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Predictors of Mortality of Primary Intracerebral Hemorrhage among the Sea Coast Population of South India

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ABSTRACT

Background and purpose Intracerebral haemorrhage (ICH) is the second most leading cause of stroke, followed by ischemic stroke, particularly Primary Intracerebral Haemorrhage (PICH) which leads to high rates of mortality and morbidity. None of the previous studies revealed the incidence of ICH among sea coast population in India.

Method The present investigation is carried with an aim to assess the major governing factors among the seacoast population presenting with primary ICH and their outcome. The present prospective study was carried in the department of Neurology at Narayana Medical College & Hospital, Nellore. The research work has been carried out for 1.5 years.

Results Hypertension was one of the most common modifiable risk factor, observed in most patients with ICH. Mortality rate of PICH was almost 50% observed in the present study. Multivariate analysis of variables revealed that patients presented with pupillary asymmetry, 2D Echo-evidence of left Ventricular Hypertrophy, High systolic blood pressure and low GCS (Glasgow coma Score) at admission and CT (computerized tomography) imaging brain (plain) studies showing high peri-hematomal edema, irregular hematoma border were the major key factors associated with high rates of mortality.

Conclusion The present study signifies that most of the people residing along the seacoast who presented with PICH were illiterate and under low economic status. Hence the life style modifications and health education were very important preventive key factors to reduce the incidence and mortality of ICH

KEYWORDS

PICH; Mortality; Hypertension; Predictors.

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most leading cause for stroke, followed by ischemic stroke, which leads to high rates of mortality and morbidity [1]. Worldwide statistics reveal the incidence of ICH is nearly up to 10-15% of all strokes and its incidence vary from region to region globally. In Asian population ICH ranges from 4 to 14% of all strokes when compared to the west [2]. Despite advances in medical and neurosurgical treatment modalities, prognosis of ICH carries poor outcome, with high rates of mortality projected worldwide up to 40% to 50% [3]. Identification of major governing factors for outcome of ICH is essential and also important in analyzing the population.

Based on the etiology ICH is classified into primary and secondary, in which primary arises due to hypertension or amyloid angiopathy, leading to dysfunction of intracranial small

vessels. The secondary ICH arises mostly due to vascular malformations, coagulopathies, vasculitis, head injury, tumors, drug induced effects and drug abuse [4]. PICH occurs in the brain commonly in the region of putamen, thalamus, cortical followed by cerebellar and brain stem. However the majority of primary ICH will be seen in elderly people whereas the secondary ICH is common in the Young age group [5]. In the elderly population cerebral amyloid angiopathy (CAA) was found to be the significant cause for the lobar ICH [6]. Earlier studies also revealed various etiologies for intracerebral hemorrhage which include chronic arterial hypertension, consumption of alcohol, treatment with anti-coagulants and anti-platelets, therapies related to thrombolytics, amphetamines usage, cocaine abuse, and usage of statins [6, 7].

In India, HTN is a burning health problem. Nearly 20% of the population under 50 years is suffering with HTN. Several studies clearly stated that HTN is the most common independent risk factor for PICH [8]. The incidence of ICH varies in various regions of India. For instance, a study conducted in Kolkata revealed that majority of stroke cases had PICH, which was higher when compared to the western world [9]. In another study conducted in northeastern parts of India it was found that tribals had more PICH [10]. Studies related to south India population identified that ICH constitutes up to 12% of all the strokes [11]. Moreover, very few studies on PICH demonstrated its impact and outcome. Since India represents its vastness and heterogeneity in population, systematic studies from different regions of the country are needed. So far most studies revealed the outcome of PICH in urban population, but very few studies have been done to show the incidence and impact of PICH along the sea coast population.

The population residing along the sea coast is more exposed to stressful environment, with a wide range of climatic factors which include high humidity and salt intake .The above mentioned factors play a role in patho-physiological changes in the small intracranial blood vessels. Hence further studies on PICH among sea coast population are needed in order to assess the risk factors and predictors of outcome in ICH and hence decrease the mortality rate. More over studying such population will pave a way for newer therapeutic approaches. Thus the present study is being carried out with an aim to assess the major predicting factors for PICH outcome among seacoast population.

MATERIALS AND METHODS

Study Design

The present prospective study was carried out in the department of Neurology at Narayana Medical College & Hospital, Nellore, which is situated within 10km radius of seacoast. The research work has been carried out for a period of 1.5 years.

Inclusion Criteria

Patients of PICH of both sexes who presented to the department of Neurology were included after obtaining permission from the institutional ethical committee. Informed consent was obtained from all the patients.

