DOI: 10.5137/1019-5149.JTN.16136-15.1
Received: 06.10.2015 / Accepted: 22.10.2015
Published Online: 26.05.2016

Original Investigation

The Relationship of Hematoma Growth to Red Blood Cell Distribution Width in Patients with Hypertensive Intracerebral Hemorrhage

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ABSTRACT

AIM: Hypertension is a primary risk factor for intracerebral hemorrhage (ICH) and is thought to be responsible for about 55% of all ICH cases. Thus, the primary goal of the study was to examine whether the status of vascular rheological factors upon admission to the hospital was associated with hypertensive ICH growth and early outcomes.

MATERIAL and METHODS: Over a 2-year period, the present study evaluated 60 ICH patients who were admitted within the first 12 hours of symptom onset. Brain computed tomography scans were performed at admission and then 24 hours later as a control. Hematoma growth was classified as an volume increase more than 6.5 ml or >33%, and good outcome was defined using the modified Rankin Scale (mRS) score (≤ 2 at 3 months).

RESULTS: The mean age of the study population was 65.07 ± 11.659 years, with 34 men and 26 women. The leading vascular risk factor was hypertension (86.7%). There were significant associations between the initial red blood cell distribution width (RDW) and hematoma growth (p=0.038). Therefore, hematoma growth in the first 24 hours after symptom onset was significantly related to a poor clinical outcome at 3 months (p = 0.050).

CONCLUSION: The study identified significant relationships between the initial RDW and poor outcome as well as the initial RDW and hypertensive hematoma growth. Additionally, this study demonstrated that these parameters are easily obtainable and could be used to effectively evaluate outcomes in ICH patients.

KEYWORDS: Intracerebral hemorrhage, Hypertensive hemorrhage, Hematoma growth, Red blood cell distribution width

INTRODUCTION

Intracerebral hemorrhage (ICH) is a subtype of stroke with morbidity and mortality accounting for about 15% of all deaths from stroke (12,13). The prevalence of ICH risk factors including older age, hypertension, diabetes mellitus and obesity are increasing, and case fatality remains high with an overall rate of 40% at 1 month (3,9,12,13,19,21). Hypertension is still the main cause, being responsible for approximately 55% of cases of ICH (3). Early hematoma growth occurs in 20%-40% of ICH patients and is a major determinant of early deterioration and poor clinical outcome (12,13).

Red cell distribution width (RDW) and platelet distribution width (PDW) are markers of variation of the size of the circulating red

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blood cells and platelets. Due to the lack of knowledge about their prognostic significance, RDW and PDW were ignored previously. Since rheologic parameters can be determined with a simple and low-cost analysis, we consider that it will be useful in risk evaluation of ICH patients.

The purpose of this study was to examine whether rheologic factors are associated with ICH growth and early clinical outcome.

MATERIAL and METHODS

This retrospective case series was conducted at the Neurology Clinic of Bezmialem Vakif University Medical School Hospital. All information was extracted from the hospital medical records. The Ethics Committee at Bezmialem Vakif University approved all described procedures.

During the two–year period (May 2011 to August 2013), we evaluated 60 patients who were admitted to our clinic in the first 12 hours after symptom onset from a cohort of approximately 1300 stroke patients. We selected patients who had undergone the first brain computed tomography (CT) at less than 12 hours and the second, follow-up brain CT at 24 hours after symptom onset. The first brain CT was immediately performed at admission to the emergency room (ER).

A blood sample was obtained from all patients included in the study for routine complete blood count (CBC), routine biochemical tests, CRP and coagulation tests (International Normalized Ratio-INR) following admission to the ER. RDW, PDW and mean platelet volume (MPV) were obtained from CBC.

Detailed data were recorded for each patient including demographics, medical history, vascular risk factors, stroke severity at admission (by means of the National Institutes of Health Stroke Scale – NIHSS), laboratory testing, imaging data and treatment.

Patient characteristics included age, sex, prior history of stroke, history of congestive heart disease and coronary artery disease, cardiovascular risk factors, admission glucose level, admission systolic/diastolic blood pressures, admission serum creatinine (Cr) level, admission INR, initial NIHSS and mRS scores, presence of underlying hemostatic abnormalities, and taking anticoagulant or antithrombotic agents. Cardiovascular risk factors were defined as: (1) hypertension, history of using antihypertensive agents, systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg before or after ≥ 2 weeks after stroke onset; (2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥200 mg/dl or glycosylated hemoglobin ≥6.5% on admission; (3) hyperlipidemia, use of antihyperlipidemic agents or a serum LDL level ≥140 mg/dl on admission; and (4) current smoking and alcohol intake.

