Research Article / Araştırma Makalesi

The Association of Whole Blood Viscosity with Clinical Outcomes After Mechanical Thrombectomy for Acute Ischemic Stroke

Akut İskemik İnme İçin Mekanik Trombektomi Sonrası Klinik Sonuçlarla Tam Kan Viskozitesinin İlişkisi

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Abstract

Background: Blood viscosity (BV) is relationship cerebrovascular events. However, the association with between BV and clinical outcomes after acute ischemic stroke (AIS) has not been studied. This study evaluated the relationship between whole blood viscosity (WBV) and clinical outcomes after AIS.
Materials and Methods: The study enrolled 240 consecutive patients with AIS who underwent mechanical thrombectomy (MT) between 2017 and 2019 years. The all patients were divided according to the modified Rankin Scale (mRS) score, as good (mRS 0–2) and poor (mRS 3–6) clinical outcomes group. WBV was calculated by the formula derived from total protein and haematocrit levels.
Results: Poor clinical outcomes group presented significantly higher WBV values both at LSR and HSR ($p < 0.001$). Multivariate analysis, both high WBV at LSR (Odd ratio: 2.679, $p < 0.001$) and high WBV at HSR (Odd ratio: 1.278, $p < 0.001$) were independent predictors for poor clinical outcomes. In receiver operating characteristic analysis, value of 16.1 WBV at HSR had 76.7% sensitivity and 76% specificity for predicting poor clinical outcomes and a value of 38.5 WBV at LSR had 75.3% sensitivity and 78% specificity for predicting poor clinical outcomes. There was a significant positive correlation between WBV at LSR and mRS score (0-6) ($r = 0.457$, $p <0.001$) and WBV at HSR and mRS score (0-6) ($r = 0.452$, $p <0.001$).
Conclusions: Increased WBC may be independent risk factor and correlated with poor clinical outcomes in AIS patients treated with MT.

Key Words: Blood viscosity, Stroke, Acute, Thrombectomy

ÖZ.

Amaç: Artmış kan viskozitesi (KV) iskemik inme ile ilişkilidir. Ancak, akut iskemik inme (Aİİ) sonrası kan viskozitesi ve klinik sonuçlar arasındaki ilişki şu ana kadar yeterince değerlendirilmemiştir. Bu çalışmanın amacı tam kan viskozitesi (TKV) ve Aİİ sonrası klinik sonuçlar arasındaki ilişkiyi değerlendirmektir.
Materyal ve Metod: Çalışmaya 2017-2019 yılları arasında mekanik trombektomi (MT) yapılan 240 ardışık Aİİ hastası alındı. Hastalar 90. günde değerlendirilen modifiye Rankin Skalası (mRS) skoruna göre iyi klinik sonuç (mRS 0-2) ve kötü klinik sonuç (mRS 3–6) olarak iki gruba ayrıldı. TKV, hem düşük kayma hızında (DKH) hem de yüksek kayma hızında (YKH) hematokrit ve total plazma protein seviyeleri kullanılarak hesaplandı.
Bulgular: Kötü klinik sonuç grubunda TKV hem DKH' de (34.9 ± 0.2'ye karşı 44.9 ± 3.2; $p <0.001$) hem de YKH'de (15.9 ± 0.28'e karşı 16.4 ± 0.42; $p <0.001$) anlamlı olarak daha yüksekti. ROC analizinde, YKH' deki TKV' nin 16,1'lik kesme değeri, kötü sonuçları tahmin etmek için % 76,7 duyarlılık ve % 76 özgüllüğe sahipti. DKH'deki TKV'nin 38,5'lik kesme değeri kötü klinik sonuçları tahmin etmek için % 75,3 duyarlılık ve % 78 özgüllüğe sahipti. Çok değişkenli analizde hem DKH'de hem de YKH'deki yüksek TKV değerleri, kötü sonuçlar için bağımsız prediktörler olarak saptandı. DKH'deki TKV değerleri ile mRS skoru (0-6) ($r = 0.457$, $p <0.001$) arasında, YKH'deki TKV değerleri ile mRS skoru (0-6) arasında anlamlı pozitif korelasyon vardı ($r = 0.452$, $p <0.001$).
Sonuç: Hem DKH de hem de YKH de artmış TKV değerleri, MT ile tedavi edilen Aİİ hastalarında kötü klinik sonuçlar için bağımsız risk faktörü olabilir, mRS skoru ile pozitif korelasyon gösterir.

