ORIGINAL ARTICLE

NAION AND ANTICOAGULANTS: BRIDGING THE GAP WITH RATIONALE-BASED THERAPY

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Background: NAION, a multifactorial disorder with an unclear mechanism has limited insight on its treatment option. Despite conflicting results in its relation to hypercoagulation, many metabolic risk factors associated with NAION are intertwined with hypercoagulation. We aim to investigate the impact of anticoagulant therapy in the vascular and visual function of NAION patients. **Methods**: A prospective interventional study was conducted in the Neuro-Ophthalmology Division, Department of Ophthalmology at FKUI-RSCM Kirana from October 2020 to April 2022, involving two groups of NAION subjects: hypercoagulation and non-hypercoagulation. All subjects received 80 mg of aspirin daily, with the hypercoagulation group additionally receiving 2 mg of warfarin. We assessed capillary perfusion (CP) and flux index (FI) using OCTA, along with changes in visual acuity (Snellen chart test) and visual field (Humphrey Visual Field - HVF) at presentation and one month after treatment. **Results:** The hypercoagulation group had 14 subjects, while the non-hypercoagulation group had 7. This research found a significant decrease for CP (p=0.003) and FI (p=0.001) in both groups. CP and FI in all quadrants decreased more in the non-hypercoagulable group without anticoagulant therapy, although the difference between the two groups was not significant (p=0.198 for CP and p=0.243 for FI). Hypercoagulation group showed significant visual field improvements (p=0.033 for MD and p=0.014 for VFI). Most subjects within hypercoagulation showed improvement although not all of it was significant, while the majority of the non-hypercoagulation group showed no changes. **Conclusion:** Anticoagulant therapy could potentially mitigate the progression of flow insufficiency and facilitate clinical enhancement.

Keywords: Non-arteritic anterior ischemic optic neuropathy; Anticoagulant, optical coherence tomography angiography; Visual field; Visual acuity; Thrombophilia

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INTRODUCTION

Suggested as ischemic disorder, the exact mechanism of NAION was not fully understood.[1,2] However, optic nerve blood flow insufficiency was believed as the main culprit in NAION.[3] The early discovery of NAION, which identified the presence of infarct suggestive thromboembolic occlusion in cadaver NAION eyes, led to the hypothesis of hypercoagulation's association with NAION. As more studies were conducted, this idea was shifted with a presumption that hypotensive disorder mainly serves the NAION pathophysiology instead.[4,5] Numerous studies have indeed produced conflicting results regarding the risk factors associated with NAION, not only for hypercoagulation but also other risk factors. Nevertheless, there are compelling reasons to explore the potential link between hypercoagulation and NAION.[3] Firstly, many of the risk factors commonly associated with NAION are metabolic conditions that are known to be associated with hypercoagulation. Secondly, the role of hypercoagulation in causing ischemic insult is a pertinent consideration. Furthermore, the impact of microvascular disease on NAION outcomes may differ from what is observed in macrovascular conditions.[1,4] In microvascular contexts, hypercoagulation might not necessarily result in elevated blood coagulation markers, making

it challenging to dismiss the possibility of coagulopathy in such settings based solely on normal coagulation markers.[3,6–8] Therefore, given the limited understanding of the pathophysiology of NAION and the conflicting findings from studies on its pathophysiology, resulting in a restricted comprehension of treatment options, our objective is to conduct a more comprehensive assessment of the potential impact of anticoagulant therapy in the vascular and visual function of NAION patients.

MATERIAL AND METHODS

This is a prospective interventional study conducted on all clinically diagnosed NAION patients at the Neuro-Ophthalmology Division, Department of Ophthalmology, FKUI-RSCM Kirana, from October 2020 to April 2022 who provided their consent for participation in this study. The research was carried out with approval from the Ethics Committee of Health Research, Faculty of Medicine, University of Indonesia. (KET-935/UN2.F1/ETIK/PPM.00.02/2020)

