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Selected Benefits of Pentoxifylline in Acute Ischemic Stroke Management: Consideration of Risk Factors

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ABSTRACT

Backgroun**d: The role of pentoxifylline in acute ischemic stroke lacks objective markers of its efficacy. In this study, we used blood viscosity as a specific marker to evaluate the efficacy of pentoxifylline.* ***Objectives: *This quasi-experimental study aimed to analyze pentoxifylline as an antihemorrheologic agent in acute ischemic stroke patients with certain risk factors, including age, smoking, hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease.* ***Method:*** *There were 22 acute ischemic stroke patients with blood hyper viscosity within 72 hours of onset who received pentoxifylline 1.200 mg/day for five days and continued with oral dose 400 mg twice daily for the next twenty-three days. All subjects received the standard treatment for acute ischemic stroke. The risk factors of stroke were recorded including smoking, hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease.* ***Results:*** *The median of baseline blood viscosity was 6.46 poise (5.20-9.73). The blood viscosity at the seventh and thirtieth day tend to decrease. The mean decrement blood viscosity level was statistically significant in smoking (p=0.009) and dyslipidemia (p=0.006) subjects. Clinical outcomes were assessed using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS), and Barthel Index (BI). All subjects had good functional outcome and statistically significant for those who had diabetes mellitus and heart disease.* ***Conclusion:*** *Pentoxifylline is beneficial for acute ischemic stroke patients with risk factors of smoking, dyslipidemia, diabetes mellitus, and heart disease.*
Keywords: blood hyper viscosity; ischemic stroke; risk factor; pentoxifylline

INTRODUCTION

The Indonesian National Health Survey (RISKESDAS) stated that stroke is the leading cause of death among the non-communicable diseases and accounted for 14.5% of deaths. The incidence of stroke increased significantly from 8.3‰ in 2007 to 12.1‰ in 2013 (Departemen Kesehatan RI, 2008; Kementrian Kesehatan RI, 2013). In 2014, 384 stroke cases were admitted to the Department of Neurology, Cipto Mangunkusumo Hospital (RSCM), Jakarta and 71.4% was ischemic stroke. The number of deaths caused by ischemic stroke during that year was 11.3% (Fadhli, Meisadona, Kurniawan, & Mesiano, 2015). Where as in the United States, it is estimated that 6.6 million people over 20 years old suffers from stroke. Every year, it is expected that 795,000 people across the world have a new or recurrent stroke (Mozzafarian et al., 2015). Stroke is the leading cause of serious long-term disability and reduces mobility in more than half of stroke survivors age 65 and over.

Ischemic stroke is defined as a temporary or permanent disturbance in the circulation of the brain, spinal cord, and retina because of occlusion (Sacco et al., 2013). On the obstructed vessel, a core ischemic zone is formed surrounded by the ischemic penumbra, an area that can still be saved by restoring blood flow to that particular area (Caplan, 2009). In a study conducted by Ott et al., hyper viscosity was found in 40% of acute ischemic stroke patients (Ott, Fazekas, Tschinkel, Bertha, & Lechner, 1983). Blood viscosity, one of the parameters used to determine peripheral resistance, plays an important role in determining the cerebral perfusion pressure and cerebral blood flow (Caplan, 2009). A hyper viscosity state in the ischemic penumbra can cause a decerease in blood flow to that area and lead to an infarction (Rasyid, 2014).

Only about 10% of acute ischemic stroke patients were able to benefit from thrombolysis therapy because of the narrow time window needed for the treatment to succeed. The other 90% of patients had to benefit from other replacement therapies to save the penumbra from infarction. Until recently, potential therapies have been developed to overcome this limitation, such as anti-platelets, anti-leucocytes, vasodilators, and neuroprotective agents. By giving optimal treatment during acute phase, we hope to reduce the number of morbidity caused by stroke (Jauch et al., 2013). Pentoxifylline is a hemoreologic agent. Its mechanism of action is improving microcirculatory flow and tissue oxygenation by increasing the deformability of erythrocytes by increasing adenosine triphosphate (ATP) content, inhibiting platelet aggregation and reducing plasma fibrinogen concentrations. These effects of pentoxifylline may contribute to the reduction of whole blood viscosity (Hsu et al., 1988).

