Correlation of Bilirubin Levels in Patients with and Without Cerebrovascular Accident

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Abstract
Stroke is 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. Bilirubin, a breakdown product of normal heme catabolism is found that in acute phase of cerebrovascular because of its antioxidant property prevents the oxidation process leading to damage of brain. In this study we correlate the total Bilirubin levels in patients with cerebrovascular accident and age and sex matched controls.

Keywords: Bilirubin, Cerebro-vascular accident, Stroke.

Introduction
Stroke is 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. Stroke is one of the leading cause of disability in developed and increasing trends in developing countries. In global perspective, stroke is the 2nd most prevalent source of death. According to WHO estimates, 5.5 million people died of stroke in 2002, and roughly 20% of these deaths occurred in south Asia. Bilirubin, a breakdown product of normal heme catabolism is found that in acute phase of cerebrovascular accident if there is an elevated level of bilirubin is significant for prognosis of patient. Bilirubin because of its antioxidant property prevents the oxidation process leading to damage of brain in acute phase. It is found that in acute phase of cerebrovascular accident if there is an elevated level of bilirubin is significant for prognosis of patient. Bilirubin because of its antioxidant property prevents the oxidation process leading to damage of brain in acute phase. In this study we correlate the total bilirubin levels in patients with cerebrovascular accident and age and sex matched controls.

Aims & Objectives
1. Oxidative injury is an important cause of the neurologic lesion in stroke.
2. Serum bilirubin -a natural antioxidant that may affect the prognosis of stroke.
3. To correlate the total bilirubin levels in patients with and without CVA.

Materials & Methods

Setting: Hospital based

Study design: Cross section study which was conducted in patients with acute CVA and general population admitted in south Indian rural based hospital.

Study participants: Patients with well-documented (clinical presentation and computed tomography-brain) first or recurrent acute stroke occurring within the 7 days before admission were included in the study.

Study duration: 1 year

Sample size: 48 (24-cases, 24-age matched controls d = relative precision of 20%)

Inclusion criteria: Patients with well-documented (clinical presentation and computed tomography of the brain) first or recurrent acute stroke occurring within the 7 days before admission were included in the study.

Exclusion criteria: Patients who have contracted aspiration pneumonia, Transient ischemic attack, any central nervous system disease such as dementia, tumour, trauma or hydrocephalus, history of depression or other psychiatric disorders, liver disease or physically unfit for interview were excluded from the study.

After obtaining a written informed consent, a clinical examination of the CNS was performed and the case details were recorded on a special proforma. Patients will be examined for parameters RFT, LFT and CT-brain.

Data entry and analysis

The data obtained were entered in the MS excel sheet and data analysis was done using SPSS v24.0

Results

In this hospital base cross sectional study totally 48 patients were taken after ethical committee approval and participation consent from all study population. Patients with cerebrovascular accident, brain imaging and blood samples were collected on the day of admission in the hospital. Age-related controls(OPD, In patient) were taken and their blood samples also taken for the study.

The study population is sub-divided based on age grouping of 30-39 years 5 (S-2,C-3), 40-49 years 6 (S-3,C-3), 50-59 years 13 (S-7,C-6), 60-69 years 13 (S-7,C-6), 70-79 years 9 (S-4,C-5), 80-89 years 2 (S-1,C-1). As we already know that cerebrovascular disease is age related it is seen in age groups 40-79 years, as our life expectancy is 68.35 years less number of cases are seen in 80-89.

Table 1

| Age group | Group | Total |
|-----------|-------|-------|
|          | Study | Control |       |
| 30-39    | 2(8.3%) | 3(12.5%) | 5(10.4%) |
| 40-49    | 3(12.5%) | 3(12.5%) | 6(12.5%) |
| 50-59    | 7(29.2%) | 6(25.0%) | 13(27.1%) |
| 60-69    | 7(29.2%) | 6(25.0%) | 13(27.1%) |
| 70-79    | 4(16.7%) | 5(20.8%) | 9(18.8%) |
| 80-89    | 1(4.2%) | 1(4.2%) | 2(4.2%) |
| Total    | 24 | 24 | 48 |

* FE test p = 1.00 (NS)

*p<0.05 statistically significant, p>0.05 Non significant, NS

Table 2

| Sex | Group | Total |
|-----|-------|-------|
|     | Study | Control |       |
| Male | 18(75.0%) | 15(62.5%) | 33(68.8%) |
| Female | 6(25.0%) | 9(37.5%) | 15(31.3%) |
| Total | 24 | 24 | 48 |

Chi square test *p<0.05 statistically significant, p>0.05 Non significant, NS

In view of sex based category it is more seen in male population in our study of 33(S-18, C-15) and female population 15 (S-6, C-9).