We evaluated the initial brain CT to calculate the baseline ICH volume. ICH volumes were measured using the "abc method". The "abc method" uses the Formula (a x b x c)/2, in which *a* is the largest diameter of the hematoma in the CT slice with the largest area of ICH; *b* is the largest diameter of the hemorrhage perpendicular to line *a*; and *c* is the number of slices with hematoma times the slice thickness and yields hematoma volume in cm^3 (11). We also evaluated the presence of intraventricular hemorrhage and cerebral shift at initial and control CT. Hematoma growth was defined as described in recent studies as absolute growth greater than 6.5 ml or a relative growth of more than 33% from initial CT to follow-up CT (2,4).

All patients were followed up at the outpatient clinic at the first and third month after discharge. On admission to ER, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional outcome was examined with the modified Rankin scale (mRS) score at the first and third month after discharge. Functional independence and good outcome were defined as a mRS score ≤ 2 at 3 months.

All statistical analyses were performed using IBM SPSS Statistics 20 (USA) and the Microsoft Office Excel Software. The Fisher exact test and Student's t-test were used to analyze significant differences between the group with low RDW values and the group with high RDW values. Age and test values were all expressed as means ± standart deviations (SD). For all tests, a two-tailed p value <0.05 was considered to indicate statistical significance with confidence intervals (CI) of 95%. A receiver operating characteristic (ROC) curve was constructed to determine the area under the curve (AUC), sensitivity, and specificity of the baseline RDW and PDW value for predicting hematoma growth at 12 hours and the outcome.

RESULTS

The patients were divided into 2 groups on the basis of a RDW level cut-off value of 13.85 based on the ROC curve. Consequently, we categorized our cohort into two groups: one group with a RDW >13.85 containing 24 patients and a second group with a RDW <13.85 containing 36 patients. Differences in the baseline clinical and laboratory characteristics in patients with low and high RDW values are listed in Table I. The mean age of the study population was 65.07 ± 11.659 years with 34 men and 26 women. Among our study population, the leading vascular risk factor was hypertension (86.7%) and we also had 14 patients who were taking antithrombotic agents.

Hematoma growth was detected in 19 patients (Table II). In our study population, we determined that the most common hematoma location was the basal ganglia region (27 patients). When we compared initial hematoma volume and hematoma volume at 24 hours with vascular risk factors, no significant relationship could be detected between them.

Similarly, we could not find statistically any significant relationship between initial blood parameters of the patients and initial hematoma volume, and hematoma volume at 24 hours. We determined a statistically significant relationship between patients who had Vitamin K antagonist (VKA) and aspirin use in their history and hematoma growth (p=0.047). We detected a statistically significant relationship between hematoma growth and RDW, which was one of the initial blood parameters of patients (p=0.038) (Table III). Initial hematoma volume and hematoma volume at 24 hours did not provide

any significant data about hematoma growth (respectively; p=0.394; p=0.577). No significant relationship was detected between initial NIHSS value and hematoma growth measured at the 24th hour (p=0.420).

We found a statistically significant relationship between initial NIHSS value and hypertension as a vascular risk factor (p= 0.044). The stroke was more serious in patients presenting with diagnosis of hypertension. A significant relationship with the other risk factors was not detected. Similarly, we did not observe any relationship between initial NIHSS value and initial blood parameters.

Among our study population, mRS score at 3 months was 0-2 in 34 patients, mRS score was 3-5 in 17 patients, mRS score was 6 in 5 patients. No significant relationship could be detected between vascular risk factors and the mRS score in the first month. We found a statistically significant relationship between the third month mRS score and the history of coronary artery disease (CAD) as a vascular risk factor (p= 0.046).

Moreover, functional addiction was observed in patients presenting with a diagnosis of CAD at the 3rd month. mRS score at the 3rd month was found to be significant between patients with higher initial SBP value (p=0.033). The relationship between initial PDW value and mRS score (0-2) at the 3rd month (p=0.047) was found to be significant.

