

Hypercoagulable States Therapy in Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

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ABSTRAK

Background

Ischemic optic neuropathy is one of the main causes of blindness or visual impairment in middle age or elderly population. Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) is the most common type of ischemic optic neuropathy. Systemic risk factors such as hypertension, diabetes mellitus, nocturnal hypotension, sleep apnea, cardiovascular disease and hypercoagulable states are related to NAION. The aim of the study was to evaluate the clinical outcome of hypercoagulable states therapy in NAION patients.

Methods

This study is a retrospective study conducted at Cipto Mangunkusumo Hospital Jakarta. All NAION patients with age more than 19 y.o were included. Patients were divided into 4 group; group 1: NAION patients treated with hypercoagulable states therapy, group 2: NAION patients treated with anticoagulant therapy, group 3: NAION patients treated with antiplatelet therapy and group 4: NAION patient without anticoagulant, antiplatelet or hypercoagulable states therapy.

Results

The total sample were 49 patients (49 eyes). Twenty-six patients (56.5%) were diagnosed with hypercoagulable state. In group 1 – 3 half of the patients (50%) had clinical improvements with anticoagulant, antiplatelet and hypercoagulable therapy.

Conclusion

Hypercoagulable states therapy may improve clinical outcome of NAION.

Kata kunci : Antiplatelet Therapy, Anticoagulant Therapy, Hypercoagulable States, Ischemic Opthic Neuorpathy, NAION

PENDAHULUAN

Ischemic optic neuropathy is one of the main causes of blindness or visual impairment in middle age or elderly population. There are two types of ischemic optic neuropathy, anterior and posterior.¹⁻³ Anterior Ischemic Optic Neuropathy (AION) divided into Arteritic Anterior Ischemic Optic Neuropathy (AAION) and Non arteritic Ischemic Optic Neuropathy (NAION).⁴ NAION is the most common type of ischemic optic neuropathy.^{2,5,6} A study in Taiwan at Kaohsiung Veterans General

Hospital, showed that there were 89 cases of NAION and 14 cases of posterior ischemic optic neuropathy (PION) out of 103 total cases from 1995 – 2005.⁷ In the United States (U.S) the annual incidence of NAION are 2.3 – 10.2/100,000 population, approximately 1500 – 6000 new cases per year.^{8,9} In Indonesia, there were 87 cases reported in Cipto Mangunkusumo Hospital from 2006 – 2011.¹⁰ A retrospective study in ophthalmology department at Kirana Cipto Mangunkusumo Hospital reported that from 2012 – 2017 there were 272 cases of NAION consist of 57% male and

43% female with the mean age of 53,49 years old.¹¹

The pathology of NAION was remain unknown, however there are systemic risk factors such as diabetes mellitus, nocturnal hypotension, sleep apnea, and cardiovascular disease.^{12,13} Previous study stated that patients with NAION who had systemic hypertension had increased risk of cerebrovascular events.¹⁴ A cohort study in Taiwan from 2000 - 2011 with 414 patients (239 men and 175 women) diagnosed with NAION and without any history of stroke before the episode of NAION were more likely to have ischemic stroke than hemorrhagic stroke. In the subgroup of patients with comorbidities, the risk of ischemic stroke was 3.35 higher in patients with NAION than those without NAION.¹⁵

Another risk factor for NAION is hypercoagulable states. According to previous study in Kirana Cipto Mangunkusumo Hospital, there were 36 (19%) patients out of 272 patients diagnosed with NAION and hypercoagulable states.¹⁶ Therefore, our aim was to evaluate the clinical outcome of hypercoagulable states therapy in NAION patients.

METHODS

Study population and data collection

This retrospective study was performed in Ophthalmology Department at Kirana Cipto Mangunkusumo Hospital. Retrospective chart review was performed in 1 year, from January – December 2019 with a clinical diagnosis of NAION. Data were analyzed using SPSS 25.0. Patients with NAION were included in this study. All patients were diagnosed by neuro-ophthalmologists and hematologist in Cipto Mangunkusumo Hospital. Patients who had medication history of anticoagulant and/or antiplatelet, refraction disorders, glaucoma, retinopathy diseases, previous

history of hypercoagulable state due to cancer, pregnancy, massive bleeding, obesity and immobility were excluded from the study.

Hypercoagulable states and Therapy

Twenty-six NAION patients were diagnosed with hypercoagulable states and treated by hematologist in Cipto Mangunkusumo Hospital. We defined hypercoagulable states as a condition with the elevation of D-Dimer >300 ug/dl and/or shorter ratio PT compare to control ≤ 0.8 and/or shorter ratio APTT compare to control ≤ 0.8 .

Hypercoagulable states therapy was defined as consumption of warfarin 2 mg daily dose and aspirin 80 mg daily dose. Anticoagulant therapy was defined as consumption of warfarin 2 mg daily dose. Meanwhile, antiplatelet therapy was defined as consumption of aspirin 80 mg daily dose.