Table 3

| Group   | N | Mean (SD) | Range | Median (Q1-Q3) | U Statistic | p-value |
|---------|---|-----------|-------|----------------|-------------|---------|
| T Bilirubin | Study | 24 | 0.88 (0.23) | 0.70 - 1.70 | 0.80 (0.80 - 0.90) | 283.00 | 0.91 (NS) |
| Control | 24 | 0.83 (0.09) | 0.70 - 1.10 | 0.80 (0.80 - 0.90) | 203.50 | 0.04* |
| D Bilirubin | Study | 24 | 0.29 (0.14) | 0.20 - 0.80 | 0.30 (0.20 - 0.30) | 203.50 | 0.04* |
| Control | 24 | 0.23 (0.06) | 0.20 - 0.40 | 0.20 (0.20 - 0.28) | 203.50 | 0.04* |

Mann Whitney U test *p<0.05 statistically significant, p> 0.05 Non significant, NS
In our study the variable total bilirubin shows a mean of 0.88 with a SD of 0.23 (R=0.7 to 1.7) mean of 0.83 with a SD of 0.09 (R=0.7 to 1.1) in study and control group respectively. The variable direct bilirubin shows a mean of 0.29 with SD of 0.14 (R=0.2 to 0.8), mean of 0.23 with a SD of 0.06 (R=0.2 to 0.4) in study and control group respectively. Using Mann Whitney U test statistic is 283 & 203.5 for total and direct bilirubin with p value of 0.91 & 0.04 respectively, which shows significant statistically for direct bilirubin.

Discussion
As already known bilirubin which is the end product of heme metabolism. In an event of oxidative stress the expression of heme-oxygenase 1 will be increased. Bilirubin which has anti-oxidative stress properties was the end product of the increased heme-oxygenase expression\(^{(4,5,6,8,11)}\). In systemic inflammatory conditions by oxidative stress, a highly inducible protein is activated, which end products are bilirubin and carbon monoxide\(^{(4,6,17,18)}\).

The neuronal cells are vulnerable to oxidative stress as brain is rich in poly unsaturated fatty acids. Bilirubin thus released from the heme-oxygenase 1 exerts cyto-protective effect\(^{(1,2,3,5,8)}\). Carbon monoxide another end product of heme-oxygenase 1 causes vasodilatation\(^{(18)}\).

Physiological levels of the bilirubin suppress the oxidation of lipids in the membranes to a greater extent than that of alpha-tocopherol. At physiological concentrations direct OH and DPPH scavenging and potent anti-oxidant activities of bilirubin are noted\(^{(21)}\). Evidence of the colocalization of HO-1 and bilirubin IX α in foam cells, suggesting a role of HO-1 induction and bilirubin in the modulation of macrophage activation in atherosclerosis\(^{(6,7,8)}\).

Various studies among individuals with general medical conditions including hepatic disease have suggested that Dbil levels may be of better prognostic value than Tbil levels\(^{(15,20)}\).

Conclusion
Bilirubin which has anti-oxidative stress properties was the end product of the increased heme-oxygenase expression.
Bilirubin thus released from the heme-oxygenase 1 exerts cyto-protective effect.
Carbon monoxide other end product of heme-oxygenase 1 causes vasodilatation.

Reference
1. DOHI K, SATOH K, OHTAKI H, SHIODA S, MIYAKE Y, SHINDO M, ARUGA T. Elevated plasma levels of bilirubin in patients with neurotrauma reflect its pathophysiological role in free radical scavenging. In vivo. 2005 Sep 1;19(5):855-60.
2. Stocker R, Yamamoto Y, McDonough AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987 Feb 27;235:1043-7.
3. Tomaro ML, del C Batlle AM. Bilirubin: its role in cytoprotection against oxidative stress. The international journal of biochemistry & cell biology. 2002 Mar 31;34(3):216-20.
4. Brouard S, Otterbein LE, Anrather J, Tobiasch E, Bach FH, Choi AM, Soares MP. Carbon monoxide generated by heme oxygenase 1 suppresses endothelial cell apoptosis. Journal of Experimental Medicine. 2000 Oct 2;192(7):1015-26.

