Pakistan
Journal of Biological Sciences

Evaluating Role of Leukocytosis and High Sedimentation Rate as Prognostic Factors in Acute Ischemic Cerebral Strokes

[1]Masoud Nikanfar, [1]Sheyda Shaafi, [1]Maziyar Hashemilar,
[1]Daioush Savadi Oskouii and [2]Mohamad Goldust
[1]Department of Neurology, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: Leukocytosis and increased Erythrocyte Sedimentation Rate (ESR) during the early phases of acute ischemic stroke has been proposed to be related with poor prognosis. The aim of this study was to evaluate these two parameters in patients with ischemic stroke. In this descriptive analytical study, 150 patients with confirmed ischemic stroke were taken under study for a period of 13 month. The White Blood Cell (WBC) count and ESR were determined on admitting and after 3 days. Any history of Diabetes Mellitus (DM), Hypertension (HTN), Heart Disease (HD), Hyperlipidemia (HLP), smoking, CT scan findings, level of consciousness and the condition of patient on admission and discharge (according to Rankin's scale) were assessed. In this study, 150 patients were enrolled, in which 75 were males and 75 were females, with the mean age of 67.3±8.2 years. Leukocytosis on day one was significantly more prevalent in patients passed away during hospitalization or discharged in not-so-well condition. High WBC and ESR levels, altered consciousness, diffused lesions in CT scan and imperfect neurological condition on day one, as well as positive history of DM and HTN were significantly related with higher in-hospital death rate and/or poor condition at discharge. Raised WBC count and ESR just after an ischemic stroke attack might be related with a poor prognosis and necessitate immediate and meticulous monitoring and therapies.

Key words: Ischemic stroke, leukocytosis, erythrocyte sedimentation rate, Rankin scale of disease

INTRODUCTION

Considering that cerebral arteries incidences are the third mortality factor in the world, patients, their relatives and physicians should always know prognosis of cerebral strokes (Nayak et al., 2011). On the other hand, neurologists are looking for ways to identify factors to determine incidence of prognosis cerebral strokes from early hours. These factors should be highly available, inexpensive and accessible without wasting time (Selvarajah et al., 2011). For this purpose, blood markers including leukocytes (WBC), Erythrocytes Sedimentation Rate (ESR), Hematocrit (HCT), blood glucose, blood platelets count and other cases have recently been evaluated. The results of these studies are controversial (Homburg et al., 2011; Lakshmi et al., 2011). Exact mechanism of ESR acute increase in patients suffering from ischemic cerebral stroke is unknown (Brouns et al., 2010). Some hypotheses have been suggested in this regard: (1) Undiagnosed infections one month before acute attack of cerebral stroke leads to this increase, (2) High ESR is regarded as indirect sign of thrombosis development and (3) there is a direct relationship between ESR and levels of inflammatory factors and proteins involved in occlusion (Bernard et al., 2010; Lidove et al., 2009; Molnar et al., 2010). Increase of WBC during acute cerebral stroke may originate from developing of inflammatory response to brain parenchyma ischemic injury (De Silva et al., 2008). Increase of cytokines is seen immediately after ischemic cerebral stroke (before increase of WBC). Additionally, there is a direct relationship between levels of inflammatory factors, proteins involved in occlusion and ESR (De et al., 2008). Laboratory samples show that increase of circulatory WBCs leads to decrease of cerebral blood flow at penumbral less injured zones (De Silva et al., 2009). We decided to conduct a study through evaluating two factors of WBC count and ESR (which can be easily be easily evaluated during first day of cerebral strokes incidence and compared with the third day) and its relationship with ischemic stroke prognosis.

