Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Comparative study of oxidative stress and antioxidant status in ischemic and hemorrhagic cases of stroke

[1]Aruna Bandi
PhD Research Scholar
Department of Biochemistry
Index Medical College Hospital and Research Center
Malwanchal University

[2]Dr Shreya Nigoskar
Professor and Head
Department of Biochemistry
Index Medical College Hospital and Research Center
Malwanchal University

Corresponding Author: Dr Shreya Nigoskar

Abstract

Introduction

Several attempts have been made to understand the molecular basis of tissue damage in stroke patients. Special attention has been paid to reactive oxygen spices (ROS) which are involved in physiological processes like aging as well as many pathologic states such as atherosclerosis, cancer, neurodegenerative diseases, and etc. It is evident from both animal and human studies that the oxidative damage of membrane lipids and cellular proteins increases during cerebral ischemia and reperfusion.

Material and Methods

This is a Prospective, Observational and Single center conducted in the Department of Biochemistry and Neurology, Index Medical College Hospital & Research Center. In this study, total 220 subjects were included; of which 110 newly diagnosed ischemic stroke patients of either sex, who clinically diagnosed in the department of Neurology and 110 newly diagnosed haemorrhagic stroke. After clinical examination and confirmed diagnosis by Physician, 220 patients of either sex, who meet the inclusion and exclusion criteria selected for the study from January 2022 to July 2024.

Results

Patients with ischemic strokes have a higher mean ceruloplasmin level (59.42 mg/dl) compared to those with hemorrhagic strokes (48.31 mg/dl). The standard deviation indicates variability in ceruloplasmin levels, with ischemic stroke patients showing slightly more variability (6.42) compared to hemorrhagic stroke patients (4.52). Ischemic Stroke: Vitamin C levels are lower, with a mean of 0.89 ± 0.12 mg/L. Hemorrhagic Stroke: Vitamin C levels are higher, with a mean of 1.29 ± 0.23 mg/L. The higher vitamin C levels in hemorrhagic stroke may indicate a better antioxidant status or a different metabolic response to oxidative stress compared to ischemic stroke. Lower vitamin C levels in ischemic stroke could suggest a deficiency in this important antioxidant, which might contribute to increased oxidative damage.

Conclusion

We determined that diabetes mellitus brings an additive oxidative stress load to acute ischemic stroke patients. These patients need to be managed carefully with regard to their

poor prognosis. We consider that high TAC levels in diabetic stroke patients render the antioxidant supplementation useless at least for the acute-phase (24 hours) treatment of stroke.

Keywords: Oxidative stress, Acute ischemic stroke, Cerebral ischemia.

Introduction

Several attempts have been made to understand the molecular basis of tissue damage in stroke patients. [1] Special attention has been paid to reactive oxygen spices (ROS) which are involved in physiological processes like aging as well as many pathologic states such as atherosclerosis, cancer, neurodegenerative diseases, and etc. [2] It is evident from both animal and human studies that the oxidative damage of membrane lipids and cellular proteins increases during cerebral ischemia and reperfusion. [3]

In the ischemic process, the circulatory arrest to brain cells can cause uncontrolled activation of calcium dependent enzymes such as phospholipase A2, cyclooxygenase and neuronal nitric oxide synthase which is followed by excessive radical production. [4] Although less studied, ROS and lipid peroxidation might also have a role in brain injury following HS. [5] Several studies in the past decade have focused on measuring oxidative biomarkers in stroke patients during the acute phase after the events and in the subsequent recovery time. [6]

Detailed biomarkers' profiles of serum, urine and CSF of stroke patients have shown a statistically significant rise in markers of oxidative damage in comparison to the controls. [7] These studies can contribute to understanding the cellular factors involved in initiation and development of stroke. Also, the possible protective role of antioxidants against brain injury can lead to new therapeutic strategies in the future for reducing mortality and morbidity among both ischemic and hemorrhagic stroke patients. [8]

Material and Methods

This is a Prospective, Observational and Single center conducted in the Department of Biochemistry and Neurology, Index Medical College Hospital & Research Center

In this study, total 220 subjects were included; of which 110 newly diagnosed ischemic stroke patients of either sex, who clinically diagnosed in the department of Neurology and 110 newly diagnosed haemorrhagic stroke.

