Original Article

Prognostic value of neutrophil-to-lymphocyte ratio in patients undergoing endovenous ablation therapy for venous insufficiency

Venöz yetmezlik nedeniyle endovenöz ablasyon tedavisi uygulanan hastalarda nötrofil/lenfosit oranının prognostik değeri

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ABSTRACT

Objectives: In this study, we aimed to investigate the role of neutrophil/lymphocyte ratio (NLR) in patients undergoing endovenous ablation (EVA) therapy in predicting success of the procedure, perioperative complications, and mid-term outcomes.

Patients and methods: A total of 284 Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification 2 to 6 patients (196 males, 88 females; mean age: 57 years; range, 23 to 87 years) who underwent EVA due to the symptoms of great saphenous vein insufficiency between January 2016 and December 2016 were retrospectively analyzed. Of these patients, 146 (52.1%) received radiofrequency ablation (RFA) and 138 (47.9%) received endovenous glue ablation (EGA) treatment. The patients were followed at three hours, on Day 7, at one and six months after the procedure. The NLR, procedural success, and perioperative complications were evaluated.

Results: The mean preoperative NLR was 3.03±0.9 in the RFA and 3.36±1.2 in the EGA group. The patients with a higher NLR had significantly a higher rate of postoperative ecchymosis (hazard ratio: 1.05; 95% confidence interval [CI]: 1.01-1.10; p=0.033) and postoperative pain (hazard ratio: 1.1; 95% CI: 1.01-1.2; p=0.04). At six months, we found that higher NLR was correlated with partial recanalization rate in the RFA (r=0.84) and high mean VCSS. The NLR was found to be predictive for complications with a sensitivity of 75% and specificity of 62%.

Conclusion: Our study results suggest that the NLR is a quick, cheap, and easily measurable inflammatory marker and is a surrogate marker of perioperative outcomes in patients undergoing EVA therapy.

Keywords: Lymphocyte; neutrophil; venous insufficiency.

ÖZ

Amaç: Bu çalışmada endovenöz ablasyon (EVA) tedavisi yapılan hastalarda işlem başarısı, ameliyat sırası komplikasyonlar ve orta dönem sonuçların öngörülmesinde nötrofil/lenfosit oranının (NLR) rolü araştırıldı.

Hastalar ve Yöntemler: Ocak 2016 - Aralık 2016 tarihleri arasında Klinik-Etiyoloji-Anatomi-Patofizyoloji (CEAP) skorları 2-6 olan ve büyük safen ven yetmezliği semptomları nedeniyle EVA yapılan toplam 284 hasta (196 erkek, 88 kadın; ort. yaş: 57 yıl; dağılım, 23-87 yıl) retrospektif olarak incelendi. Bu hastaların 146'sına (%52.1) radyofrenkans ablasyon (RFA) ve 138'ine (%47.9) endovenöz yapıştırıcı ablasyon tedavisi yapıldı. Hastalar işlemden sonra üçüncü saatte, yedinci günde, birinci ve altıncı aylarda takip edildi. Nötrofil/lenfosit oranı, işlem başarısı ve ameliyat sırası komplikasyonlar değerlendirildi.

Bulgular: Ameliyat öncesi ortalama NLR RFA grubunda 3.03±0.9 ve EGA grubunda 3.36±1.2 idi. Daha yüksek NLR'li hastalarda ameliyat sonrası ekimoz (risk oranı: 1.05; 95% güven aralığı [GA]: 1.01-1.10; p=0.033) ve ameliyat sonrası ağrı (risk oranı: 1.1; 95% GA: 1.01-1.2; p=0.04) oranı daha yüksekti (hazard ratio: 1.05; 95% GA: 1.01-1.10; p=0.033) Altıncı ayda RFA'da yüksek NLR parsiyel rekanalizasyon oranı (r=0.84) ve yüksek ortalama VCSS ile ilişkili bulundu. Nötrofil/lenfosit oranı, %75 duyarlılık ve %62 özgüllük ile komplikasyonlar açısından öngördürücü idi.

Sonuç: Çalışma sonuçlarımız NLR'nin çabuk, ucuz ve kolaylıkla hesaplanabilen bir enflamasyon belirteci olup, EVA tedavisi yapılan hastalarda ameliyat sırası sonuçların destekleyici bir belirteci olduğunu göstermektedir.