NAION patients were divided into two groups, hypercoagulation and non-hypercoagulation, based on blood coagulation markers (D-dimer, fibrinogen, PT, aPTT, and International Normalized Ratio (INR). An experimental clinical trial was conducted to evaluate the effectiveness of hypercoagulation therapy within one month. The hypercoagulation group was given antiplatelet and anticoagulant, while the non-hypercoagulation group was given antiplatelet alone. Daily 80 mg of aspirin were given for all subjects whereas 2 mg of warfarin were given in addition to the hypercoagulation group. To assess the efficacy of both forms of treatment, the patients were evaluated for the optic nerve blood flow for its capillary perfusion (CP) and flux index (FI) using OCTA examination and clinical improvement of visual acuity obtained by Snellen chart test and visual field by Humphrey Visual Field (HVF) examination at presentation and one-month post treatment. The success of each treatment in preserving NAION perfusion was the capillary perfusion (CP) and flux index (FI) value by OCTA. The success of each form of treatment in visual acuity was categorized as improvement (VA increased ≥2 rows), insignificant improvement (VA increased 1 row), insignificant deterioration (VA decreased 1 row), and deterioration (VA decreased ≥2 rows). In the visual field test, the success of each treatment was categorized as improvement (MD≥3), insignificant improvement (3>MD>0), no change (VA 0), insignificant deterioration (0>MD>-3), and deterioration (MD≤ -3).[3,9] The results were collected and analyzed using SPSS ver. 26.

RESULT

A total of 42 subjects were included in this study, ranging from 41–79 years old, with a mean age of 53 years old. There were 14 and 7 subjects within hypercoagulation and non-hypercoagulation groups respectively.

This research found a significant decrease for both CP and FI despite given therapy. As seen in Table 1, CP in the affected quadrant showed a significant decrease from a mean of 0.3954 pre-therapy to a mean of 0.3600 post-therapy (p=0.003). A significant decrease was also found in the FI of the affected quadrant (p=0.001). The mean FI decreased from 0.45 pre-therapy to 0.43 post-therapy.

Interestingly, we found that CP and FI decreased more in the non-hypercoagulable group who did not receive anticoagulant therapy compared to the hypercoagulation group who received anticoagulant therapy (Table 2). Although the difference between the two groups was insignificant (p=0.198 and p=0.243), these findings were found in all quadrants of CP and FI, including the affected quadrant.

Not only evaluating from the perspective of objective measurement, we also try to allude this statistically insignificant result into the possibly clinically significant result. Thus, we further evaluate the visual field and visual acuity of the subjects. In the evaluation of 1 month follow-up, generally all NAION subjects showed improvements in visual acuity and visual field based on the numerical values of MD, VFI, UCVA, and BCVA (Table 3). When compared between the two groups, it was found that the hypercoagulation group, who had received anticoagulant for 1 month, showed significant visual field improvements while the non-hypercoagulation group did not.

Clinical improvement was also assessed based on clinical category (Table 4). Concerning the changes in visual acuity, no significant deterioration was observed in any of the subjects. Most subjects within hypercoagulation showed improvement although not all of it was significant. However, minority of this group underwent insignificant deterioration of visual acuity. On the other hand, majority of the non-hypercoagulation group did not show any changes after one month follow-up. Based on visual field function, both groups showed improvement in most subjects. However, minority of hypercoagulation group showed deterioration of the visual field.

Table 1. Comparison of Pre-therapy and Post-therapy Capillary Perfusion and Flux Index of NAION subjects

OCTA	Pra-therapy	Pasca-therapy	*p*-value
Capillary perfusion			
Superior	0,4000 ± 0,0596	0,3597 ± 0,0466	**0,002***
Inferior	0,4150 ± 0,0462	0,3960 ± 0,0458	**0,041***
Nasal	0,4302 ± 0,0357	0,4007 ± 0,0311	**0,001***
Temporal	0,4549 ± 0,0487	0,4242 ± 0,0311	**0,021***
Affected quadrant	0,3954 ± 0,0503	0,3600 ± 0,0492	**0,003***
Average	0,4250 ± 0,0389	0,3952 ± 0,0290	**< 0,001***
Flux index			
Superior	0,442 (0,341–0,529)	0,435 (0,304–0,467)	**0,001****
Inferior	0,452 (0,328–0,519)	0,442 (0,303–0,480)	**0,005****
Nasal	0,460 (0,334–0,543)	0,448 (0,301–0,505)	**0,001****
Temporal	0,460 (0,325–0,570)	0,434 (0,290–0,494)	**0,019****
Affected quadrant	0,450 (0,328–0,517)	0,434 (0,286–0,493)	**0,001****
Average	0,459 (0,339–0,527)	0,441 (0,300–0,476)	**0,001****

*Paired T-test **Wilcoxon test

Table-2: Comparison of the Difference Values of Pre-therapy and Post-therapy Capillary Perfusion and Flux Index based on Hypercoagulability.

