ORIGINAL ARTICLE

Association of Serum Bilirubin with Acute Ischemic Stroke – An Observational Study

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ABSTRACT

Introduction: Stroke is a common cause of mortality and morbidity and has an increasing prevalence across the world.1 Bilirubin is now being considered an antioxidant which increases in response to diseases associated with increased oxidative stress. Hence the present observational study was undertaken to assess the bilirubin levels with the outcome of acute ischemic stroke. **Methods:** This observational study was conducted from January 2018 to December 2018 on 64 ischemic stroke patients admitted at KLE'S Dr. Prabhakar kore hospital at Belagavi, Karnataka. All adult patients above 18 years of age presenting with cerebrovascular accident and proved as ischemic stroke on CT scan or MRI scan were included. The patients were empirically divided into different Groups based on the bilirubin level. They were then analysed with their NIHSS scores for assessing stroke severity. **Results:** A total of 64 patients were included in the final analysis. The mean total bilirubin level in the patients was 0.68±0.34 mg/dl (mean±SD). 34.3% (22) of ischemic stroke patients in the study had serum total bilirubin levels 0.7 mg/dl or more. Mean NIHSS Score for Group 1(Low) total bilirubin group was 9.37 and for Group 2(High) bilirubin group was 10.9, which was statistically not significant. This indicates that there was no significant correlation between total bilirubin and severity of symptoms at the time of admission.There was no statistically significant correlation between NIHSS and direct bilirubin levels **Conclusion:** The current study has documented no association between the bilirubin levels and stroke severity and prognosis.

Keywords: Bilirubin, Stroke severity, Acute ischemic stroke, Prognosis, NIHSS

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INTRODUCTION

Stroke is known to be one of the commonest causes of mortality across the world.(1) Stroke is an important risk factor for disability and premature death among developing countries specially like India. Recently over a decade demographic changes and increase in the prevalence lead to rise in Non communicable Diseases specially stroke. Bilirubin is now considered as an antioxidant that can cause the progression of diseases caused by oxidative stress, stroke being one such disease. Oxidative stress that leads to the production of free radicals is found to be an important mechanism of brain damage in acute ischemic stroke(AIS). Bilirubin being an antioxidant, it is synthesised in response to oxidative stress and can indicate the severity of it. In the study, we aimed to find the association of serum bilirubin with AIS. Various studies conducted during the acute phase of ischemic stroke found that lower levels of serum bilirubin are related to positive outcomes in stroke patients and hence, bilirubin can indicate the severity of oxidative stress.Yun Luo et al (2012) (2) reported that both Direct Bilirubin(DB) and Total Bilirubin(TB) are indicative of the severity of ischemic stroke.Sandra Pineda et al (2008)(3) reported an association between higher direct bilirubin on admission and greater stroke severity.Rapid modernization and increased life expectancy has resulted in increased incidence of mortality due to stroke. Worldwide, each year 15 million people suffer from stroke.(4)Of those one third die and one third are left permanently disabled.(5) By 2040, in lowand middle-income countries, around a billion adults over the age of 65 years are estimated to be at a risk of developing a stroke.(6) Various studies have revealed the effect of level of billirubin as predictor of vascular events that are risk factors for Ischemic stroke. Some studies also have revealed that low level of billirubin was associated with stroke.(7,8) In addition to the age, hypertension and tobacco use are the major risk factors worldwide. Thus, various studies have been done to see the role of bilirubin in conditions like coronary artery disease which are associated with oxidative stress. Bilirubin being an antioxidant may limit the neurologic damage after a stroke. Hence the present observational study was undertaken to assess the bilirubin levels with

the outcome of acute ischemic stroke.

MATERIALS AND METHODS

This was a one year hospital based observational study carried out during 1 January 2018 to 31 December. Sample size was calculated using the formula N= za^2 P(1-P) / d^2 .For a 5% level of significance, za is 1.96P is the prevalence of the disease which is 20%d is the percentage likely difference in the prevalence which is 10%. Hence sample size of 64 was taken using purposive sampling. Ethical clearance was obtained from KLE University Institutional Ethical Committe (JNMC\ DOME\EC-132) and Informed consent was taken from participants before commencement of the study.