MATERIALS AND METHODS

One hundred and fifty patients having 75 males and 75 females were considered under analytical study which

---

Corresponding Author: Mohamad Goldust, Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
Tel: 00989111289630

were hospitalized with diagnosis of ischemic cerebral stroke. The patients necessarily excluded from the study, if they received intervenient drugs before hospitalization or if there is a disturbing factor in their medical history. The patients of in-hospital mortality and in-hospital survived groups as well as two groups of desired and undesired results while releasing from hospital (in those patients who were survived) were compared. Desired and undesired results of Rankin's scale at the time of releasing from hospital were respectively regarded as 0-2 and 3-5. Rankin's scale was considered as follow:

Grade 0: Asymptomatic
Grade 1: Symptomatic but performs routine activities well
Grade 2: Trivial disability but performs daily activities without asking others' help
Grade 3: Average disability, looking for other's help to do activities but walk by him/herself
Grade 4: Need other's help to walk but fulfils personal needs and requirements without help
Grade 5: Severe disability, he/she cannot walk, suffers from feces incontinency and needs a nurse
Grade 6: Mortality has been considered. WBC higher than 10,000 mm^{-3} is regarded as leukocytosis

ESR was measured using Western green method in a single laboratory and considering normal amounts for the desired age range. The obtained data was stated as Mean±standard deviation ($\mu \pm SD$), frequency and percentage and SPSS-16 is the used statistical software. Quantitative variables were compared using student t-test (independent samples) or paired samples t-test. Contingency tables using chi-square test or Fischer's exact test (considering conditions) were used to compare categorical variables. Pearson's correlation coefficient was used to evaluate correlation. Logistic regression test was used to conduct a multivariable study. In all understudy cases, the results were known as statistically meaningful, if $p \leq 0.05$.

RESULTS

The understudy patients were consisted of 75 females and 75 males with mean age of 67.33±8.17 (48-88) years and the patient's mean Rankin scale was 4±0.57 (1-5) while admission. Mean WBC was 10972.00±3617.47 (5600-24000) and 10319.33±2693.96 (5000-18600) per mm^3 while admission and after three days, i.e., mean WBC during the third day is meaningfully less than that of the first day (p = 0.004). In-admission leukocytosis was observed in 70 patients (46.7%). Mean ESR was 28.69±6.73 (16-45) and 24.8±10.1 (8.48) mL h^{-1} while admission and after three days, i.e., mean ESR during the third day is meaningfully less than that of the first day (p<0.001). Mean Rankin scale of release (or mortality) time was 3.92±1.53 (0-6). Table 1 demonstrates comparison of the studied variables in two groups with desired and undesired results at the time of release. According to Table 1, mean WBC level of serum and ESR in the first day of admission in the group with undesired results was meaningfully higher than that of the group with desired results while releasing from hospital. Additionally, frequency of cases with in-admission leukocytosis, records of diabetes and hypertension and lowering of consciousness level in the group with undesired results was higher than that of the group with desired results while releasing from hospital. In order to find independent risk factor, the above-mentioned cases entered a multivariable study and following results were obtained: Lowering of consciousness level (p<0.674) and increasing in-admission ESR level (p = 0.123) were not independent risk factors for undesired results while releasing from hospital in patients suffering from cerebral ischemic stroke. Hypertension (p = 0.013), increasing in-admission blood WBC level (p = 0.014) and in-admission Rankin scale (p = 0.028) were regarded as independent risk factors for undesired results while releasing from hospital in patients suffering from cerebral ischemic stroke. In-admission WBC serum and ESR level as well as Rankin scale in predicting of obtaining weak results while releasing from the hospital were respectively 0.719, 0.677 and 0.679 meaning that all three parameters are appropriate to predict weak results while releasing from the hospital (p<0.05). Distributed cerebral lesions observed in CT-scan (p<0.001), increasing in-admission blood WBC level (p = 0.037), increasing in-admission ESR level (p = 0.006) and increasing in-admission Rankin scale (p = 0.004) were regarded as independent risk factors for in-hospital mortality of patients suffering from cerebral ischemic stroke. Increasing in-admission serum WBC level has increased weak results at the time of releasing from hospital as well as in-hospital mortality. Increasing in-admission ESR level has led to increase of weak results at the time of releasing from hospital as well as in-hospital mortality. In-admission Rankin scale is significantly higher in the dead group. In-admission WBC serum and ESR level as well as Rankin Scale in predicting of in-hospital mortality were respectively 0.739, 0.816 and 0.771 meaning that all three parameters are appropriate to predict in-hospital mortality (p<0.05). There is weak and significant correlation between in-admission serum WBC level and in-admission Rankin scale (p = 0.001, r = 0.271), fair and meaningful correlation between

