ORIGINAL ARTICLE

Study of red blood cell distribution width and carotid intima-media thickness in acute ischemic stroke patients and its correlation with neurological scoring systems

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Abstract

Background: There is no widely used, rapidly determined and sensitive biomarker of acute ischemic stroke. There are limited studies done to evaluate the association between Red Blood Cell Distribution (RDW), Carotid Intima-Media Thickness (CIMT) and severity of acute ischemic stroke. *Aim and Objectives*: To identify the correlation of RDW and CIMT with neurological scoring system in acute ischemic stroke patients. *Material and Methods*: This was hospital based observational, case control study. Sixty-eight patients and 68 age and sex matched controls were included in study after applying inclusion and exclusion criteria. RDW and CIMT in all subjects were compared regarding various clinical and biochemical parameters along with severity of stroke on neurological scales. *Results*: Mean RDW in case group was 15.23 ± 1.70 while in control group was 13.51 ± 1.31 and this was statistically highly significant. Higher RDW was associated with raised CIMT ($p = 0.0364$, correlation coefficient (r) = 0.081). The relationship of severity of stroke on neurological scales with RDW and CIMT was statistically significant. *Conclusion*: RDW and CIMT are strongly associated with increased risk of occurrence as well as with severity of acute ischemic stroke. As they are inexpensive investigations, they can be used as screening tools to assess early atherosclerotic changes in people with risk factors for stroke.

Keywords: Acute Ischemic Stroke, Red Blood Cell Distribution Width, Carotid Intima-Media Thickness

Introduction

A stroke or cerebrovascular accident is defined as an abrupt onset of neurological deficit that is attributable to a focal vascular cause. The clinical manifestations of stroke are highly variable because of complex anatomy of the brain and its vasculature [1].

Stroke is becoming an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors. The poor are increasingly affected by stroke, because of both the changing population exposures to risk factors and, most tragically, not being able to afford the high cost for stroke care. Majority of stroke survivors continue to live with disabilities, and the costs of on-going rehabilitation and long term-care are largely undertaken by family members, which impoverish their families [2-3].

In most of the ischemic strokes the underlying pathophysiology is atherosclerosis. The risk factors for stroke are modifiable and non-modifiable. The modifiable risk factors are mostly related to the atherosclerotic burden and include diabetes, hypertension, smoking, and dyslipidemia [4].

Acute ischemic stroke is diagnosed by history, physical and neurological examination, and

imaging methods. The diagnosis of acute ischemic stroke is based on cerebral imaging techniques, but biochemical examination of tissue damage can be an alternative strategy for early diagnosis. It would be helpful to have a biomarker to screen and identify patients who have had acute ischemic stroke, especially in patients before hospitalization who may be candidates for thrombolytic therapy. However, there is no widely used, rapidly determined, and sensitive biomarker of acute ischemic stroke [5]. For prediction of the severity and mortality of acute ischemic stroke, scoring systems such as the Glasgow Coma Scale (GCS), Canadian Neurological Scale (CNS), and National Institutes of Health Stroke Scale (NIHSS) are used. These scoring systems quantify the severity of acute ischemic stroke based on the physical examination of patients.

Red Cell Distribution Width (RDW) measures the range of red cell volumes. It is a measure of the variability in size of circulating erythrocytes and is indicated as the coefficient of variation of the erythrocyte size.

High RDW levels may be observed in various disorders. In disorders other than anemia, the prognostic importance of high RDW levels previously received insufficient attention because of lack of knowledge. However high RDW levels are associated with a poor prognosis in certain disorders such as acute myocardial infarction, stroke and peripheral artery disease [6-7].

RDW is a predictor of mortality in patients who have cardiovascular disease, cancer, chronic lung disease, symptomatic chronic congestive cardiac insufficiency, acute stroke, or acute cardiac insufficiency [8]. The reason for the association between RDW and mortality is still unknown, and it is unclear whether RDW is associated with increased incidence of stroke. However, there are several factors that could potentially link RDW to the risk of stroke. While many studies have shown the relationships between RDW and stroke, the pathophysiological mechanisms remain unclear. Elevated RDW level may have a direct impact on stroke, or it may be merely a marker, reflecting something else going on in the body. The existing hypothesis mainly includes the microvascular disorder, inflammatory cytokines, and so on.

Carotid Intima-Media Thickness Test (CIMT) is a measure used to diagnose the extent of carotid atherosclerotic vascular disease. The test measures the thickness of the inner two layers of the carotid artery the intima and media; and alerts physicians to any thickening when patients are still asymptomatic. Since carotid artery atherosclerosis is caused by several inflammatory responses of vascular endothelial injuries, it is inferred that RDW could be involved in the process of carotid artery atherosclerosis. Since limited studies have been done evaluating the association between RDW, CIMT and severity of acute ischemic stroke, we planned this study to further explore the association between them in north-western part of Rajasthan.

