Clinical Research

Are hypertension and the using of amlodipin increase the risk of Parkinson's disease?

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative in central nervous system, characterized by tremor, rigidity, akynesia, and postural instability. Previous studies showed hypertension and certain drug, such as amlodipin, increasing PD risk. But the results from previous studies are conflicting. **Objective**: This study aimed to measure the risk of PD related to hypertension and use of amlodipin. **Method**: This study is a case control study. The case group were 59 PD patients and the control group were 118 patients without PD at Bethesda Hospital, matched by age and gender. Each subject on both group were agree to be interviewed and signed the informed consent form. Supplementary data obtained from medical record. The data were analyzed using chi square test and fisher test, continued by multivariate analysis using logistic regression analysis. **Results**: The subjects were dominated by male (50.8%) and >60 years old (87.7%). The proportion of hypertension in PD group is 35 subjects. The proportion of hypertension in control group is 84 subjects. This study showed that hypertension did not increase the risk of PD (p: 0.113). The most common prescribed antihypertensive drug was amlodipine 5 mg. Most of subjects using amlodipin alone rather than combination (66.2% vs 2.6%) and have been using amlodipin for ≥2.5 years. Bivariate analysis showed that among patients with hypertension, the use of amlodipin does not increase the risk of PD (p: 0.733). **Conclusion**: The results of this study showed that hypertension and the using of amlodipin do not increase the risk of PD.

Keyword**:** Parkinson, hypertension, amlodipin, anti hypertensive drug

Introduction

Parkinson's Disease (PD) is a neurodegenerative disease and considered as a movement disorder (Biaggioni, 2007). PD characterized by loss of dopaminergic neurons in the central nervous system, most notably in the basal ganglia and substantia nigra (Gallo and Garber, 2011). PD's main symptoms are tremor, bradykinesia, rigidity and postural instability (Jankovic, 2008). The inability of cells to regulate Ca^{2+} is one of pathological mechanism in PD (Zaichick et al., 2017). Understanding the mechanisms by which Ca^{2+} signaling contributes to the progression of this disease will be crucial for the development of effective therapies and to slow PD progression (Rios et al., 2014).

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PD is affecting approximately 7 to 10 million people around the world, according to the Parkinson's Disease Foundation (Pringsheim et al., 2014). The prevalence rate of PD in European countries is estimated from 65.6 per 100 000 to 12500 per 100 000, and the incidence from 5 per 100 000 to 346 per 100 000. In Asian countries, the crude prevalence rates seem to be lower and range from 15 per 100 000 to 328 per 100 000 (Chen and Tsai, 2010). Indonesia's death rate caused by PD was in the 5th place in Asia or the 12th in worldwide (Noviani, 2010).

Blood pressure (BP) abnormalities have been known in PD patients (Tsukamoto et al., 2013). Previous study did not support an association between hypertension (HT) and PD and the risk of PD seems to be lower in hypertensive than in normotensive subjects (Mazza et al., 2013). Calcium channel blockers (CCB) is frequently used for treatment of HT and there was a report of drug induce parkinsonism caused by CCB (Pinzon and Adnyana, 2015). Some studies stated CCB decrease the PD risk (Biglan and Simuni, 2014).

But the results from previous studies are conflicting. This study aimed to measure the risk of PD related to hypertension and use of CCB.

Materials and method

Study design

This study was a case control study matched by gender and age (±5 years). The case subjects were PD patients and the control subjects were non PD patients at Bethesda Hospital, Yogyakarta, Indonesia. The information were obtained from interview after given an informed consent. Other data were collected from subjects' medical record.

Subjects and sampling method

The inclusion criteria of case subjects i.e.: (i) have a PD, (ii) agreed to be interviewed, and (iii) signed the informed consent form. The inclusion criteria of control subjects i.e.: (i) have not a PD, (ii) agree to be interviewed, and (iii) signed the informed consent form. The exclusion criteria of case and control subjects were incomplete data. This study was using consecutive sampling method. All subjects matched the inclusion criteria would be taken until reach the desired number.