Exclusion Criteria

Patients presenting with secondary ICH like tumor bleed, head injury, aneurysmal rupture, anticoagulant therapy, infective endocarditis were excluded from this study.

METHODOLOGY

The demographic data of all the patients were documented. The premorbid history and major risk factors of ICH such as arteriopathies, vasculitis, smoking, diabetes, hypertension, alcohol dependence and Cardiac diseases were noted. Along with this, therapies like anti-platelets, anticoagulant agents, and drug abuse were also documented. The routine clinical examination; baseline biochemical tests were carried out followed by specific investigations like ECG, 2D-Echo and CT (plain) brain were done. For certain patients MRA (Magnetic Resonance Arteriography) CT scan reports focused on hematoma size, location, intra-ventricular extension, peri-hematomal edema,and midline shift. Outcome was analysed based on alive and dead patients. Dead patients were categorised as patients who were dead and patients with very poor GCS (3-5) who left against medical advice despite counseling due to poor outcome and grave prognosis.

Statistical Analysis

To determine various predictors of outcome in patients with primary ICH, the analysis was performed in two stages. For this purpose, the quantitative variables were categorized. Variables showing significant association with the outcome (mortality) at $p<0.20$ were considered as candidate variables for inclusion in the multivariate model. Step–wise multivariate logistic regression analysis was performed with the potential candidate variables as co-variates and the backward stepwise method was applied to determine independent predictors of mortality. SYSTAT 7.0 (SPSS Inc., Chicago, IL, USA) and SPSS (version 10.0, SPSS Inc., Chicago, IL, USA) were used for statistical analysis. All statistical tests performed were two tailed. In this study, $p<0.05$ was considered as statistically significant.

RESULTS

In the present study we tried to assess outcome of PICH among the seacoast population. 158 patients who presented with PICH were enrolled in the study according to inclusion and exclusion criteria with their informed consent after obtaining permission from the institutional ethical committee. Initially various demographic variables were assessed.

Demographic Characteristics

Results indicate that the incidence of PICH was higher in males compared to females and the mean age was found to be 56.8 yrs in both sex (Table1). Assessment of variables like economic status and literacy rate revealed that most of them were of low socio economic status and illiteracy rate was also high. The patients presented with various clinical signs and symptoms which includes Limb weakness, altered sensorium, headache, vomiting, dysathria, and aphasia. Limb weakness was the most common presenting complaint. Their mean systolic blood pressure was 154 ± 21 mmHg and the mean diastolic blood pressure was 94 ± 15 mmHg.

Very low percentage of patients had a family history of stroke. GCS at presentation was > 12 in 53.7% of patients. Out of 158 ICH patients assessed, 80 were alive and 78 were dead (Table 1). The mean duration from ictus to admission was 27.8 ± 3.73 hours. Recovered patients had a lengthy stay at hospital when compared to patients who were dead (median 14 Vs 7, p value: <0.001).

Table 1: Univariate analysis for predictors of mortality based on Demographics, Risk factors, symptoms & signs, CT Brain Plain image findings of 158 Primary Intracerebral haemorrhage patients of Sea coast population of south India.