Material and Methods

This was a hospital based case control study conducted from May 2019 to October 2019 in Sardar Patel Medical College and AGHs, Bikaner. Ethical approval was obtained from Institutional Research Ethics Committee and written informed consent was taken from all subjects.

Patients with acute ischemic stroke were included in this study using simple random sampling method. Assuming a pooled standard deviation of

2.1 units, the study required a sample size of 58 for each group (i.e. a total sample size of 116, assuming equal group sizes), to achieve a power of 80% and a level of significance of 5% (two sided), for detecting a true difference in means between the test and the reference group of 1.09 (i.e. 14.7 - 13.6) units. To improve power of study, all eligible candidates were included in the study who were admitted in the hospital during study period. Therefore total sample size in cases group increased to 68. Same number of patients admitted in hospital for any reason other than stroke were recruited as controls after age and sex matching with application of inclusion and exclusion criteria. All participants were subjected to detailed clinical examination and relevant investigations, and recruited only after satisfying the inclusion and exclusion criteria.

Inclusion criteria:

1. Patients who presented with symptoms for < 24 hours duration and were diagnosed with acute ischemic stroke based on the history and CT scan report.
2. Patients willing to participate in study. Written informed consent was taken from study participants.

Exclusion criteria:

1. Minor patients.
2. Patients with established diagnosis of cerebral hemorrhage, subdural hematoma, intracerebral mass or cerebrovascular damage secondary to trauma.
3. Patients with presence of infection.
4. Patients with known immunological disorders, malignancy, or pregnancy.
5. Patients with presence of hemoglobinopathy or other conditions that may be associated with abnormal RDW such as sickle cell anemia, thalassemia, or other anemias or current use of iron, folic acid, or vitamin B12 supplements [9].
6. Patients on drugs like benzodiazepines, opiates, tricyclic antidepressants, cortico-steroids and anticonvulsants in previous 6 months.
7. Patients with chronic diseases like chronic liver disease and chronic kidney disease.
8. Those patients or their family members who were uncooperative for the study.

All the subjects included in the study were interviewed regarding age, gender, education level, history of smoking, history of alcohol abuse, sleep status, history of diabetes, hypertension, and dyslipidemia using a predesigned and pretested proforma. Medication history regarding use of lipid-lowering medications, anti-diabetic medications, antihypertensive medications, antiplatelet medications or any drug causing cognitive impairment were recorded through questionnaires and pill bottle review.

For each patient the following data were collected: biochemical parameters (complete blood count including haemoglobin, RDW, total and differential leucocyte count, total platelet count, fasting plasma glucose, blood urea, serum creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, urine analysis, serum triglycerides, serum HDL cholesterol, serum LDL cholesterol, serum VLDL, serum total cholesterol, ESR). Severity of stroke was assessed using GCS (mild 14-15, moderate 9-13, severe 3-8), CNS (mild 8.5-10, moderate 2.5-8, severe 0-2) and NIHSS (mild -less than equal to 8, moderate 9-15, severe - more than equal to 16).

Statistical analysis

Collected data were entered in Microsoft Excel spreadsheet and presented in the form of tables, figures, graphs, and diagram. Epi-Info Software (7.2.5.0 version) was used for data analysis. Quantitative variables were presented as mean and Standard Deviation (SD). Qualitative variables were presented as frequencies and percentages using the descriptive statistical method. To analyze the data, the inferential statistical methods were used. For comparing means between more than two groups the ANOVA test was applied.

Results

In the present study, comparison of RDW was performed in both case and control group. Mean RDW in case group was 15.23 ± 1.70 while in control group was 13.51 ± 1.31. This relationship was found to be statistically highly significant ('t' = 43.495 p <0.001) (Table 1).

A total 68 cases had acute ischemic stroke. Sixty-eight healthy controls were taken in the same age groups. RDW value was studied in relation to all three scoring systems i.e. GCS, CNS, and NIHSS. It was found that on GCS scale, 42 out of 68 cases with mild severity stroke had mean RDW 14.8310 ± 1.6083. While 21 cases with moderate severity stroke had mean RDW 15.7714 ± 1.7036. Five cases with severe stroke on GCS scale had mean RDW 16.4400 ± 1.5566. This relationship between severity of stroke on GCS score and RDW was statistically significant. (p = 0.0188). Similarly on CNS and NIHSS also we found that with increasing severity of scale, RDW values also increased and these findings were statistically significant (Table 2).