Table 1: Comparing the evaluated parameters in patients with desired and undesired results while releasing from hospital

Parameter	Desired results	Undesired results	p-value
Age (year)	66.90±6.3000*	67.50±7.4000	0.682
In-admission WBC (mm^{-3})	8861.54±1821.1	10732.71±3080.8	0.001
WBC after three days (mm^{-3})	8907.70±2228.3	9541.30±2732.8	0.106
In-admission ESR (mm h^{-1})	24.10±5.7000	27.90±6.0000	0.004
ESR after three days (mm h^{-1})	20.60±9.9000	24.70±9.8000	0.100
In-admission Rankin scale	3.50±0.90000	4.00±0.30000	<0.001
In-admission leukocytosis	4.00 (15.4)	44.00 (47.8)	0.003
Gender			
Male	10.00 (38.5)	45.00 (48.9)	0.346
Female	16.00 (61.5)	47.00 (51.1)	
Disease duration (h)			
<6	18.00 (69.2)	52.00 (56.5)	0.494
6-12	4.00 (15.4)	18.00 (19.6)	
12-24	4.00 (15.4)	22.00 (23.9)	
Hospitalization duration (week)			
<1	26.00 (100.0)	68.00 (73.9)	-
1-2	0.00	18.00 (19.6)	
2-4	0.00	6.00 (6.5)	
Diabetes	2.00 (7.7)	24.00 (26.1)	0.046
Cardiac disease	2.00 (7.7)	20.00 (21.7)	0.154
Hypertension	12.00 (46.2)	68.00 (73.9)	0.007
Receiving anti-hypertension drugs	12.00 (46.2)	54.00 (58.7)	0.255
Hyperlipidemia	5.00 (19.2)	18.00 (19.6)	0.970
Smoking	8.00 (30.8)	18.00 (19.6)	0.224
Decreasing consciousness level	4.00 (15.4)	34.00 (37.0)	0.038
Cerebellar symptoms	0.00	2.00 (2.20)	1.000
Methods of brain involvement			
Non-involvement	10.00 (38.5)	24.00 (26.1)	0.107
Topical	16.00 (61.5)	56.00 (60.9)	
Distributed	0.00	12.00 (10.2)	

*Values are as Mean±SD, Values in brackets are percentages

in-admission serum WBC level and Rankin Scale while releasing from hospital (p = 0.001, r = 0.399) and between in-admission serum ESR level and in-admission Rankin scale (p<0.001, r = 0.446) and strong and meaningful correlation between in-admission serum ESR level and Rankin scale while releasing from hospital (p<0.001, r = 0.508) and between in-admission Rankin scale and Rankin scale while releasing from hospital (or in-hospital mortality) (p<0.001, r = 0.628). As observed, increasing in-admission serum WBC level increases weak results while releasing from hospital and in-hospital mortality.

DISCUSSION

This simple and practical system can quickly and accurately evaluate patient's condition without need to any special facilities. This is one of the most important advantages of the present study. Efficiency of the system in evaluating these patients has previously confirmed by Balestrino *et al.* (1998). Use of multivariable studies to identify independent factors involved in prognosis of patients with ischemic stroke is another advantage of our study. These studies concluded that in-admission higher WBC and Rankin scale as well as records of hypertension are of independent predictors of weak results while