OCTA	Hypercoagulation (n = 14)	Non-hypercoagulation (n = 7)	*p*-value
Capillary Perfusion Difference			
Superior	-0,0387 ± 0,0572	-0,0431 ± 0,0485	0,863**
Inferior	-0,0089 ± 0,0273	-0,0401 ± 0,0534	0,082**
Nasal	-0,0302 ± 0,0349	-0,0280 ± 0,0320	0,890**
Temporal	-0,0325 (-0,0800–-0,1430)	-0,0450 (-0,1530–0,0330)	0,370*
Affected quadrant	-0,0135 (-0,1670–0,0160)	-0,0640 (-0,1230–(-0,0030))	0,062*
Average	-0,0241 ± 0,0273	-0,0413 ± 0,0288	0,198**
Flux Index Difference			
Superior	-0,025 ± 0,031	-0,033 ± -0,026	0,558**
Inferior	-0,016 ± 0,030	-0,038 ± 0,031	0,138**
Nasal	-0,021 ± 0,027	-0,043 ± 0,035	0,139**
Temporal	-0,021 ± 0,048	-0,032 ± 0,032	0,615**
Affected quadrant	-0,026 ± 0,027	-0,041 ± 0,031	0,281**
Average	-0,020 ± 0,028	-0,037 ± 0,027	0,243**

Table-3: Comparison of HVF and VA Before and After Intervention Between Hypercoagulation and Non-hypercoagulation NAION Subjects.

Clinical Parameters	Hypercoagulation (n=14)			Non-hypercoagulation (n=7)		
	Pra Therapy	Pasca Therapy	*p* value	Pra Therapy	Pasca Therapy	*p* value
Mean Deviation (dB)	-18,00 ± 7,35	-15,05 ± 7,27	**0,033***	-21,19 ± 7,02	-16,65 ± 7,49	0,120*
Visual Field Index	0,46 ± 0,29	0,58 ± 0,28	**0,014***	0,38 ± 0,23	0,54 ± 0,26	0,076*
UCVA (decimal)	0,18 (0,02–0,67)	0,20 (0,05–1,00)	0,074*	0,33 (0,05–1,00)	0,50 (0,05–1,00)	0,285*
BCVA (decimal)	0,23 (0,02–1,00)	0,30 (0,05–1,00)	0,068*	0,49 ± 0,38	0,56 ± 0,43	0,354*

*Wilcoxon test **Paired T-test

Table-4: Comparison of Clinical Improvement by Category between Hypercoagulation and Non-hypercoagulation NAION Subjects.

Clinical Changes	Hypercoagulation (n=14)	Non-hypercoagulation (n=7)	Total (n = 21)
UCVA			
Deterioration	0 (0,0%)	0 (0,0%)	0 (0,0%)
Insignificant deterioration	2 (14,3%)	0 (0,0%)	2 (9,5%)
No changes	4 (28,6%)	4 (57,1%)	8 (38,1%)
Insignificant improvement	4 (28,6%)	1 (14,3%)	5 (23,8%)
Improvement	4 (28,6%)	2 (28,6%)	6 (28,6%)
MD			
Deterioration	1 (7,1%)	0 (0,0%)	1 (4,8%)
Insignificant deterioration	3 (21,4%)	1 (14,3%)	4 (19%)
No changes	0 (0,0%)	0 (0,0%)	0 (0,0%)
Insignificant improvement	5 (35,7%)	3 (42,9%)	8 (38,1%)
Improvement	5 (35,7%)	3 (42,9%)	8 (38,1%)

DISCUSSION

The pathophysiology of NAION still cannot be explained with certainty.[1,2] Several studies are contradictory in stating the mechanism of NAION and the factors that influence it. Hypercoagulation used to be linked in the mechanism of NAION, but later studies denied it. Endothelial damage can result in activation of coagulation so that blood viscosity increases.[3] To a certain degree, the coagulation process continues until a hypercoagulable condition occurs. In hypercoagulable states, increased blood viscosity and thrombosis cause slowing and obstruction of blood flow in the short posterior ciliary artery (SPCA) thus resulting in axonal damage of the optic nerve.[3] Therefore, we tried to investigate the rationale of anticoagulant therapy for NAION patients.

