Prognostic value of routine haematological and biochemical parameters on 30 day fatality in patients with acute hypertensive intracerebral hemorrhage

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Abstract

Objective: This prospective study aimed to study the prognostic value of routine haematological and biochemical parameters in patients of acute hypertensive intracerebral hemorrhage (ICH) on fatality occurring during first 30 days, and to estimate its case fatality rate, demographic and clinical correlates. *Methods:* One hundred and eleven consecutive patients with proved hypertensive ICH within 72 hours of symptom onset were studied. After clinical evaluation and neuroimaging, blood investigations including hemoglobin, total leukocyte count, platelet count, erythrocyte sedimentation rate, random blood sugar, urea, creatinine, sodium, potassium, serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), albumin estimations were performed. The patients were followed up for a maximum period of 30 days from the onset of stroke. *Results:* Logistic regression analysis demonstrated that a low Glasgow Coma Scale (GCS) score (Odd`s ratio (OR) 17.54, p=0.001); high serum bilirubin (OR=7.97, p=0.021), and low serum albumin (OR=13.31, p=0.001) correlated significantly with death.
Conclusions: Our study shows that low GCS, raised serum bilirubin, and low serum albumin are marker of poor outcome in ICH.

INTRODUCTION

Primary (spontaneous) intracerebral hemorrhage (ICH) is the most fatal type of acute stroke with almost 50% mortality. Also compared to western countries hemorrhagic stroke are much more common in India comprising about 32% of all stroke.[1] A number of ICH scores had been devised to predict the prognosis of the patients with intracerebral hemorrhage that includes age, Glasgow Coma Scale (GCS), ICH volume and intraventricular extension.[2,3] Apart from clinical and neuroimaging parameters, many studies have highlighted the prognostic importance of various laboratory parameters such as blood sugar, total leukocyte count, and erythrocyte sedimentation rate (ESR).[4-7] Some recently published studies have demonstrated that parameters such as hematocrit, serum creatinine are significant yet underestimated predictor of mortality in acute stroke.[6,7] Aminotransferase levels are known to be associated with hemorrhagic stroke as well as its incidence[8-11], however whether or not they have a prognostic value is not clear. In our study we tried to confirm the finding of previously published studies regarding these parameters, as well as to investigate new parameters such as serum aminotransferase with multivariate analysis; hoping to better guide the physicians in the management of hemorrhagic stroke patients.

METHODS

This study was conducted on patients of acute stroke with primary (spontaneous) intracerebral hemorrhage (ICH) admitted to the Department of Medicine and Department of Neurology, C. S. M. Medical University Lucknow, from April 2008 to July 2009. All patients included in the study had a diagnosis of hypertensive intracerebral hemorrhage presented within 72 hours of symptom onset. Stroke was defined according to the WHO definition[7], as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than of vascular origin. The time of onset of the stroke was defined as the time when the patient or observer first became aware of the symptoms. Proven hypertensive intracerebral hemorrhage was defined as: Patient is a known case of hypertension having documented blood pressure of more than 140/90 mm Hg with or without treatment[15] (Table 1A); Having electrocardiographic (ECG)

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/Two dimensional echocardiogram (2D Echo) changes of left ventricular hypertrophy due to hypertension (Table 1B); with at least hypertensive intracerebral hemorrhage on neuroimaging (Table 1C). Patient's ECG were interpreted according to the Romhilt and Estes point score system and a score of 5 or more is considered positive indicator of left ventricular hypertrophy (Table 1B).We choose Romhilt Estes criteria because it is having similar sensitivity but greater specificity among different ECG criterias.[12] LVH was defined on 2D echo as left ventricular mass index (LVMI) greater than 150 g/m2, according to data from the Framingham Heart Study.[13] (Table 1B).

All the patients who presented within 72 hours of onset, irrespective of age, sex were included in the study. Patients with previous history of stroke or who are alcoholic, or having previous episodes of jaundice/documented deranged liver function test were excluded. Those with significant alcohol consumption were classified as alcoholic. We defined significant alcohol intake as consumption of up to one drink per day for women and up to two drinks per day for men. Twelve fluid ounces of regular beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits is taken as one drink. This definition is not intended as an average over several days but rather as the amount consumed on any single day. These patients were excluded because alcohol is known to produce derangement in liver function tests.