Anahtar kelimeler: Kan viskozitesi, İnme, Akut, Trombektomi

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Introduction

Blood viscosity (BV) is an important blood property. Blood viscosity is determined by haematocrit, plasma viscosity, red blood cells and shear rate (1). WBV can be calculated from hematocrit (Hct) and plasma total protein levels (TP) for low and high shear rates. Increased blood viscosity (BV) is relationship atherothrombotic events and in many studies with ischemic stroke (2-4).

Mechanical thrombectomy (MT) is a standard treatment for acute ischemic stroke (AIS) patients with large vessel occlusion (LVO) if they undergo the procedure within an appropriate time interval (5). Several meta-analyses showed a substantial clinical efficacy of MT in AIS (6). Despite experienced stroke teams, a good outcome is not achieved in all patients treated. Many factors can affect functional outcome after MT. However, an association between WBV and functional outcomes have not yet been studied.

In this study, the effect of WBV on clinical outcomes of AIS due to a LVO treated with MT was investigated.

Materials and Methods

Study population

In the present study, 240 consecutive patients with AİS who underwent MT between 2017 and 2019 who were registered in the database of Samsun Training and Research Hospital were investigated. Patients with anticoagulant drug use for any reason, acute coronary syndromes, important hypertrophy of the left ventricle, severe valvular disorders and prosthetic valve, acute decompensated heart failure, chronic infectious diseases, chronic inflammatory or autoimmune diseases, and oncologic pathologies, severe anemia, and missing data were excluded from the study. Demographical data, medical history, drugs used and laboratory values were obtained using the hospital's database. Ethics Committee of University of Health Sciences, Training and Research Hospital (TUEK1-2019 BADK /1-5).

Study Procedure

In all patients, large cerebral artery occlusions were detected on computed tomographic angiography. MT was performed in case of occlusion of LVO (middle cerebral artery, internal carotid artery, basilar artery). MT was initiated within the first 6 hours after stroke onset. MT was performed using stent retrievers. Stroke subtype was determined according to TOAST (Trial of Org 10172 in the Acute Stroke Treatment) classification. Successful recanalization was defined as modified TICI (Thrombolysis in Cerebral Infarction Scale) ≥2b. ICH (intracerebral hemorrhage) was evaluated computed tomography or magnetic resonance imaging after 24 hours. Neurological deficit was evaluated using the NIHSS (National Institutes of Health Stroke Scale) after 24 hours and clinical outcome after 90 days using the modified Rankin scale (mRS). The mRS is evaluated of patient functional independence following a stroke, with scores ranging from 0 (fully independent) to 6 (dead) (7). The mRS scoring was evaluated by a neurologist at outpatient clinic visits. The all patients were divided into two groups according to the mRS score evaluated on day 90, as good clinical outcomes (mRS 0–2 group) and poor clinical outcomes (mRS 3–6 group).

WBV was calculated according to Hct and TP values evaluated at the time of emergency application. The WBV value was calculated using De Simone's formula and blood values at the time of admission (8). The WBV value was calculated separately for both shear rates.

Whole Blood Viscosity Measurement via De Simone's Formula (8).

WBV at HSR = 208/sec^{-1}, and WBW at LSR = 0.5/sec^{-1} were calculated using Hct and TP values.