Participants were the patients admitted in the wards and Intensive Care Unit (ICU) of Departments of general medicine, neurology at KLES Dr.Prabhakar Kore Hospital, Belagavi fulfilling the following inclusion criteria: patients above 18 years of age presenting with cerebrovascular accident and proved as ischemic stroke on (Computarised Tomography) CT scan or (Magnetic Resonance Imaging) MRI scan within 24 hours of stroke. Exclusion criteria were hemorrhagic stroke, hemolyticanemias, hepatobiliary disease and on hepatotoxic drugs.

Confirmed Acute ischemic stroke were included in the study after obtaining informed consent and Institutional ethical clearance. A detailed history was taken and clinical features, basic labrotary tests, total and direct billirubin level as well as national Institute of Health Sroke Scale were assessed at the time of admission.. Patients were arbitrarily divided into Group 1(high) total bilirubin ≤ 0.7mg/dL and Group 2(low) total bilirubin ≥ 0.7mg/dL.Group 1(low) direct bilirubin ≤0.2mg/dL and Group 2(high) direct bilirubin ≥ 0.2mg/dL. Severity of stroke was based on the NIHSS scores mild (0-4), moderate (5-15), moderate to severe (16-20) and severe (21-42).

For analysis, BP ≥ 140/90mmHg was considered high. HDL levels ≥ 40mg/dL were considered high and <40mg/dL as low.LDL levels ≥100mg/dL were considered high and <100mg/dL were considered low. Triglyceride levels ≥ 150mg/dL were considered as high and < 150mg/dL were considered low.Total cholesterol levels ≥ 200mg/dL were considered as high and <200mg/dL were considered as low.All the patients fulfilling the inclusion criteria and willing to participate, were included in the study.

Advanced excel has been used for the statistical analysis. Continuous variables are represented by mean ± sd form and categorical variables by frequency table. Chi-square/Fisher Exact test has been used to check the association between categorical variables. Comparison has been done using t-test/Mann Whitney U-test. P-Value less than 0.05 was considered as significant.

RESULTS

Sample data contains 64 subjects of age 60.25 ± 12.54 years consisting of 45 (70.3%) male subjects and remaining 19 (29.6%) female subjects. We observe that majority (31.2%) of the subjects were of the Age group "60-69", followed by "50-59" (21.8%), "70-79"(20.3%). There are only 3 and 2 subjects with age above 80 and between 30-39 respectively. With reference to the clinical presentation 56(87.5%) subjects had motor chief complaints whereas 43(67.1%) had complaints related to Cranial Nerve abnormalities, followed by 39(60.9%) with speech related complaints and 11(17.1%) with sensory complaints.We also observe that Hypertension is present in 50% of the total subjects, 34% subjects have Diabetes Mellitus whereas 30% of the total subjects are Alcoholic and 23% subjects are smokers. 28% of the total subjects have High blood pressure and 56% subjects have Normal blood pressure.From table 12, we observe that majority- 73.4% of the subjects had a stroke of the MCA territoryfollowed by "MCA-PCA" territory with 10.9% (Table I).

Table I: Clinical and Risk factors among patients

Factor	Sub-category	Percentage (%)
Chief Complaints	Motor	87.5%
	Cranial Nerve	67.1%
	Speech	60.9%
	Sensory	17.1%
Risk Factor	DM	34%
	HTN	50%
	Smoker	23%
	Alcoholic	30%
Blood Pressure	High (> or equal to 140/90 mmHg)	44%
	Normal (<140/90mmHg)	56%
Stroke Territory	ACA	1.5%
	MCA	73.4%
	PCA	3.1%
	ACA-MCA	7.8%
	MCA-PCA	10.9%
	Cerebellar	9.3%
Clinical Features	Motor	85.93%
	Cranial Nerve	67.19%
	Speech	15.63%
	Sensory	18.75%

