

A Study on Association between Serum Bilirubin and Acute Ischemic Stroke and Its Prognostic Significance

Prof.Dr.S.Ushalakshmi, M.D¹, Dr. Ramya. A,²

¹Professor, Head of the Department of Medicine, Kilpauk Medical College and Hospital, Chennai-600010

²Department of Medicine, Kilpauk Medical College, Chennai-600010, India

Corresponding Author: Prof.Dr.S.Ushalakshmi,M.D

Abstract: Stroke is the third commonest cause of death across the world. Stroke is becoming a very important cause of disability and premature death in developing countries like India. Over the last few decades, a rise in non communicable diseases including stroke has been considered to be related primarily to demographic changes and enhanced by the prevalence of the risk factors. Bilirubin the final product of heme catabolism was thought to be only a waste end-product. However, it is now considered as an antioxidant that may have role in the progress of diseases caused by oxidative stress, such as stroke. Oxidative stress resulting in the production of free radicals is found to be an important mechanism of brain damage in acute ischemic stroke and the bilirubin being an antioxidant, its synthesis is induced in response to oxidative stress. Bilirubin can reflect the severity of oxidative stress. In this study, we found the association of increased serum bilirubin level correlating with severity of acute ischemic stroke.

Date of Submission: 29-06-2019

Date of acceptance: 15-07-2019

I. Introduction

In developing countries there is decreasing trend of infectious and malnutrition related diseases, whereas stroke incidence is increasing in recent decades as a result of dietary changes, decreased physical activity, and increased tobacco use. Stroke occurs as a result of disruption of blood flow to a part of brain either because of blood vessel occlusion as in acute ischemic stroke (AIS) or blood vessel rupture causing bleeding either into the brain (Intracerebral hemorrhage-ICH) or around the brain (subarachnoid hemorrhage -SAH). High metabolic activity and oxygen consumption which results in the production of high levels of ROS, along with relatively low levels of endogenous antioxidant enzymes, mainly catalase make the neurons vulnerable to oxidative stress. Various studies found that different forms of bilirubin are powerful antioxidants: Unconjugated, conjugated, free and albumin-bound bilirubin were all found to be effective scavengers of peroxy radicals. They are able to protect LDL against peroxidation.

II. Material And Methods

This case control study was carried out on patients at Department of Medicine, Kilpauk Medical College, Chennai, Tamilnadu from April 2014 to September 2014. A total 100 (50 stroke patients and 50 normal control subjects) were included in this study.

Study Design: Case control study.

Study Location: This was a tertiary care teaching hospital based study done in Department of Medicine, Kilpauk Medical College, Chennai

Study Duration: April 2014 to September 2014.

Sample size: 100 patients.

Subjects & selection method: Fifty patients who had acute ischemic stroke and fifty controls were included for study. Patients who got admitted within 48 hours of stroke onset only were taken under study. All the subjects in control group were selected in respect to age (group match), gender, co-morbid conditions (diabetes and hypertension) matched with cases.

Inclusion criteria:

All patients presenting with new onset neurological deficit following ischemic stroke admitted within 48 hours of onset of stroke.

Exclusion criteria:

- Patients with
 - o H/O alcoholism
 - o Known liver disease
 - o Known Chronic Kidney disease
 - o Known Coronary artery disease
 - o Known Malignancy
 - o Known Connective Tissue Disorders
 - o Hemodynamic instability – BP<90/60mmHg
 - o Hepatotoxic drug intake in past 30 days
 - o Infection identified through history and clinical examination
 - o Haemorrhagic Stroke Patients (ICH,SDH,EDH) - with the aid of CT/MRI scan.

Procedure methodology

Fifty patients who had acute ischemic stroke and fifty controls were included for study. Patients who got admitted within 48 hours of stroke onset only were taken under study. Then complete relevant medical history, neurological examination, relevant blood investigations and CT/MRI scan were done and all data were recorded in a standardized proforma.

CT/MRI scan was done for the exclusion of hemorrhagic stroke. Blood sample for Serum total and direct bilirubin and other baseline investigations was taken as soon as patient got admitted . National Institute of Health Stroke Scale (NIHSS) scoring was assessed at the time of admission and these patients were grouped according to score of <10 and ≥10. These patients were treated according to standard protocols. None of the patients were thrombolysed.. Modified Rankin Scale was assessed to know the functional recovery of the patient after 7 days either in ward or in review opd if got discharged. Similarly subjects in control group were studied by relevant medical history, and clinical examination and relevant blood investigations.