WBV at HSR formula (208/sec^{-1}): (0.12 × HcT) + 0.17 (TP − 2.07)

WBV at LSR formula (0.5/sec^{-1}): (1.89 × HcT) + 3.76 (TP − 78.42)

All data were compared between the two groups. Two different logistic regression models were established for LSR and HSR (Models 1 and 2) to determine the risk factors affecting poor clinical outcomes. Independent risk factors affecting poor clinical outcomes were compared using these models.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences V23 (SPSS Inc., Chicago, IL, USA) program. The independent samples *t*-test was used to compare normally distributed quantitative data and the Mann–Whitney *U*-test was used to analyze data that did not follow a normal distribution. Categorical data were analyzed using the chi-square test. The individual effects of all variables were examined in a univariate binary logistic regression analysis. Two different logistic regression models were established separately for LSR and HSR; independent risk factors affecting poor clinical outcomes were calculated using multivariate logistic regression analysis, and the comparative results are presented. The cut-off values for LSR and HSR regarding clinical outcome were examined using ROC analysis and area under the curve (AUC), positive-negative predictive value and accuracy values corresponding to each cut-off value are presented. Spearman correlation analysis was performed to examine the correlation between WBV and mRS score. A p-value less than 0.05 is statistically significant.

Results

Demographic characteristics and clinical outcomes data of the study groups are summarized in Table 1. Hemoglobin (13.3 ± 1.7 g/ dL vs. 14.4 ± 1.2 g/dL; p = 0.002), Hct (38.9% ± 3.8 vs. 41.7% ± 3.3; p < 0.001) and TP (6.8 ± 1.2 g/ dL vs. 7.1 ± 1.4 g/L; p = 0.013) levels were found to be higher in the In poor clinical outcomes group than the good clinical

outcomes group. There were no significant difference between the two groups in terms of other demographic characteristics, procedural results and medical history. In addition, there was no significant difference between the two groups in terms of occlusion site, mTICI score, symptomatic ICH and stroke subtypes (p > 0.05). In poor clinical outcomes group, WBV values were significantly higher compared to the good clinical outcomes group [both HSR (15.9 ± 0.28 vs. 14.4 ± 1.2 16.4 ± 0.42; p < 0.001) and LSR (34.9 ± 0.2 vs. 44.9 ± 3.2; p < 0.001)].

Table 1. Demographic, procedural and medical history data for the study group.

Variables	mRS 0-2 (n=124)	mRS 3-6 (n=116)	p-value
Age, years	68± 7.5	71± 8.5	0.053
Gender, female n,(%)	62(50)	6556)	0.805
Hypertension n,(%)	98 (79)	90 (77)	0.204
Diabetes Mellitus n,(%)	41 (33)	45 (38)	0.895
Congestive Heart Failure n,(%)	21 (16)	19 (16)	0.766
Coronary Artery Disease n,(%)	53 (42)	49 (26)	0.255
Atrial Fibrillation n,(%)	38 (32)	36 (31)	0.166
Smoking n,(%)	25 (20)	24 (20)	0.086
NIHSS	14.5 ± 0.2	15 ± 0.3	0.852
Hemoglobin (g/dL)	13.3 ± 2.5	14.4 ± 1.2	**0.002**
Hematocrit (%)	38.9 ± 3.8	41.7 ± 3.3	**< 0.001**
White Blood Cell (10^3 µl)	10.2 ± 2.3	9.7 ± 2.3	0.755
Platelet (10^3 µl)	329 ± 38	332 ± 41	0.569
Total Protein (g/L)	6.8 ± 1.2	7.1 ± 1.4	**0.013**
Albumin (g/dL)	3.5 ± 0.5	3.4 ± 0.6	0.067
Total cholesterol, mg/dl	171 ± 81.4	169.5 ± 74.5	0.592
LDL-C, mg/dl	104 ± 31	107 ± 300	0.064
HDL-C, mg/dl	37.7 ± 11.3	38.3 ± 11.5	0.112
TG, mg/dl	148.8 ± 62.2	138.7 ± 60.2	0.095
Symptomatic ICH n,(%)	7 (5)	10 (8)	0.308
mTICI score 2b-3 n,(%)	101(81)	91(78)	0.326
Stroke subtype n,(%)			
Cardioembolism	61 (49)	61 (52)	0.165
Large artery atherosclerosis	43 (35)	40 (34)	0.153
Other	20 (16)	15 (14)	0.096
Occlusion site n,(%)			
MCA, M1 segment	66 (53)	63 (54)	0.103
MCA, M2 segment	28 (23)	23 (20)	0.098
ACA, A1 segment	3 (2)	5 (4)	0.203
Basiller artery	7 (5)	8 (7)	0.156
Internal Carotis Artery	20(17)	17 (15)	0.088
WBV at LSR ($0,5/s^{-1}$)	34.9 ± 2.2	44.9 ± 3.2	**<0.001**
WBV at HSR ($208/s^{-1}$)	15.9 ± 0.28	16.4 ± 0.42	**<0.011**