Patient Selection:

After clinical examination and confirmed diagnosis by Physician, 220 patients of either sex, who meet the inclusion and exclusion criteria selected for the study from January 2022 to July 2024.

Ischemic stroke patients

- Magnetic resonance imaging (MRI) proven ischemic stroke patients attending the neurology Department included.
- For the assessment of stroke subtypes the classification of the trial of ORG 10172 in acute stroke treatment (TOAST) considered.
- A detailed medical history on risk factors namely systemic hypertension (systolic blood pressure (SBP)> 140 mm Hg and diastolic blood pressure (DBP)>90

mm Hg, diabetes (Fasting blood sugar > 106 mg/dl, 2h post prandial blood sugar > 200 mg/dl or as oral hypoglycemic or insulin therapy, dyslipidemia, smoking, alcohol consumption, tobacco chewing, family history of stroke recorded.

- Patients were then finally grouped in to 3 groups: large artery disease, small vessel disease group and a group of strokes with other determined and unknown etiology.
- Due to their small sample size, we have only included large artery and small vessel disease group for performing statistical analysis of subgroups of ischemic stroke.

Patients were included on the basis of inclusion and exclusion criteria as follows:

Inclusion criteria:
• MRI proven Ischemic stroke
• Age above 40 years
• Place of birth and ethnicity - North India.

Exclusion criteria:
The patients with following disorders were excluded
• Cardio embolic stroke
• Liver and kidney failure
• Thyroid disorder and
• Cerebral venous sinus thrombosis

Hemorrhagic stroke patients

- Patients with computerized tomography (CT) proven intracerebral hemorrhage examined by the neurologist to confirm the diagnosis and included in the study.
- CT scans were reviewed for the location of hematoma.
- A detailed medical history reviewed on blood pressure, diabetes mellitus, smoking, alcohol consumption, tobacco chewing and family history of stroke. Magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) done to exclude the vascular malformations.
- Patients were grouped in to 2 major groups namely; lobar and non lobar hemorrhages.

Patients were included on the basis of inclusion and exclusion criteria as follows:

Inclusion criteria:
• CT proven Hemorrhage,
• Above 40 years of age
• Place of birth and ethnicity- North India

Exclusion criteria: patients with
• Head injury
• Vascular malformation,
• Tumour bleed
• Vasculopathy
• Subarachnoid hemorrhage

We have excluded subarachnoid hemorrhage cases under hemorrhagic group as to maintain biological plausibility of hemorrhagic stroke studied in our case control analysis because

subarachnoid hemorrhage is so different regarding pathophysiology, clinical picture and management that is often discussed separately.

Healthy Controls:
Healthy control group comprised of age and sex- matched healthy volunteers free of any neurological disorder. We have excluded the volunteers who had any sort of cardiac disease, diabetes, and hypertension.

Inclusion criteria
• Absence of stroke
• Free from any neurological disorder, cardiac disease
• Age, gender and ethnicity matched Exclusion criteria
• Anybody suffering from following
• Hypertension
• Diabetes
• No family history of stroke
• Any other chronic debilitating disease

Full examination (general and neurological) including evaluation of stroke severity on admission using: The National Institute of Health Stroke Scale (NIHSS) was performed for initial evaluation of stroke severity, within the first 24 h on admission, in this study, a score of (0) is measured for no stroke symptoms, (1-4) is measured for minor, (5-15) is measured for moderate, (16-20) is measured for moderate to severe, and (21-42) measured for severe.

Follow-up assessment of the patients: Modified rankin scale (mRS) was performed after 3 months post stroke to assess short-term outcome and dis- ability of stroke. Modified rankin scale scores the disability of patients into points from 0-6 according to the degree of disability. Patients with score < 2 were considered had favorable outcome, while patients with score 2-5 were considered had unfavor- able outcome and dead patients had score 6, in this study a score of (6) is measured for dead, (2-5) is measured for unfavorable outcome and (< 2) is measured for favorable outcome.