Blood samples were taken as soon as the patient admitted in case group and in control group randomly. Serum bilirubin was measured by spectrophotometry method in the laboratory using Jendrassik-Grof allied methods.

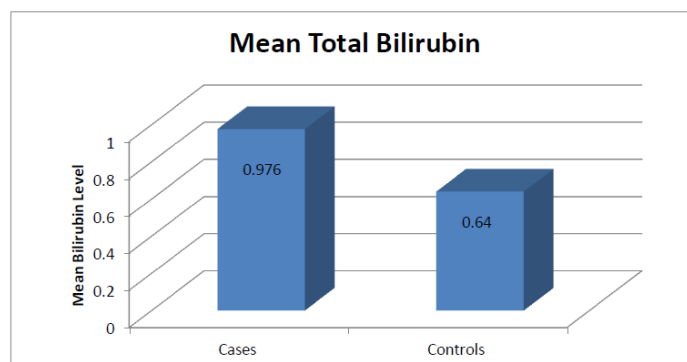
Statistical analysis

Continuous variables like age and bilirubin level were expressed as mean (Standard Deviation). Association between ischemic stroke and total bilirubin level was tested by comparing serum bilirubin levels in ischemic stroke patients with that of controls using unpaired (Independent) t test. A P value of <0.05 was considered as statistically significant.

Severity of stroke on admission was assessed by NIHSS severity scale (NIHSS> 10 was considered as Severe stroke) and the prognosis of stroke on 7th day of stroke was assessed by Modified Rankin functional outcome Scale (MRS >3 was considered as poor prognosis). Total bilirubin levels were divided in to three groups, (Group 1: < 0.6mg/dl, Group 2: 0.7 to 0.9mg/dl, Group 3: >1.0 mg/dl). Severity of stroke, prognosis of stroke was expressed as percentages and its correlation with three groups of bilirubin was tested by Chi Square analysis. A P value of <0.05 was considered as statistically significant.

III. Result

| Parameter | Cases(n=50) | Controls(n=50) | P value |
|-------------------------|--------------|----------------|---------|
| MeanTotal Bilirubin(SD) | 0.976(0.328) | 0.64(0.249) | <0.001 |



MEAN (SD) INDIRECT BILIRUBIN IN CASE AND CONTROL GROUP

| .Parameter | Cases(n=50) | Controls(n=50) | P value |
|-----------------------------|--------------|----------------|---------|
| Mean Indirect Bilirubin(SD) | 0.714(0.286) | 0.403(0.186) | <0.001 |

The mean indirect bilirubin in cases was 0.714 and in control group was 0.403,so there is a positive correlation between indirect bilirubin and acute ischemic stroke and it is statistically significant.

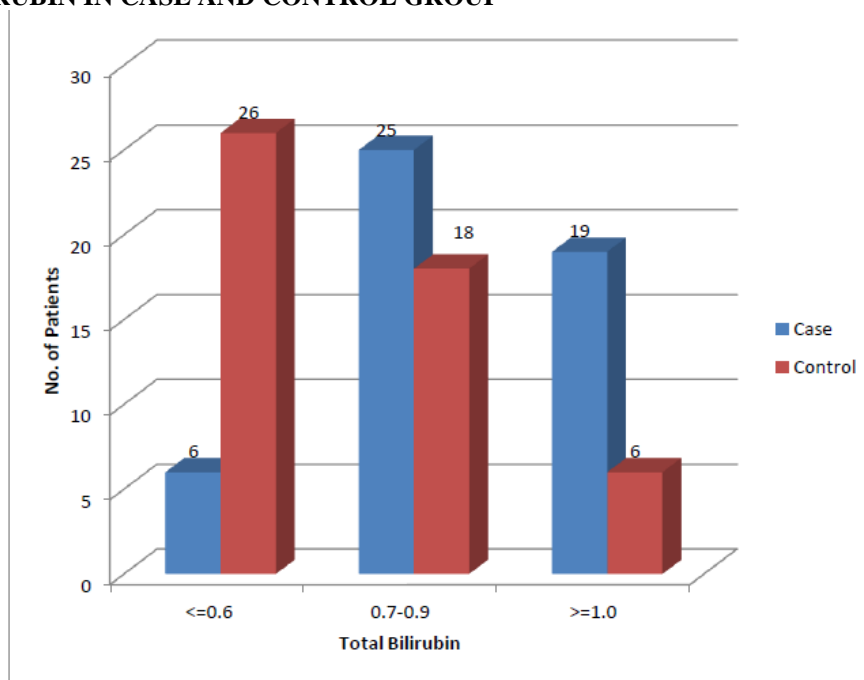
TOTAL BILIRUBIN IN CASE AND CONTROL GROUP