Table I: Baseline Characteristics of the Patients at Admission

	Patients			
	All (n=60)	**RDW<13.85 (n=36)**	**RDW>13.85 (n=24)**	**p value***
Demographics				
Age÷ (years)	65.07± 11.65(36-90)	64.67±12.25 (36-90)	65.67±10.92 (42-83)	.500
Sex				.132
Female	34 (43.3)	13 (36.1)	13 (54.2)	NA
Male	26 (56.7)	23 (63.9)	11 (48.8)	NA
Medical and drug history				
Hypertension	52 (86.7)	31 (86.5)	21 (87.5)	.598
Diabetes Mellitus	12 (20)	5 (13.9)	7 (29.2)	.132
Hyperlipidemia	9 (15)	8 (22.2)	1 (4.2)	.055
Congestive Heart Failure	1 (1.7)	0	1 (4.2)	.400
Coronary Artery Disease	10 (16.7)	6 (16.7)	4 (16.7)	.643
Previous Stroke/Transient Ischemic Attack (TIA)	7 (11.7)	4 (11.1)	3 (12.5)	.456
Current Smoking	6 (10)	3 (8.3)	3 (12.5)	.456
Bleeding history	4 (6.7)	1 (2.8)	3 (12.5)	.171
Taking antithrombotic drugs	14 (23.3)	7 (19.4)	7 (29.3)	.372

Data in parantheses are percentages, unless otherwise specified.

÷Data are the mean ± SD. Data in parantheses are the range
** NA indicates not applicable.*

Table II: Neuroimaging Database of Population RDW>13.85 and RDW<13.85

	Patients			
Neuroimaging	**All (n=60)**	**RDW<13.85 (n=36)**	**RDW>13.85 (n=24)**	**p value***
Initial Hematoma Volume÷ (cm^3)	26.12± 46.7 (1-313)	17.11±17.54 (1-75)	39.64±69.41 (1-313)	.441
Control Hematoma Volume÷ (cm^3)	32.95 ± 51.197(1 -315)	19.81±22.31 (1-113)	52.66±72.73 (2-315)	.406
Hematoma Growth	19 (31.7)	8 (22.2)	11 (45.8)	**.038**

Data in parantheses are percentages, unless otherwise specified.

÷Data are the mean ± SD. Data in parantheses are the range
** NA indicates not applicable.*

Table III: Baseline Clinical and Laboratory Parameters of the Patients at Admission

	Patients			
	All (n=60)	**RDW<13.85 (n=36)**	**RDW>13.85 (n=24)**	**p value***
Clinical and laboratory parameters				
NIHSS on presentation∔	7.97±5.86 (7-25)	7.97±5.86 (0-25)	9.83±5.03 (2-20)	.195
Systolic Blood Pressure∔ (mmHg) at admission	150.02±32.73 (80-240)	180.30±36.57 (120-170)	178.70±29.74 (110-230)	.857
Diastolic Blood Pressure (mmHg) at admission∔	79.3±13.463 (40-110)	92.27±19.92 (50-145)	94.35±13.76 (60-120)	.647
Glucose (mg/dl) at admission∔	159.84±72.56 (88-447)	131.79±50.96 (85-329)	138.54±66.99 (80-357)	.680
Creatinine (mg/dl) at admission∔	0.95 ±0.64 (1-5)	0.82±0.15 (1-1)	1.15±0.96 (1-5)	.108
Blood Urine Nitrogen (BUN) (mg/dl) at admission∔	17.33 ±6.27 (5-40)	16.14±4.39 (5-25)	19.06±8.09 (7-40)	.117
C-Reactive Protein (CRP) (mg/dl) at admission∔	0.68±0.87 (0-4)	0.45±0.50 (0-2)	0.99±1.16 (0-4)	**.042**
INR at admission	1.32 ± 0.86 (1-6)	1.27±0.74 (1-4)	1.39±1.04 (1-6)	.652
Haemoglobin (Hb). (g /dl)∔	13.5±1.93 (7.9-17.3)	14.19±1.55 (9.60-17.30)	12.47±2.02 (7.90-16.10)	**.001**
Platelet count. (10^3/µl)∔	247.6±65.48 (110-450)	244.44±63.76 (110-440)	252.33±69.10 (141-450)	.657
RDW (%)∔	14.06±2.14 (10.50-25.7)	12.96±0.68 (10.50-13.80)	19.67±2.51 (13.90-25.7)	**<.000**
MPV(fl) ∔	9.73 ±1.14 (7.70-13)	9.66±1.21 (7.70-13)	9.85±1.05 (7.80-11.70)	.515
PDW(fl) ∔	14.23±3.08 (9-22)	14.06±3.17 (9-22)	14.49±2.97 (9.80-20.80)	.601

Data in parantheses are percentages, unless otherwise specified.
∔Data are the mean ± SD. Data in parantheses are the range
** NA indicates not applicable.*

No significant relationship was determined between hematoma values of both the initial period and at 24 hours and mRS scores in the first month and third months (mRS for first month: p=0.478, p=0.188; mRS for third month: p=0.821, p=0.337). A significant relationship was detected between the severity of patient during the application and mRS score of the first month and third month (p = 0.014). Therefore hematoma growth in the first 24 hours was significantly related to poor clinical outcome at the 3rd month (p=0.050).