Measurement

The interview was conducted based on previous research entitled Association of Blood Pressure and Hypertension With the Risk of Parkinson Disease: The National FINRISK Study. The data obtained from interview and medical record include: age, gender, family history of PD, HT, type 2 diabetes mellitus (DM), hypercholesterolemia, alcohol consumtion, coffee consumtion, tea consumtion, smoking, exercise, antihypertensive medication, and head trauma history.

Age differed into 2 groups: > 60 years and ≤ 60 years. Family history of PD defined as subjects who had PD on first degree relative(s), thus classified into subjects with family history of PD and subjects without family history of PD. HT defined as subjects with systolic blood pressure ≥ 140 mmHg diastolic blood pressure ≥ 90 mmHg, and/or consuming antihypertensive drug. DM defined as subjects with fasting plasma glucose ≥ 126 mg/dL, 2 hours plasma glucose ≥ 200 mg/dL during oral glucose tolerance test, random plasma glucose ≥200 mg/dL with classic symptoms of hyperglycemia, A1C ≥6.5%, consuming antidiabetic drugs, and/or using insulin. Hypercholesterolemia defined as subjects with total cholesterol level > 200 mg/dL and/or consuming lipid lowering drug.

Alcohol consumtion defined as subjects with regular consumtion of alcohol, thus differed into subjects with regular alcohol consumtion and subjects without regular alcohol consumtion. Coffee consumtion classified into 3 groups: (i) no regular coffee consumtion, (ii) 2 cups per day, and (iii) 3-4 cups per day. Tea consumtion classified into 3 groups: (i) no regular tea consumtion, (ii) 1-2 cup(s) per day, and (iii) ≥ 3 cups per day. Smoking classified into 4 groups: (i) no regular smoking, (ii) 1-9 cigarette(s) per day, (iii) 10-19 cigarettes per day, and (iv) ≥ 20 cigarettes per day. Exercise classified into 4 groups: (i) no regular exercise, (ii) 1-2 time(s) per week, (iii) 3-4 times er week and (iv) ≥ 5 times per week. Head trauma history defined as any repetitive trauma on head, or any trauma on head which is causing decrease/loss of consciousness and/or hospitalization.

Antihypertensive medication differed into subjects with CCB medication and subjects without CCB medications. CCB medication assesed in this study include amlodipin and nifedipin. Subjects with amlodipin medication further differed into subjects with amlodipin medication only and subjects with amlodipin combination with other antihypertensive drug(s). Duration of amlodipin medication classified into < 2.5 years and ≥ 2.5 years. There were 2 amlodipin dosage measure in this study: 5 mg and 10 mg.

Statistical analysis

All of data were analyzed by using SPSS programme. Univariate analysis was performed to identify subjects characteristics. Chi square test and fisher test as bivariate analysis was conducted to analyse factor(s) contributing to PD. A logistic regression analysis was performed to determine the independent factor(s) increasing risk of PD. Statistical significance was set at $p < 0.05$.

Ethical clearance

This study was verified by Duta Wacana Christian University Ethical Research Committee. The number of ethical clearance was 252/C.16/FK/2016.

Results

There were total 177 subjects consist of 59 case subjects and 118 control subjects. Subjects were dominated by male (50.8%) and age > 60 years (87%). Most of subjects had not a family history of PD (91%). Only 20.9% subjects with DM and 38.4% with hypercholesterolemia (Table 1). Four percent of subjects consume alcohol, 26% consume coffee, 75.7% consume tea, 4.6% smoking, and 55.9% doing an exercise regularly. As much as 71.2% subjects had not a head trauma.

Most of subjects had a hypertension (67.2%) and was using CCB (63.2%) as their antihypertensive drug, especially amlodipin (93.1%). More than half of subjects have been using amlodipin for ≥ 2.5 years. Table 2 showed the detail of subjects' antihypertensive medication.