The study patient was subjected to a detailed

Table 1: Proven hypertensive intracerebral hemorrhage is defined as either patient is a known case of hypertension (A), or having electrocardiographic (ECG) / 2D echo changes of left ventricular hypertrophy (B); with at least hypertensive intracerebral hemorrhage on neuroimaging (C)

(A) Patient is a known case of hypertension having documented blood pressure of more than 140/90 mm Hg with or without treatment[15]

(B) Patient is having hypertensive left ventricular hypertrophy detected either on 2D echo or on ECG.
  • LVH was defined on 2D echo as left ventricular mass index (LVMI) greater than 150 g/m², according to data from the Framingham Heart Study.[13] Comprehensive 2D and Doppler echocardiography was performed as described previously Left ventricular dimensions (interventricular septal thickness [IVS], posterior wall thickness [PW], and left ventricular end-diastolic diameter [LVEDD] were measured at end of diastole by using the leading edge to leading-edge convention.
  • Left ventricular mass was determined by using the Troy formula according to the recommendations of the American Society of Echocardiography (ASE)[13]
 	
LVM (gm) = 1.05 [(LVEDD +TVS + PW)^3 - LVEDD^3].
 	
Left ventricular mass was divided with body surface area to obtain the left ventricular mass index (LVMI).
 	
  • patient's ECG is interpreted according to The Romhilt and Estes point score system, a score of 5 or more point is considered positive evidence of left ventricular hypertrophy
 	
The Romhilt and Estes point score system
  • Increased QRS magnitude   3 points
  • ST-T abnormality   3 points
  • A P Wave of left atrial enlargement   3 points
  • Left axis deviation   2 points
  • Increased ventricular activation time   1 point

(C) Hypertensive intracerebral hemorrhage on neuroimaging is defined as cerebral hemorrhage on these sites on computed tonmography (CT)/ magnatic resonance angiography (MRI)
  • Putamens and adjacent internal capsule
  • The central white matter of temporal parietal or frontal lobes
  • Thalamus
  • Cerebeller hemisphere
  • Pons

clinical evaluation. The risk factors of stroke recorded included diabetes mellitus, hypertension and smoking. Diabetes mellitus was defined based on WHO criteria, which was a fasting plasma glucose of more than or equal to 126 mg/dl or a two hour plasma glucose of more than or equal to 200 mg/dl.[14] Hypertension was defined according to the JNC-7 criteria[15], which was a blood pressure of more than or equal to 140/90 mm Hg. Smoking status was defined according to Nina *et al*.[16] Subjects were asked about the amount smoked (in absolute numbers), duration, inhalation, and preferred type of tobacco (cigarettes, cigars, cheroots, pipes, and mixed types). Total tobacco consumption expressed in grams per day was calculated by equating a cigarette to 1 g of tobacco, a cheroot to 3 g, and a cigar to 5 g. Both sustained (having no period of smoking abstinence longer than 3 month) light smokers (1–14 g/day), and sustained heavy smokers (≥15 g/day) were included in the study as smokers.

A GCS score was obtained for each patient. Apart from computed tomography (CT), blood investigations which were performed included hemoglobin, total leukocyte count, platelet count, blood sugar, urea, creatinine, sodium, potassium and erythrocyte sedimentation rate (ESR). For the assessment of liver function, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and albumin estimations were performed. Blood samples were collected immediately after admission, before starting any intravenous infusion preferably within 1 hour in plastic disposable syringes. Blood samples were immediately sent to the laboratory for evaluation. Informed consent was taken for each patient.

These patients were treated according to the standard treatment protocols of our hospital. The study in no way interfered with the treatment. Nevertheless an ethical committee clearance was taken for the study. The patients were followed up for a maximum period of 30 days from the onset of stroke, and patients who expired were grouped as 'expired' and the rest as 'survivors'. Patients discharged from the hospital before this period was asked to visit the outpatient department at weekly intervals. Those who failed to attend the weekly follow-up were contacted by phone about their outcome, or had a home visit. Those patients who were discharged from the hospital against medical advice or on persistent request were excluded from the study. The haematological and biochemical investigations were carried out in the Hematology and Biochemistry Laboratory of our Hospital. The result were analyzed by the Student 't' test and by univariate analysis. The difference was considered significant if 'p' value was less than 0.05.Multiple logistic regression analysis was done for parameters found significant in univariate analysis. The statistical programme used was SPSS.

RESULTS

A total of 111 patients fulfilled the inclusion criteria and were enrolled in the study. They consisted of 72 males and 39 females. Among these 111 patients 18% were diabetic, 31% were hypertensive and 28.9% were smokers. Expired patients have a slightly higher mean age then survived patient (66.4 years vs 64.5 years, p=0.06) which is statistically not significant. The female patients had significantly higher mortality, 24 out of 39 females (61%) versus 30 out of 72 males (41%), p=0.046). There was however, no significantly increased mortality among the smokers versus non-smokers (50.6% vs 48.0%, p=0.66), and diabetics mellitus versus non-diabetics (49.7% vs 48.4%, p=0.71).