Majority 55(85.93%) subjects had clinical features of the motor system whereas 43(67.19%) had features of cranial nerve dysfunction. The mean HDL value is 38.20±9.75mg/dL. 37(57.81%) subjects are in the low HDL category whereas 27(42.18%) are in the high HDL category. The mean Low density lipoprotein value in the sample is 97.53±40.94 mg/dL. Also, 45.31%

have high low density lipoprotein values.Amongst the total subjects,28.12% have high triglyceride levels. 20.31% of total subjects have high total cholesterol levels. Also, mean total cholesterol level in the sample is 160.19±45.00mg/dL.42(65.62%) subjects in the sample fall into group 1 with lower bilirubin levels and 22(34.37%) had higher total bilirubin and fell into group 2. Majority of the subjects i.e. 40 in the sample had high level direct bilirubin and fell into group 2 while 24 had lower direct bilirubin and fell into group 1.38 subjects with moderate NIHSS score followed by 13 subjects with minor NIHSS score, 9 with moderate-severe NIHSS score and 4 subjects are with severe NIHSS score in the sample. 51 subjects with Good outcome MRS value and 13 subjects with Poor outcome MRS value (Table I and II).

Using spearman correlation, we conclude that there is no significant correlation between NIHSS and Total bilirubin (rho=0.1881, p=0.1366). Also, there is no significant correlation of MRS with Total Bilirubin (rho=0.1486, p=0.2413).

DISCUSSION

Bilirubin in recent days has gained importance because of its antioxidant properties. Various studies proposed the role of bilirubin in oxidative stress mediated diseases including diseases like coronary artery disease, stroke. There are studies which concluded that greater admission serum bilirubin levels were associated with greater stroke severity and poor short-term outcome. Mean age of patients in this study was 60.25 years (SD - 12.54 years). 53% of ischemic stroke patients belonged to age group of 50 to 69 years of age suggesting that advancing age is a risk for development of ischemic stroke. This is comparable to the population-based studies done by Dalal et al., (9) in Mumbai in which 66 years was the mean age of stroke, Sridharan et al., (10) in Trivendrum in which mean age for stroke was 67 years and Nagaraj et al., (11) from which mean age was 54 years. This implies that elderly age is a risk factor for stroke.

Out of 64 patients included in the study, 45 patients were male and 19 were females.Majority of the patients were males, constituting 70.3%. This is comparable to a study done by Nagaraj et al.,(11) in Bangalore where males constituted 67%. Dalal et al.,(9) from Mumbai reported that males had higher stroke incidence. This implies that males are at a higher risk of ischemic stroke compared to females.Majority of the patients presented with motor weakness (87.5%), followed by cranial nerve abnormalities (67.1%), speech abnormalities (60.9%) and sensory abnormalities (17.1%) being the least common. This is comparable to the study done by Nagaraj et al.,(11) where motor weakness or paresis (92%) was the commonest presentation.

Middle cerebral artery territory was the most common site of involvement; in 73.4% patients, followed by cerebellar artery in 9.3%, posterior cerebral artery involvement in 3.1% and anterior cerebral artery in 1.5%. Middle cerebral-posterior cerebral artery involvement was found in 10.9%, whereas middle cerebral artery-anterior cerebral artery involvement was found in 7.8%. This indicates that Middle cerebral artery is the most common territory involved in ischemic stroke and this is comparable to study done by Paciaroni M et al.,(12) in Perugia in which middle cerebral artery was the most common vascular territory involved.

The mean HDL levels were 38.20 mg/dl with standard deviation of 9.75 mg/dl. HDL levels in blood less than 40mg/dl were considered as low HDL. HDL levels were low in 37 patients (57.81%). LDL levels in blood ≥ 100 mg/dl were taken as high LDL. LDL levels were 97.53±40.94 mg/dl (mean±SD) and 45.31% (29 patients) had high LDL levels. We considered 150mg/dl or more levels of triglycerides (TG) in blood as high triglycerides. Triglycerides levels (TG) were 135±81.59 mg/dl (mean±SD) and 20.3% had high levels of triglycerides. Cholesterol levels were 160.19±45.00 (mean±SD) and high levels of cholesterol was seen in 13 (20.31%) ischemic stroke patients included in the study. Total cholesterol levels of 200mg/dl or more were considered as high cholesterol. This in comparable to studies done by Mary Grace et al., in which 63.3% cases had high LDL cholesterol, 38.3% had high total cholesterol, 33.3% had low HDL and 21.7% had high triglycerides