The total of twenty-six NAION patients with hypercoagulable states are then categorized into 4 groups; (1) group 1: NAION patients treated with hypercoagulable states therapy, (2) group 2: NAION patients treated with anticoagulant therapy, (3) group 3: NAION patients treated with antiplatelet therapy and (4) group 4: NAION patient without anticoagulant, antiplatelet and hypercoagulable states therapy.

Clinical Outcome Improvement

Clinical outcome improvement defined as improvement of visual acuity measured by Snellen chart and improvement of visual field measured by Humphrey. All patients were followed up within 1 month period.

Ethical Consideration

This research has been approved by The Ethical Committee Faculty of Medicine Univeristas Indonesia.

RESULTS

The total of 46 patients (49 eyes) were evaluated consists of 25 male and 21 female. Mean ages was 58.9 ± 11.3 years old, as 36 years old was the youngest and 84 years as the oldest, as shown in Table 1. Total number of diabetics hypertension and hypercoagulable states were 19 (41.3%) and 16 (34.8%), and 26 (56.5%) respectively. The mean of visual acuity (VA) and intraocular pressure (IOP) were 0.9 and 12.001. There was an arcuate inferior defect in 3 (6.1%) patients. Fundus examination revealed swollen optic disc in the affected eyes 12 (36%) while 34 (74%) had optic atrophy.

Table 1. Baseline Characteristics of NAION Patients

Variable	NAION (n=46 patients, 49 eyes)
Age (<i>mean</i>)	58.9±11.3
Gender	
Male	25 (54.3%)
Female	21 (45.7%)
NAION risk factors	
Diabetes mellitus	19 (41.3%)
Hypertension	16 (34.8%)
Hypercoagulable states	26 (56.5%)
Visual acuity (<i>mean</i>)	0.9
IOP (<i>mean</i>)	12.001
Visual field	
Arcuate superior	1 (2%)
Arcuate inferior	3 (6.1%)
Altitudinal superior	1 (2%)
Altitudinal inferior	1 (2%)
Non specific	43 (87.8%)
Atrophy papil	34 (74%)
Edema papil	12 (26%)

Twenty-six patients (56.5%) diagnosed with NAION and hypercoagulable state were divided into 4 different sub-group. According to Table 2., Two out of 4 (50%) patients in group 1 had clinical outcome improvement with hypercoagulable states therapy, meanwhile 3 out of 6 (50%) patients in group 2 had a clinical outcome

improvement with anticoagulant therapy, 5 out of 7 (71.4%) patients in group 3 had an clinical outcome improvement with antiplatelet therapy, and 2 out of 9 (22%) patients in group 4 had an improvement without any therapy.

Table 2. Clinical outcomes improvement in NAION patients with hypercoagulable states

Group	Clinical outcomes improvement (n=26)	
1	Yes	2 (50%)
	No	2 (50%)
2	Yes	3 (50%)
	No	3 (50%)
3	Yes	5 (71.4%)
	No	2 (28.6%)
4	Yes	2 (22.2%)
	No	7 (77.8%)

Table 3. Laboratory Findings in NAION Patients with Hypercoagulable States

Variable	NAION (n=26)
PT	0.92 ± 0.08
APTT	0.98 ± 0.19
Fibrinogen	383.53 ± 108.34
D-dimer	968.34 (320 – 9210)
INR	0.99 ± 0.09

DISCUSSION

Demographic

The mean age of this study was 58.9 ± 11.3 years old. A population-based study in Los Angeles, California, reported that the majority age of NAION was older than 50 years old. Another study showed that the age of NAION patients ranged from 57 to 65 years.⁸ Study from Repka et al, stated that 169 (86%) patients out of 196 patients were diagnosed with NAION with an average age of 64 years, ranging from 42 to 88 years old.¹⁷ A Recent study with 1.381.477 patients, 977 (0.1%) were diagnosed with NAION with the mean age 64.0 ± 9.2 years old.¹⁸ Our study showed the similarity of mean age with previous studies, ranging from 57 to 65 years old.^{8,17,18}

Systemic Vascular Risk Factors

The etiology of NAION is known to be an ischemia due to occlusion of posterior ciliary vessels. Arterial hypertension, dyslipidemia, diabetes mellitus (DM) and hypercoagulation are some of risk factors that influence the occlusion process.^{19,20} Study from Ischemic Optic Neuropathy Decompression Trial (IONDT), reported that 60% of NAION patients had at least one vascular risk factor, 47% had hypertension and 26% had diabetes.²¹

Hypertension

Systemic hypertension is an important risk factor for ischemic cerebrovascular disease due to the decrease in endothelium dependent and flow-mediated vasodilation.^{22,23} One study reported that there was a decreased of flow mediated vasodilation in patients with NAION.²⁴ Hypertension has been found to be associated with patients under 65 years old.¹⁴ Cestari et al¹⁸, stated that patients with uncomplicated hypertension had a 62% risk of getting NAION ($p = 0.0001$), with 536 (54.8%) out of 977 patients diagnosed with NAION and uncomplicated hypertension which is hypertension without end organ damage.

