**ORIGINAL ARTICLE**

# Frequency of Low Serum Zinc Levels in Patients with Cerebral Infarction

SHEHLA TABASSUM, GHULAM MUSTAFA, IJAZ-UL-HAQUE TASEER

## ABSTRACT

**Aim:** To determine the frequency of low serum zinc levels in patients with cerebral infarction.
**Study design:** Descriptive cross-sectional study
**Setting:** Department of Medicine, Nishtar Hospital, Multan.
**Duration:** Six months from December 2011 to June 2012
**Methods:** One hundred and eighty (180) patients between the ages of 50-80 years were included in the study after identification of clinical features of stroke, on history and detailed clinical examination, and Computed Tomography (CT) scan brain was carried out in all such patients to establish cerebral infarction. Serum samples were obtained within 24 hours of admission and analyzed for serum Zinc levels. All the relevant data were taken and recorded in a specially proforma.
**Results:** One hundred and eighty patients with cerebral infarction were included in the study. Out of 180 patients studied, 103(57.2%) were male while 77(42.8%) were female. Mean age was 62.74±8.55 years. Among those 180 patients, 56(31.1%) patients reached hospital within the first 12 hours of the onset of cerebral infarction, 65(36.1%) patients reached within 13-24 hours, while 59(32.8%) patients reached within 25-48 hours after the onset of stroke. Mean serum zinc level was 12.294±3.18 µmol/L, 59(32.8%) patients had serum zinc level less than the normal reference range while 121(67.2%) patients had serum zinc level within the normal reference limits.
**Conclusion:** The results of this study show that zinc is found to be deficient in a significant proportion of patients with cerebral infarction. The development of new treatment and preventive strategies for the CNS insults need to take into account the role of zinc in neuronal function, damage and repair.
**Keywords:** Stroke, Cerebral infarction, Serum zinc level.

## INTRODUCTION

Stroke is the main cause of adult disability and the third most common cause of mortality in the world. Worldwide more than 16 million people suffer an acute stroke each year. Over 80% survive acute insult but most victims are unfortunately left with long-term neurological deficits, making stroke the leading cause of chronic disability in adults[1]. Stroke together with other atherosclerosis related diseases are global problems of immense proportion. About 87% of strokes worldwide are caused by infarction and the remainder by hemorrhage. About 3.5 million of deaths occur from stroke each year in developing countries. Asians have a higher prevalence of stroke[2]. Incidence of stroke ranges from 182 to 342 per 100,000 population in Asia[3]. The burden of stroke in Asia is predicted to increase, both in absolute terms and as a proportion of total disease burden, due to increased population aging and lifestyle changes. There is no sizeable community based epidemiological studies on stroke from Pakistan. Estimated annual incidence is 250/100,000[4]. Out of this, 69% of stroke cases are ischemic in origin[5]. These figures pose a great challenge to the health care system in Pakistan. Control of risk factors of cerebral infarction remains an important target for intervention. Zinc is essential for the structure and function of regulatory, structural and enzymatic proteins. From its former marginal status as a "trace element", zinc has risen to assume a position along with calcium, potassium and sodium as a key modulator of neuronal excitability. The "glutaminergic" synapse is the most abundant synapse type in the cerebral cortex, giving zinc a privileged role in cortical communication[6]. About 10% of all zinc in the brain exists in the pre-synaptic vesicles of glutamitergic neurons and it is released into synaptic cleft upon the excitation of nerves[7], mediating several vital physiological functions. Dietary zinc deprivation may influence zinc homeostasis in the brain, resulting in brain dysfunction[8]. Preclinical studies have extensively investigated the role of zinc in cerebral infarction. The clinical study conducted by Bhatt et al, in USA showed low zinc levels in 35.7% patients of cerebral

*Department of Medicine, Nishtar Medical College and Hospital, Multan*
*Correspondence to Dr. Ijaz ul Haque Taseer, Chief Research Officer, PMRC Research Centre, Nishtar Medical College, Multan Email: dritaseer@hotmail.com, pmrcnmc@gmail.com , Cell: 300-9638246*

ischemia and concluded that low serum zinc concentrations are associated with more severe stroke on admission and poor functional status at discharge[9]. It has also been proposed that pre-treatment with zinc-protoporphyrin complexes reduced the size of infarct and the edema associated with transient cerebral ischemia[10]. Throughout the world, very limited clinical studies have investigated an association of serum zinc levels with severity of cerebral infarction. No such study has ever been carried out in Pakistan. Very little of the meager resources are allocated for prevention and treatment of stroke in Pakistan. By better understanding of the immensity of the problem and appropriate knowledge about the role of micronutrients in the pathogenesis of cerebral infarction, this can be a ray of hope to the population at risk.