Risk factors for ischemic stroke can be divided into two categories, which are non-modifiable and modifiable risk factors. Non-modifiable risk factors include age, gender, race, ethnicity, and hereditary, whereas modifiable risk factors include hypertension, cardiac disease, diabetes, dyslipidemia, cigarette smoking, alcohol, illicit drug use, other lifestyle factors (obesity, physical activity and diet), migraine, hemostatic, and inflammatory factors, homocysteine, asymptomatic carotid stenosis and transient ischemic attacks (Sacco et al., 1997). In this study, we analyzed the efficacy of pentoxifylline in stroke patients with certain risk factors, including age, smoking, hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease, by evaluating functional outcome using National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS) and Barthel Index (BI) as well as a change in blood viscosity after treatment.

METHOD

This was a quasi-experimental study of acute ischemic stroke patients with blood hyper viscosity. A total of 22 consecutive subjects were enrolled from September 1st, 2016 until June 31st, 2017. All subjects underwent standard clinical examination and had brain computed tomography (CT) imaging without contrast at admission. The clinical examination was assessed by the doctor on duty at the emergency room or at the ward.

Our inclusion criteria were age 18-80 years old, ischemic stroke with onset within 72 hours, and evidence of blood hyper viscosity. If patients had signs and symptoms of total anterior cerebral infarction (TACI) or posterior circulation infarction (POCI), received thrombolysis therapy or other hemoreologic drugs, had chronic kidney disease stage 4 or 5, and had dehydration, they were excluded from the study.

All subjects willing to participate in this study were hospitalized during acute phase stroke and were given the acute stroke standard treatment, including antithrombotic agent (antiplatelet or anticoagulant), atorvastatin, and other drugs that were adjusted to their risk factors or conditions (hypertension and/ or diabetes). Pentoxifylline was given as an add-

on therapy. Intravenous pentoxifylline 1,200 mg per day was administered in 5 days and followed by oral pentoxifylline 400 mg twice daily for the next 23 days. They also received standard hematologic laboratory examination.

The blood viscosity was examined with digital microcapillary instrument by Rasyid (2014) at admission, day 7, and day 30. Neurological deficits were assessed using the NIHSS at day of admission and day 30. The mRS score and Barthel Index were used to assess disability and functional outcome.

Risk factor definitions were defined as followed. Hypertension was present if systemic blood pressure is elevated above 140 mmHg and or diastolic blood pressure above 90 mmHg for at least 1 week before stroke onset, or is currently consuming anti-hypertensive medication. Diabetes mellitus diagnosis was in accordance to American Diabetes Association (ADA) definition where at least two random glucose tests showed above 200 mg/dL or fasting blood glucose was above 126 mg/dL. Dyslipidemia was present if total serum cholesterol was above 200 mg/dL or triglycerides (TGs) serum was above 150 mg/dL, or low-density lipoprotein (LDL) was above 130 mg/dL or high-density lipoprotein (HDL) below 40 mg/dL or currently taking statin medication. Smoking and ischemic heart disease was assessed during history taking and electrocardiography (ECG) recording.

All data were inputted and analyzed using SPSS software version 20.0 for Macintosh. Subject characteristics and blood profiles were shown with mean and standard deviation if normally distributed or mean and range if not so. Mean difference of blood viscocity value after intravenous and oral pentoxifylline treatment, NIHSS, mRS, and Barthel Index improvement were compared among associated risk factors with Student t-test if they were normally distributed or otherwise Mann-Whitney test.