Another study reported 13 out of 41 patients diagnosed with NAION and hypertension.²⁵ Hayreh et al,¹² also reported that hypertension was present in up to 49% of NAION patients. A pilot study in Pakistan showed that there were 3 out of 24 patients were diagnosed with NAION and hypertension.²⁶ In line with our study, 16 (34.8%) out of 46 patients were also diagnosed with NAION and hypertension.

Diabetes Mellitus

Prior studies have shown a positive correlation between Diabetes Mellitus (DM) and NAION. One study reported that DM has been found to be associated in all ages. Our study showed that there were 19 (41.3%) patients with DM. This results is

comparable with previous study from Talks et al., which reported that 6 patients out of 41 with DM.

Our result is strengthened with another prior study that reported the prevalence of DM has ranged from 5% to 40%.²⁷ Another study also reported that there were 107 patients diagnosed with NAION and 40% of them had DM.²⁸ The largest cohort of NAION reported that 206 (31%) out of 655 NAION patients had DM.²⁷ A meta-analysis study with 2.0996 participants from 12 case control studies showed that these studies indicated that DM is related with the increased risk of NAION.²⁹

Cestari et al¹⁸, stated that patients with uncomplicated hypertension had a 62% risk of getting NAION ($p = 0.0001$) and patients with DM complicated by end-organ damage had 27% risk of getting NAION ($p = 0.04$).

Hypercoagulable states

Hypercoagulable states as a potential causes of NAION have been reported in several studies and case reports. There were five cases reported that NAION is associated with antiphospholipid antibodies, two cases with protein C deficiency, and one cases each with anti-thrombin III deficiency and tissue plasminogen activator deficiency.^{20,30,31}

Another study also reported that there was a significant association between incidence of NAION and raised level of fibrinogen.³² Fibrinogen is an acute phase protein, and coagulating factors which affects whole body viscosity.^{19,33} Increased level of fibrinogen is related with platelet aggregation and increases the activity of monocytes and macrophages. Thus will leads to thrombotic vascular occlusion.^{19,33,34} The current study showed that there were 26 (56.5%) patients diagnosed with NAION and hypercoagulable states, which are similar to previous studies reported.

Hypercoagulable states therapy and NAION

The therapy of NAION still remains an open question. Several alternative therapies for NAION are systemic corticosteroid, optic nerve sheath decompression, aspirin, intravitreal triamcinolone acetonide and intravitreal bevacizumab.^{35–41} However, multiple risk factors may contribute to NAION. Managing NAION risk factors is important to reduce the risk of NAION in the fellow eye or progressing of NAION in the same eye.³⁵

Prior studies have shown that hypercoagulable states may contribute to NAION.^{30,31,42} Anticoagulant, antifibrinolytic and antiplatelet aggregation were drug of choices for hypercoagulable states therapy in Indonesia.⁴³ Anticoagulant such as heparin and warfarin, and antiplatelet aggregation such as aspirin and clopidogrel, are often used in clinical setting.⁴³

Our study used a combination of warfarin and aspirin as hypercoagulable states therapy, warfarin as anticoagulant therapy and aspirin as antiplatelet therapy. Our study demonstrated an improvement in clinical outcome of NAION patients who received hypercoagulable states therapy (50%), anticoagulant therapy (50%), and antiplatelet therapy (71.4%). Meanwhile in the last group, 22% of patients had clinical outcome improvement.

Similar findings were found in previous studies. Aftab et al²⁶, stated that anticoagulation therapy using heparin and warfarin does benefit patients with NAION presenting within 4 weeks of onset of symptoms. They postulated that hypotension and (or) thrombotic/embolic event leads to decreased perfusion pressure of the optic nerve head blood supply and caused sluggish blood flow in the short posterior ciliary arteries. These may cause a predisposition of thrombus formation.

The ischemic insult affected through this mechanism causes optic nerve head edema and disruption of axonal flow leading to nerve fiber layer (NFL) swelling. This evokes a vicious cycle further compromising blood supply to optic nerve head.²⁶

Another study also reported a slightly improvement in visual acuity of NAION patients with double thrombophilia (protein S deficiency and prothrombin G20210A mutation) receiving warfarin. Even though, the inferior altitudinal field defect had remained unchanged.⁴⁴ A case series study with total of 6 patients also reported that there were improvement in visual acuity and visual field after treated with anticoagulant.⁴⁵ Beck et al.⁴⁶ observed that aspirin therapy significantly reduced NAION development in the fellow eye. Similarly, Kupersmith et al.⁴⁷ found aspirin therapy effective in NAION patients with regard to second eye involvement.

Limitation of our study are that the sample size was too small and the duration of follow-up was too short. Therefore, we suggest another study with larger sample size with randomized clinical trial for a better result.

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