| Total Bilirubin | Case, n (%) | Control, n (%) |
|-----------------|-------------|----------------|
| ≤0.6 | 6 (12%) | 26 (52%) |
| 0.7-0.9 | 25 (50%) | 18 (36%) |
| ≥1.0 | 19 (38%) | 6 (12%) |
| Total | 50 (100%) | 50 (100%) |

P value <0.001

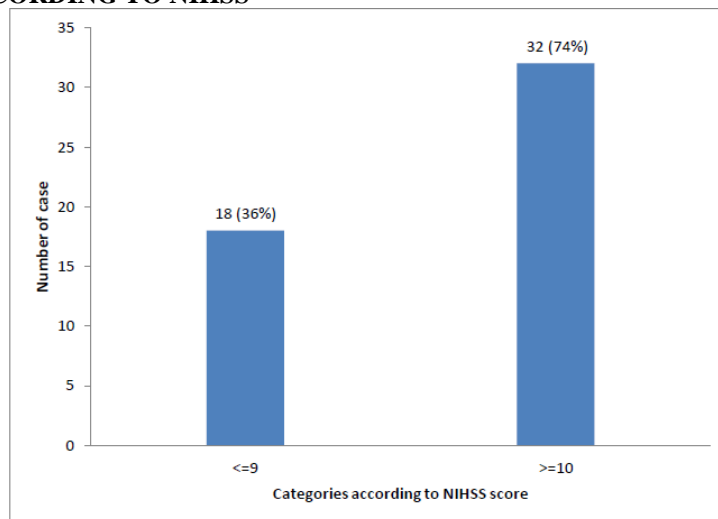
In the study,out of 50 cases 12%,6 cases had total bilirubin in the range ≤ 0.6,50%,25 cases had total bilirubin in the range of 0.7 -0.9,38%,19 cases had total bilirubin in the range ≥1.0. Among the control group,52%,26 subjects had total bilirubin in the range ≤0.6, 36%,18 subjects had total bilirubin in the range of 0.7 -0.9, 12%,6 cases had total bilirubin in the range of ≥1.0.

TOTAL BILIRUBIN IN CASE AND CONTROL GROUP



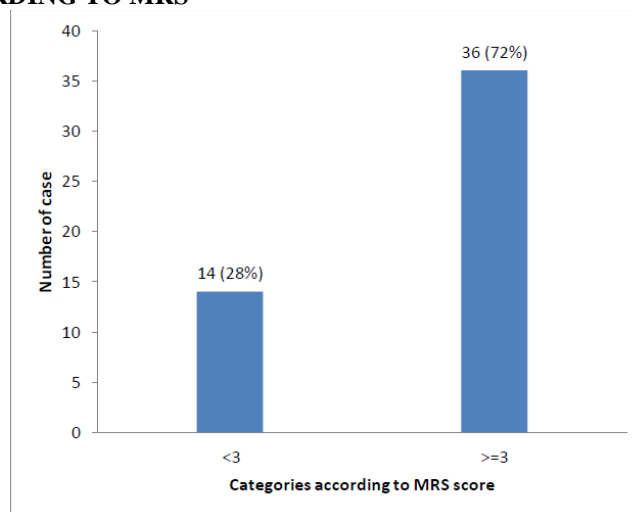
Thus 44 cases had total total bilirubin in the range ≥0.7 and only 6 cases had total bilirubin ≤0.6. So the association between the acute ischemic stroke and admission total bilirubin is statistically significant comparing with control group.

CATEGORIES ACCORDING TO NIHSS



In the study, out of the 50 cases (36%) 18 cases had NIHSS ≤ 9 at admission and (74%) 32 cases had severe stroke NIHSS ≥ 10 at admission.