WBV at HSR, Whole blood viscosity at high shear rate; WBV at LSR, Whole blood viscosity at low shear rate; LDL-C, low-density lipoprotein cholesterol; TG,Trigliserid

NIHSS, National Institutes of Health Stroke Scale; ICH, Intracranial hemorrhage; mTICI, Modified treatment in cerebral ischemia; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; TG, Triglycerides; ACA, Anterior cerebral artery MCA, Middle cerebral artery; WBV at HSR, Whole blood viscosity at high shear rate; WBV at LSR, Whole blood viscosity at low shear rate.

In ROC analysis, a cut-off value of 16.1 WBV for HSR had an 76.7% sensitivity and 76% specificity for predicting poor clinical outcomes [(AUC): 84.3%, 95% CI 72.53-87.25; p < 0.001] and a cut-off value of 38.5 WBV for LSR had an 75.3% sensitivity and 78% specificity for predicting poor clinical outcomes [(AUC: 83.8%, 95% CI 72.4-87.2; p < 0.001)] (Figure 1).

In univariate and multivariate analyzes, both high LSR at WBV (OR: 2.679, p < 0.001) and high HSR at WBV (OR: 1.278, p < 0.001) were independent predictors for the poor clinical outcomes (Table 2).

There was a significant positive correlation between LSR at WBV and mRS score (0-6) (r = 0.457, p <0.001) and HSR at WBV and mRS score (0-6) (r = 0.427, p <0.001) (Figure 2A-B, respectively).

Table 2. The effects of variables on poor outcomes in logistic regression analysis

Univariate logistic regression analysis			
Variables	**Odds Ratio (OR)**	**95% CI**	**p-value**
Age	1.029	(0.990 – 1.050)	0.129
LDL-C, mg/dL	1.113	(0.994 – 1.127)	0.035
TG, mg/dl	1.006	(0.995 – 1019)	0.198
Hypertension	0.971	(0.259 – 3.634)	0.045
Diabetes Mellitus	1.149	(0.511 – 2.584)	0.036
Smoking	0.949	(0.234 – 1.025)	0.058
White Blood Cell (10^3 µl)	0.993	(0.878 – 1.121)	0.074
Platelet (10^3 µl)	1.001	(0.996 – 1.006)	0.048
WBV at LSR ($0,5/s^{-1}$)	1.247	(1.147 – 1.356)	<0.001
WBV at HSR ($208/s^{-1}$)	1.622	(1.123 – 2.331)	<0.001
Multivariate logistic regression analysis			
Variables	**Odds Ratio (OR)**	**95% CI**	**p-value**
MODEL-1			
Hypertension	0.852	(0.096 – 7.523)	0.885
Diabetes Mellitus	1.792	(0.498 – 6.447)	0.372
Smoking	0.531	(0.157 – 1.797)	0.309
White Blood Cell (10^3 µl)	1.073	(0.866 – 1.329)	0.519
Platelet (10^3 µl)	1.002	(0.993 – 1.01)	0.260
LDL-C, mg/dL	1.003	(0.991 – 1.016)	0.593
WBV at LSR ($0,5/s^{-1}$)	1.278	(1.015 – 1.421)	<0.001
MODEL-2			
Hypertension	1.057	(0.106 – 19.989)	0.778
Diabetes Mellitus	1.097	(0.391 – 6.526)	0.515
Smoking	0.948	(0.125 – 1.847)	0.286
White Blood Cell (10^3 µl)	1.123	(0.884 – 1.427)	0.341
Platelet (10^3 µl)	1.006	(0.995 – 1.016)	0.215
LDL-C, mg/dL	1.007	(1.001 – 1.012)	0.292
WBV at HSR ($208/s^{-1}$)	2,679	(1.174 – 3.920)	<0.001