Collection of blood samples:
All the volunteer patients and normal healthy individuals (Control group) were told to fast (overnight) 12 – 14 hours, and then with all aseptic precautions the venous blood withdrawn from the anterior cubital vein, in fluoride, plain bulb and heparinised tubes for biochemical measurements. One & half hours after the meal, a second blood samples were withdrawn in a similar way for measurement of post prandial blood glucose level. For both samples, blood allowed to clot at room temperature for about 30 minutes and then centrifuged at 3000 rpm for 10minutes. The separated

STATISTICAL ANALYSIS

At the end of the data collection, all statistical analysis done using window based software SPSS, Version 29. Results were expressed as arithmetic means ± SD (Standard deviation) Before and after treatment levels difference between each groups were evaluated using, paired student "t" test and considered statistically significant at probability values less than 0.05 ($P \leq 0.05$). One-Way analysis of variance (ANOVA) done to assess the significance within and between groups.

Result

Table 1: Distribution of Gender

Characteristics	**Ischemic stroke Frequency (Percentage)**	**Haemorrhagic stroke Frequency (Percentage)**
Males	69 (62.7%)	71 (64.5%)
Female	41 (37.2%)	39 (35.4%)

In table 1, Both types of strokes are more prevalent in males, with males comprising over 62% of cases for both ischemic and hemorrhagic strokes. The percentage of females affected is notably lower, at around 37% for ischemic strokes and 35% for hemorrhagic strokes.

Table 2 Clinical severity (National Institute of Health Stroke Scale) of the ischemic stroke and Haemorrhagic stroke patients

NIHSS	**Ischemic stroke Frequency (Percentage)**	**Haemorrhagic stroke Frequency (Percentage)**
No stroke symptoms (0)	0	0
Minor (1-4)	2 (1.8%)	1 (0.9%)
Moderate (5-15)	31 (28.1%)	41 (37.2%)
Moderate to severe (16-20)	77 (70%)	68 (61.8%)
Severe (21-42)	0	0

In table 2, the majority of patients with ischemic strokes fall into the "moderate to severe" category (70%). For hemorrhagic strokes, a significant portion is also in the "moderate" (37.2%) and "moderate to severe" (61.8%) categories. There are no patients with severe symptoms or no symptoms for either type of stroke.

Table 3: Distribution of Ceruloplasmin of the ischemic stroke and Haemorrhagic stroke patients

Parameters	**Ischemic stroke Mean± SD**	**Haemorrhagic stroke Mean± SD**
Ceruloplasmin (mg / dl)	59.42 ± 6.42	48.31 ±4.52

In table 3, Patients with ischemic strokes have a higher mean ceruloplasmin level (59.42 mg/dl) compared to those with hemorrhagic strokes (48.31 mg/dl). The standard deviation indicates variability in ceruloplasmin levels, with ischemic stroke patients showing slightly more variability (6.42) compared to hemorrhagic stroke patients (4.52).

Table 4: Comparison of mean cholesterol, TG, HDL, LDL and VLDL between cases of ischemic stroke and cases of hemorrhagic stroke

Parameter	**Ischemic stroke Mean± SD**	**Haemorrhagic stroke Mean± SD**	**P value**
Total cholesterol (mg/dl)	257.0±24.40	194.35±22.66	0.0001
TG(mg/dl)	191.32±20.41	181.43±18.52	0.2315
HDL(mg/dl)	31.32±3.43	34.31±4.32	0.009
LDL(mg/dl)	187.40±26.41	123.8±28.32	0.001
VLDL(mg/dl)	38.26±4.31	36.29±3.89	0.2373

In table 4, total Cholesterol: Significantly higher in ischemic stroke patients (257.0 mg/dl) compared to hemorrhagic stroke patients (194.35 mg/dl) with a p-value of 0.0001, indicating a strong statistical significance. HDL: Ischemic stroke patients have lower HDL levels (31.32 mg/dl) compared to those with hemorrhagic strokes (34.31 mg/dl), with a p-value of 0.009, also indicating significance. LDL: The mean LDL level is significantly higher in ischemic stroke patients (187.40 mg/dl) compared to hemorrhagic stroke patients (123.8 mg/dl) with a p-value of 0.001. Triglycerides and VLDL: No significant difference was observed between the two groups, with p-values of 0.2315 and 0.2373, respectively. These findings suggest that certain lipid parameters, particularly total cholesterol, HDL, and LDL, are significantly different between ischemic and hemorrhagic stroke patients, which may have clinical implications.

