ORIGINAL ARTICLE

PROGNOSTIC SIGNIFICANCE OF SERUM BILIRUBIN IN STROKE

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Background: Oxidative injury is an important cause of the neurologic lesion in stroke. Serum bilirubin is considered a natural antioxidant that may affect the prognosis of stroke. The purpose of this study was to evaluate the prognostic significance of bilirubin in stroke patients. **Methods:** A prospective cross-sectional study was conducted in Medical Units of Khyber Teaching Hospital, Peshawar. Inpatients admitted with acute attack of stroke were included in this study. Data regarding serum bilirubin and concurrent cerebrovascular risk factors were collected. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were used to analyse stroke's severity and functional outcomes, respectively. **Results:** Hypertension, diabetes mellitus and heart diseases were the most common risk factors. Patients were divided into 3 groups on the basis of serum bilirubin, i.e., ≤0.6 mg/dl (Group-1), 0.7–0.9 mg/dl (Group-2), and ≥1.0 mg/dl (Group-3). The mean pre-hospitalisation NIHSS score for Groups 1, 2 and 3 was 5.62, 11.66 and 25.33, respectively; and post-hospitalisation score was 0.875, 3.76 and 16.26, respectively. The pre-hospitalisation mRS score was 4 for Group-1, 4.52 for Group-2 and 4.93 for Group-3; while post-hospitalisation Mrs Score was 1.50, 2.38 and 4.26, respectively. Average serum bilirubin level was significantly higher in patients with poor outcomes as compared with good outcomes (p<0.01). **Conclusions:** This study suggests that higher serum bilirubin levels were associated with increased stroke severity, longer hospitalisation and poor prognosis.

Keywords: Stroke severity, stroke outcome, stroke prognosis, serum bilirubin, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS)

INTRODUCTION

Stroke is defined as a clinical syndrome of rapid onset of focal cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.[1] Stroke is the first leading cause of disability in developed and developing countries.[2] In global perspective, stroke is the 2nd most prevalent source of death.[3] According to WHO estimates, 5.5 million people died of stroke in 2002, and roughly 20% of these deaths occurred in south Asia.[4] No large scale epidemiological studies are available to determine the true incidence of stroke in Pakistan. Estimated annual incidence is 250/100,000, translating to 350,000 new cases every year and this is expected to go up because of the amplified prevalence of stroke's risk factors.[4] One study, conducted in Karachi, reported an overall prevalence of 4.8%.[5]

Stroke causes neuronal cell injury which arises from destructive biochemical substances, released from a variety of sources. Bilirubin, the final product of heme catabolism, was thought to be only a waste end-product. However, it is now considered an antioxidant that may have some role in diseases caused by oxidative stress, such as stroke.[6–9] It can neutralise free radicals and prevent peroxidation of lipids. In addition, there is evidence that bilirubin protects the cardiovascular and neuronal systems.[10,11] Because of its neuroprotective actions, it is proposed that it can influence the prognosis of stroke. Higher bilirubin level was reported to be associated with reduced stroke prevalence and favorable stroke outcomes.[12] On the other hand, some researchers have found inverse relationship between serum bilirubin and positive outcomes in stroke patients.[13] It has also been pointed out that such studies are limited in various ethnic groups.[13] To the best our knowledge, no data are available regarding the relationship of serum bilirubin with the prognosis of stroke in Pakistani population. Therefore, the purpose of this work was to investigate the relationship of serum bilirubin with severity and prognosis of stroke in Pakistani population.

MATERIAL AND METHODS

This was a prospective, cross-sectional study conducted in Medical Units of Khyber Teaching Hospital (KTH), Peshawar, Pakistan, which is a tertiary-care hospital. The study included patients admitted to hospital for an acute attack of stroke during a three-month period, from 8th November 2010 to 8th Feb 2011. Patients with recurrent stroke and those who contracted aspiration pneumonia were excluded from the study.

For this study, stroke was defined as clinical syndrome of rapid onset of focal cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.[14] It was classified as either ischemic or hemorrhagic on the basis of the findings of the CT- scan. Following patients' data were prospectively collected: brain CT-scan (performed 24

hour after stroke), serum bilirubin, ESR (erythrocyte sedimentation rate), lipid profile and blood glucose (24 hour after acute phase of stroke). Cerebrovascular risk factors were recorded for each patient that included hypertension, diabetes mellitus, hyperlipidemia, smoking and heart diseases (coronary artery disease, arthrosclerosis, myocardial infarction and atrial fibrillation). Hypertension was diagnosed when its presence was documented in medical records or when at least two readings of blood pressure were ≥140 mm of Hg (systolic) or ≥90 mm of Hg (diastolic) after acute phase of stroke. Diabetes mellitus was diagnosed if its presence was shown in medical records or when patient was taking oral hypoglycaemic or insulin. Heart disease was diagnosed on the basis of medical history. Hyperlipidemia was diagnosed when it was present in medical record or when it was confirmed from the lipid profile of the patient after the acute phase of stroke. Patient was defined as smoker when there was history of smoking in the past 5 years.