Anahtar sözcükler: Lenfosit; nötrofil; venöz yetmezlik.

Chronic venous disease (CVD) is a highly prevalent cosmetic and physiological problem which has serious consequences such as pain, discomfort, and reduced quality of life and can cause complications including skin lesions and ulcerations. Consequently, it can be life-threatening, leading to the loss of the affected limb.[1,2]

Radiofrequency ablation (RFA) of the great saphenous vein (GSV) causes thermal damage in the vein wall resulting in fibrosis and clot formation. The ClosureFast catheter (Covidien, Mansfield, MA, USA) allows a simultaneous coagulation of a vein segment in 7 cm in length for 20 sec at a temperature of 120°C. An adhesive substance (a tissue glue derived from cyanoacrylic glue) is applied into the GSV lumen in endovenous glue ablation (EGA) technique.

The neutrophil/lymphocyte ratio (NLR) is defined as the ratio of absolute counts of neutrophils and lymphocytes. Neutrophils mediate inflammation by several mechanisms such as release of arachidonic acid metabolites and platelet-aggravating factors and reflect the inflammatory response.[3] Low lymphocyte counts reflect the cortisol-induced stress response.[4] Therefore, this simple, relatively cheap marker correlates with the markers of a proinflammatory state. The NLR has been adopted for the prognostic evaluation in various areas, such as peripheral artery disease,[5] bladder cancer,[6] coronary artery disease,[7] colorectal cancer,[8] prostatic hyperplasia,[9] pancreatic cancer,[10] and pulmonary embolism,[11] although it has never been studied in CVD and endovenous ablation therapy (EVA).

In this study, we aimed to investigate the role of the NLR in patients undergoing EVA for predicting success of the procedure, perioperative complications, and mid-term outcomes.

PATIENTS AND METHODS

This retrospective study included a total of 284 Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification 2 to 6 patients (196 males, 88 females; mean age: 57 years; range, 23 to 87 years) who were suffering from the symptoms of GSV insufficiency such as pain, itching, limb heaviness, cramps, restless leg, ankle swelling, tenderness, or pain along bulging varicose veins and underwent EVA between January 2016 and December 2016. Of these patients, 146 (52.1%) received RFA and 138 (47.9%) received EGA treatment. The study protocol was approved by the Ankara Numune Training and Research Hospital Ethics Committee. A written informed consent was obtained from the patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic variables and Doppler measurements (Aloka Prosound Alpha 7-Hitachi Aloka Medical, Japan) of the GSV are shown in Table 1.

The patients whose vein diameter <20 mm[12] and saphenous vein reflux higher than the cut-off value of 0.5 sec, were included in the study. Patients who had deep vein thrombosis and a vein diameter of >20 mm were excluded.

Operative technique

The patients were placed in supine position. Before the procedure, Doppler ultrasonography was

Table 1. Demographic and operative variables

Variables	Received radiofrequency ablation (n=146)					Endovenous glue ablation (n=138)					
	n	%	Mean±SD	Mean	Min-Max	n	%	Mean±SD	Mean	Min-Max	p
Age (year)		46.15					45.23				>0.05
Gender											
Female	102					64					0.0016
Body Mass Index		1.86					1.75				>0.05
Clinical-Etiology-Anatomy-Pathophysiology					2-6					2-6	>0.05
SFJ diameter (mm)				8.54	5.5-19.8				7.74	5.5-11.2	0.0534
Above knee (mm)				5.42	2.9-11.3				5.32	3.5-9.7	>0.05
Ablation length (cm)		34.73					34.29				>0.05
Venous Clinical Severity Score			4.75±1.2					4.48±1.5			>0.05
Tumescent anesthesia volume (mL)					500-1000					0	0.0001
Distance of GSV from the skin (SFJ)		12.63					12.74				>0.05
Distance of GSV from the skin (middle of the thigh) (cm)		11.69					10.87				>0.05
Distance of GSV from the skin (above the knee) (cm)		11.98					11.16				>0.05
Mean operation time (min)			23.8±9.6					12.5±7.3			0.014

SD: Standard deviation; Min: Minimum; Max: Maximum; GSV: Great saphenous vein; SFJ: Saphenofemoral junction.