CIMT value was also studied in relation to all three scoring systems. It was found that on GCS scale, 42 out of 68 cases with mild severity stroke had mean CIMT value of 0.8518 ± 0.1252. While 21 cases with moderate severity stroke had mean CIMT value of 0.9143 ± 0.0989. Five cases with severe stroke on GCS scale had mean CIMT value of 1.0000 ± 0.1061. This relationship between severity of stroke on GCS score and CIMT was statistically significant (p = 0.003). Similarly on CNS and NIHSS also we found that with increasing severity of scale, CIMT values also increased and these findings were statistically significant (Table 3). On evaluating the relationship between smoking habit and CIMT, it was found that CIMT of smokers was significantly higher (0.8813 ± 0.1044) than non-smokers (0.8173 ± 0.1136) (p = 0.0016) (Table 4).

RDW was divided in quartiles and compared with mean CIMT. The first quartile of RDW had mean CIMT 0.81 ± 0.09 while in second, third and fourth quartile it was 0.81 ± 0.07, 0.84 ± 0.12 and 0.89 ± 0.14 respectively. And this relationship between RDW and CIMT was statistically significant (Table 5). Correlation between RDW and CIMT of all subjects (both cases and control) were conducted to further explore possible CIMT and RDW relationship. Our results showed positive relation between RDW and CIMT (p = 0.036474, correlation coefficient (r) = 0.081).

Table 1: Distribution of cases according to Red cell Distribution Width [RDW-CV (%)]

RDW-CV (%)	Cases	Control	Total
	N (%)	N (%)	N (%)
≤14	49 (72.06)	17 (25)	66 (48.53)
>14	19 (27.94)	51 (75)	70 (51.47)
Total	68 (100)	68 (100)	136 (100)
Mean ± SD	15.23 ± 1.70	13.51 ± 1.31	
t	43.4959		
p	<0.001		

Table 2: Relation of RDW (%) with severity of stroke

Scales	Mean RDW			*p*
	Mild	Moderate	Severe	
GCS	14.8310	15.7714	16.4400	0.0188
CNS	14.7750	15.3333	16.2917	0.0180
NIHSS	14.8310	15.6769	16.1231	0.0207

GCS-Glasgow Coma Scale, CNS-Canadian Neurological Scale, NIHSS -National Institutes of Health Stroke Scale

Table 3: Relation of CIMT (mm) with severity of stroke

Scales	Mean CIMT (mm)			*p*
	Mild	Moderate	Severe	
GCS	0.8518	0.9143	1.0000	0.003
CNS	0.8352	0.9125	0.9458	0.002
NIHSS	0.8518	0.9115	0.9500	0.006

GCS-Glasgow Coma Scale, CNS-Canadian Neurological Scale, NIHSS -National Institutes of Health Stroke Scale

Table 4: Relationship between smoking habit and CIMT (mm)

Age group	Smoker		Non-Smoker		Total
	N (%)	CIMT Mean	N (%)	CIMT Mean	N (%)
< 60	6 (12.50)	0.8667	18 (20.45)	0.7769	24 (17.65)
61 - 70	17 (35.42)	0.8588	41 (46.59)	0.7919	58 (42.65)
71 - 80	11 (22.92)	0.8636	15 (17.05)	0.8060	26 (19.12)
> 80	14 (29.16)	0.9215	14 (15.91)	0.9012	28 (20.59)
Total	48 (100)	**Total**	88 (100)	**Total**	136 (100)
Mean ± SD	0.8813 ± 0.1044		0.8173 ± 0.1136		
t	10.4016				
p	0.0016				

Table 5: Comparison of RDW (%) quartiles with mean CIMT (mm)

	RDW Quartiles				Total
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	N (%)	N (%)	N (%)	N (%)	N (%)
	34 (25)	34 (25)	34 (25)	34 (25)	136 (100)
RDW Range	11.6-13.2	13.2-14.1	14.1-15.5	15.6-19.8	11.6-19.8
CIMT Mean ± SD	0.81 ±0.09	0.81 ± 0.07	0.84 ± 0.12	0.89 ± 0.14	
t	4.558423				
p	0.036474				

Discussion

In the present study, mean RDW in case group was 15.23 ± 1.70 while in control group was 13.51 ± 1.31. This relationship was found to be statistically highly significant (F statics = 43.495, p <0.001). Our results are similar to study done by Hasan *et al*. (2015) [10]. They found mean RDW of 14.7 in stroke cases while 13.7 in healthy controls (p = 0.001). Similarly Jia *et al*. (2015) [11] found correlation of RDW with ischemic stroke (odds ratio 1.14, p = 0.023). Soderholm *et al*. (2015) [12] in their large study on 28449 patients also found similar correlation of RDW with acute ischemic stroke. Similarly Ramirez-Moreno *et al*. (2013) [13] in their case control study on ischemic stroke patients found that higher level of RDW is associated with increased risk of stroke (p <0.0001). Feng (2017) [15] did a meta-analysis in which they analyzed the available scientific literature on the putative role and the potential epidemiological association between RDW and ischaemic stroke (including carotid artery atherosclerosis). They found overall, considerable and convincing evidence which demonstrated that an increased RDW value is likely associated with ischaemic cerebrovascular disease, carotid artery atherosclerosis and cerebral embolism. Higher RDW could independently predict adverse outcomes in patients with these conditions. In a study by Agarwal (2012) [22] RDW is proposed as inflammatory marker. Chronic inflammation is one of the mechanisms of developing atherosclerosis thereby predisposing affected persons to increased risk to stroke.

