Relationship Between Carotid Stenosis and Infarct Volume in Ischemic Stroke Patients

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Data Collection B
Statistical Analysis C
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Background: Stroke is a serious health problem all over the world. Ischemia causes 85% of strokes and 75% of these ischemic strokes occur within the area supplied by the internal carotid artery (ICA).

Material/Methods: This study included 47 acute stroke patients who were in the large-artery atherosclerosis group according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and who had an infarct in the area supplied by the internal carotid artery. We sought to determine whether there was a significant correlation between the infarct volume of the patients as measured by diffusion-weighted magnetic resonance imaging (DW MRI), their National Institutes of Health Stroke Scale (NIHSS), and degree of carotid stenosis as identified by carotid computed tomography angiography (CTA).

Results: A significant correlation was observed between the percentage of carotid artery stenosis and infarct volume ($p<0.001$). In addition, there was a significant positive correlation between the NIHSS and infarct volume; the correlation was of moderate strength ($r=0.366$, $p=0.001$).

Conclusions: Our findings indicate that the percentage of carotid artery stenosis could be useful in predicting the infarct volume of the stroke.

MeSH Keywords: Angiography • Carotid Stenosis • Stroke • Tomography, X-Ray Computed

Abbreviations: ICA – internal carotid artery; CTA – computed tomography angiography; MRI – magnetic resonance imaging; TOAST – Trial of ORG 10172 in Acute Stroke Treatment; NIHSS – National Institutes of Health Stroke Scale; NASCET – The North American Symptomatic Carotid Endarterectomy Trial

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Background

Stroke is the third most common cause of mortality and the primary cause of disabilities in the world. It is also an important cause of morbidity and high health care costs in industrialized countries. There is no reliable information about the prevalence or incidence of stroke in Turkey [1,2]. In industrialized countries, 85% of strokes are associated with ischemia and 15% with hemorrhage. In a hospital-based multicenter study examining the general characteristics and risk factors of stroke patients in Turkey, it was found that the rate of ischemic stroke was 72%, while the rate of hemorrhagic stroke was 28% [3]. Of the ischemic strokes, about 75% occur in the area supplied by the internal carotid artery [2].

Based on the etiological TOAST classification, stroke subtypes include: large-artery atherosclerosis (LAA), small-vessel occlusion (SVO), cardioembolism (CE), stroke of other determined etiology, and stroke of undetermined etiology [4].

Recently, the morbidity and mortality associated with stroke has declined due to better identification and treatment of risk factors linked to stroke. For instance, late diagnosis and treatment of hypertension, one of the most common risk factors, is known to increase mortality [5]. There is a growing body of evidence supporting the need for treating hypertension to prevent recurrent ischemic stroke. A systematic review of the 7 studies collectively registering more than 15 000 patients with a history of ischemic stroke showed that anti-hypertensive therapy reduced risks associated with stroke, non-fatal stroke, myocardial infarction (MI), and general vascular cases, but not the mortality risk related to all vascular and other causes [6].

As another significant risk factor – high-risk carotid plaques and recurrent thromboembolic events – are believed to be among the leading causes of ischemic cerebrovascular events. Therefore, early diagnosis of predisposition to carotid plaques has been a key target for preventing cerebrovascular cases [7,8]. High-risk carotid plaques associated with ischemic cerebrovascular events have characteristics such as large lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH), and fibrous cap rupture (FCR) [9–11]. Apart from the high risks posed by carotid plaques, several studies explored the degree of carotid stenosis as a risk factor in ischemic stroke patients, and a significant association was established between the recurrence of stroke and degree of carotid stenosis [8].

Our study also examined whether there was a correlation between the size of the anterior system infarct zone as identified by the diffusion-weighted magnetic resonance imaging (DW MRI), NIHSS of the patients, and degree of carotid stenosis as determined by carotid computed tomography angiography (CTA) in acute stroke patients. It was speculated that the correlation between the degree of carotid stenosis on one hand and the infarct volume and the patient's clinical condition on the other hand could provide information in advance about the severity of ischemic strokes.

Material and Methods

This prospective study was performed in our Neurology Clinic from January to December 2015, after obtaining local Ethics Committee approval. Patient consent was obtained for the study.

This study registered 47 patients who presented at the Emergency Unit of our hospital, ages 51–89 years, who had an acute anterior system infarct in the ICA supply area (anterior system). Among the 47 ischemic stroke patients, those who were in the Large Artery Atherosclerosis Group according to TOAST classification were included in the study, and met the specified criteria.