releasing from hospital (Dulli *et al.*, 1999). They introduced in-admission higher WBC, ESR and Rankin scale as well as distributed or wide lesions observed through initial CT-scan as independent predictors of in-hospital mortality (Suwanwela *et al.*, 2006). Several studies have evaluated the relation between leukocytosis and prognosis of patients suffering from cerebral stroke (especially ischemic stroke) while there are few studies considering ESR (Swartz *et al.*, 2005). In a previous research, 400 patients are found with acute cerebral stroke in Poland. In this study, the patients' prognosis was evaluated based on modified Rankin Scale. Accordingly, increasing in-admission WBC independently was accompanied by worse prognosis and higher mortality rate. The main difference of the study with our study is related to considering hemorrhagic cerebral stroke along with its ischemic type (Kazmierski *et al.*, 2004). They evaluated 13555 African-American and whites suffering from acute ischemic cerebral stroke. In this study, meaningful relationship was observed between in-admission higher levels of blood WBC and patients' weak prognosis (Lee *et al.*, 2001). Zaremba *et al.* (2004) studied the relation between in-admission leukocytosis and undesired prognosis of ischemic cerebral stroke in patients with coronary heart disease and reported a meaningful result. Different studies have emphasized the

relation between increasing of in-admission WBCs and serious prognosis of those patients with ischemic cerebral stroke (Vila *et al.*, 2000; Zeltser *et al.*, 2001). In the previous researches, it is demonstrated that increasing of ESR in patients suffering from cerebral stroke at carotid artery area at 6 first h may be accompanied by a serious prognosis (Elneihoum *et al.*, 1996; Zeltser *et al.*, 2001). In another study, Suzuki *et al.* (1995) indicated the relationship found between increased ESR level during initial stages of cerebral stroke and the patients' worse prognosis. In another study on 208 patients with ischemic cerebral stroke, Chamorro *et al.* (1995) suggested that increasing in-admission ESR is independently accompanied by a worse prognosis in these patients.

CONCLUSION

Higher in-admission WBC and ESR is accompanied by weak results at the time of release from hospital. Also, higher WBC is known as independent predictor of weak results while releasing from the hospital. Higher in-admission WBC and ESR and CT-scan findings indicating wide or distributed lesion are accompanied by in-hospital mortality. Higher WBC and ESR and wide or distributed lesion observed through CT-scan are known as independent predictors of in-hospital mortality.

REFERENCES

Balestrino, M., D. Partinico, C. Finocchi and C. Gandolfo, 1998. White blood cell count and erythrocyte sedimentation rate correlate with outcome in patients with acute ischemic stroke. J. Stroke Cerebrovasc Dis., 7: 139-144.

Bernard, T.J., L.Z. Fenton, S.D. Apkon, R. Boada and G.N. Wilkening *et al.*, 2010. Biomarkers of hypercoagulability and inflammation in childhood-onset arterial ischemic stroke. J. Pediatrics, 156: 651-656.

Brouns, R., R. Verkerk, T. Aerts, D. de Surgeloose, A. Wauters, S. Scharpe and P.P. de Deyn, 2010. The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. Neurochem. Res., 35: 1315-1322.

Chamorro, A., N. Vila, C. Ascaso, A. Saiz, J. Montalvo, P. Alonso and E. Tolosa, 1995. Early prediction of stroke severity: Role of the erythrocyte sedimentation rate. Stroke, 26: 573-576.

De Silva, D.A., F.P. Woon, C. Chen, H.M. Chang and M.C. Wong, 2009. Serum erythrocyte sedimentation rate is higher among ethnic South Asian compared to ethnic Chinese ischemic stroke patients. Is this attributable to metabolic syndrome or central obesity? J. Neurol. Sci., 276: 126-129.

De Silva, D.A., F.P. Woon, H.Y. Gan, C. Chen and H.M. Chang *et al.*, 2008. Arterial stiffness is associated with raised levels of the inflammatory marker erythrocyte sedimentation rate among ischaemic stroke patients. Intern Med J., 38: 918-920.

De, G.L., N.D. Brunetti, A. Cuculo, P.L. Pellegrino and M. di Biase, 2008. Systemic inflammation in nonischemic dilated cardiomyopathy. Heart Vessels., 23: 445-450.

Dulli, D.A., H.S. Schutta, R.L. Levine and P.S. Rahko, 1999. Ischemic stroke associated with activated protein C resistance and aortic valvular papillary fibroelastoma. J. Stroke Cerebrovasc Dis., 8: 45-48.