In the present study, severity of stroke was compared on GCS score, CNS and NIHSS with RDW. In all three scoring systems, it was found that with increasing severity of scale, RDW values also increased and these findings were statistically significant. (GCS and RDW p = 0.0188, CNS score and RDW p = 0.0180, NIHSS score and RDW p = 0.0207). These results are similar to findings by Hasan *et al*. (2015) [10]. They found similar results in their study on neurological scoring systems (GCS, CNS and NIHSS) and RDW in acute stroke patients. Our findings showed that there is a strong association between RDW value and severity of stroke. Thus RDW value in acute ischemic stroke patients may be helpful in predicting prognosis.

In the present study, severity of stroke was also compared on all three scoring systems (GCS, CNS and NIHSS) with CIMT value. In all three scoring systems we found that with increasing severity of scale, CIMT values also increased and these findings were statistically significant. (GCS and CIMT p = 0.003, CNS score and CIMT p = 0.002, NIHSS score and CIMT p = 0.006). No study previously compared CIMT with severity of stroke on neurological scales. Our results showed statistically significant association between CIMT and severity of stroke on all three neurological scales included in study. So increased CIMT is strongly associated with increased risk of occurrence as well as severity of acute ischemic stroke. Hence assessment of CIMT in people having various risk factors for stroke may be helpful in early appropriate intervention thereby decreasing overall morbidity and mortality in such people.

In our study, we compared mean CIMT of smokers and non-smokers in all age groups. Overall mean CIMT of smokers was 0.8813 ± 0.1044 while of non-smokers was 0.8173 ± 0.1136.

This relationship between smoking habit and CIMT was found to be statistically significant (p = 0.0016). Our findings are similar to results of study done by Ren *et al*. (2017) [14]. They studied carotid intima media thickness in metabolic syndrome patients and found statistically significant ($p < 0.001$) higher CIMT in smokers compared to non-smokers. Jia *et al*. (2015) [11] also found similar results in acute ischemic stroke patients. They found higher number of smokers in acute ischemic stroke patients with significant carotid artery atherosclerosis than in patients without significant carotid artery atherosclerosis. CIMT is easily accessible tool to detect carotid atherosclerosis. Since smoking is an established cause of premature atherosclerosis so CIMT could be used as important screening tool to assess early atherosclerotic changes in people with high risk factors for stroke such as smoking.

In the present study, correlation was carried out between RDW and CIMT of all subjects (both cases and control) to further explore possible CIMT and RDW relationship. The first quartile of RDW had mean CIMT 0.81 ± 0.09 while in second, third and fourth quartile it was 0.81 ± 0.07, 0.84 ± 0.12 and 0.89 ± 0.14 respectively. And this relationship between RDW and CIMT was statistically significant (p = 0.036474 r = 0.081). Wen *et al*. (2010) [16] in their cross sectional study on 156 patients observed higher baseline RDW in patients with increased CIMT (p = 0.008). Kaya *et al*. (2013) [17] in their prospective study on 153 patients with heart failure found that patients with RDW value > 15.2% on admission had 87% sensitivity and 74% specificity in predicting stroke ($p < 0.001$). Wonnerth *et al*. (2014) [18] did a prospective cross sectional cohort study on 1286 neurologically asymptomatic carotid atherosclerosis patients and found statistically significant association ($p < 0.001$) with raised RDW. Vijayshree *et al*. (2014) [19] did a retrospective cross sectional study on young infarct patients and found significantly higher ($p < 0.001$) RDW in them. Soderholm *et al*. (2015) [12] in their population based cohort study on 26879 patients found statistically significant higher incidence of stroke/cerebral infarct in subjects with high RDW. In population based prospective study on 25992 subjects Lappegard *et al*. (2016) [20] found high risk of stroke in subjects with high RDW. Ren *et al*. (2017) [14] also found similar relation in CIMT and RDW in their cross sectional study on 803 patients of metabolic syndrome. Considering that RDW and CIMT are inexpensive tests, further multicenter research with larger sample size is certainly needed to investigate the potential mechanistic role of RDW and CIMT in stroke occurrence.

Conclusion

A strong association of RDW and CIMT with severity of stroke was found. Patients having higher RDW and who are at higher risk of having ischemic stroke should be evaluated for CIMT for early identification of carotid atherosclerosis, so as to initiate timely intervention of modifiable risk factors to decrease stroke occurrence thereby decreasing overall morbidity and mortality in such patients.

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