Bivariate analysis was performed to identify

Table 1. Subjects' Characteristics

Characteristics	n (%)		Total (%)
	Parkinson	Without Parkinson	
Age			
- ≤ 60 years	6 (10.2)	17 (14.4)	23 (13.0)
- > 60 years	53 (89.8)	101 (85.6)	154 (87.0)
Gender			
- Male	30 (50.8)	60 (50.8)	90 (50.8)
- Female	29 (49.2)	58 (49.2)	87 (49.2)
Family History of PD			
- Yes	10 (5.6)	6 (5.1)	16 (9.0)
- No	49 (27.7)	112 (94.9)	161 (91.0)
DM			
- Yes	4 (6.8)	33 (28.0)	37 (20.9)
- No	55 (93.2)	85 (72.0)	140 (79.1)
Hypercholesterolemia			
- Yes	24 (40.7)	44 (37.3)	68 (38.4)
- No	35 (59.3)	74 (62.7)	109 (61.6)
Alcohol Consumtion			
- Yes	6 (10.2)	1 (0.9)	7 (4.0)
- No	53 (89.8)	117 (99.1)	170 (96.0)
Coffee Consumtion (per day)	40 (67.8)	91 (77.1)	131 (74.0)
- No	17 (28.8)	26 (22.0)	43 (24.3)
- 2 cups	2 (3.4)	1 (0.9)	3 (1.7)
- 3-4 cups			
Tea Consumtion (per day)			
- No	11 (18.6)	32 (27.1)	43 (24.3)
- 1-2 cup(s)	42 (71.2)	73 (61.9)	115 (65.0)
- ≥3 cups	6 (10.2)	13 (11)	19 (10.7)
Smoking (per day)			
- No	55 (93.2)	114 (96.6)	169 (95.5)
- 1-9 Cigarette(s)	2 (3.4)	2 (1.6)	4 (2.3)
- 10-19 Cigarettes	2 (3.4)	1 (0.9)	3 (1.7)
- ≥ 20 Cigarettes	0	1 (0.9)	1 (0.6)
Exercise (per week)			
- No	30 (50.8)	48 (40.7)	78 (44.1)
- 1-2 time(s)	5 (8.5)	18 (15.2)	23 (13.0)
- 3-4 times	6 (10.2)	8 (6.8)	14 (7.9)
- ≥5 times	18 (30.5)	44 (37.3)	62 (35.0)
Head Trauma History			
- Yes	22 (37.3)	29 (24.6)	51 (28.8)
- No	37 (62.7)	89 (75.4)	126 (71.2)

PD: Parkinson's Disease; DM: Type 2 Diabetes Mellitus

Table 2. Hypertension and Antihypertensive Drugs

Characteristics	n (%)		Total (%)
	Parkinson	Without Parkinson	
Hypertension			
- Yes	35 (59.3)	84 (71.2)	119 (67.2)
- No	24 (40.7)	34 (28.8)	58 (32.8)
Antihypertensive Drug			
- Non CCB	11 (34.4)	31 (37.8)	42 (36.8)
- CCB	21 (65.6)	51 (62.2)	72 (63.2)
Amlodipin Drug			
- Amlodipin	21 (65.6)	51 (62.2)	72 (63.2)
- Amlodipin+Combination	3 (14.3)	2 (3.9)	5 (6.9)
Duration Using Amlodipin			
- < 2.5 years	9 (42.9)	25 (49.0)	34 (47.2)
- ≥ 2.5 years	12 (57.1)	26 (51.0)	38 (52.8)
Amlodipin Dosage			
- 5 mg	11 (52.4)	34 (66.7)	45 (62.5)
- 10 mg	7 (33.3)	15 (29.4)	22 (30.6)
Nifedipin Dosage			
- 5 mg	0	0	0
- 10 mg	3 (14.3)	2 (3.9)	5 (6.9)

CCB: Calcium Channel Blocker

significant factor(s) increasing risk of PD. Family history of PD (p: 0.009), DM (p: 0.001), and alcohol consumtion (p: 0.006) were significant increasing the risk of PD. Bivariate analysis was continued by multivariate analysis (Table 3).

Multivariate analysis was made based on the result of bivariate analysis. Multivariate analysis showed alcohol consumtion and family history of PD were significant increasing risk of PD (Table 4). Alcohol consumtion increasing risk of PD by 15.744 times, whereas family history of PD increasing risk of PD by 3.450 times.