Table 2. Complications

Complications	Received radiofrequency ablation		Endovenous glue ablation		
	n	%	n	%	p
Ecchymosis	13	8.9	2	1.44	0.00115
Thrombophlebitis	0	0	0	0	>0.05
Paresthesia	6	4.1	0	0	0.0021
Postoperative pain	14	9.5	2	1.44	0.00031
Skin burns	0	0	0	0	>0.05
Deep vein thrombosis	0	0	0	0	>0.05
Pulmonary thromboembolism	0	0	0	0	>0.05

performed. A linear 7 Mhz probe of the Doppler was inserted into a sterile cover. Under the ultrasound guidance, the GSV was punctured at or above the knee joint and cannulated. A 0.025 inch guidewire was introduced into the GSV and a 6-Fr introducer sheath was advanced over it. The tip of the RFA catheter (ClosureFast RFA, NYSE:COV) or the EGA catheter (Invamed venaBLOCK Vein Sealing System, HealthLink Europe BV, The Netherlands) was placed 2 to 3 cm inferior to the saphenofemoral junction (SFJ) under the ultrasonographic guidance.

In the RFA group, a tumescent solution was infiltrated into the saphenous compartment between the superficial and deep fascia. We performed infiltration from proximal to the distal direction, as it could help to relieve pain at the time of distal infiltration due to the proximal anesthetic effect. The solution consisted of 500 mL normal saline + 2% lidocaine 20 mL + sodium bicarbonate 2.5 mL + epinephrine 0.5 mL. After infiltration of the tumescent solution, the position of the catheter tip was confirmed using ultrasound. The radiofrequency generator (VNUS medical Technologies Inc., San Jose, CA, USA) allowed simultaneous coagulation of a 7 cm vein segment, while the generator monitored and maintained a temperature of 120°C. The time of energy application was 20 sec. We recommended two cycles of ablation for the first segment of the saphenous vein and the segments where the incompetent perforators were located. We also applied a manual external compression along the heating element to create a bloodless field.

In the EGA group, no tumescent anesthesia was used. After positioning the tip of the catheter, an adhesive substance about 2 mL (a tissue glue derived from cyanoacrylic glue) was applied into the vein lumen to obliterate the vessel. As the final step, we performed concomitant ambulatory phlebectomy to remove refluxing tributary veins. A compression bandage was wrapped around the leg and the patients were encouraged to walk. At three hours, it was worn out and the patients wore compression stocking for at least seven days.

NLR definition

The pre-treatment white blood count and differential counts were evaluated on admission before the operation. The postoperative counts evaluated taken seven days later after the operation. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[13]

The patients were followed at three hours, on Day 7, at one and six months after the procedure. The Venous Clinical Severity Scores (VCSS) of the patients were recorded. Also the possible complications, such as ecchymosis, thrombophlebitis, paresthesia, postoperative pain, and skin burns were noted. At each visit, Doppler ultrasonography was performed.

Statistical analysis

Statistical analysis was performed using the PASW version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in mean ± standard deviation (SD), and number and frequency. The Student's t-test and paired samples t test were used for the statistical analysis, if the data were normally distributed; otherwise, the non-parametric Mann Whitney U and Wilcoxon's test were used. The chi-square test was performed to compare categorical variables. A p value less than 0.05 was considered statistically significant.

RESULTS

The demographic data of the patients are shown in Table 1. There was no statistically significant difference between the groups in terms of age,

CEAP classification, and Doppler ultrasonographic measurements among the groups. The number of female patients was higher in the RFA group. The mean diameter of the SFJ was 8.54 mm in the RFA group and 7.74 mm in the EGA group (p=0.0534). Tumescent anesthesia was not used in the EGA group, while all operations in the RFA group were performed with tumescent anesthesia. The mean operation time was longer in the RFA group (23.8±9.6 min vs 12.5±7.3 min, respectively; p=0.014). The immediate occlusion rate was 100% for both groups.

Complications are shown in Table 2. The number of patients who suffer from postoperative ecchymosis, paresthesia, and pain in the RFA group was more than the patients in the EGA group. Thrombophlebitis, skin burns, deep vein thrombosis, and pulmonary thromboembolism were observed in both groups.

The mean preoperative NLR was 3.36±1.2 in the RFA group and 3.03±0.9 in the EGA group. Within the groups, the patients with a higher NLR had significantly a higher rate of postoperative ecchymosis (hazard ratio: 1.05; 95% CI: 1.01-1.10; p=0.033) and postoperative pain (hazard ratio: 1.1; 95% CI: 1.01-1.2; p=0.04).