Elneihoum, A.M., P. Falke, L. Axelsson, E. Lundberg, F. Lindgarde and K. Ohlsson, 1996. Leukocyte activation detected by increased plasma levels of inflammatory mediators in patients with ischemic cerebrovascular diseases. Stroke, 27: 1734-1738.

Homburg, P.J., Plas G.J., S. Rozie, A. van der Lugt and D.W. Dippel, 2011. Prevalence and calcification of intracranial arterial stenotic lesions as assessed with multidetector computed tomography angiography. Stroke, 42: 1244-1250.

Kazmierski, R., P. Guzik, W. Ambrosius, A. Ciesielska and J. Moskal, W. Kozubski, 2004. Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. Clin. Neurol. Neurosurg, 107: 38-43.

Lakshmi, A.B., P. Uma, C. Venkatachalam and R.G.S. Nageswar, 2011. A simple slide test to assess erythrocyte aggregation in acute ST-elevated myocardial infarction and acute ischemic stroke: Its prognostic significance. Indian J. Pathol. Microbiol., 54: 63-69.

Lee, C.D., A.R. Folsom, F.J. Nieto, L.E. Chambless, E. Shahar and D.A. Wolfe, 2001. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: Atherosclerosis risk in communities study. Am. J. Epidemiol., 154: 758-764.

Lidove, O., M.P. Chauveheid, C. Caillaud, R. Froissart and L. Benoist *et al.*, 2009. Aseptic meningitis and ischaemic stroke in Fabry disease. Int. J. Clin. Pract., 63: 1663-1667.

Molnar, T., V. Papp, M. Banati, L Szeredayand G. Pusch *et al.*, 2010. Relationship between C-reactive protein and early activation of leukocytes indicated by leukocyte antisedimentation rate (LAR) in patients with acute cerebrovascular events. Clin. Hemorheol. Microcirc., 44: 183-192.

Nayak, A.R., R.S. Kashyap, D. Kabra, P. Deoras, H.J. Purohit, G.M. Taori and H.F. Daginawala, 2011. Evaluation of routinely performed hematological and biochemical parameters for the prognosis of acute ischemic stroke patients. Neurol. Sci., 32 : 855-860.

Selvarajah, J.R., C.J. Smith, S. Hulme, R. Georgiou and C. Sherrington *et al.*, 2011. Does inflammation predispose to recurrent vascular events after recent transient ischaemic attack and minor stroke. The North West of England transient ischaemic attack and minor stroke (NORTHSTAR) study. Int. J. Stroke., 6: 187-194.

Suwanwela, N.C., A. Chutinet and K. Phanthumchinda, 2006. Inflammatory markers and conventional atherosclerotic risk factors in acute ischemic stroke: Comparative study between vascular disease subtypes. J. Med. Assoc. Thai., 89: 2021-2027.

Suzuki, S., R.E. Kelley, Y. Reyes-Iglesias, V.M. Alfonso and W.D. Dietrich, 1995. Cerebrospinal fluid and peripheral white blood cell response to acute cerebral ischemia. South. Med. J., 88: 819-824.

Swartz, J.E., B.F. Jacobson, M.D. Connor, P.L. Bernstein and V.U. Fritz, 2005. Erythrocyte sedimentation rate as a marker of inflammation and ongoing coagulation in stroke and transient ischaemic attack. S. Afr. Med. J., 95: 607-612.

Vila, N., J.C. Reverter, J. Yagueand A. Chamorro, 2000. Interaction between interleukin-6 and the natural anticoagulant system in acute stroke. J. Interferon Cytokine Res., 20: 325-329.

Zaremba, J., P. Skrobanski and J. Losy, 2004. Acute ischaemic stroke increases the erythrocyte sedimentation rate, which correlates with early brain damage. Folia Morphol., 63: 373-376.

Zeltser, D., N.M. Bornstein, R. Rotstein, V. Prochorov and I, Shapira, *et al.*, 2001. The erythrocyte adhesiveness/aggregation test in the peripheral blood of patients with ischemic brain events. Acta Neurol. Scand., 103: 316-319.