Table 3. Bivariate Analysis

Characteristics	p	OR (95% CI)
Age ≤ 60 years	0.429	-
Male	1.000	-
Family History of PD	0.009	3.810 (1.311-11.066)
DM	0.001	0.187 (0.063-0.558)
Hypercholesterolemia	0.662	-
Alcohol Consumtion	0.006*	13.245 (1.556-112.773)
Coffee Consumtion: 2 cups per day	0.196	-
Tea Consumtion: 1-2 cup(s) per day	0.424	-
Smoking: 1-9 cigarette(s) per day	0.479	-
Exercise: 1-2 times per week	0.333	-
Head Trauma	0.078	-
Hypertension	0.113	-
Antihypertension drug: amlodipin	0.733	-
Antihypertension drug: amlodipin + combination	0.172*	-
Duration of using CCB: < 2.5 years	0.634	-
Amlodipin dosage: 10 mg	0.523	-

PD: Parkinson's Disease; DM: Type 2 Diabetes Mellitus; CCB: Calcium Channel Blocker; *Fisher Test

Table 4. Multivariate Analysis

Characteristics	p	OR (95% CI)
Family History of PD	0.031	3.450 (1.118-10.644)
DM	0.006	0.194 (0.060-0.623)
Alcohol Consumtion	0.019	15.744 (1.579-157.004)

PD: Parkinson's Disease; DM: Type 2 Diabetes Mellitus

Discussion

Most of subjects in this study had a hypertension (67.2%). This results is parallel to previous study. PD is characterized by peculiar blood pressure (BP) abnormalities. Vetrano et al. (2017) stated the prevalence of hypertension was 60% according to office and 69% according to ambulatory BP measurements (p <0.001). In the PRIAMO (Parkinson Disease Non-Motor Symptoms) study conducted in Italy, HT was the most frequently reported concomitant, non-neurological disorder (Barone et al., 2009).

Further analysis in this study showed HT did not increasing PD risk (p: 0.113). Simon et al. conclude the same statement. There was no association between HT and PD (Simon et al, 2007). PD risk was not significantly related to history of HT (RR: 0.96; 95% CI: 0.80-1.15) (Zhang and Tian, 2011). Research on 59 540 subjects showed there was no significant association between blood pressure and PD

risk in men (Qiu et al., 2011).

Most previous studies found CCB have a protective effect to PD or decreasing PD risk. The long term use of CCB has shown a significant reduction in risk of PD (Mullapudi et al., 2016). The pooled estimate of 7 studies on the association between use of CCBs and PD showed a significant reduction in the risk of PD in the users of CCBs (RR 0.82, 95% CI 0.71–0.93) (Mullapudi et al. [2], 2016). Lee et al. (2014) suggest there is a benefit by using dihydrophyridine CCB to PD.

Dopaminergic neuron in substansia nigra have L-type Ca^{2+} channels in the surface. Dysregulation of L-type Ca^{2+} channels known as one of pathology process in PD. Continuous Ca^{2+} influx via L-type Ca^{2+} channels into the dopaminergic neurons of substantia nigra may facilitate a downstream cascade of events leading to the cell death and the progressive degeneration of PD (Belardetti and Zamponi, 2012). The Ca^{2+} intracellular level > 10.4 mol/L may blocked dopamine release, which is disturbance on dopamine release and/or production causing PD (Satyanegara, 2010). Target effect of dihydrophiridine CCB is on L-type Ca^{2+} channels. Amlodipin is one of dihydrophiridine CCB that pass the blood brain barier. By these mechanism, the using of CCB, especially dihydrophiridine CCB, reduce the PD risk and PD progression. The mechanism of lowering risk of PD was though by potential neuroprotective effect of CCB, not by lowering BP (Ritz et al., 2010; Gudala et al., 2015).

Another studies showed an different results, as stated by Ascherio and Schwarzchild (2016) the use of dihydropyridine CCB was associated with reduced PD risk in some but not all studies (. Current study conclude the using of CCB (p: 0.733) and CCB combination (p: 0.172) did not increasing or decreasing PD risk. The duration of CCB medication was not correlate to PD risk (p: 0.634). The using of amlodipin, did not significant influencing PD risk (p: 0.523). These results are similar to previous study. Ton et al. (2007) stated there was no correlation between CCB medication and PD risk. Amlodipine prescription drug use was not associated with risk of PD (Ritz et al., 2010)

Current study showed family history of PD and alcohol consumtion were increasing the risk of PD. Family history of PD increasing risk of PD by 3.450 times (95% CI: 1.118-10.644, p: 0.031). This result is parallel to some previous studies stated a family history of PD related to a higher risk of PD. Genetic studies of the glucocerebrosidase, parkin, and LRRK2 genes have contributed to our understanding of familial PD (Chen and Tsai, 2010). Wells (2009) mentioned family history of PD significantly increasing risk of PD 8.8 times on age < 70 year and 2.8 times on age > 70 year (Wells et al., 2009). Compared with never smokers with no family history of PD, never smokers who did have a family history had an OR of 2.81 (95% CI: 1.91-4.13) and for smokers with a family history, the OR was 1.60 (95% CI: 1.15-2.23) (Kenborg et al., 2015).

