

PENTOXIFYLLINE IN ACUTE ISCHEMIC STROKE PATIENTS WITH BLOOD HYPERVERSICOSITY

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ABSTRACT

Objective: This study evaluated the efficacy of pentoxifylline, a hemorrheologic agent, for treating acute ischemic stroke in patients with blood hyperviscosity.

Methods: Patients were randomly allocated within 3 days of stroke onset to study or control treatment. All the patients received the standard acute ischemic stroke treatment. The study treatment was intravenous pentoxifylline 1200 mg/day for 5 consecutive days and oral pentoxifylline 800 mg in two divided doses for 23 days. Blood viscosity was evaluated on days 7 and 30. The outcomes were assessed by the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale, and Barthel index (BI) criteria.

Results: The median baseline viscosity was 6.89 poise in the study and 6.46 poise in the control groups and had decreased in all the patients on days 7 and 30. The decrease in the study group on day 7 (1.13 poise) was greater than that in the control group (0.57 poise); the difference was not significant. The NIHSS score improved by 32% in the study group (relative risk [RR]=1.00, 95% confidence interval [CI]: 0.421–3.556; p=1.00). At 1-month, 67% of the study group had a good functional outcome (RR=1.026, 95% CI: 0.656–1.605; p=0.909).

Conclusion: Pentoxifylline decreased blood viscosity and improved clinical outcome in this patient series.

Keywords: Blood hyperviscosity, Digital microcapillary, Ischemic stroke, Pentoxifylline.

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INTRODUCTION

In Indonesia, the most common cause of death from a noncommunicable disease is stroke. The incidence of stroke increased from 8.3/1000 population, in 2007, to 12.1/1000 population, in 2013 [1]. Stroke can cause long-term disability [2], in 2014, 71.4% of the stroke patients admitted to the Neurology Department of Cipto Mangunkusumo General Hospital RSCM (*Rumah Sakit Cipto Mangunkusumo*) experienced ischemic stroke [3]. Ischemic stroke is caused by sudden loss of blood circulation to the brain, spinal cord, or retina due to embolism, thrombosis, or perfusion abnormalities such as blood hyperviscosity [4]. Regions of cerebrovascular ischemia include two areas of injury, a core zone of cell death and an ischemic penumbra that can be salvaged [5].

Blood hyperviscosity is present in 40% of patients with acute ischemic stroke and contributes to the severity of clinical outcome [6]. Hematocrit, erythrocyte deformability, erythrocyte aggregation, and fibrinogen determine blood viscosity [7]. It is important to determine blood viscosity because hyperviscosity in the penumbra can decrease cerebral blood flow and lead to infarction [8]. In Indonesia, the measurement of blood viscosity in patients with acute ischemic stroke is not routine because until now it could be done in large laboratories only and the result could not be obtained right away. In this study, a novel digital microcapillary instrument was used to screen blood viscosity [9].

The Indonesian national health insurance values effective, efficient treatment. Since intravenous thrombolysis can only be administered to 10% of acute ischemic stroke patients due to the narrow time window [10], 90% of patients require an alternative therapy to protect the penumbra from infarction. Pentoxifylline, a methylxanthine derivative, inhibits cyclic adenosine monophosphate phosphodiesterase and cyclic guanosine monophosphate hydrolysis and blocks the

adenosine transporter and the phospholipase. Methylxanthines inhibit platelet aggregation and thromboxane A₂ synthesis, increase phagocytic activity, and increase the synthesis of prostacyclin from endoperoxidase. They lower blood viscosity by increasing erythrocyte stability, by reducing the aggregation of erythrocytes and plasma fibrinogen concentration, and may be neuroprotective by inhibiting glutamate release [11]. Pentoxifylline may improve cerebral blood flow and may suppress inflammation in acute stroke [12,13], but a marker of its efficacy is lacking. In this study, blood hyperviscosity was used as a marker of the effectiveness of pentoxifylline in acute stroke patients. The device used in this study called "Digital Microcapillary" is a portable device to measure blood viscosity that has been patented in Indonesia since 2016 with patent number 0000431D8 from the Ministry of Law and Human Rights of Republic of Indonesia.