WBV at HSR, Whole blood viscosity at high shear rate; WBV at LSR, Whole blood viscosity at low shear rate; LDL-C, low-density lipoprotein cholesterol; TG,Trigliserid

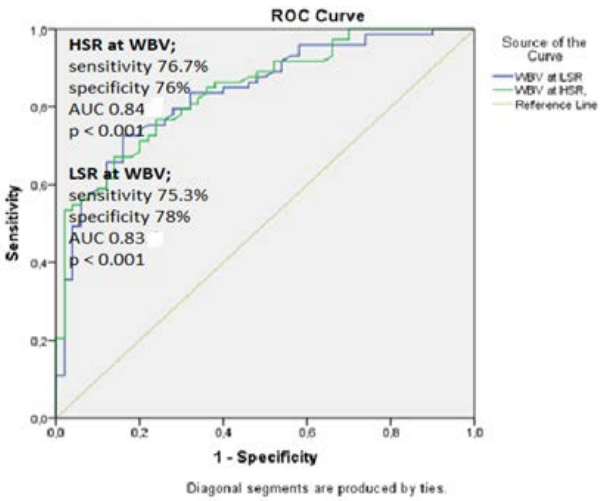

Fig 1. ROC curve analysis showing the predictive cut-off value of WBV at a high shear rate (blue line) and low shear rate (green line) for poor clinical outcomes. *AUC, area under the curve; HSR, high shear rate; LSR, low shear rate; ROC, receiver operating characteristic; WBV, whole blood viscosity.*

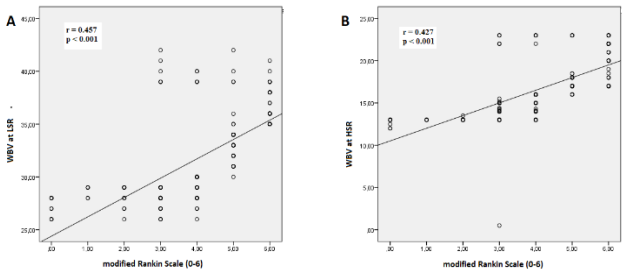

Fig 2. (A) Correlation between WBV at LSR and mRS score, (B) Correlation between WBV at HSR and mRS score

Discussion

Our study is the first to evaluate the relationship between WBV and functional status (evaluated after 90 days) in patients treated with MT. The results of this study demonstrate that the increased WBV values at LSR and HSR were an independent risk factor for poor clinical outcomes in AİS patients treated with MT. Besides, increased WBV values both at LSR and HSR were positively correlated with higher mRS score.