The study protocol adhered to the Declaration of Helsinki and was approved by the Health Research Ethics Committee - University of Indonesia and Cipto Mangunkusumo Hospital (HREC-FMUI/CMH). All subjects or their family gave written informed consent. The subject's identity will be kept as confidential

RESULTS AND DISCUSSION

There were 22 subjects that met criteria for this study. Two subjects did not come back for blood viscosity evaluation test at day 30 but the clinical outcome (mRS and BI) still could be assessed by phone. Four subjects did not complete the study protocol after they were discharged out of hospital (Fig 1). In this study, we used the intention to treat analysis method so that all the subjects that had already received pentoxifylline were still analyzed.

Baseline Characteristics

The median age of our subjects were 55 years with the range between 36 to 64 years old. Eighteen subjects (82%) were above 45 years old and 4 subjects (18%) were 45 years old or younger. There were more males than females, 14 subjects (64%) were male and 8 subjects (36%) were female. Based on stroke risk factors, hypertension is the most common risk factor (82%), followed by smoking (73%), dyslipidemia (45%), diabetes mellitus (41%) and heart disease (23%). The most common risk factors of stroke from our study was consistent with the Indonesian National Health Survey that was hypertension (Kementerian Kesehatan RI, 2013). In our data, the incidence of stroke also increased with age.

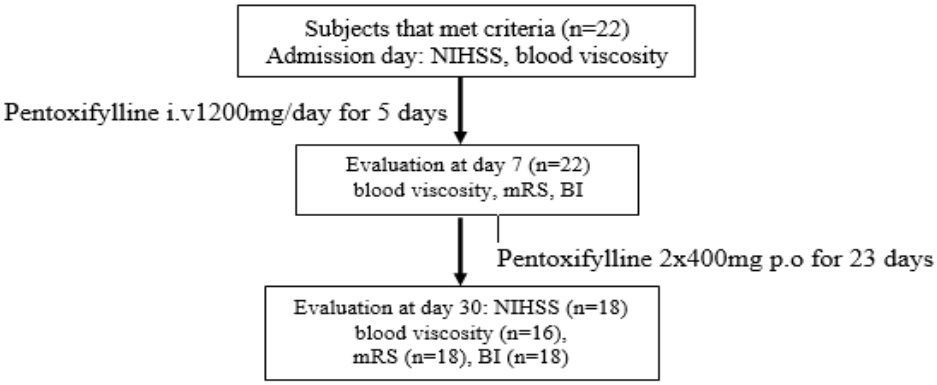

Fig 1. Flow diagram of patients participating in this study

Table 1 Baseline characteristics of the subjects

Variable	Subjects (n=22)
Demographic Variables	
Age	55 (36-64)
Age Groups	
- ≤45 years old	4(18%)
- >45 years old	18(82%)
Gender	
- Male	14(64%)
- Female	8(36%)
Smoking	
-Yes	16(73%)
-No	6(27%)
Clinical Variables	
Hypertension	
- Yes	18(82%)
- No	4(18%)
Diabetes Mellitus	
- Yes	9(41%)
- No	13(59%)
Heart Disease	
- Yes	5(23%)
- No	17(77%)
Dyslipidemia	
- Yes	10(45%)
- No	12(54%)
Stroke Symptoms	
- PACI	3(14%)
- LACI	19(86%)

More of than half of the subjects (91%) came to the hospital with onset within 24 hours. The most common stroke type is lacunar stroke (86%). From a study done by Harris et al., lacunar stroke was indeed the most common type of ischemic stroke (Harris et al, 2016). The range of the subject's NIHSS score during admission was 1 to 11 with a median score of 4. Eighteen subjects (82%) had a NIHSS score above 5 and 4 subjects (18%) had a NIHSS score of 5 or less. The subjects' baseline characteristics are shown in Table 1.