METHODS

Subjects

Adult acute ischemic stroke patients with blood hyperviscosity treated at the Cipto Mangunkusumo General and Prikasih Hospital between September 1st, 2016, and June 31, 2017, were recruited within 3 days of onset. Physical and neurologic examinations were performed by the doctor on duty. Ischemic stroke was diagnosed by cerebral computed tomography. Stroke symptoms were classified by the Bamford criteria; patients with posterior circulation infarct or total anterior cerebral infarct were excluded. Patients with dehydration (a urea/creatinine ratio >32 on admission), previous history of stroke or transient ischemic attack, previous intravenous or intra-arterial thrombolysis, or an estimated glomerular filtration rate of <30% were excluded.

Study design and procedures

In this single-blind controlled study, eligible patients were assigned by block randomization to receive pentoxifylline or control treatment

(no pentoxifylline). All the subjects received the standard treatment for acute ischemic stroke, including an antithrombotic agent, statin, and other medications if indicated, such as antiepileptic agents for seizures or antibiotics for pneumonia or other infections. The study group received intravenous pentoxifylline 1200 mg/day for 5 consecutive days followed by oral pentoxifylline 800 mg in two divided doses for 23 days. The study protocol was approved by the Health Research Ethics Committee of the University of Indonesia and Cipto Mangunkusumo Hospital (HREC-FMUI/CMH) and was conducted following the ethical principles of the Declaration of Helsinki. All the participants gave written informed consent.

Blood viscosity was measured on the day of admission, day 7, and day 30 day using a digital microcapillary device previously described by Rasyid *et al.* [9]. The neurological deficit was assessed on admission and day 7 by the National Institutes of Health Stroke Scale (NIHSS) score. Significant improvement was defined as a 4-point change from the baseline score or a score of 0. Disability and functional outcome were assessed by the modified Rankin Scale (mRS) and Barthel index (BI) on day 30. A poor disability outcome was defined as an mRS score of >3, and a poor functional outcome was defined as a BI score of <60.

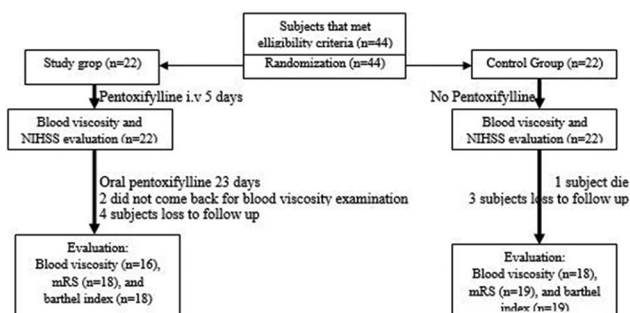


Fig. 1: Patients participating in this study

Statistical analysis

Numerical data were reported as means \pm standard deviation if normally distributed or as median and range if not normally distributed. Categorical data were reported as frequencies and percentages. Statistical analysis was performed with SPSS version 20 (IBM Cor., Armonk, NY, USA). Independent t test or Mann-Whitney U-tests was used to compare means; Chi-square or Fisher's exact tests were used to compare percentages.

RESULTS AND DISCUSSION

A total of 44 patients met the eligibility criteria and were willing to participate; 42 were admitted to RSUPN Cipto Mangunkusumo and two were admitted to Prikasih Hospital. 22 patients received pentoxifylline; 22 received standard (control) treatment. One patient from the control group died on day 20 from a heart attack. Two patients in the study group did not return for the blood viscosity measurement, and seven (three in the control group and four subjects in the study group) were lost to follow-up. Intention to treat analysis was performed so that all randomized patients were included in the analysis. The patient selection, treatment, and disposition are shown in Fig. 1.

Most patients (68%) were 50–80 years of age. The median was 55 (range 19–70) years of age, 70% were men, 80% were hypertensive, 64% were current smokers, 50% had dyslipidemia, 30% had diabetes mellitus, and 23% had ischemic heart disease. Lacunar stroke was the most common stroke type (86%), and the main manifestation was motor paralysis. There were no statistically significant differences in baseline demographic, clinical, or laboratory characteristics in the study and control groups (Tables 1 and 2).