Inclusion criteria

According to the criteria, the following patients were included in the study:
1. Patients who had an acute infarction in the area supplied by ICA,
2. Patients whose cerebral DW MR imaging was of a quality that would allow an adequate volumetric measurement within 12 h after the onset of symptoms,
3. Patients who were in the Large Artery Atherosclerosis Group according to TOAST classification,
4. Patients whose carotid CT angiography was performed, and
5. Patients whose NIHSS scores were calculated before MR imaging.

Exclusion criteria

1. Patients who had an infarct in multiple vessel supply areas and in the posterior system,
2. Patients who had a chronic infarct,
3. Patients who developed hemorrhagic transformation,
4. Patients who were not in the Large Artery Atherosclerosis Group according to TOAST classification were not included in the study.

Radiological measurements

Measurements of the infarct volume in cerebral DW MRI were conducted by a radiologist and a neurologist blinded to the clinical conditions of the patients. In the DWI sequence, the hyperintense area with restricted DWI was measured manually. Lesion

Table 1. Descriptive statistics for numeric variables in the study.

	N	Mean average	Median	SD	Minimum	Maximum
Percentage of left ICA stenosis	26	75.2000	68.5500	16.86884	54.00	100.00
Percentage of right ICA stenosis	21	72.6571	65.6000	16.95681	51.00	100.00
Infarct volume	47	4.4409	2.7300	4.27040	1.50	17.77
NIHSS	47	4.9574	4.0000	4.49617	.00	23.00
Age	47	71.2979	71.0000	9.06238	51.00	89.00
Percentage of ICA (right and left) stenosis	47	74.0638	68.0000	16.77195	51.00	100.00

Table 2. Results of the comparisons within left carotid and right carotid degree of stenosis groups with regard to infarct volume*.

		N	%	Mean	Median	SD	p
Degree of left carotid stenosis groups	1	14	53.8	3.21	2.37	2.863	
	2	6	23.1	5.87	4.06	5.419	0.096
	3	6	23.1	5.81	3.75	5.278	
Degree of right carotid stenosis groups	1	12	57.1	2.33	2.22	0.721	
	2	6	28.6	7.65	6.65	6.609	0.234
	3	3	14.3	6.61	6.82	4.893	

* Kruskal-Wallis test has been used.

volume was found by multiplying it by slice thickness (+inter-slice gap). The patients' infarct volumes were calculated using the DW MRIs performed up to 12 h after the event. Grouping by infarct volume was as follows: Group A: 1.5–5 cm^2; Group B: 5–10 cm^2; and Group C: over 10 cm^2. Following the first MRI, the patients' clinical conditions were assessed according to NIHSS. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) classification was used in the evaluation of carotid stenosis using carotid CTA. According to the grouping, Group 1 had 50–69% occlusion, Group 2 had 70–99% occlusion, and Group 3 had complete occlusion. Since the study included only those who were in the large-artery atherosclerosis group, stenoses below 50% were not included in the study.

Statistical analysis

Descriptive statistics for numeric variables were calculated as mean, standard deviation, minimum, and maximum, while descriptive statistics for categorical variables are presented as numbers and percentages. Differences between carotid stenosis groups and infarct volume groups in terms of numeric variables were examined using the Kruskal-Wallis test and the differences between right and left hemispheres were analyzed with the Mann-Whitney U test. Correlations between numeric variables were analyzed with Spearman correlation coefficient. Additionally, a multiple regression analysis was conducted to predict the infarct volume and NIHSS results. When the p value

was <0.05 in the statistical evaluations, the result was considered to have statistical significance. PASW (ver. 18) software was used in the calculations. Descriptive statistics for numeric variables in the study are presented in Table 1.

Results

The study registered 47 patients who presented at the Emergency Unit of our hospital, age 51–89 years, who had an acute anterior system infarct in the ICA supply area (anterior system). The average values and standard diversion of the age and body mass index (BMI) values of the patients were 71.30/9.062 and 23.52/3.84, respectively. As definitive statistics, it was calculated that 32 (68.1%) patients had HT and 24 (51.1%) were active smokers.

The study also determined whether there was a significant difference between left carotid groups and right carotid groups with regard to mean infarct volumes, but no significant difference was found between right and left carotid groups (p value, 0.096 and 0.234, respectively) (Table 2).

Additionally, without grouping according to degree of stenosis for the right or left carotid, the relation between the percentage of stenosis and infarct volume was studied and we found no significant correlation. We established that the infarct

Table 3. Correlations between age and carotid stenosis percentage, and infarct volume*.