Table 2 Laboratory result at the baseline

Variable	Value
Blood viscosity at admission	6.46 (5.20-9.73)
Hematocrit	45.41±5.89
Leukocytes	9,197.62±2097.91
Fibrinogen	362.72±118.72
LDL cholesterol	118.75±43.76
HDL cholesterol	37±9.70
Triglycerides	107.50 (57-234)

Laboratory baseline characteristics of the subjects are shown in Table 2. The median baseline are as follows 6.46 poise (5.20-9.73) for blood viscosity, 45.41+5.89 cells/□l for hematocrit, 9,197.62+2097.91 cells/□l for leukocytes, 362.72+118.72 mg/dL for fibrinogen, 118.75+43.76 mg/dL for LDL-C, 37+9.70 mg/dL for HDL-C, and 107.50 (57-234) mg/dL for triglycerides. After pentoxifylline administration, the level of blood viscosity tends to be decrease. At day 7, mean of the blood viscosity was 5,64 poises and at day 30 was 5,33 poises (Fig 2).

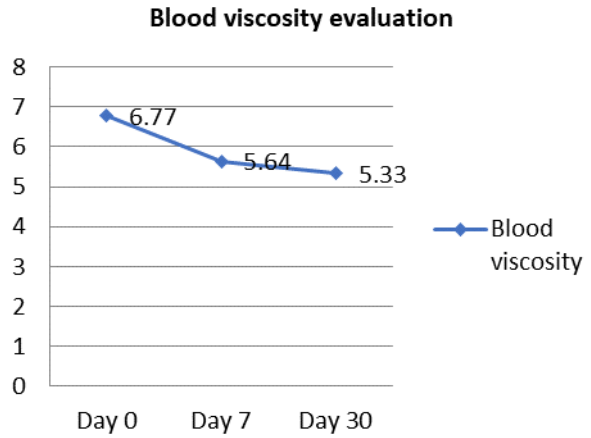

Fig 2. The Decrement Level of Blood Viscosity

Blood Viscosity Analysis

Blood hyper viscosity was found in 40% acute ischemic stroke patients and in the patients with the risk factor of stroke such as smoking, diabetes mellitus, dyslipidemia, and heart disease (Ott et al., 1983; Coull et al., 1991). Pentoxifylline, a metilxantine derivative, has been used as an intermittent claudication therapy in patients with peripheral arterial disease. It has seven metabolites identified in human urine (M1-M7). Metabolites M1 and M5 of pentoxifylline have significant haemorheologic effects while others do not. Pentoxifylline improves peripheral blood flow by decreasing blood viscosity and increasing red blood cell flexibility (Hsu et al., 1988). In this study, pentoxifylline was administered intravenously and orally as an add-on therapy for acute ischemic patients. At day 7 and day 30, the mean level of blood viscosity has decreased. The decrement of blood viscosity was statistically significant for those who had dyslipidemia both in day 7 and day 30 (p=0,009 and p=0,006; Table 3 and Table 4).

Dyslipidemia is an elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. From the baseline laboratory data, the abnormal lipid profile of this study was HDL cholesterol (mean 37+9.70 mg/dL; Table 2). HDL cholesterol (HDL-C) is one of

lipoprotein classes that carry cholesterol in the blood. It is considered to be beneficial because it removes excess cholesterol from tissue and carries it to liver for disposal. Lee et al. conducted a study in patients with intermittent claudication and concluded that pentoxifylline can improve maximal walking distance, but did not affect lipid profile (Lee et al., 2001). Previous studies correlating the effects of pentoxifylline with lipid profiles in ischemic stroke patients are not available yet.