This study found alcohol consumtion was increasing risk of PD by 15.744 times (95% CI: 1.579-157.004, p: 0.019). This result is consistent to previous studies. Sipetic et al. (2012) stated alcohol consumtion increasing PD risk significantly (OR: 4.78, 95% CI:2.67-8.55). Inversely, research on 214 cases within 6 years of PD onset and 327 controls without neurodegenerative disease did not find any significant interactions between alcohol drinking (Fukushima et al., 2010). There are some possibilities causing the different result i.e.: this study did not measure the amount of alcohol daily intake percisely. Subjects' bias also considered as an important factor of this differences.

This study found age ≤ 60 years was not significant increasing PD risk (p: 0.429). This results is reasonable because increasing age has been found to be the most consistent risk factor for the development of PD (Tan, 2013). A research in Italian population by Pupillo et al. (2016) reported older age, but not younger age, was associated with increased PD risk. Young onset Parkinson's disease (<50 years) is more likely to be genetic than older onset Parkinson's disease, particularly with a positive family history, and there are also racial differences (Malek et al., 2013). In old age, the dopaminergic neurons seem increasingly rely on L-type calcium channels for their activation and so were more vulnerable to neurologic damage (Chan et al., 2007). Bivariate analysis on gender showed the p value was 1.000. Thus, there is no association between gender and PD risk. This statement is same to study by Taylor et al. (2007) reported no gender differences on PD prevalence.

DM was found to be a protective factor to PD in this study (OR: 0.194, 95% CI: 0.060-0.623, p: 0.006). Study by Driver et al. (2008) did not suggest that diabetes is a preceding risk factor for PD. Previous case control studies stated the association between DM and PD risk was not significant (OR: 0.75, 95% CI: 0.50–1.11; p: 0.835) (Cereda et al., 2011). Lu et al. (2014) reported a decrease of PD risk among DM subjects (OR: 0.75, 95% CI: 0.58–0.98).

Other study showed a different result. PD among subjects with DM, compared with those without it, were 1.80 (95% CI 1.03–3.15) in men, 1.93 (1.05–3.53) in women, and 1.85 (1.23–2.80) in men and women combined (adjusted also for sex) (Hu et al., 2007). Current study did not make a differentiation between DM after PD onset or DM before PD onset and may lead to different result.

Hypercholesterolemia was not significant increasing risk of PD in the present study (p: 0.662). Previous case control study including 124 PD cases and 112 controls had

the same result, serum total cholesterol did not differ significantly between PD patients and controls (Huang et al., 2007). A large retrospective case-control study did not find any association between serum total cholesterol and the occurrence of idiopathic PD (Hu, 2010).

On the contrary, the secondary analysis of the DATATOP trial provides preliminary evidence that higher total serum cholesterol concentrations may be associated with a modest slower clinical progression of PD (Huang et al., 2011). Present study only asked the subjects about their history of hypercholesterolemia and/or look at their medical record, but did not measure the actual total cholesterol level when the study conducted. This study also did not differentiate between hypercholesterolemia before or after PD onset. It may be the caused of the difference of the result.

Current study stated coffee consumtion (p: 0.196) and tea consumtion (p: 0.424) were not significant increasing or decreasing PD risk. These results is contrary to many previous studies. Coffee and tea consumtion found to be a protective factors of PD. Tanaka et al. (2011) stated the intake of coffee and caffeine reduced the risk of PD. Coffee and black tea, but not green tea, seemed to be protective to PD (Gaba, 2015). A meta-analysis by Li et al. (2012) showed tea drinking can lower the risk of PD, the pooled OR (95% CI) was 0.85 (0.74–0.98), which suggests the protective effect of tea drinking in PD risks. The differences between current study to previous study differences may be caused by several reasons. This study did not differentiate the type of coffee (decaffeinated coffee and caffeinated coffee) and tea (black tea and green tea).

