <0.05 to the TUG test in bivariate analysis. This showed a significant correlation between age (p: 0,000), gender (p: 0,037), history of falls (p: 0,004), and comorbid disease (p: 0,001). Multivariate analysis with multiple linear regression performed to see the effect of antihypertension (amount and duration) on the TUGT with the presence of confounding variables shows that only the age and gender entered the regression model with a correlation strength value of 0.622 indicating that age and gender have a strong correlation in influencing the TUGT.

Table 5. Correlation of counfounding variables and TUGT

Variable	TUGT
	p value
Age	0.000*
Body mass index	0.096
Comorbid	0.001*
Sistolic	0.196
Diastolic	0.298
Gender	0.037*
History of fall	0.004*
Living alone	0.259
Other drug therapies	0.127

* = Significant (p value < 0.05)

This was a match with previous studies where the incidence of falls increased significantly with increasing age (Chi2 = 101.42; df = 43, p <0.001) [20], [21]. Progressive loss of balance and changes in muscle and bone mass, which is the process of aging was the cause of the high risk of falling with age. Gender influences the TUGT score according to previous studies which stated that the risk of falling in women increased by two times from men (95% CI 1.40 – 2.92) [22]. Women were more risker than men because of the low amount of body mass and muscle strength compared to men. According to Foldvari et al, women lose muscle strength earlier than men [23].

Of the two variables, the variable most related to the risk of falling is age with a Beta value of 0.564. The final model in the multivariate analysis with the TUG dependent variable is:

$$Y = -25{,}440 + (0{,}497 \times X_1) + (3{,}594 \times X_2)$$

*Y = risk of fall, X1 = age, X2 = gender

Based on the line equation model, the meaning of the coefficient B for each variable is:

1. For every additional 1 year of age, a required time to complete a fall risk test (TUGT) will increase by 0.497 seconds after controlling the gender variable (X2 = 0)
2. If the gender of the elderly is female, then the time needed to complete the fall risk test (TUGT) will increase by 3.594 seconds after controlling for age variable (X1 = 0)

Conclusions from the results of multivariate analysis with the dependent variable TUG is the risk of falling will increase as age increases and gender is female. The risk of falling will be lower at the younger age and the male gender

4. CONCLUSION

Antihypertensive therapy did not have a significant correlation to timed-up-and-go-test (TUGT) as a fall risk approach in elderly. Although this study has not shown that antihypertensive therapy could increase the risk of falling in elderly patients, practitioners should consider deprescribing (the process of reducing, discontinuing, or withdrawing drugs, to manage polypharmacy and improve the patient's clinical condition) and considering the benefits and risks of each drug administration to the elderly. Further research is needed to determine the effect of antihypertensive therapy in increasing

the risk of falling in the elderly with a larger sample of patients and a more balanced therapy group so that data will be better distributed and better results can be obtained.

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