Variables	Total	Response		P-value
Demographic Characteristics		Dead(no:78)	Alive (no: 80)	
Mean Age (years)	56.8	57.5±11.5	56±11	0.42
Sex				
Male	104(66)	48(61.5)	56(70)	0.337
Female	54(34)	30(38.5)	24(30)	
Low socioeconomic status	129(81.6)	69(88.5)	60(75)	0.029
Illiteracy	113(71.5)	57(73)	56(70)	0.353
Family history of stroke	7(4.4)	2(2.6)	5(6.3)	0.260
Ictus to hospitalization (hours)	27.8±3.73	25 ±3.1	30.5±4.3	0.353
Hospital stay (days)	10.7±8.5	7±6.6	14±8.7	**<0.001**
Risk factors				
Hypertension	113(71.5)	59(75.6)	54(67.5)	0.356
Diabetes mellitus	41(26)	24(30.8)	17(21.3)	0.367
Smoking	74(47)	38(48.7)	36(45)	0.640
Alcoholism	66(42)	32(41)	34(42.5)	0.851
Symptoms				
Limb weakness		58(74.4)	69(86.3)	0.416
Altered sensorium		48(61.5)	47(58.7)	0.720
Head ache		47(60.3)	44(55)	0.323
Vomiting		40(51.3)	37(46.2)	0.319
Dyasrthria		27(34.6)	47(58.8)	0.002
Giddiness		32(41)	40(50)	0.321
Aphasia		13(16.7)	24(30)	0.048
Convulsion		10(12.8)	17(21.2)	0.435
Stroke recurrence		12(15.4)	10(12.5)	0.601
Physical Examination				
Glasgow Coma Scale				
≤ 9	56 (35.4)	49(63)	7(8.8)	<0.001
10 – 12	50 (31.6)	20(25.6)	30(37.5)	
> 12	52 (33)	9(11.4)	43(57.8)	
Pupillary asymmetry		42(53.8)	3(3.8)	<0.001
Hemiplegia		57(73)	61(76.3)	
Ataxic hemiparesis		6(8)	14(17.5)	0.048
Undetermined *		15(19)	5(6.3)	
Cerebellar signs		1(1.3)	5(6.3)	1.107
Electrocardiogram †		64(82)	42(52.5)	<0.001
Echocardiography ‡		42(62.7)	19(24.7)	<0.001
Systolic blood pressure(at admission)		184 ±33	154±21	<0.001
Pulse pressure		88±27	60±17	<0.001
CT Brain (Plain) Imaging Findings				
Location of hemorrhage				0.651
Putamen	99	45(57.7)	54(67.5)	
Thalamus	29	16(20.5)	13(16.3)	
Cortical	13	7(9)	6(7.5)	
Cerebellum	10	5(6.4)	5(6.3)	
Brain stem	7	5(6.4)	2(2.5)	
Bleed volume(ml)		51.8 ± 32.5	23±17	**<0.001**
Perihematomal edema volume(ml)		33.2±26.4	16±13.5	**<0.001**
Intraventricular extension		53(68)	27(33.8)	**<0.001**
Hydrocephalus		39(50)	15(18.8)	**<0.001**
Irregular hematoma border		49(62.8)	14(17.5)	**<0.001**

Note: *Undetermined as decorticate and decerebrate posturing , †Electrocardiogram evidence of left ventricular hypertrophy (LVH) , ‡Echo cardiographic evidence of LVH.

Comorbid conditions and risk factors

In general risk factors include Hypertension (HTN), Diabetes mellitus, smoking and alcoholism, which are considered as modifiable risk factors in PICH. We observed HTN and diabetes were the major modifiable risk factors involved in the present study. The other modifiable risk factors like smoking and alcohol were also found to be closely associated with PICH.

CT Brain (Plain) Image findings

The CT Brain findings showed that maximum number of cases of PICH were in the region of putamen (62.6%) followed by thalamus, cortical or lobar, cerebellar and brain stem. The putamen was the most common site of PICH in both alive and dead patients (57.5%).The hematoma size was also significantly higher in the dead group of patients with a significant P value (<0.001). Other findings that were observed to be significant in predicting mortality were perilesional edema, midline shift, intraventricular extension and irregular hematoma border (Table 1).

DISCUSSION

As evidenced by various studies intracerebral hemorrhage (ICH) is the leading cause for stroke causing high rates of mortality and morbidity worldwide [12]. Many studies have shown that the etiology of ICH is multi-factorial, however, none of the studies in India revealed the incidence and outcome of PICH among sea coast South Indian population. Hence, the present study is carried out with an aim to assess the major predictors of mortality among the seacoast population presenting with PICH. In the present study 158 patients who presented with PICH were enrolled according to our inclusion and exclusion criteria with their informed consent.

The demographic variables data clearly represent their livelihood status. Most of them are illiterate, with low socio-economic status (Table-1). In the present study PICH is noted in wide age range with peak incidence in the 6th decade of life and the mean age was found to be 56.8 yrs. However the present study revealed that age is of no significance in determining the outcome following PICH after performing both uni and multivariate analysis. Sex is also not found to be significant when using the unilabiate analysis where male were 66% and female were 34%. The demographic data findings are similar in studies of western countries and India [13, 14].

Many studies demonstrated the role of various comorbid conditions and risk factors among PICH patients [15]. The comorbid conditions observed were Hypertension (HTN), Diabetes mellitus, Coronary artery disease (CAD) smoking and alcoholism. Findings showed that HTN was the most common modifiable risk factor for PICH. Earlier studies clearly mentioned that PICH and Coronary artery disease (CAD) will have common risk factors which include age, sex, hypertension, smoking, alcoholism and diabetes, etc. The incidence of PICH and coronary heart disease (CHD) rises with the aging process [16]. Along with this, few studies have also showed that higher levels of Fasting Blood Glucose (FBG) in diabetes mellitus will have more chances of PICH rather than on CHD [17]. Studies in India revealed that HTN is the most common cause of PICH when compared with the western world [18]. Few studies stated that HTN related PICHs have deep seated hematomas with raised intracranial pressure and poor outcome [19]. In one study it has been reported that high diastolic blood pressure damages the endothelium of the intracerebral arteries, leads to hemorrhagic stroke. Thus, the finding obtained in the study clearly demonstrates the impact of various variables assessed and also well correlated with other studies which reported similar findings [20].