Blood viscosity

The baseline blood viscosities in the study (6.46, range 5.20–9.73 poise) and control (6.89 poise, range 5.57–14.10 poise) groups were not significantly different ($p=0.105$, Table 2). On day 7, the blood viscosity had decreased in both of the groups; however, the decrement was larger in the pentoxifylline group than in the control group (1.22

Table 1: Patient baseline demographic and clinical characteristics

Variable	Study group (n=22)	Control group (n=22)	Total (n=44)	p
Demographic variable				
Age, y	55 (36–64)	55 (19–70)	14 (32%)	0.503**
18–49	6 (27%)	8 (36%)	30 (68%)	0.517†
50–80	16 (73%)	14 (63%)		
Sex				0.322†
Male	14 (63%)	17 (77%)	31 (70%)	
Female	8 (36%)	5 (23%)	13 (30%)	
Smoking				0.210†
Yes	16 (73%)	12 (54%)	28 (64%)	
No	6 (27%)	10 (45%)	16 (36%)	
Clinical variable				
Hypertension				1.000†
Yes	18 (82%)	17 (77%)	35 (80%)	
No	4 (18%)	5 (23%)	9 (20%)	
Diabetes mellitus				0.099†
Yes	9 (41%)	4 (18%)	13 (30%)	
No	13 (59%)	18 (82%)	31 (70%)	
Ischemic heart disease				1.000†
Yes	5 (23%)	5 (23%)	10 (23%)	
No	17 (77%)	17 (77%)	34 (77%)	
Dyslipidemia				0.546†
Yes	10 (45%)	12 (54%)	22 (50%)	
No	12 (54%)	10 (45%)	22 (50%)	
Stroke symptom				1.000†
PACI	3 (14%)	3 (14%)	6 (14%)	
LACI	19 (86%)	19 (86%)	38 (86%)	
Onset				0.412†
<24 h	20 (91%)	17 (77%)	37 (86%)	
24–72 h	2 (9%)	5 (23%)	7 (16%)	
NIHSS score	4.0 (1–11)	5.95 \pm 3.484		0.354**

†Chi-square test; †Fischer's exact test; *unpaired t test; **Mann-Whitney U-test, $p<0.05$. NIHSS: National Institutes of Health Stroke Scale

poise vs. 0.56 poise, $p=0.465$, Fig. 2). On day 30, the blood viscosity had decreased further; however, the decrement was not statistically significant ($p=0.665$, Fig. 2).

Clinical outcomes

Improvement in NIHSS score was achieved in 32% of the study group patients (relative risk [RR]=1.00; 95% confidence interval [CI]: 0.421–3.556; $p=1.00$, Table 3). At the 1-month follow-up, the mRS and BI scores confirmed good functional and disability outcomes in 67% of the patients (RR=1.026; 95% CI: 0.656–1.605; $p=0.909$, Table 3).

DISCUSSION

The hematocrit, erythrocyte deformability, erythrocyte aggregation, and fibrinogen levels determine blood viscosity, the thickness, and stickiness of blood [7]. Blood hyperviscosity is present in most patients with acute ischemic stroke [14] and patients with stroke risk factors such as smoking, diabetes mellitus, dyslipidemia, and heart disease [15]. There were no significant differences in the presence of stroke-risk factors in the study groups. Hypertension was present in 80% of the patients, consistent with the Indonesian demographic data

that indicate hypertension as a principal risk factor for stroke [1]. Other risk factors present in this study population included smoking (64%), dyslipidemia (50%), diabetes mellitus (30%), and heart disease (23%). The incidence of stroke increased with age.

Pentoxifylline is a nonselective phosphodiesterase inhibitor used to treat intermittent claudication in patients with the peripheral arterial disease. Pentoxifylline significantly improves erythrocyte function, inhibits platelet aggregation, and decreases plasma fibrinogen, and blood viscosity in patients with cerebrovascular insufficiency [11]. The effectiveness of pentoxifylline was shown in this study by its effect on blood viscosity and association with the improvement of the clinical outcomes.

Mediators of inflammation such as tumor necrosis factor- α , interferon- β , interleukin (IL)-1 β , and (IL-6) are released in the acute phase of stroke. Plasma fibrinogen also increases in the acute phase [16]. Blood viscosity increases in the acute stroke phase in response to inflammation and is also affected by coexisting stroke-risk factors [15]. Blood hyperviscosity contributes to stroke severity and outcome [14, 17-19].