As shown in Table 2, with univariate analysis, among the clinical parameters, a low GCS and a higher initial blood pressure; among the hematological parameters, high hematocrit and high total leukocyte count on admission correlated significantly with death. Among the biochemical parameters, elevated blood urea, serum creatinine, serum transaminases (AST and ALT), serum ALP, and lower serum albumin level correlated significantly with death. However, serum sodium, serum potassium and ESR had no significant correlation with being expired. With logistic regression analysis on the factors found significant in univariate analysis, low GCS, low serum albumin and high serum bilirubin were significantly correlation with death (Table 3).

DISCUSSION

In this study, we have found on univarriate analysis, low GCS, higher mean blood pressure, high hematocrit, high leukocyte count, higher blood sugar, deranged renal function (blood urea and creatinine), deranged liver function (serum bilirubin, AST,ALT) and a low serum albumin to be significantly associated with mortality. On multiple logistic regression analysis, a low GCS, low serum albumin and high serum bilirubin had significant association with mortality

The association of low GCS with mortality

Table 2: distribution of parameters in relation to outcome (discharged/expired)

Parameter	Outcome		P value
	Discharged N =57 Mean ± SD	Expired N=54 Mean ± SD	
Glasgow coma scale	11.2 ± 3.2	6.6 ± 2.8	0.001
Mean blood pressure (mm Hg)	167.5 ± 34.1	183.4 ± 29.8	0.01
Hematocrit (%)	37.7 ± 4.2	38.3 ± 6.1	0.03
Total leukocyte count (/mm³)	8573.6 ± 3904.5	12950.1 ± 4511.0	0.001
Blood sugar (mg/d L)	128.1 ± 48.07	181.2 ± 56.1	0.001
Sodium (mEq/L)	141.4 ± 145.7	163.2 ± 176.1	NS
Potassium (mEq/L)	4.1 ± 0.5	4.2 ± 0.4	NS
Blood urea (mg/d L)	38.4 ± 32.9	71.4 ± 37.3	0.01
Creatinine (mg/d L)	1.2 ± 0.8	2.3 ± 1.3	0.04
Bilirubin (micromole/L)	1.3 ± 0.8	2.0 ± 0.9	0.001
Aspartate transaminase (IU/L)	35.7 ± 27.0	66.7 ± 42.7	0.001
Alanine transaminase (IU/L)	55.7 ± 58.8	86.8 ± 72.8	0.01
Alkaline phosphatise (IU/L)	119.6 ± 108.8	133.1 ± 122.0	0.02
Albumin (g/l)	3.8 ± 0.7	3.1 ± 0.5	0.0012
Erythrocyte sedimentation rate (By Westergreen)	11.2 ± 12.2	17.9 ± 20.4	NS

NS: Not significant

was in accordance with the previous studies.[2,3] In fact GCS is one of the components of different types of ICH scores used to predict the mortality of stroke patients.[17,18]

Bilirubin has been shown to be a natural antioxidant.[19,20] In previous studies, a U-shape correlation between bilirubin and cardiovascular risk was described[21,22] or suggested[23,24]; that is, the risk of cerebrovascular disease and stroke was increased at both low and high serum level. However there was no previous report of association between high serum bilirubin and early mortality of hemorrhagic stroke patients. Pathophysiological basis of high serum bilirubin and high early mortality of ICH patients is not well understood. The association can partly be explained by a close relationship between liver dysfunction and abnormality of almost all major

Table 3: Multivariate logistic regression model showing most significant parameters predicting prognosis of spontaneous intracerebral hemorrhage

Outcome	Standard error	Z value	P>Z	+95% CI	−95% CI	Odds ratio
Glasgow Coma Scale	13.07	3.86	0.001	4.101	75.034	17.543
Serum bilirubin (micromole/L)	7.17	2.30	0.021	1.365	46.587	7.971
Aspartate transaminase (IU/L)	2.05	1.41	0.159	0.668	11.780	2.802
Serum albumin (gm/L)	8.85	3.89	0.001	3.615	49.032	13.31

hemostatic parameters governing the progress of hematoma.[25-27] Raised aminotransferase level has traditionally been thought to be a risk factor for development of intracerebral hemorrhage.[28] The role of aminotransferase may be partly explained by the aminotransferase levels being correlated with the gamma glutamyltransferase level[29-31], which has been reported to be associated with ischemic heart disease and stroke.[32-37] Gamma glutamyltransferase may also be a marker of oxidative stress, and may be involved in the generation of oxygen free radicals.[34,37,38] Thus, raised aminotransferase level can indirectly predict the extent of oxidative damage to brain cells.