CATEGORIES ACCORDING TO MRS



In the study ,out of the 50 cases (28%) 14 cases had good outcome after 7 days of onset of stroke(MRS <3) and(72%)36 cases had poor outcome after 7 days of onset of stroke(MRS ≥ 3)

ASSOCIATION OF NIHSS AND MRS

| NIHSS | MRS | | Total |
|-----------|-----------|-----------|----------|
| | <3 | ≥ 3 | |
| ≤ 9 | 10 (55.6) | 8 (44.4) | 18 (100) |
| ≥ 10 | 4 (12.5) | 28 (87.5) | 32 (100) |
| Total | 14 (28) | 36 (72) | 50 (100) |

P value = 0.001

In the study, among 18 cases who had NIHSS ≤ 9 at admission, 10 cases (55.6%) had good outcome (MRS <3) after 7 days and 8 cases (44.4%) had poor outcome (MRS ≥ 3) after 7 days. Among 32 cases who had NIHSS ≥ 10 at admission, only 4 cases (12.5%) had good outcome (MRS <3) and 28 cases (87.5%) had poor outcome (MRS ≥ 3) after 7 days.

ASSOCIATION OF TOTAL BILIRUBIN WITH NIHSS SCORE AMONG CASES

| Total Bilirubin | NIHSS | | |
|-----------------|------------|------------|-----------|
| | ≤9 | ≥10 | Total |
| ≤0.6 | 6(100%) | 0(0%) | 6(100%) |
| 0.7-0.9 | 10 (40.0%) | 15 (60.0%) | 25 (100%) |
| 1.0 and above | 2 (10.5%) | 17 (89.5%) | 19 (100%) |
| Total | 18 (36%) | 32 (64%) | 50 (100%) |

P value = 0.0003

In the study, among 18 cases (36%) who had (NIHSS ≤9), six cases had total bilirubin in the range of ≤ 0.6, 10 cases had total bilirubin in the range of 0.7-0.9 and only 2 cases had total bilirubin ≥ 1. Among 32 cases (64%) who had (NIHSS≥10), none of them had total bilirubin in the range of ≤ 0.6, 15 cases had total bilirubin in the range of 0.7-0.9 and 17 cases had total bilirubin ≥ 1.

IV. Discussion

Bilirubin once considered to be the toxic waste product, in recent days gained importance because of its antioxidant property. Various studies proposed about the role of bilirubin in oxidative stress mediated diseases like stroke, coronary artery diseases, cancer etc. There are studies which concluded that greater admission serum bilirubin levels were associated with greater stroke severity and poor short term outcome. Several studies have proved that the synthesis of bilirubin is induced in response to oxidative stress.

So the high bilirubin level at the admission found in ischemic stroke patients may be simply due to oxidative stress pathway induction and bilirubin may play no role in protection against neurological damage. In this Case control Study (Ischemic stroke patients as cases and non stroke persons as control group) conducted in Department of Medicine, Kilpauk Medical College, Chennai during the period of April 2014 to September 2014, I analysed 50 patients who had Ischemic stroke were taken as cases, 50 patients who did not have stroke were taken as control group.

All the cases and controls were subjected to complete investigation and were analyzed for difference in serum total bilirubin levels between cases and controls. Further analysis was done to find any association exists between total bilirubin and stroke severity at admission and prognosis after 7 days.

In the study, mean total bilirubin was higher in cases than controls and the difference is statistically significant (p <0.001) and also the indirect bilirubin was also higher in cases significantly but the direct bilirubin didn't showed such results. Among the cases, 74 % had severe stroke on admission and 72% had poor functional outcome after 7 days. Patients with higher total bilirubin level (i.e in the second and third group of total bilirubin) at admission had severe stroke (p0.0003) and it was positively correlated with significance. This is supported by the study conducted by Tian Xu et al , concludes that elevated serum total bilirubin positively correlates with stroke severity. Patients with higher total bilirubin level (i.e in the second and third group of total bilirubin) at admission had poor outcome and it was positively correlated with significance. (p 0.0002)

Most of the studies conducted on ischemic stroke and bilirubin found statistically significant association between admission bilirubin and short term clinical outcome.

