Investigating Elevated E-Selectin and P-Selectin Levels in Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) Patients: The Stepping Stone to a Future Clinical Approach

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ABSTRACT

Background**: Studies regarding hypercoagulation in Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) patients have produced conflicting results. With a presumption that the early coagulation phase may affect the occurrence of NAION, this study aims to investigate the early coagulation markers, E-selectin and P-selectin, to determine whether these biomolecular changes play a significant role in NAION, thus potentially leading to a better clinical approach. **Methods**: A cross-sectional study involving two groups of NAION subjects, a hypercoagulation group and a non-hypercoagulation group, was conducted in the Neuro-Ophthalmology Division, Department of Ophthalmology, FKUI-RSCM Kirana from October 2020 to April 2022. All patients were evaluated for E-selectin and P-selectin levels measured using flow cytometry. **Results**: A total of 42 subjects comprising 14 hypercoagulation and 28 non-hypercoagulation subjects were included. In all subjects, E-selectin was strongly correlated with P-selectin (r = 0.862, p < 0.001). There was no significant difference in E-selectin* *and P-selectin values between the groups (p = 0.317 for E-selectin, and p = 0.575 for P-selectin). Prothrombin time and international normalized ratio (INR) were inversely correlated with both E-selectin and P-selectin in the hypercoagulation group (p = 0.032, p = 0.030 for E-selectin and p = 0.044, p = 0.036 for P-selectin). There was no significant correlation between E-selectin and P-selectin for NAION-associated metabolic risk factors. However, higher E-selectin and P-selectin values were found in the presence of risk factors except for P-selectin in the hypertension group.* ***Conclusion*: This interesting finding opens up the potential for considering the involvement of E-selectin and P-selectin in the diagnostic strategy for NAION. It prompts consideration of whether assessing E-selectin and P-selectin levels should be recommended for all NAION patients. Furthermore, considering the role of E-selectin and P-selectin in the early coagulation process, future studies are also needed to further evaluate whether anticoagulants could play a role in the choice of treatment for NAION despite a clinically hypercoagulable state.*

Keywords*: non-arteritic anterior ischemic optic neuropathy, NAION, e-selectin, p-selectin, hypercoagulation*

INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) remains a complex and enigmatic ocular disorder. While the precise mechanisms driving NAION are not fully understood, it is widely believed to be the consequence of a multifactorial interplay.[1-2] Prior studies have reported conflicting results in the evaluation of the role of hypercoagulation in NAION.

The alteration in the natural course of the vascular system triggers the release of specific molecules to maintain homeostasis, among which E-selectin and P-selectin stand out as prominent endothelial biomarkers.[3] E-selectin signifies endothelial injury, while P-selectin denotes platelet activation, both indicative of the early coagulation process.[4]

Studies have revealed elevated levels of E-selectin and P-selectin in individuals with risk factors associated with NAION.[5] However, the pivotal question that remains unanswered is whether these risk factors directly contribute to the pathology of NAION at such a molecular level. To address this knowledge gap, our study aims to evaluate the levels of E-selectin and P-selectin in NAION patients. By conducting this research, we intend to elucidate whether the damage in NAION initiates at this biomolecular juncture, thus potentially providing foundational insight that may guide the development of targeted treatment approaches and ultimately lead to improved patient outcomes.

METHODS

This is a cross-sectional 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. The research was carried out with approval from the Ethics Committee of Health Research, Faculty of Medicine, Universitas Indonesia.

We obtained demographic data and assessed the presence of risk factors associated with NAION, including diabetes mellitus (DM), hypertension, dyslipidemia, hypercoagulation, obesity, smoking, and snoring. To evaluate the results of E-selectin and P-selectin, NAION patients were divided into two groups, hypercoagulation and non-hypercoagulation, based on their blood coagulation markers. D-dimer > 440 μg/dL and/or PT ratio ≤ 0.8, and/or aPTT ratio ≤ 0.8 qualified subjects to the hypercoagulation group. All patients were examined for blood E-selectin and P-selectin levels using flow cytometry. The results were collected and analyzed using SPSS ver. 26.

RESULTS

A total of 42 subjects were included in this study, dominated by male patients (54.8%). The ages ranged from 41–79 years old, with a mean age of 53 years old. Notably, 40.4% of subjects were under 50 years old. Seven systemic risk factors associated with NAION were identified as follows: hypercoagulation, diabetes mellitus, hypertension, obesity, dyslipidemia, smoking, and snoring. Every subject had at least one NAION-associated risk factor. As seen in **Table 1**, hypercoagulation was found in 33% of subjects.

Table 1. Clinical characteristics of NAION subjects.