Hypertension causing primary ICH is believed to be primarily a monophasic event. HTN enhances intracranial pressure, leads to cerebral edema and further promotes re-bleeding in the brain causing cerebral/cerebellar herniation and subsequent neurological deterioration and death [21]. HTN also affects the perforating arteries, which undergo lipohyalinosis and aneurysms, thereby causing PICH. Besides this, auto-regulation in the rate of blood flow in the brain is impaired in HTN and the vessels undergo severe stress for the increased blood pressure, which leads to bleeding [22-24]. Moreover, in the preset study all the patients were residing along the sea coast and have the habit of high salt intake in their diet and as well as exposed to varied environmental factors like severe humidity . Uncontrolled HTN was the primary cause for PICH and most common etiology observed in the present study, which was correlated with earlier studies [25-27].

The findings in the present study revealed putamen as the most common site for PICH followed by thalamus ,cortex and brainstem(Table 1) which is suggesting higher incidence of hypertension related PICH. These results correlated with other studies [28, 29].

The multivariate analysis (Table2) confirmed the following clinical and imaging variables emerged as independent predictors of mortality in PICH: high systolic blood pressure (>160mmHg) at admission; LVH (left ventricular hypertrophy) evident on Echocardiogram, low GCS score ≤9; pupillary asymmetry ; high perihematomal edema volume (>25ml) and irregular hematoma border. However when we compared the results of various studies regarding predictors of mortality, in the present study few new variables have emerged as predic-

tors of mortality in PICH like LVH evident on echocardiogram, pupillary asymmetry, high perihematomal edema volume and irregular hematoma border. Similar findings were observed from results of previous studies [30].

Table 2: Multivariate analysis for predictors of mortality in PICH.

Variable	Co-efficient	Standard Error	Standard coefficient	F-value	p–value
Pupillary asymmetry	0.357	0.070	0.321	26.072	**< 0.001**
ECHO cardiographic evidence of LVH	0.151	0.060	0.149	6.306	0.013
Irregular hematoma border	0.157	0.064	0.151	6.119	0.015
High systolic blood pressure at admission	-0.209	0.067	-0.229	15.070	0.001
High perihematomal edema	-0.261	0.067	-0.229	15.070	**<0.001**
Low Glasgow Coma Scale score	-0.169	0.069	-0.169	5.958	0.016

LVH as evident by echocardiogram is another independent predictor of mortality and It denotes a marker of long standing poorly controlled hypertension, leading to the vasculopathy of chronic hypertension mainly affecting the perforating arteries and these are subjected directly to changes in blood pressure and similarly the small arteries undergo lipohyalinosis, Charcot Bouchard aneurysms. In addition, autoregulation of blood flow is altered in chronic hypertension and the vessels are unable to compensate for increased blood pressure predisposing to bleeding as well as impaired compensation after the ictus.

Earlier studies stated that the presence of Irregular hematoma border clearly indicates active bleeding from multiple arterioles and causing an enlargement of hematoma (hematoma growth) [31] and worsening their clinical course. The present study also highlighted that irregular hematoma border is an independent predictor of mortality for PICH.

Hematoma size on admission CT did not emerge as predictor of mortality in multivariate analysis. Since the level of consciousness and size of the hematoma are closely independent variables, both factors were found to be significant predictors of mortality in studies that have used univariate analysis [32].

Ventricular enlargement did not appear as a significant predictor of mortality in the final multivariate model. It could be argued that such an enlargement could be attributable to senile cortical atrophy rather than post obstructive hydrocephalus secondary to intra ventricular hemorrhage.

CONCLUSION

The present study revealed following factors as independent predictors of mortality of PICH which includes pupillary asymmetry, 2D Echo evidence of LVH, irregular hematoma Border, high systolic blood pressure >160 mm of Hg at admission, high peri hematomal edema and low GCS <9 .The present study signifies that most of the people residing along the seacoast presented with PICH were illiterate and under low economic status. Hence the life style modifications and health education are very important preventive key factors to reduce the incidence and mortality of PICH among sea coast population by primarily focussing on primary prevention of Hypertension.

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