Hematoma growth in-group cut-off value was measured as 13.85 for RDW. Sensitivity was 57%, specificity was 68% and AUC was 0.641 on the basis of the ROC curve. The cut-off value was 14.65 for PDW, sensitivity was 59%, specificity was 63% and AUC was 0.657 on the basis of the ROC curve.

■ DISCUSSION

Intracerebral hemorrhage is a subtype of stroke with morbidity and mortality accounting for about 15% of all deaths from stroke (2,3,12,16). Hypertension is still the main cause, being responsible for approximately 55% of cases of ICH. Cerebral amyloid angiopathy is the other major cause of primary ICH in the elderly (3,12). The most common sites of hypertensive ICH are the cerebral hemispheres, basal ganglia, thalamus, brain stem (predominantly the pons) and cerebellum (3,10).

The association between RDW and increased ischemic events in patients with cardiovascular disease is well known and there have been a few studies on its relation to bleeding events. However, its relation to bleeding events in patient with cerebrovascular disease has not been established. In

our study, RDW was a predictor of hematoma growth in ICH patients.

RDW and PDW are markers of variation of the size of the circulating red blood cells and platelets. Due to the lack of knowledge about their prognostic significance, RDW and PDW were ignored previously. It has been speculated that RDW is a marker of chronic health status but recent studies have shown that elevated RDW may also reflect recent hemorrhage (14). Since rheologic parameters depend on a simple and low cost analysis, we believe that these parameters will be useful in the risk evaluation of ICH patients.

García et al. (7,10) have described in detail the sequential histologic changes that take place in the hematoma to investigate the ICH-inflammation relationship. RDW may have a role in the pathogenesis by inflammation (6). Possible mechanisms may include the fact that higher levels of RDW may reflect an underlying inflammatory state, which is related to poor patient outcomes (17). Inflammatory cytokines and neurohumoral mediators are activated in acute and chronic cardiovascular diseases. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, and the increased immature erythrocytes may therefore reflect higher RDW levels (15). Admission RDW (aRDW) has recently been shown to predict mortality in trauma patients by an unclear mechanism (14).

Ani and Owbiagele showed that the mean RDW was significantly higher among persons with stroke compared to individuals without stroke (1, 20). Ye et al. found a 10% greater risk of mortality for a 1% increase in RDW for patients with peripheral arterial disease (23). Gonçalves et al. showed that RDW was associated with higher in-hospital mortality and was an independent predictor of in hospital major bleeding in a population of patients with non-ST elevation acute coronary syndromes (8). Similar results were found in an another study (18). Fatemi et al. found that RDW was independently associated with in-hospital major bleeding in 6.689 patients undergoing PCI after adjustment for major covariates of bleeding (5). In our study, we demonstrated that a greater admission RDW value was independently associated with hypertensive hematoma growth in the first 12 hours.

PDW is a potentially useful marker for the early diagnosis of thromboembolic disease. PDW is easily measured with platelet indices, which increase during platelet activation. Varasteh-Ravan and colleagues found the desired cut-off point of PDW to predict the no-resolution of ST- segment 12.85 fl with 71.2% sensitivity and 83.6% specificity (22). In our study we found that PDW value is significantly related with morbidity at the 3rd month.

LIMITATIONS

High RDW values may indicate accelerated red blood cell destruction, nutritional deficiency (folic acid or vitamin B12), a proinflammatory state or renal dysfunction that impairs erythropoiesis and RBC maturation. Levels of erythropoietin, iron, folic acid or vitamin B12 were not included in our analysis.

CONCLUSION

RDW and PDW are inexpensive and powerful prognostic factors routinely reported as a part of CBC and could therefore be a useful risk assessment tool in different clinical settings. Future studies are needed to externally cross-validate our findings in a larger prospective cohort of hypertensive ICH patients.