	Regression coefficient	Standard error of regression coefficient	p
Model constant	5.296	4.396	0.235
Age	.159	.063	**0.015**
Percentage of carotid stenosis	.142	.034	**<0.001**

* Multiple regression analysis has been used.

Table 4. Results of the comparisons between the infarct volumes of the groups found after left and right carotid percentages were merged*.

Carotid stenosis groups (left and right carotid percentages were merged)	Infarct volume			p
	N	Mean**	SD	
1	27	2.7641[a]	2.13419	
2	11	7.2182[b]	5.89198	0.004
3	9	6.0767[b]	4.85345	

* Kruskal-Wallis test has been used; ** Different letters on the mean indicate significant differences.

Table 5. Relation between NIHSS and infarct volume*.

		NIHSS
Infarct volume	r (correlation number)	0.506*
	p	0.001
	N	47

* Spearman's rank correlation analysis has been used.

volume did not change according to stenosis percentage in either the right or left carotid. The correlation between carotid stenosis percentage and infarct volume for the left was 0.331 (p=0.098) and the correlation between carotid stenosis percentage and infarct volume for the right was 0.381 (p=0.088). However, when the stenosis percentages for right and left carotid arteries were assessed together, a significant (p<0.001) correlation was found between stenosis percentage and infarct volume, probably due to the increased number of patients. We established that when carotid stenosis percentage increased by 1 unit, the infarct volume grew by 0.142 unit (Table 3).

In the multiple regression model used to predict the infarct volume in consideration of the carotid stenosis percentage and age in combination, infarct volume was the dependent variable and age and carotid stenosis percentage were independent variables. In light of these results, when we tried to predict the infarct volume, taking age and carotid stenosis percentage into account, it is seen that the accuracy of the prediction was 55%. Thus, it was established that there was a significant correlation

between age and carotid stenosis percentage, and infarct volume, and that infarct volume decreased with advancing age such that a 1-year increase in age would result in a 0.159-unit decrease in the infarct volume (p=0.015). Accordingly, when age and carotid stenosis percentage are considered together, infarct volume can be reliably predicted (Table 3).

Additionally, after left and right carotid stenosis percentages were combined, they were re-grouped and compared in relation to infarct volume. An examination of the results obtained in these comparisons revealed that mean infarct volume in Group 1 was significantly lower than that in Group 2 (p=0.007) and was significantly lower than that in Group 3 (p=0.049). Mean infarct volumes by groups are presented in Table 4.

We found that as the NIHSS values of the patients increased, so did their infarct volumes. A moderate and significant (r=0.366, p=0.001) positive correlation was found between the NIHSS and infarct volume (Table 5). This result increases the reliability of our study.

4957

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Discussion

Besides being a major cause of disability and death, stroke also causes significant financial loss due to increasing hospital admissions and high treatment costs; therefore, pre-determination of stroke-causing risk factors is significant for preventing the disease [1].

Atherosclerosis is a serious risk factor for a number of diseases, including stroke. Models have been used to determine the carotid artery atherosclerosis and identify the associated stroke risk. For this purpose, certain factors (e.g., carotid artery stenosis, intimal medial thickness, and carotid plaque burden and composition) have been measured. Work on the measurement of carotid artery calcification as a risk factor is still in progress [12]. The ability to make non-invasive calcification measurements to determine atherosclerosis and risks associated with it would be a distinct advantage, particularly in unstable carotid plaques. CTA is the first-line diagnostic modality for vascular imaging commonly used in acute stroke patients [13]. Just as it reliably demonstrates occlusions and stenoses in the intra-cranial vascular structure, it can also determine the severity of atherosclerotic stenosis in the extra-cranial arteries, especially carotid arteries, with high precision [14]. In our study we utilized CTA as a reliable technique to identify the degree of carotid artery stenosis.

Having measured the calcium deposits of the cervical carotid artery using non-enhanced conventional CT, Culebras et al. found calcium deposits in internal and common carotid arteries were denser in their posterior half. The presence of these deposits was associated with atheromatous plaques that disrupt the hemodynamics in arteries. The authors also established a correlation between calcium scores and age. However, no significant difference was found between the calcification scores of symptomatic and asymptomatic groups, and as such, calcification scores were not associated with symptoms [15]. Nandalur et al., on the other hand, measured the carotid artery calcium burden using MDCT angiography, and showed a significant and independent correlation between the scores and symptoms. The study reliably quantified the cervical calcium burden using MDCT angiography and this was considered an appropriate marker for luminal stenosis. As a potential independent risk factor for TIA and stroke, calcium scores are critical in identification of risk groups among patients and in administration of effective therapy [16].