Table II: Comparison of NIHSS and MRS with total and direct Billirubin

Factor	Sub category	Total Bilirubin Category		p-value	Direct Bilirubin Category		p-value
		Group 1	Group 2		Group 1	Group 2	
NIHSS		9.6904 ± 6.590	11.6363 ± 5.678	0.2448	9.375 ± 5.87	10.950 ± 6.57	0.3381
MRS		2.0 ± 1.5848	2.5 ± 1.4690	0.1786#	2.21± 1.61	2.23 ± 1.54	0.8933#
NIHSS	**Mild**	10	3	0.6627 F	6	7	
	Moderate	25	13		15	23	0.3352 F
	Moderate to severe	5	4		1	8	
	Severe	2	2		2	2	
MRS	**Good**	33	18	1 F	19	32	1 F
	Poor	**9**	**4**		**5**	**8**	

level. Siddeswari et al.,(13,14) had reported low HDL in 77%, high LDL in 21%, high triglycerides in 17% and high cholesterol in 21% of ischemic stroke cases.

The mean total bilirubin levels in the patients was 0.68±0.34 mg/dl (mean±SD). The range of total bilirubin was 1.61mg/dl to 0.24mg/dl. Serum total bilirubin 0.7mg/dl or more was considered as Group 2(high). 34.3% (22) of ischemic stroke patients in the study had serum total bilirubin levels 0.7 mg/dl or more. Direct bilirubin levels were also measured and were 0.25+/-0.15 mg/dl (mean+/-SD) with a range of 0.1 – 1.1 mg/dl. 40 patients (62.5%) had high direct bilirubin values (Group 2).

National Institute of Health Stroke Scale (NIHSS) was used to assess the severity of stroke at the time of admission. NIHSS score of 1-4 indicated minor/mild severity, 5-15 as moderate, 16-20 as moderate to severe and >20 as severe. NIHSS score of mild severity was seen in 20.3% cases, 59.3% had moderate, 14% had moderate-severe and 6.2% had severe severity.

In this study, we found no correlation between severity of stroke and serum bilirubin (total and direct) at the time admission. This was in contrast to the study done by Ademiluyi et al.(15), where they found significant correlation between severity of stroke and serum total bilirubin at the time admission. They took 120 ischemic stroke patients and divided them into two bilirubin groups; high and low, and compared the NIHSS score among the two groups. The group with higher total bilirubin had a greater stroke severity. Yun Luo et al.(2), compared 531 Ischemic stroke patients and assessed serum bilirubin (total and direct) levels with NIHSS score between the two groups. The level of serum total bilirubin and direct bilirubin were significantly higher in acute ischemic stroke. Arsalan et al(16) in their study divided ischemic stroke cases into three groups of serum total bilirubin and compared them with NIHSS score at the time of admission. Patients with higher total bilirubin were associated with higher stroke severity.

Sandra Pineda et al.,(17)conducted a prospective study for five years on ischemic stroke patients. They measured serum bilirubin (total and direct) on admission, NIHSS on admission and MRS at discharge. A total of 743 ischemic stroke patients were studied with mean age being 67.3 years and 52.5% were males. It was found that there was no significant association between total bilirubin and severity of stroke (NIHSS) on admission. The direct bilirubin levels were significantly higher in patients with severe stroke on admission (NIHSS).They did not find any significant relationship between admission (total and direct) bilirubin and discharge outcome similar to our study. Perlstein et a1.,(18) reported that a 0.1 mg/dl increment in bilirubin level was associated with a 10% reduced odds of an adverse stroke outcome.

CONCLUSION

In this study we found no significant correlation between severity of stroke at the time of admission (NIHSS) with serum bilirubin levels.At the time of discharge, both the bilirubin groups (total and direct) were not statistically different in terms of prognosis as evaluated by MR score.

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