Neurological function and stroke severity were measured with the National Institutes of Health Stroke Scale (NIHSS).[15] The NIHSS is a widely used tool for measurement of stroke severity with established validity. It is a 15-item instrument addressing the severity of cerebral damage. The score represents the observed-levels of wakefulness, vision, sensation, movement, language function and perception. Total scores range between 0 (zero) to 42, with higher scores indicating increased severity. NIHSS was scored at the time of admission (pre-hospitalisation) and at the time of discharge (post-hospitalisation). When the NIHSS score was between 1 to 4, stroke was ranked as mild stroke; when it was from 5 to 15, stroke was ranked as moderate; when the score was from 16 to 20, it was ranked as moderate-severe and when the score was from 21 to 42, it was ranked as severe stroke.

Functional outcomes were operationalised using the modified Rankin Scale (mRS).[16] The mRS is a stroke-specific measure of level of functional independence as compared with pre stroke activity. A score of 0 (zero) to 5 is assigned, with scores indicating the stroke survivor's disability level from 'no symptoms' (0) to 'severe disability' (5), while death is scored as 6.

Statistically, data were presented in the form of frequencies and percentages, where appropriate. Difference in the means of two variables was determined using student *t*-test. P≤ was considered statistically significant. SPSS-16 was used for all statistical analyses.

RESULTS

Initially 62 patients were enrolled in the study. Ten patients with recurrent stroke and eight patients with aspiration pneumonia were excluded. Of 44 patients, 34 (72%) patients were of ischemic stroke and 10 (28%) of haemorrhagic stroke. Hypertension was the most prevalent cerebrovascular risk factor followed by concurrent heart diseases (Table-1).

In order to assess the impact of serum bilirubin on various stroke variables and prognosis, patients were divided into 3 groups on the basis of their serum bilirubin levels: (1) below ≤0.6 mg/dl, (2) from 0.7–0.9 mg/dl and (3) ≥1.0 mg/dl. Various stroke variables of each group were then analysed (Table-2). The mean pre-hospitalisation NIHSS score of the patient's with serum bilirubin below 0.6mg/dl was found to be 5.62 while post-hospitalisation score was 0.87. The average hospital stay for this group was six days. The mean pre-hospitalisation mRS was found to be 4 while post-hospitalisation score was 1.50. The stroke variables of the second group (bilirubin level 0.7–0.9 mg/dl) were different from first group. The mean NIHSS pre-hospitalisation score was 11.66 while post-hospitalisation score was 3.76. The average hospital stay was 6.57 days. Pre-hospitalisation mRS score was 4.52 while post-hospitalisation mRS score was 2.38. For the third group, the mean pre-hospitalisation NIHSS score was 25.33 and the post-hospitalisation score was 16.26. The average hospital stay for this group was nine days. Pre-hospitalisation mRS score was 4.93 while post-hospitalisation score was 4.26. The results show that higher serum bilirubin levels were associated with increased stroke severity, longer hospital stay and poor functional outcomes and vice versa (Table-2). Furthermore, the study population was divided into two groups: poor outcome and good outcome (Table-3). Poor outcome group patients were those whose mRS score at discharge was from 4 to 6 showing bad prognosis and physical dependency. Good outcome group patients were those whose mRS score at discharge was from 0–3. Bilirubin level was 1.05 mg/dl (rang: 0.7–1.4) in poor outcome group, while 0.76 mg/dl (rang: 03–1.4) in good outcome group. Statistically, bilirubin level was significantly lower in the patient with good outcome ($p<0.01$). Likewise, the study population was divided into three groups on the basis of mRS at discharge: 0–1, 2–3 and 4–6 (Table–4).

The mean age of the three groups were found to be different from each other. The group having the best outcome (mRS=0–1) had the lowest mean age (56 years), while mean age of the patients with poorest outcome (mRS=4–6) was 63.5 years. Thus it can be concluded that increased age had a negative impact on the stroke outcome. Hypertension and diabetes were more prevalent in the group with poor outcome. Mean bilirubin was lowest in the first group having best functional outcomes at discharge and it was highest in the group with poorest outcome showing that higher bilirubin is associated with poor outcomes (Table-4).