Table 5: Distribution of the Vitamin C (mg/L) among Ischemic stroke group and Haemorrhagic stroke

Characteristics	**Ischemic stroke Mean± SD**	**Haemorrhagic stroke Mean± SD**
Vitamin C (mg/L)	0.89 ± 0.12	1.29 ± 0.23

In table 5, Ischemic Stroke: Vitamin C levels are lower, with a mean of 0.89 ± 0.12 mg/L. Hemorrhagic Stroke: Vitamin C levels are higher, with a mean of 1.29 ± 0.23 mg/L. The higher vitamin C levels in hemorrhagic stroke may indicate a better antioxidant status or a different metabolic response to oxidative stress compared to ischemic stroke. Lower vitamin C levels in ischemic stroke could suggest a deficiency in this important antioxidant, which might contribute to increased oxidative damage.

Table 6: Distribution of the Vitamin E (mg/L) among Ischemic stroke group and Haemorrhagic stroke.

Characteristics	**Ischemic stroke Mean± SD**	**Haemorrhagic stroke Mean± SD**
Vitamin E (mg/L)	8.23± 1.21	11.32± 1.73

In table 6, Ischemic Stroke: Vitamin E levels are lower, with a mean of 8.23 ± 1.21 mg/L. Hemorrhagic Stroke: Vitamin E levels are higher, with a mean of 11.32 ± 1.73 mg/L. The higher vitamin E levels in hemorrhagic stroke may suggest a better antioxidant status, which can help mitigate oxidative stress. Conversely, the lower levels in ischemic stroke might indicate a deficiency that could contribute to oxidative damage.

Table 7: Distribution of the Total Antioxidant capacity (TAC) (mmol/L) among Ischemic stroke group and Haemorrhagic stroke

mRS	**Ischemic stroke Frequency (Percentage)**	**Haemorrhagic stroke Frequency (Percentage)**
Dead = 6	**1 (0.9%)**	**1 (0.9%)**
Unfavorable outcome (2-5)	38 **(34.5%)**	43 **(39.0%)**
Favorable outcome (< 2)	**71 (64.5%)**	**66 (60%)**

In table 7, mRS Outcomes The majority of patients in both groups had favorable outcomes (mRS < 2), with ischemic stroke showing a slightly higher percentage (64.5%) compared to hemorrhagic stroke (60%). The proportion of patients with unfavorable outcomes (mRS 2-5)

is relatively similar between the two groups, with ischemic stroke at 34.5% and hemorrhagic stroke at 39.0%.

Discussion

In this study, both types of strokes are more prevalent in males, with males comprising over 62% of cases for both ischemic and hemorrhagic strokes. The percentage of females affected is notably lower, at around 37% for ischemic strokes and 35% for hemorrhagic strokes.

Lipid peroxidation, with accumulation of thiobarbiturate reactive material, is consistently found in cerebral ischemia. Amount of oxidative stress and acute changes of antioxidant capacity might influence the prognosis of cerebral ischemia. [10] Keeping this in view, we measured lipid profile (total cholesterol, HDL cholesterol, TG, LDL cholesterol, VLDL cholesterol), serum MDA and serum SOD levels in patients of cerebrovascular stroke.

In current study the majority of patients with ischemic strokes fall into the "moderate to severe" category (70%). For hemorrhagic strokes, a significant portion is also in the "moderate" (37.2%) and "moderate to severe" (61.8%) categories. There are no patients with severe symptoms or no symptoms for either type of stroke. This is in agreement with the results of Mendioroz et al. [11] who stated that 59.9% of patients (on admission) showed NIHSS score (16-20). Also, Mansour et al. [12] recorded in a cohort study that their patients NIHSS median value at 24 h was 22 (16–30) and at 72 h was 20 (11–30), otherwise Soliman et al. [13] reported that 61.7% of their patients show NIHSS moderate score (5– 15), and moderate to severe in 11.4.