Neuroprotective efficacy of albumin is attributable to its multifunctional properties.[39] These include hemodilution and osmotic effects, antioxidant action, binding of copper ions, fatty-acid transport, and intravascular actions. The latter include salutary interactions with vascular endothelium[40], platelet antiaggregatory effects[41], antagonism of erythrocyte sedimentation in low-flow states[42], reaction with nitric oxide to form a stable S-nitrosothiol with endothelium-derived relaxing factor-like properties[43], and antagonism of the binding of activated neutrophils to endothelial cells in response to inflammatory stimuli.[44] In the ALIAS pilot clinical trial, subjects who received thrombolysis (IV tissue plasminogen activator) plus high-dose albumin were twice as likely to attain a favourable neurological outcome at 3 months as did tissue plasminogen activator–treated subjects who received lower-dose lbumin.[45] Dziedzic et al.[46] showed that relatively high serum albumin level in acute stroke patients decreases the risk of poor outcome.

Hematocrit plays an important role in blood rheology and in cerebral blood flow (CBF) dynamics. It has been shown that reduction of hematocrit improves CBF, so hematocrit reduction may thus improve circulation and ameliorate the clinical manifestation of stroke. Tanne[7] observed that mortality of stroke patients is significantly increased at both extremes of haemoglobin. Anemia may induce hypoxia at the most vulnerable regions when hemoglobin is reduced below a critical level, while high hemoglobin may increase blood viscosity, affect cerebral blood flow and is associated with pulmonary disease.

There has been previous studies reporting the association of leukocytosis in stroke.[47-49] The mechanisms by which leukocytes are implicated in parenchymal brain injury include vessel plugging, release of hydrolytic enzymes, oxygen free radicals or initiation of thrombosis.[47] Leukocytosis might also be a manifestation of some common causes of fever (e.g., pulmonary or urinary tract infections, sepsis, or pulmonary embolism from deep vein thrombosis) which may be the cause of mortality. Recent development in the ability to selectively modify leukocyte adhesion with antiadhesion molecule and the potential clinical application of this therapeutic approach have spurred a resurgence of experimental studies examining the role of leukocyte in acute stroke.

The association of high ESR and increased stroke mortality has been reported in some previous studies.[5,50] An elevated ESR may indicate an increase in fibrinogen concentration, leading to reduction in the cerebral blood flow, a larger lesion and poorer outcome.[50] This may also be indicate a displacement of the concentration of natural anticoagulant.

Song et al.[51] found that in brain oedema after ICH with hyperglycemia, the oedema was in lesion and non-lesion hemispheres. This may be attributable more to vasogenic edema. There has been previous studies reporting high blood glucose predicting increased mortality and poor outcome in ICH with and without diabetes.[52-54] A randomized trial has shown improved outcomes with tight glucose control (range 80 to 110 mg/dl) using insulin infusions in mainly surgical critical care patients.[55] However, recent studies have demonstrated increased incidence of hypoglycemic with possible increased mortality in patients treated with this regimen.[56,57] The optimal management of hyperglycemia in ICH and the target glucose remains to be clarified.

The increase in cardiovascular risk with worsening renal dysfunction is partly explained by factors associated with renal decline. This includes anemia, oxidative stress, increase in plasma asymmetrical dimethylarginine, a powerful inhibitor of nitric oxide synthesis, inflammation, and conditions promoting coagulation[58,59], all of which are associated with accelerated atherosclerosis and endothelial dysfunction. Other factors that progressively increase with renal decline include albuminuria, proteinuria, fibrinogen, homocystinemia, and elevated uric acid levels.[60,61] Data on the association between renal dysfunction and outcome after acute stroke are scarce.[62]

This study has limitations of firstly, we did not included body mass index (BMI) of the patient as a risk factor while obesity is known to be associated with both increase cardiovascular mortality and aminotransferase elevation.

Secondly we tried to exclude the patient with significant alcohol consumption with the help of self reported questionnaire which may have reporting bias, as even alcohol in small amount can cause derangement in liver function. Thirdly, time interval between stroke onset and admission, and so between stroke onset and sample collection was not standardised. This could also affect the prognosis. We could not find any way to overcome this.

In conclusion, we have shown that a low GCS score, a high serum bilirubin, and a low serum albumin at admission are independent predictors of increased 30 day fatality in primary ICH.

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DISCLOSURE

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