Arsalan et al found statistically significant correlation between bilirubin and short term outcome. In the study, direct bilirubin levels were not correlated both with severity and functional outcome. But this result is not supported by any of the previous similar studies. In the study, indirect bilirubin levels were elevated in cases significantly (p0.001) and also correlates with stroke severity (p0.003) and functional outcome. (p0.001). In the study the mean AST, ALT between two groups didn't have any statistically significant differences. This association has not been analysed extensively. In the study, there is a positive correlation between severe stroke and poor outcome and it is statistically significant.

Above findings support the hypothesis that serum bilirubin might act as the endogenous antioxidant, but during the acute phase of stroke it acts as the marker of oxidative stress damage. Whatever the preventive or destructive function in ischemic stroke, bilirubin is elevated in ischemic stroke which is related to stroke severity and poor functional outcome and bilirubin can act as the marker of oxidative stress.

V. Conclusion

In summary, this study found that serum total and indirect bilirubin levels are higher in acute ischemic stroke patients. Serum total and indirect bilirubin levels were correlated positively and significantly with stroke severity NIHSS \geq 10 and poor short term functional outcome MRS \geq 3.

CLINICAL IMPLICATIONS

Since bilirubin acts as the marker of oxidative stress in stroke patients, measures to reduce oxidative stress in patients with higher bilirubin will be taken as therapeutic measure to reduce morbidity and mortality. And also with this basic investigation, severity and prognosis of stroke can be assessed and Ischemic stroke patients with higher bilirubin levels can be monitored to avoid complications

References

- [1]. Association of Serum Bilirubin with Ischemic Stroke Outcomes. Sandra Pineda, BS, Oh Young Bang, MD, PhD and Bruce Ovbiagele, MD J Stroke Cerebrovasc Dis. 2008; 17(3): 147–152.
- [2]. UN Chronicle Health Watch. Atlas of Heart Disease and Stroke. 2005; 0105: 46.
- [3]. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock, P. Stroke. Lancet 2003; 362: 1211–24.
- [4]. Reddy K, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998; 97:596–601.
- [5]. Davidson's principles and practices of Medicine, 20th edition.
- [6]. Ischemic Stroke: Pathophysiology and Principles of Localization Editor: Alireza A tri, MD, PhD www.turner –white .com. Hospital Physician Board Review Manual
- [7]. Harrison's Principles of Internal Medicine Volume 2, Page: 3275
- [8]. Challa V. Atherosclerosis of the Cervicocranial arteries. In Toole JF (ed) cerebrovascular disorders. 5th edition. Lippincott Williams and Wilkins, Philadelphia, 1999.
- [9]. Glaglov S, Zarins CB. What are the determinants of plaque instability and its consequences? J VascSurg 198; 9: 389-390. 1.
- [10]. Falk E. Why do plaques rupture? Circulation 1992; 86:30-42.
- [11]. Garcia JH, HoKhang-Loon, Pantoni L. Pathology in Barnett, Henry JM, Mohr JP, Stein BM, Yatsu FM (eds), Stroke Pathophysiology, Diagnosis and Management. Third edition, Philadelphia, PA: Churchill Livingstone; 1998.
- [12]. Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia: Mechanisms and incidence. Cerebrovasc Brain Metab Rev. 1993; 5:1-16.
- [13]. Garcia JH, Anderson ML: Circulatory disorders and their effects on the brain. pp 715-822. In Davis RL, Robertson DM (eds): Textbook of Neuropathology, 3rd edition. Williams & Wilkins, Baltimore 1997
- [14]. Fisher M., Schaebitz W. An overview of acute stroke therapy. Past, present, and future. Arch Intern Med 2000; 160:3196-3206.
- [15]. Lee J-M., Zipfel G.J., Choi D.W. The changing landscape of ischaemic brain injury. Nature 399:A7-A14; 1999
- [16]. Labovitz DL, Boden-Albala B, Hauser WA, Sacco RL. Lacunar infarct or deep intracerebral hemorrhage: who gets which? The Northern Manhattan Study. Neurology 2007; 68:606–8.
- [17]. Bansal recent concept of stroke, Medicine update 135 -137 Guidelines for the Early Management of Patients With Acute Ischemic Stroke AHA/ASA Stroke guidelines <http://stroke.ahajournals.org/lookup/doi/10.1161/STR>.

Prof. Dr. S. Ushalakshmi, M.D. "A Study on Association between Serum Bilirubin and Acute Ischemic Stroke and Its Prognostic Significance." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 7, 2019, pp 64-69.