BV is determined by blood components and varies with the shear rate as a non-Newtonian fluid (1,9). Blood viscosity is affected by many rheologic components. Blood cells and plasma components are closely related to BV. As a result of increased BV, blood flow rate decreases and stasis occurs. Besides, changes in BV may effect the endothelial shear stress, an important component of atherosclerosis, and therefore trigger the development of atherosclerosis (9-11). The complex effects of BV accelerate the atherothrombotic process and development of cardiovascular diseases and may also effect the prognosis of these diseases (11). Lowe et al. demonstrated that BV is a risk factor similar to diastolic blood pressure, low-density lipoprotein cholesterol, and smoking in patients with stroke and myocardial infarction (12). Resch et al. reported that high BV is associated with death due to recurrent stroke, myocardial infarction, and cardiovascular disease (13). But, in routine clinical practice, evaluation of WBV with viscometer is limited owing to the necessity of technical equipment and lack of standardization in its assessment. De Simone et al. offered that WBV can be extrapolated from its primary constituents including hematocrit and total plasma protein at the desired shear rate with a simple formula . The different shear rates used when calculating WBV are indicators of different hemodynamic settings. LSR reflects the low velocity blood flow at the end of diastole and HSR reflects the high velocity blood flow at the systolic peak in the major arteries. The accuracy of this formula has been supported in large patient populations and in validation analyses performed with a viscometer device, which measures blood viscosity (8). This De Simone formula has been used in many different cardiovascular patient populations (14-16). Some recent studies have explored the relationship between acute stroke and blood viscosity: Furukawa et al. and Song et al. observed increased blood viscosity in stroke patients with small artery occlusion (17,18); Fisher et al. demonstrated that increased BV is associated with cerebral ischemia (19); and Li et al. found that increased BV in patients with low shear stress is associated with silent cerebral ischemia (20). This close relationship between increased BV and cerebral ischemia may affect the clinical outcomes of the AIS patients as demonstrated in our study.

MT with stent-retrievers results in higher recanalization rates. In the study of Nogueira et al., Despite successful recanalization rates, good clinical results evaluated with the mRS score ≤ 2 were obtained in only half of the patients (21). Some authors have identified a lot of clinic factors that influence poor outcomes in patients with AIS treated with MT (22, 23). In some studies, the association of laboratory parameters with poor functional results was evaluated (24, 265). Wang et al described the PREDICT scale after successful MT for poor outcomes for early prediction (26). Given the relationship between BV and ischemic cerebrovascular events, increased WBV induced endothelial dysfunction, peripheral vascular resistance, thrombosis, stasis, and impaired collateral flow can lead to increased neuronal ischemia at the micro and macrovascular level. These changes may affect functional outcomes negatively despite successful recanalization with MT in AIS patients. In our study, for the first time in literature, we evaluated the relationship between long-term outcomes of AIS patients undergoing MT and WBV calculated using De Simone formula. Herein, it was shown that increased blood viscosity was an independent predictor of poor functional outcomes. Also, the fact that the increased WBV value correlated positively with the increased mRS score supports this relationship. Considering the results of our study, clinicians may use WBV, a practical, easy and inexpensive parameter, as a predictor of long-term outcomes during the early evaluation of patients undergoing endovascular treatment for AIS. Accordingly, blood viscosity may also be included as one of the variables in the scoring tools designed to predict post-MT clinical outcomes.

Limitations

Our study has several limitations. Sample size, retrospective analysis of prospectively collected data, non-randomized and single-center study are important methodological shortcomings. The possibility of an unknown confounding factor affecting the results cannot be ruled out completely. The calculated WBV value has not been verified using a viscometer. The extrapolation formula that we used in our study has been validated and utilized in several other studies but direct comparison of estimated and directly measured WBV in this patient population may strengthen our results and serve precision. In addition, other hemorheological factors that may affect BV such as erythrocyte aggregability and rigidity were not evaluated.

Conclusion

This study demonstrates for the first time in the literature

that the increased WBV is an independent risk factor and correlated with poor clinical outcomes in AIS patients treated with MT. BV may be added to the scoring systems which predict the long-term outcomes in these patients if our results are confirmed with large scale, prospective studies.

Ethical Approval: *Ethics Committee of University of Health Sciences, Training and Research Hospital (TUEK1-2019 BADK / 1-5).*
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Concept: M.Y.,Ç.K.A.,E.G.
Literature Review: M.Y.
Design : M.Y.,Ç.K.A.,E.G.
Data acquisition: M.Y.
Data analysis and interpretation: Ç.K.A,E.G.,M.Y.,U.A.
Writing manuscript: M.Y.,Ç.K.A.
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