Animal studies indicate that caffeine is neuroprotective. The administration of caffeine to maneb- and paraquat-treated rodents reduced the number of degenerating dopaminergic neurons (Kachroo et al., 2010; Yadav et al., 2012). Genetic and pharmacological data from rodent studies indicate that caffeine reduces dopaminergic toxicity and slows disease progression (Xiao et al., 2011; Sonsalla et al., 2012). Polyphenols in green and black tea extracts provide a highly potent antioxidant-radical activities in brain mitochondrial membrane fractions (Zhao, 2009). Polyphenols in tea reduce occurrence of disease and provide neuroprotection in cell culture and animal models (Seidl et al., 2014).

Smoking was not increasing or decreasing risk of PD significantly (p: 0.479). Many previous studies conclude smoking as a protective factor or decreasing risk of PD. Ritz et al. (2007) stated a dose-dependent reduction of PD risk associated with cigarette smoking. A matched case-control study on 92 individuals with PD and 184 people without PD found that individuals with PD are significantly less likely to have smoked regularly than those without PD (Masoud, 2008). Stratified analyses indicated that smoking duration was associated with lower PD risk within fixed intensities of smoking. Compared with never smokers, the ORs among past smokers who smoked > 20 cigarettes/day were 0.96 for 1 - 9 years of smoking, 0.78 for 10-19 years, 0.64 for 20-29 years, and 0.59 for 30 years or more (p for trend: 0.001) (Chen et al., 2011). The possibilities reasons of these differences i.e.: current study did not measure the duration of smoking.

Nicotine has long been considered as a possible therapeutic agent for PD (Quik et al., 2008). Cigarette smoke has been shown to inhibit monoamine oxidase (MAO) activity, which is MAO is known to breakdown dopamine. Several studies also suggest that nicotine stimulates dopamine release (Miller and Das, 2007).

Exercise was not correlate to PD risk (p: 0.333). Past study showed an inverse result. The risk of developing PD appeared to be inversely associated with the amount of exercise practiced throughout life (OR: 0.65, 95% CI: 0.51–0.83, p <0.0001). People who practice physical exercise during these two periods of their life have a 40% lower risk of PD than people who remained inactive during the same periods (Xu et al., 2010). PD risk in late adult life was strongly inversely associated with physical exercise during high school and college or at age 35-39 years (Ascherio and Schwarzchild, 2016). Research by Yang, et al. (2015) found that a medium level of daily total physical activity is associated with a lower risk of PD, especially in males. Current study did not measure the duration of exercise and years of physically active. It may be the reason of the different results.

Exercise could potentially influence endogenous production and release of dopamine in patients with PD, leading to enhanced dopaminergic neurotransmission. Exercise could also postpone the onset of parkinsonism (Speelman et al., 2011). Exercise limits the alteration in dopaminergic neurons in the substantia nigra and contributes to optimal functioning of the basal ganglia involved in motor commands and control by adaptive mechanisms involving dopamine and glutamate neurotransmission. In response to exercise, the concentration of dopamine increases and the receptors of this neurotransmitter enhance their sensitivity (Paillard et al., 2015).

History of head trauma did not correlate to PD risk in present study (p: 0.078). This result is parallel to research by Kenborg et al. (2015) stated examination of number of head injuries or hospitalization for a head injury did not show an association with PD. For 954 study subjects with at least one

head injury, there was no evidence of an association between loss of consciousness, duration of loss of consciousness, or amnesia and risk for PD. Another studies by Lee et al. (2012) and Jafari et al. (2013) suggested a different results. In logistic regression analyses, we observed a 2-fold increase in risk of PD for subjects who reported a traumatic brain injury (Lee et al., 2012). The pooled OR for the association of PD and head trauma was 1.57 (95% CI: 1.35-1.83) (Jafari et al., 2013).

Conclusion

Hypertension and amlodipin do not increase the risk of PD. Family history of PD and alcohol consumtion are increasing risk of PD, whereas DM is a protective factor of PD.

Conflicts of Interests

All authors have none to declare.

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