Table 3 The correlation between stroke risk factors with the decrement of blood viscosity at day 7

Risk Factor	Yes	No	*p*
Smoking	1,63±1,03	-0,39±1,45	0,074*
Hypertension	1,27±1,134	0,74±1,19	0,469*
Diabetes Melitus	1,38±1,01	1,03±1,50	0,518*
Heart Disease	1,73±0,38	1,01±1,43	0,290*
Dyslipidemia	1,85±1,09	0,39±1,37	**0,009***

**Unpaired T-test*

At day 30, mean of the blood viscosity decrement level in smoking subjects was statistically significant compared to nonsmoking subjects (p=0.009; Table 4). Smoking is one of the risk factors for stroke. Smoking leads to the raise of hematocrit. Smoking can also alter the rheological behavior of erythrocytes and increases both plasma viscosity and fibrinogen levels (Ernst, 1995). The exact mechanisms of how pentoxifylline alters red blood cell physiology is not entirely understood. It might be due to reduction of inhibition of calcium influx or by increasing the amount of ATP. Pentoxifylline inhibits the activation of Ca2+ dependent transglutaminase. The enzyme irreversibly crosslinks membrane proteins and therefore rigidifies erythrocytes (Magnusson, 2009).

Table 4 The correlation between stroke risk factors with the decrement of blood viscosity at day 30

Risk Factor	Yes	No	*p*
Smoking	1,86±1,47	0,17±0,67	**0,009***
Hypertension	1,67±1,63	0,78±0,79	0,178*
Diabetes Melitus	1,39±1,22	1,47±1,70	0,911*
Heart Disease	1,42±0,29	1,44±1,67	0,966*
Dyslipidemia	2,38±1,44	0,49±0,82	**0,006***

**Unpaired T-test*

Clinical Outcome Analysis

The main goal treatment in acute ischemic stroke is to preserve the ischemic penumbra area. Tissue in this area can be preserved by restoring blood flow and optimizing the collateral flow. The adequate cerebral blood flow (CBF) can maintain consciousness and normal mental status. The decrease in cerebral blood flow will lead to the death of brain cells. The blood flow of the brain is determined by the cerebral perfusion pressure that results from the reduction of systemic blood pressure and intracranial pressure. Systemic blood pressure is affected by peripheral resistance. Peripheral resistance is arterial resistance to blood flow. Peripheral resistance is determined by autonomic activity, pharmacological agents, blood viscosity, and endothelial dysfunction (Caplan, 2009).

Clinical outcomes of ischemic stroke patients are determined by several factors. In this study, after 1-month administration of pentoxifylline, the median of mRS score and the mean of Barthel index were found to be statistically significant in diabetic patients

(p=0.031 and p=0.013; Table 5 and Table 6). Various vascular complications can occur in chronic hyperglycemia. The mechanisms of those complications are the increased production of advanced glycation end products, activation of protein kinase C, stimulation of the polyol pathway and enhanced reactive oxygen species generation, regulates vascular inflammation, altered gene expression of growth factors and cytokines, and platelet and macrophage activation (Yamagishi & Imaizumi, 2005). There are a number of studies documenting increased blood and plasma viscosity, enhanced RBC aggregation and altered RBC deformability in diabetes mellitus. Impaired deformability of polymorphonuclear leukocytes was also reported in diabetes and this alteration may also be associated with tissue perfusion problems (Cho, Mooney, & Cho, 2008).

The effect of pentoxifylline in diabetic patients has been widely investigated due to its anti-inflammatory, antifibrotic, and hemorheological properties. In the study conducted by McCormick et al. (2008) pentoxifylline significantly decreased proteinuria compared with placebo or usual care. In patients with diabetic retinopathy, the potential role of pentoxifylline still needs further investigation (Lopes de Jesus, Atallah, Valente, & Trevisani, 2008). In diabetic rats, the correction of sensory nerve conduction velocity in sciatic motor and saphenous were 56.5% and 69.8%, respectively, with pentoxifylline treatment (Flint, Cotter, & Cameron, 2000).