Baseline blood viscosity was higher in control than in the pentoxifylline group; however, the difference (7.78 poise vs. 6.77 poise) was not significant. The blood viscosity had decreased from the baseline on both days 7 and 30. Blood hyperviscosity indicates a poor prognosis in patients with acute ischemic stroke. It leads to further loss of blood flow in the ischemic penumbra and can lead to the expansion of the infarct area and the worsening of the neurological deficit [5]. On day 7, the neurological deficit had improved in 32% of the patients in both groups (RR=1.00; 95% CI: 0.421–3.556; $p=1.00$, Table 3). On day 30, 67% of the pentoxifylline group and 68% of the control group had good clinical outcomes (RR=1.026; 95% CI: 0.656–1.605; $p=0.909$; Table 3). The similar clinical outcomes in both groups indicate that the standard acute stroke treatment that was given to all patients was adequate to improve the clinical outcome.

The study results differ from those reported by a double-blind, randomized trial of pentoxifylline in no hemorrhagic stroke patients. Intravenous pentoxifylline 1200 mg/day was given for 3 days and continued orally 400 mg t.i.d for the next 28 days. The neurological deficit improved but did not differ from the placebo control after the first few days. The improvements in the level of consciousness, motor function, and cranial nerve function were better in the study group than in the control group [20].

The study limitations include the small number of patients to assess the effect of pentoxifylline therapy for acute ischemic stroke and the loss of seven patients at the 1-month clinical evaluation.

CONCLUSION

A decrease in blood viscosity and improvement of clinical outcome was seen after pentoxifylline administration but was not significantly different from those seen in control patients with standard therapy after 7 days. The efficacy of pentoxifylline as an ischemic stroke therapy

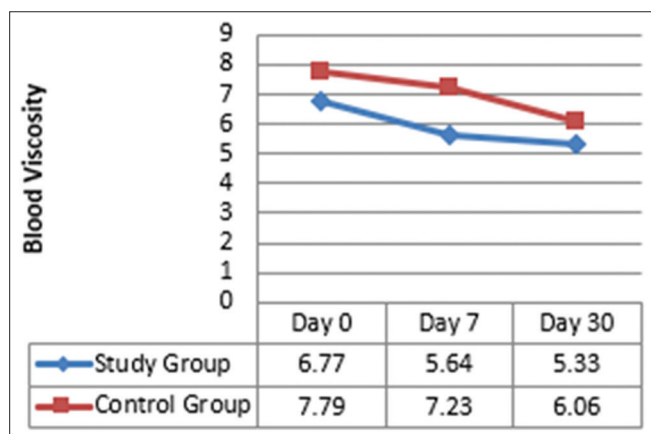


Fig. 2: The level of blood viscosity

Table 2: Patient baseline laboratory characteristics

Variable	Study group (n=22)	Control group (n=22)	p
Blood viscosity	6.46 (5.20–9.73)	6.89 (5.57–14.10)	0.105**
Hematocrit	45.41±5.89	43.52±3.64	0.108*
Leukocyte	9.197.62±2097.91	9.748.64±2.425.35	0.430*
Fibrinogen	362.72±118.72	384.62±116.39	0.564*
LDL cholesterol	118.75±43.76	117±39.12	0.886*
HDL cholesterol	37±9.70	41.53±10.50	0.081*
Triglyceride	107.50 (57–234)	100 (65–280)	0.695**

*Unpaired t test, **Mann-Whitney U-test, $p<0.05$

Table 3: Clinical outcomes

Variable	Study group	Control group	Total	RR (95% CI)	p
NIHSS improvement					
Yes	7 (32%)	7 (32%)	14 (32%)	1.00 (0.421–3.556)	1.000 [†]
No	15 (68%)	15 (68%)	30 (68%)		
mRS (day 30)					
Good	12 (67%)	13 (68%)	25 (67%)	1.026 (0.656–1.605)	0.909 [†]
Poor	6 (33%)	6 (32%)	2 (33%)		
BI (day 30)					
Good	12 (67%)	13 (68%)	25 (67%)	1.026 (0.656–1.605)	0.909 [†]
Poor	6 (33%)	6 (32%)	12 (33%)		

[†]Chi-square test, $p<0.05$. NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale, BI: Barthel index, CI: Confidence interval

warrants investigation in a large clinical trial with more specific inclusion criteria to confirm these results.

CONFLICTS OF INTEREST

All authors have none to declare.

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