Table-1: Patients' demographics and cerebrovascular risk factors

Variable	Frequency	Percentage
Men	26	59.0
Women	18	41.0
Ischemic stroke	34	77.3
Hemorrhagic stroke	10	22.7
Deaths	4	9.0
Hypertension	23	52.3
Diabetes	19	43.2
Dyslipidemia	14	31.8
Heart disease	20	45.5
Smoking	9	20.5

Table-2: Stroke variables of study population according to bilirubin levels

Variables		Groups on the basis serum bilirubin (mg/dl)		
		≤0.6 (n=8)	0.7–0.9 (n=21)	≥1.0 (n=15)
Average hospital stay: days (ranges)		6.12 (5-7)	6.57 (4–8)	9.06 (6–12)
NIHSS score	Pre hospitalisation	5.62 (4-10)	11.66 (5–25)	25.33 (16–31)
	Post hospitalisation	0.875 (0-2)	3.76 (1–11)	16.26 (2–42)
mRS score	Pre hospitalisation	4 (4-4)	4.52 (4–5)	4.93 (4–5)
	Post hospitalisation	1.50 (1-3)	2.38 (1–4)	4.26 (3–6)

Table-3: Serum bilirubin and clinical outcome

Outcome*	Mean serum bilirubin (mg/dl)	*p*-value
Good	0.76	<0.01**
Poor	1.05	

*Outcome is based on modified Rankin Scale (mRS). For Good outcomes, mRS score = 0–3; while for poor outcomes, mRS score=4–6.
**Difference is statistically significant

Table-4: Main traits of the study population according to the functional outcome at discharge

Variables	mRS at discharge		
	mRS 0–1 (n=10)	mRS 2–3 (n=18)	mRS 4–6 (n=16)
Age (mean)	56 (4–60)	61.7 (50–75)	63.5 (55–70)
Male(n) Female (n)	8 2	9 9	7 9
NIHSS (admission mean)	6.5 (4–10)	11.55 (4–21)	24.8 (15–31)
NIHSS (discharge-mean)	1.5 (0–3)	2.8 (0–6)	16.5 (4–42)
Ischemic (n)	9	13	12
Hemorrhagic (n)	1	5	4
Hypertension (n)	4	10	9
Diabetes (n)	2	9	8
Smoking (n)	5	1	3
Dyslipidemia (n)	3	5	6
Heart Disease (n)	2	10	8
Bilirubin (mean)	0.69 (0.5–0.9)	0.8 (0.3–1.2)	1.05 (0.7–1.4)

DISCUSSION

Results of this study suggest that patients with higher serum bilirubin levels were having greater stroke severity and poor functional outcomes. The higher the serum bilirubin, the poor was the prognosis of stroke. In this study, no beneficial effects of higher serum bilirubin levels were found on the prognosis of stroke. Therefore, these results suggest that the role of higher serum bilirubin in limiting the oxidative damage in stroke patients by exerting its antioxidant effects is questionable. Higher bilirubin levels observed in severe stroke patients may be caused by induction of bilirubin production in response to oxidative stress. But these higher bilirubin levels may not reduce the neurological damage caused by these oxidants possibly because the antioxidant activity of bilirubin is in serum while the actual oxidative damage occurs in tissue where bilirubin may not penetrate in sufficient concentration to produce anti-inflammatory and antioxidant actions.[17,18] These findings are consistent with many other studies. Pineda *et al*. reported that bilirubin was independently associated with greater stroke severity at admission and poor outcome.[19] Another study has shown that serum bilirubin is a marker of oxidant stress in hemorrhagic stroke.[20] Several studies have suggested that bilirubin acts as a physiologic antioxidant, with its synthesis being induced in response to oxidative stress. In some experimental studies, in which halogentated hydrocarbons were used to induce oxidative stress, it is shown that oxidative stress increases the serum bilirubin.[19] As neurologic injury in stroke is also related to oxidative radicals damage this may cause increase in the serum bilirubin levels.

This study is limited by its small sample size. Therefore it should be considered a preliminary work in Pakistani stroke-population. It is suggested that further larger studies, preferably multi-center, should be conducted to investigate the relationship of bilirubin with severity and outcome of stroke.

CONCLUSIONS

This study suggests that higher serum bilirubin levels were associated with increased stroke severity, longer hospitalisation and poor prognosis. Larger studies are required to further explore the role of serum bilirubin in the prognosis of stroke.

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