Table 5 The correlation between stroke risk factors with 1 month modified ranking scale (mRS) score

Risk Factor	Yes	No	*P*
Smoking	0,00 (0-1)	0,00(0-1)	0,485**
Hypertension	0,00 (0-1)	0,50 (0-1)	0,274**
Diabetes Melitus	1,00 (0-1)	0,00 (0-1)	**0,031****
Heart Disease	0,00 (0-1)	-	0,253**
Dyslipidemia	0,50 (0-1)	0,00 (0-1)	0.067**

** *Mann Whitney*

Table 6. The Correlation Between Stroke Risk Factors with 1 Month Barthel Index (BI) score

Risk Factor	Yes	No	*P*
Smoking	-11,54±11,25	-24,00±10,84	0,065*
Hypertension	-14,29±12,54	-17,50±12,58	0,671*
Diabetes Melitus	-22,86±6,99	-10,00±12,45	**0,013***
Heart Disease	-6,67±11,55	-16,67±12,05	0,269*
Dyslipidemia	-19,38±11,78	-11,50±12,03	0,183*

**Unpaired T-test*

Beside diabetes mellitus, another risk factor for stroke that was found to be statistically significant at 1-month follow up was ischemic heart disease when assessed with mRS and BI (p=0,025; Table 7 and Table 8). Pentoxifylline has demonstrated the beneficial effect on ischemic and myocardial and vascular disorders in previous studies. After pentoxifylline administration in heart disease patients, level of glyceryl trinitrate consumption was decreased, ability to exercise was improved, and tachycardia was decreased. Reduction in TNF-α production has been shown to be an important mechanism by which pentoxifylline protects against ischemic injury; this has been shown to be occur both in vitro and in vivo. Pentoxifylline acts as an inhibitor of PDE and induces prolonged cAMP levels resulting in the activation of protein kinase A, which blocks the nuclear factor kappa-B-induced TNF- α messenger RNA transcription (Zhang, Xu, Mengi, Arneja, & Dhalla, 2004).

Table 7 The Correlation between stroke risk factors and 1 month modified ranking scale (mRS) category (mRS >3 is considered poor)

Variable	Good	Poor	*p* value
Age Group			
- ≤45 years old	1	1	1,000**
- >45 years old	11	5	
Gender			
- Male	8	6	0,245**
- Female	4	0	
Smoking			
- Yes	7	6	0,114**
- No	5	0	
Clinical Variable			
Hypertension			1,000**
- Yes	9	5	
- No	3	1	
Diabetes Mellitus			0,316**
- Yes	6	1	
- No	6	5	
Heart Disease			**0,025****
- Yes	0	3	
- No	12	3	
Dyslipidemia			0,152**
- Yes	7	1	
- No	5	5	
Stroke Symptoms			0,098**
- PACI	0	2	
- LACI	12	4	
Onset			0,615**
- <24h our	8	5	
-24-72 hour	4	1	
NIHSS at admission grouping			0,321**
- ≤5	8	2	
- >5	4	4	

Table 8 The correlation between stroke risk factors with 1 month Barthel Index (BI) category (BI<60 is considered poor)

Variable	Good	Poor	*p* value
Age Group			1,000**
- ≤45 years old	1	1	
- >45 years old	11	5	
Gender			0,245**
- Male	8	6	
- Female	4	0	
Smoking			0,114**
- Yes	7	6	
- No	5	0	
Clinical Variable			
Hypertension			1,000**
- Yes	9	5	
- No	3	1	
Diabetes Mellitus			0,316**
- Yes	6	1	
- No	6	5	
Heart Disease			**0,025****
- Yes	0	3	
- No	12	3	
Dyslipidemia			0,152**
- Yes	7	1	
- No	5	5	
Stroke Symptoms			0,098**
- PACI	0	2	
- LACI	12	4	
Onset			0,615**
- <24h our	8	5	
-24-72 hour	4	1	
NIHSS at admission grouping			0,321**
- ≤5	8	2	
- >5	4	4	

CONCLUSIONS

Pentoxifylline is a potential therapy for acute ischemic stroke patients with blood hyper viscosity with the risk factors of smoking, dyslipidemia, diabetes mellitus, and heart disease. A large scale clinical trial with those specific risk factors is required to confirm this result.

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