5. Barañano DE, Rao M, Ferris CD, Snyder SH. Biliverdin reductase: a major physiologic cytoprotectant. Proceedings of the national academy of sciences. 2002 Dec 10;99(25):16093-8.

6. Stocker R, Porrella MA. Heme oxygenase-1. Circulation. 2006 Nov 14;114(20):2178-89.

7. Stocker R. Antioxidant activities of bile pigments. Antioxidants & redox signaling. 2004 Oct 1;6(5):841-9.

8. CLARK JE, FORESTI R, GREEN CJ, MOTTERLINI R. Dynamics of haem oxygenase-1 expression and bilirubin production in cellular protection against oxidative stress. Biochemical Journal. 2000 Jun 15;348(3):615-9.

9. Nakayama M, Takahashi K, Komaru T, Fukuchi M, Shioiri H, Sato KI, Kitamura T, Shirato K, Yamaguchi T, Suematsu M, Shibahara S. Increased expression of heme oxygenase-1 and bilirubin accumulation in foam cells of rabbit atherosclerotic lesions. Arteriosclerosis, thrombosis, and vascular biology. 2001 Aug 1;21(8):1373-7.

10. Wu TW, Wu J, Li RK, Mickle D, Carey D. Albumin-bound bilirubins protect human ventricular myocytes against oxyradical damage. Biochemistry and cell biology. 1991 Oct 1;69(10-11):683-8.

11. Bakken AF, Thaler MM, Schmid R. Metabolic regulation of heme catabolism and bilirubin production. I. Hormonal control of hepatic heme oxygenase activity. Journal of Clinical Investigation. 1972 Mar;51(3):530.

12. Pineda S, Bang OY, Saver JL, Starkman S, Yun SW, Liebeskind DS, Kim D, Ali LK, Shah SH, Ovbiagele B. Association of serum bilirubin with ischemic stroke outcomes. Journal of Stroke and Cerebrovascular Diseases. 2008 Jun 30;17(3):147-52.

13. Dohi K, Mochizuki Y, Satoh K, Jimbo H, Hayashi M, Toyoda I, Ikeda Y, Abe T, Aruga T. Transient elevation of serum bilirubin (a heme oxygenase-1 metabolite) level in hemorrhagic stroke: bilirubin is a marker of oxidant stress. ACTA Neurochirurgica-Supplementum Then Supplement-Wien-. 2003 Jan 1;86:247-50.

14. Doré S, Takahashi M, Ferris CD, Hester LD, Guastella D, Snyder SH. Bilirubin, formed by activation of heme oxygenase-2, protects neurons against oxidative stress injury. Proceedings of the National Academy of Sciences. 1999 Mar 2;96(5):2445-50.

15. Perlstein TS, Pande RL, Creager MA, Weuve J, Beckman JA. Serum total bilirubin level, prevalent stroke, and stroke outcomes: NHANES 1999–2004. The American journal of medicine. 2008 Sep 30;121(9):781-8.

16. Kawamura K, Ishikawa K, Wada Y, Kimura S, Matsumoto H, Kohro T, Itabe H, Kodama T, Maruyama Y. Bilirubin from heme oxygenase-1 attenuates vascular endothelial activation and dysfunction. Arteriosclerosis, thrombosis, and vascular biology. 2005 Jan 1;25(1):155-60.

17. True AL, Olive M, Boehm M, San H, Westrick RJ, Raghavachhari N, Xu X, Lynn EG, Sack MN, Munson PJ, Gladwin MT. Heme oxygenase-1 deficiency accelerates formation of arterial thrombosis through oxidative damage to the endothelium, which is rescued by inhaled carbon monoxide. Circulation research. 2007 Oct 26;101(9):893-901.

18. Durante W. Carbon monoxide and bile pigments: surprising mediators of vascular...
function. Vascular Medicine. 2002 Aug;7(3):195-202.

19. Lindenblatt N, Bordel R, Schareck W, Menger MD, Vollmar B. Vascular heme oxygenase-1 induction suppresses microvascular thrombus formation in vivo. Arteriosclerosis, thrombosis, and vascular biology. 2004 Mar 1;24(3):601-6.

20. Xu T, Zhang J, Xu T, Liu W, Kong Y, Zhang Y. Association of serum bilirubin with stroke severity and clinical outcomes. Canadian Journal of Neurological Sciences. 2013 Jan;40(1):80-4.

21. Kang SJ, Lee C, Kruzliak P. Effects of serum bilirubin on atherosclerotic processes. Annals of medicine. 2014 May 1;46(3):138-47.