Several other studies aiming to assess the risk of future stroke found that changes in the white matter was a proven risk factor for all stroke types. The relationship between white-matter changes and future stroke was attributed to the diffuse demyelinization of the white matter, probably due to advanced-stage atherosclerosis. Bots et al. demonstrated that white matter lesions were associated with atherosclerosis in the cardiac peripheral artery and carotid artery; however, they could not find a correlation between carotid CT calcium scores and the severity of white matter disease. Thus, it they concluded that the identification of carotid calcium score would not be useful in preventing subsequent stroke [17,18].

Based on the contradictory results about the relationship between carotid calcium burden and stroke risk, Sarikaya et al. explored the correlation between carotid bifurcation calcium burden identified by non-enhanced CT and the degree of carotid luminal stenosis found in DSA. They established a moderate correlation between carotid calcium volume and degree of stenosis [19].

Carotid artery calcium burden may not decisively reveal carotid atherosclerosis and the stroke risk associated with it. Compositional features like the stability of carotid plaques are more relevant in terms of predicting the stroke risk. There are multiple studies showing that symptomatic carotid plaques are ulcerated, less-organized, and hemorrhagic [20], whereas calcified plaques are associated with stroke and TIA symptoms to a lesser extent [21]. Arterial-intimal calcification is a stable indicator for atherosclerotic disease, and there is a linear relation between calcium area and total plaque area. As the burden increases, a compensatory expansion occurs in the artery to prevent luminal stenosis. However, when the burden exceeds the capacity that this mechanism can handle, atherosclerotic disease causes a growing obstruction and leads to ischemic symptoms like hypoperfusion, thrombosis, and emboly [16,22].

In a cross-sectional study, Zhao et al. examined whether carotid plaque compositions characterized by cerebral infarcts in ischemic stroke patients, as well as high-risk carotid lesions, could be more effectively identified than stenosis using vessel wall imaging. They reported that many carotid arteries with low degrees of stenosis developed high-risk plaque characteristics like IPH and FCR. They found that morphological and compositional properties of carotid plaques are associated to a significant extent with the dimensions of ipsilateral ICAs, before and after correcting for critical demographic factors or carotid lumen stenosis. These results suggest that direct imaging of the vessel wall can be useful in better identification of the etiology and selection of the most appropriate treatment option in stroke patients [8]. In fact, in a recent study, after using plaque imaging in assessment, Freilinger et al. concluded that cryptogenetic stroke could be partly related to carotid atherosclerosis [23]. This result demonstrates that identification of the risk for stroke on the basis of atherosclerotic changes in the carotid artery may prove useful in helping a larger group of patients.

It has been maintained in certain studies that luminal stenosis levels could be an efficient marker in characterizing high-risk

carotid plaques [24]. However, although there was a strong correlation between plaque burden quantifications and luminal stenosis in the study conducted by Zhao et al., they found a remarkable number of LRNC and IPH in carotid arteries with low-level stenosis (<50% lumen decrease). Other studies support these findings. For instance, Saam et al. showed that complicated plaques were formed in 21.7% of carotid arteries with 16–49% stenosis. These present through the presence of IPH, FCR, or a calcium nodule [25]. Dong et al. demonstrated the presence of IPH in 8.7% of patients who had 0% stenosis in their arteries [26]. Similarly, recent studies showed that there was LRNC and IPH in 98.2% and 28.6%, respectively, of carotid arteries that had <50% stenosis [27]. This phenomenon can be explained by the positive remodeling hypothesis [28]. Research on the characteristics of high-risk plaques in arteries with low degrees of stenosis provides convincing evidence that luminal stenosis has limitations as a marker of carotid high-risk plaques [8].

Conclusions

We found that degree of carotid artery stenosis, a vascular risk factor, is a strong indicator for future stroke, and that it will be helpful in predicting the infarct volume of a future stroke. When the degree of carotid stenosis increases, infarct volume grows, and infarct volume is positively correlated with NIHSS values. This finding can inform the choice of treatment in consideration of the identified degree of carotid narrowing. There are no similar studies in the literature, and further multicenter studies with larger patient groups are needed to confirm the validity and reliability of our results.

Statement

The authors declare that they have no competing interests.

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