Clinical Characteristic	Total (%)
Associated Risk Factors	
Dyslipidemia	42 (100%)
Hypercoagulation	14 (33.3%)
Hypertension	26 (61.9%)
Diabetes Mellitus	23 (54.8%)
Obesity	20 (47.6%)
Smoking	12 (28.6%)
Snoring	5 (11.9%)

We observed the early coagulation markers, E-selectin and P-selectin, as we aimed to discover whether the hypercoagulability in NAION may occur in the earlier phase, causing an increased level of the early coagulation markers without increasing the late coagulation marker. We found that E-selectin is strongly correlated with P-selectin ($r = 0.862$, $p < 0.001$). This data also shows that E-selectin and P-selectin are proportionally correlated. Evaluation between groups, as seen in **Table 2**, shows that NAION subjects in the hypercoagulation group exhibited a mean E-selectin value of 68.25 MP/µL and P-selectin value of 55.04 MP/µL, while mean values for E-selectin and P-selectin within the non-hypercoagulation group were 92.53 MP/µL and 65.52 MP/µL, respectively. There was no significant difference in E-selectin and P-selectin values between the groups ($p = 0.317$ for E-selectin and $p = 0.575$ for P-selectin).

Furthermore, the correlation between both E-selectin and P-selectin with other coagulation markers was assessed in each group. As seen in **Table 3**, prothrombin time and international normalized ratio (INR) were inversely correlated in the hypercoagulation group. On the other side, the non-hypercoagulation group did not reveal any correlation between E-selectin and P-selectin with other coagulation markers.

This study analyzed the comparison of early hypercoagulation marker values in each risk factor group, which are DM, hypertension, and obesity. As seen in **Table 4**, no significant differences were found for each early coagulation marker among the respective risk factor groups. However, all data showed higher E-selectin and P-selectin values in the presence of risk factors except for P-selectin in the hypertension group.

Table 2. Comparison of E-selectin and P-selectin values between the hypercoagulation and non-hypercoagulation groups.

Parameters	Hypercoagulation (n = 14)	Non-hypercoagulation (n = 28)	P-value
E-selectin (MP/µL)	68.25 (38.13–241.50)	92.53 (14.21–241.50)	0.317*
P-selectin (MP/µL)	55.04 (8.78–214.67)	65.52 (8.94–211.30)	0.575*

*Mann-Whitney Test

Table 3. Correlation between E-selectin and P-selectin values between groups.

	Hypercoagulation (n = 14)		Non-hypercoagulation (n = 28)	
	E-selectin (MP/µL)	P-selectin (MP/µL)	E-selectin (MP/µL)	P-selectin (MP/µL)
PT	−0.574 (p = 0.032)	−0.544 (p = 0.044)	0.038 (p = 0.848)	−0.033 (p = 0.867)
aPTT	0.049 (p = 0.867)	−0.154 (p = 0.599)	0.290 (p = 0.134)	0.344 (p = 0.073)
D-dimer	−0.083 (0.778)	−0.303 (0.292)	0.032 (p = 0.871)	0.057 (p = 0.773)
Fibrinogen	0.263 (p = 0.364)	0.219 (p = 0.451)	0.156 (p = 0.427)	0.090 (p = 0.647)
INR	−0.578 (p = 0.030)	−0.564 (p = 0.036)	−0.160 (p = 0.416)	−0.238 (p = 0.222)

*Pearson Test

Table 4. Comparison of E-selectin and P-selectin in each NAION risk factor group

	E-selectin (MP/μL)	P-value	P-selectin (MP/μL)	P-value
Diabetes Mellitus				
Yes	91.38 (26.83–241.50)	0.390	69.00 (8.78–214.67)	0.318
No	86.69 (14.21–228.71)		54.00 (8.94–173.57)	
Hypertension				
Yes	88.625 (26.83–241.50)	0.938	60.38 (8.78–214.67)	0.928
No	82.755 (14.21–241.50)		65.52 (8.94–211.30)	
Obesity				
Yes	91.69 (14.21–241.50)	0.450	63.655 (8.78–214.67)	0.623
No	78.025 (26.83–228.71)		54.58 (13.42–169.05)	

*Mann-Whitney Test

DISCUSSION

The search for the mechanism of NAION has been a long journey in NAION research, yet there is still no definitive understanding of its pathophysiology. However, it is known to be a multifactorial disease.[1,2,6] Studies have revealed conflicting results regarding hypercoagulation as the factor underlying NAION pathology. Later studies have even stated that NAION is a hypotensive disorder instead of an occlusive disorder, therefore belittling the role of hypercoagulation. Nevertheless, to the best of our knowledge, most studies conducted so far have not considered early coagulation markers in their efforts to discover the role of hypercoagulation in NAION. We assume that NAION is a microvascular disease in which hypercoagulation can occur without elevating the later coagulation markers, as seen in more macrovascular conditions. We believe that hypercoagulation still plays a role in NAION physiology. As found in this study, we observed that 33.3% of NAION subjects had hypercoagulation. Aligned with this finding, a previous retrospective study between January 2012 and December 2017 in Cipto Mangunkusumo Hospital Jakarta revealed that 19% of NAION subjects had hypercoagulation.[6]