All patients reached the six-month follow-up point. The total occlusion rate at one and six months were 98.5% (136/138) and 97.1% (134/138) in the EGA group, respectively. The total occlusion rate at one and six months were 97.3% (142/146) and 96.0% (140/146), respectively. The mean VCSS was improved to 1.44±1.1 in the RFA group and 1.29±0.7 in the EGA group at the postoperative sixth month, respectively (p<0.001). The mean NLR was calculated as 1.95±0.6 in the RFA group and 1.71±0.4 in the EGA group at six months during follow-up. We found that higher NLR was correlated with partial recanalization rate in the RFA (r=0.84) and high mean VCSS (r=0.75).

The receiver operating characteristic analysis revealed that, using a cut-off point of 3, NLR could predict complications with a sensitivity of 75% and specificity of 62%.

DISCUSSION

The contribution of the inflammatory process to the pathophysiology of the chronic venous disease was well documented by Coleridge Smith et al.[14] and named as the white cell trapping hypothesis. This theory suggests that increased venous pressure leads to leukocyte activation, adhesion, and extravascular migration with the release of proteolytic enzymes and free radicals. Furthermore, neutrophil degranulation and activation have been shown in normal individuals[15] and patients with chronic venous disease exposed to short-term venous hypertension.[16]

Recently, the NLR has emerged as a new inflammatory biomarker which can be used as an indicator of inflammation. It is simple, quick, relatively inexpensive, and more available than any other markers and has shown to be a good predictor for cardiovascular outcomes such as pulmonary embolism[11] and peripheral arterial occlusive disease.[4,17] White blood cell subtypes, particularly neutrophils, play a key role in the atherosclerotic process.[18] Diabetic nephropathy, retinopathy, and cancer may be also seen in conditions where the NLR is evaluated and a significant positive correlation is shown.[19] Lymphopenia in the inflammatory process can be explained by apoptosis and is a frequent finding secondary to increased levels of corticosteroids in stress conditions such as acute coronary syndrome and stroke.[20] On the other hand, patients who have a relative constitutional lymphopenia would be easily classified as having a high NLR without an increased inflammatory activity. Therefore, clinicians should be careful with the false-positive results. In addition, it has been used in the prediction of coronary artery disease mortality, prognosis of ST-elevation myocardial infarction, and assessment of stent thrombosis risks.[21-23] In almost all of these studies, high NLR levels were found to be associated with worse outcomes.[17-20] The necessity of easily accessible and cost-effective parameters to predict the peri- and postoperative outcomes in patients undergoing EVA has been the basis of our study.

In our study, at six months of follow-up, we found out that the VCSS was improved and the NLR became lower in both groups. This result suggests that EVA treatment with medication and compression therapy can reduce inflammation.

Furthermore, postoperative pain, ecchymosis, and paresthesia were observed more frequently in the RFA group, compared to the EGA group. This result can be explained with the energy delivered by the RF generator, resulting in a temperature of 120°C, multiple needle insertions to deliver tumescent anesthesia, and the possible cutaneous nerve damage caused by the phlebectomy incisions. However, the stunning result that in the same group, patients

with a higher NLR had a significantly higher rate of postoperative ecchymosis and postoperative pain can be only explained by the degree of inflammation. In addition, we found that a higher NLR was correlated with a higher partial recanalization rate in RFA with high mean VCSS.

Several studies have suggested that leukocytes contribute to venous thrombosis by damaging the endothelium.[24] Elevated NLR levels indicate a higher level of inflammation, indicating that it can be correlated with a more severe form of disease and an increased risk for adverse events, including deep venous thrombosis or pulmonary embolism. However, in our study group, we observed no deep venous thrombosis or pulmonary embolism.

Our study is the first study which used the NLR to predict the peri- and postoperative results and prognosis in the patients who underwent EVA. Since it is the first study, there is a lack of information in the cardiovascular literature. In addition, a few limitations of our study deserve to be mentioned. Other inflammatory parameters such as interleukin-6, C-reactive protein, and intercellular adhesion molecule-1 could have been studied to correlate the results.

In conclusion, our study results indicate that the NLR, which is quick, cheap, and easily measurable novel inflammatory marker with routine complete blood count analysis, is a surrogate marker of peri- and postoperative outcomes in patients undergoing EVA.

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