Evaluation of blood flow insufficiency was assessed by measuring CP and FI value through serial OCTA. This study reports significant decrease for both CP and FI despite given therapy. These findings might indicate the natural course of NAION which causes worsen blood flow insufficiency over time. This phenomenon was also reported by other studies. A study by Rebolleda *et al*.[10] found that perfusion density decreased by 17.2% within three months. Similar results were also reported in a study by Fard *et al*.[11] which observed a significant decrease in capillary density from 41.77±4.05% in the acute phase to 34.35±7.30% in the chronic phase. Liu et al.'s study also noted a decline in vessel density in the initial examination and at 1–2 weeks, 1–2 months, and 3–6 months. Given that we only assessed the CP and FI values after a one-month follow-up, it's plausible that these values could worsen even further over time. Comparison between groups showed that the reduction in CP and FI in the hypercoagulation group showed a smaller decline compared to the non-hypercoagulation group in all quadrants. The administration of anticoagulant therapy to the hypercoagulation group is assumed to inhibit the decline in CP and FI. With an extended follow-up period, there is a chance that the CP and FI of the hypercoagulation group may either cease declining or continue to decline further.

Diverging from the prevailing studies attributing NAION to a hypoperfusion etiology, our study challenges this notion by uncovering a significant association between coagulation factors and NAION development. While a separate study contends that NAION is primarily a hypoperfusion-related issue, our findings demonstrate a notable impact of anticoagulants on NAION, even within the subset of patients not exhibiting hypercoagulation.[1,2,4,5] Clinically, all groups exhibit improvement based on numerical value of visual acuity and HVF. However, the group which received anticoagulant showed significant visual field improvement while the untreated group did not. The role of anticoagulants in NAION has been studied in research by Aftab *et al*.[3] The study found that anticoagulant therapy yielded positive results in terms of visual acuity, with an improvement in visual acuity observed in 66.6% of the subjects. Although the study did not evaluate CP and FI, it can be assumed that clinical improvement can be achieved because anticoagulant therapy can enhance blood circulation. Further, we categorized the clinical changes to assess the clinical significance of the difference value.[3,9] Most subjects within the hypercoagulation group experienced improvement of visual acuity and visual field after anticoagulant therapy while the majority of the untreated group did not show any clinical changes. The clinical improvements found in the subjects of this study are in line with studies conducted by Huang, *et al*[12] evaluating visual acuity improvement of more than 0.3 logMAR occurred in 52% of NAION patients at examination 12 months after onset, while visual acuity worsening occurred in 13% of patients. In spite of possible natural improvement in the clinical course of NAION, there were also subjects who experienced deterioration of VA and HVF from the hypercoagulation group. Unlike the hypercoagulation group, in the non-hypercoagulation group, no subjects were found to experience clinical deterioration in visual acuity, and there were no subjects who underwent a significant decrease in visual field. This might be due to the relatively short follow-up duration, considering that previous studies have indicated a decline in visual field at 3 months after onset, followed by a return to baseline. Furthermore, the severity of coagulopathy may result in worse clinical outcomes in NAION.

Although our study revealed clinical improvements, it is crucial to recognize its limitations. Firstly, the sample size was small, and secondly, the follow-up period was relatively short. These constraints may impact the generalizability and our ability to capture long-term outcomes.

CONCLUSION

All the findings presented in this study indicate that anticoagulant therapy could potentially mitigate the progression of flow insufficiency and facilitate clinical enhancement. Considering these results, we recommend that future investigations take into account the potential existence of a hypercoagulable state in NAION and undertake larger-scale studies to evaluate the use of anticoagulants for NAION.

AUTHORS' CONTRIBUTION

SN: Contributed to study conceptualization of study design, data collection, data analysis, writing, and editing. AR, AK, MS, SP, ARH, AK & TDDG: Contributed to study conceptualization of study design. BMB, LRE: Contributed to data analysis, writing, and editing. NDA: Contributed to writing, and editing.

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