Cerulopasmin is the primary antioxidant and barrier against free radicals in the blood stream. Ceruloplasmin ferroxidase activity is of greatest importance in conversion of Fe^{++} to Fe^{+++} and may reduce oxidation by inhibition of the Fenton reaction. Cenuloplasmin inhibits the oxidation of lipids, poly unsaturated fatty acids and phospholipids. Ceruloplasmin antioxidant activity also blocks protein and DNA damage and removes reactive intermediate hydrogen peroxide. Increase in the levels of ceruloplasmin in ischemic stroke patients without diabetes may be due to an adaptive mechanism to increased oxidative stress. A decrease in the ceruloplasmin levels as observed in Ischemic stroke indicates that antioxidant defense is impaired in these patients [14].

In this study, total Cholesterol: Significantly higher in ischemic stroke patients (257.0 mg/dl) compared to hemorrhagic stroke patients (194.35 mg/dl) with a p-value of 0.0001, indicating a strong statistical significance. HDL: Ischemic stroke patients have lower HDL levels (31.32 mg/dl) compared to those with hemorrhagic strokes (34.31 mg/dl), with a p-value of 0.009, also indicating significance. LDL: The mean LDL level is significantly higher in ischemic stroke patients (187.40 mg/dl) compared to hemorrhagic stroke patients (123.8 mg/dl) with a p-value of 0.001. Triglycerides and VLDL: No significant difference was observed between the two groups, with p-values of 0.2315 and 0.2373, respectively. These findings suggest that certain lipid parameters, particularly total cholesterol, HDL, and LDL, are significantly different between ischemic and hemorrhagic stroke patients, which may have clinical implications.

Comparing lipid profile parameters between ischemic and hemorrhagic stroke, we found that mean levels of total cholesterol and LDL were significantly higher and mean HDL levels were lower in ischemic stroke as compared to hemorrhagic stroke. There was no statistical significant difference levels of TG and VLDL cholesterol. Ahmed W *et al.* [117] who showed

in their study that, the difference in values of TC, HDL, LDL, TG in study group and controls was found to be highly significant ($p<0.001$). This reflects the anti-atherogenic role, of HDL cholesterol in facilitating reverse cholesterol transport.

In contrast high LDL and total cholesterol levels favors atherogenesis and plaque formation. Muhammed nazim *et al.* [15] in their study on 370 stroke patients found that Ischemic stroke patients had significantly higher frequency of hypercholesterolemia and reduced HDL-Cholesterol levels than patients of hemorrhagic stroke**.**

Asad mehmood *et al.* [16]in their study on comparison of serum lipid profile between two categories of stroke showed a raised serum total cholesterol and low HDL ischemic stroke as compared to hemorrhagic stroke No statistical significance was found on comparing serum values of triglycerides, LDL-cholesterol and VLDL-cholesterol in ischemic and hemorrhagic. Thus difference in lipid profile parameters between ischemic and hemorrhagic stroke should be taken into consideration while initiating lipid lowering therapy for primary prevention in high risk cases and secondary preventive measure in cases of ischemic stroke. [17]

We noticed that Ischemic Stroke: Vitamin C levels are lower, with a mean of 0.89 ± 0.12 mg/L. Hemorrhagic Stroke: Vitamin C levels are higher, with a mean of 1.29 ± 0.23 mg/L. The higher vitamin C levels in hemorrhagic stroke may indicate a better antioxidant status or a different metabolic response to oxidative stress compared to ischemic stroke. Lower vitamin C levels in ischemic stroke could suggest a deficiency in this important antioxidant, which might contribute to increased oxidative damage.

Supplementation with the antioxidant vitamin C, which directly removes ROS and RNS as well as increases NO synthesis through eNOS, may reduce the risk of ischemic and hemorrhagic stroke and lipid peroxidation. Vitamin E reduces infarct volume by 45–55% in transient and permanent cerebral ischemia models. [18]

Conclusion

We determined that diabetes mellitus brings an additive oxidative stress load to acute ischemic stroke patients. These patients need to be managed carefully with regard to their poor prognosis. We consider that high TAC levels in diabetic stroke patients render the antioxidant supplementation useless at least for the acute-phase (24 hours) treatment of stroke. Oxidative stress and TAC in the later periods of acute ischemic stroke need to be explored in further studies.

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