E-selectin is a glycoprotein that endothelial cells express in response to injury. Endothelial damage triggers the initial stages of coagulation, including adhesion, accumulation, platelet activation, and the generation of thrombin.[7-8] P-selectin, another glycoprotein, plays a role in promoting adhesion and platelet activation, and it becomes expressed on the surface of activated platelets.[3] The expression of E-selectin and P-selectin may suggest the early activation of the coagulation process, hence making them early coagulation markers. E-selectin and P-selectin have been used as biomarkers for coagulopathy in various thrombosis-related diseases.[3,7-8] P-selectin has also been employed in microvascular coagulopathy research, as seen in Ogata et al.'s[9] study, where diabetic retinopathy patients exhibited elevated procoagulant levels, including P-selectin. Assessing coagulation status in the early phases may offer a different perspective in NAION. In this study, E-selectin levels were proportionally correlated with P-selectin. The activation of E-selectin in NAION patients, indicating endothelial damage, is followed by platelet activation marked by P-selectin activation, hence the activation of the intrinsic coagulation pathway in NAION patients. This presumption was strengthened by comparing E-selectin and P-selectin values between groups and their correlation with the late coagulation markers between groups.

There was no statistically significant difference in the levels of E-selectin and P-selectin between individuals with hypercoagulation and those without hypercoagulation. Interestingly, the non-hypercoagulation group even displayed higher values for both E-selectin and P-selectin. Due to this lack of statistical difference, it can be inferred that individuals with NAION exhibit E-selectin and P-selectin levels on par with those of hypercoagulation patients. This observation is consistent with a study conducted by Nagy et al., which reported elevated levels of P-selectin in NAION patients.

Moreover, we found a correlation between prothrombin time and INR and E-selectin and P-selectin in the hypercoagulation group. The significant correlation implies that the intrinsic coagulation system activated by E-selectin and P-selectin was then followed by shortened prothrombin time and INR, the late coagulation markers, suggestive of coagulopathy. These results were not found in the non-hypercoagulation group, indicating that activated E-selectin and P-selectin might not be followed by elevated late coagulation markers. Looking back to the comparison between groups, there was no statistically significant disparity in E-selectin and P-selectin levels. Interestingly, the non-hypercoagulation group exhibited higher levels of both E-selectin and P-selectin than the hypercoagulation group, yet this was not accompanied by a rise in the late coagulation markers. There is a possibility, however, that this might lead to increased late coagulation markers over time.

Besides coagulopathy, increased levels of E-selectin and P-selectin were also found in metabolic diseases associated with NAION. Studies have reported increased soluble E-selectin and P-selectin levels in hypertensive patients. Studies by Bolbou et al.[10] showed high E-selectin and P-selectin levels in diabetic patients. Lee et al.[11] reported the same result in obese patients. The risk factor found in all of the NAION subjects, dyslipidemia, is also known to exhibit increased P-selectin levels. These studies showed that most NAION-associated risk factors themselves revealed high levels of E-selectin and P-selectin. We report quite similar results. Albeit insignificant, higher E-selectin was found in diabetic, hypertensive, and obese patients compared to the subjects without those risk factors. Additionally, P-selectin was also found to be higher in diabetic and obese patients.[12]

Although hypercoagulation was still found in NAION patients and the early coagulation markers were considered equal between groups, we should not neglect the potential of hypercoagulation in NAION. Those insights give rise to the idea that there might be an escalated initiation of the coagulation process that potentially leads to microvascular hypercoagulation, in which, hypothetically, coagulopathy may occur despite the normal hypercoagulation biomarkers usually detected in macrovascular disorders. In addition, NAION is known as a multifactorial disease. Despite its relation to coagulopathy, most NAION-associated risk factors also showed high levels of E-selectin and P-selectin. Thus, we suggest that the pathology of NAION begins at the level of biomolecular alteration of E-selectin and P-selectin.

CONCLUSION

This interesting finding opens up the potential for considering the involvement of E-selectin and P-selectin in the diagnostic strategy for NAION. It prompts consideration of whether assessing E-selectin and P-selectin levels should be recommended for all NAION patients. Furthermore, considering the role of E-selectin and P-selectin in the early coagulation process, future studies are also needed to further evaluate whether anticoagulants could play a role in the choice of treatment for NAION despite a clinically hypercoagulable state.

COMPETING INTEREST

The authors report no conflict of interest.

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