REFERENCES

1. Ani C, Ovbiagele B: Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 277: 103–108, 2009
2. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, Skolnick BE, Davis SM: Determinants of intracerebral hemorrhage growth: An exploratory analysis. Stroke 38: 1072-1075, 2007
3. Chakrabarty A, Shivane A: Pathology of intracerebral hemorrhage. ACNR 8(1): 20-21, 2008
4. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger JM, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Kosior J, Bhatia R, Tymchuk S, Subramaniam S, Gladstone DJ, Hill MD, Aviv RI, PREDICT/Sunnybrooke ICH CTA study group: Prediction of hematoma growth and outcome in patients with intracerebral hemorrhage using the CT-angiography spot sign (PREDICT): A prospective observational study. Lancet Neurol 11: 307–314, 2012
5. Fatemi O, Torguson R, Chen F, Ahmad S, Badr S, Satler LF, Pichard AD, Kleiman NS, Waksman R: Red cell distribution width as a bleeding predictor after percutaneous coronary intervention. Am Heart J 166: 104-109, 2013
6. Fukuta H, Ohte N, Mukai S, Saeki T, Asada K, Wakami K, Kimura G: Elevated plasma levels of B-type natriuretic peptide but not C-reactive protein are associated with higher red cell distribution width in patients with coronary artery disease. Int Heart J 50: 301–312, 2009
7. Garcia JH, Ho KL, Caccamo DV: Intracerebral hemorrhage: Pathology of selected topics. In: Kase CS, Caplan LR (eds), Intracerebral Hemorrhage. Boston: Butterworth-Heinemann, 1994: 45-50
8. Gonçalves S, Ferreira Santos J, Amador P, Rassi L, Rodrigues AR, Seixo F, Neves Soares L: Impact of red blood cell distribution width on risk for bleeding events in patients with non-ST elevation acute coronary syndromes. Rev Port Cardiol 32: 27-33, 2013
9. Howard G, Cushman M, Howard VJ, Kissela BM, Kleindolfer DO, Moy CS, Switzer J, Woo D: Risk factors for intracerebral hemorrhage. The reasons for geographic and racial differences in stroke (REGARDS) study. Stroke 44:1282-1287, 2013
10. Kase CS, Mohr JP, Caplan LR: Intracerebral hemorrhage. In: Mohr JP, Wolf PA, Grotta JC, Moskowitz MA, Mayberg MR, von Kummer R (eds), Stroke. Elsevier, 2011: 327-376
11. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. Stroke 27:1304, 1996

12. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, Macdonald RL, Messe SR, Mitchell PH, Selim M, Tamargo RJ: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 41: 2108-2129, 2010
13. Mustanoja S, Strbian D, Putaala J, Meretoja A, Curtze S, Haapaniemi E, Sairanen T, Hietikko R, Siren J, Kaste M, Tatlisumak T: Association of prestroke statin use and lipid levels with outcome of intracerebral hemorrhage. Stroke 44: 2330-2332, 2013
14. Paulus EM, Weinberg JA, Magnotti LJ, Sharpe JP, Schroeppel TJ, Fabian TC, Croce MA: Admission red cell distribution width: A novel predictor of massive transfusion after injury. Am Surg 80: 685-689, 2014
15. Pierce CN, Larson DF: Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 20: 83–90, 2005
16. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. N Engl J Med 344: 1450-1460, 2001
17. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators: Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 344: 1959–1965, 2001
18. Sánchez-Martínez M, López-Cuenca A, Marín F, Flores-Blanco PJ, García Narbon A, de las Heras-Gómez I, Sanchez-Galian MJ, Valdes-Chavarri M, Januzzi JL, Manzano-Fernandez S: Red cell distribution width and additive risk prediction for major bleeding in non-ST-segment elevation acute coronary syndrome. Rev Esp Cardiol 67: 830-836, 2014
19. Tetri S, Juvela S, Saloheimo P, Pyhtinen J, Hillbom M: Hypertension and diabetes as predictors of early death after spontaneous intracerebral hemorrhage. J Neurosurg 110: 411–417, 2009
20. Uyarel H, Isik T, Ayhan E, Ergelen M: Red cell distribution width (RDW): A novel risk factor for cardiovascular disease. Int J Cardiol 154: 351-352, 2012
21. Van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ: Incidence, case fatality and functional outcome of intracerebral hemorrhage over time, according to age, sex, and ethnic origin: A systematic review and meta-analysis. Lancet Neurol 9:167–176, 2010
22. Varasteh-Ravan HR, Ali-Hassan-Sayegh S, Shokraneh S, Mozayan MR, Karimi-Bondarabadi AA: Relationship of admission mean platelet volume, platelet distribution width and white blood cells with ST resolution in patients with acute ST segment elevation myocardial infarction treated with streptokinase without history of previous cardiovascular surgery. Perspect Clin Res 4:125-129, 2013
23. Ye Z, Smith C, Kullo IJ: Usefulness of red cell distribution width to predict mortality in patients with peripheral artery disease. Am J Cardiol 107: 1241–1245, 2011