The rationale of this study was to detect the serum zinc levels among stroke patients secondary to cerebral infarction at Nishtar Hospital, Multan. The study will work as a pilot project for further studies on this subject. If frequency of low serum zinc will be high among these patients, then it will be emphasized for estimation of routine serum zinc level in cerebral infarction patients and it will be recommended to supplement zinc treatment for ischemic stroke patients and for general population at risk for this disease.

## MATERIALS AND METHODS

This descriptive cross-sectional study was conducted in the Department of Medicine Nishtar Hospital and Medical College, Multan from December, 2011 to June, 2012 on one hundred and eighty (180) patients of cerebral infarct. The sampling technique non-probability purposive was used. Patients suffering from cerebral infarction having age between 50 to 80 years irrespective of gender were included in the study. While patients suffering from stroke due to the reasons other than cerebral infarction and who are already on zinc supplementation were excluded.

The hospital ethical committee reviewed and permitted to conduct this study. Informed consent was taken from patients or their attendants. Patients between the ages of 50-80 years were included in the study after identification of clinical features of stroke, on detailed history and detailed clinical examination. CT scan brain was carried out in all such patients from Department of Radiology, Nishtar Hospital, Multan to establish cerebral infarction. Patients suffering from stroke due to the reasons other than cerebral infarction or already on zinc supplementation were excluded. Blood samples were taken for estimation of zinc level within 24 hours of admission. Blood samples were analyzed by photometric method using a manual kit by Multan branch of Chughtai Laboratory, Lahore. All the information was recorded in especially designed proforma. All data were entered and analyzed through SPSS-16. The expenditures of the tests of all the patients were borne solely by the researcher.

Descriptive statistics for numerical data was applied to calculate mean and standard deviation for the age of patients and duration of onset of stroke. Frequency and percentages were calculated for categorical data i.e. gender of patients and low serum zinc levels. Chi-square test was applied to see the effect of these on outcome variable. $P<0.05$ was to be taken as significant.

## RESULTS

We identified 180 patients with cerebral infarction. Mean patient age was 62.74±8.55 years. Maximum number 68 (37.8%) of patients belonged to the age group 50-59 years (Table l).

Table-1: Age groups (n=180)

| Age Groups (years) | Frequency | Percent |
|---|---|---|
| 50-59 | 68 | 37.8 |
| 60-69 | 62 | 34.4 |
| 70-80 | 50 | 27.8 |

Out of 180 patients, 103(57.2%) were male and 77(42.8%) were female. Gender distribution was not significant for stroke due to cerebral infarction. Male to female ration was 1.34:1.

Among those 180 patients, 56(31.1%) patients reached the hospital within the first 12 hours of the onset of cerebral infarction, 65(36.1%) patients reached within 13-24 hours, while 59(32.8%) patients reached within 25-48 hours after the onset of stroke. Overall, 59(32.8%) patients had low serum zinc levels. Mean zinc levels (mean±SD) were 12.29±3.18µmol/L.

## DISCUSSION

Stroke is a medical emergency requiring immediate treatment. Worldwide more than 16 million people suffer from acute stroke every year. Over 80% survive acute insult but most victims unfortunately are left with long-term neurological deficits making stroke the leading cause of chronic disability in the world. Proper treatment improves the chances of survival and increases the degree of recovery. Improved medical treatment of all types of stroke may result in dramatic decline in death rates. Likewise, comprehensive preventive measures can significantly improve both survival and recovery. Investigations have documented that nutritional interventions can enhance the recovery of neurocognitive functions in

individuals with ischemic stroke. This supports the need for targeted nutritional therapies aimed at improving the mortality and morbidity associated with ischemic stroke. To the best of our knowledge, our study is the first in Pakistan to show an association between low serum zinc levels and cerebral infarction. Our study showed that a significant proportion of people with cerebral infarction are zinc-deficient.

Zinc mediates several vital physiological roles in the body. Preclinical studies have extensively evaluated the role of zinc in cerebral ischemia. Animal-based studies have shown that zinc supplementation reduces infarct size[11], while zinc chelation is neurotoxic. In view of the potential relationship between cerebral ischemia and zinc status, He Z et al designed a study to examine whether dietary zinc deficiency would affect the outcome of focal cerebral ischemia in rats. He concluded that dietary zinc-deficiency increases infarct size following permanent middle cerebral artery (MCA) occlusion in rats[12]. In addition, the aggravation of cerebral ischemia may depend on the severity of zinc deficiency, duration and the timing of dietary restriction.

The clinical study conducted by Bhatt et al in USA showed low serum zinc levels in 35.7% patients of cerebral ischemia and concluded that low serum zinc concentrations are associated with more severe stroke on admission and poor functional status at discharge[9]. Munshi et al also suggested through their study that low zinc levels may represent an independent risk factor for stroke and therefore a possible target for prevention[13]. The study undertaken by Soresen documented the disappearance of zinc positive neuronal terminals in the ischemic neocortex and related areas, most likely due to a neuronal release of vesicular zinc in response to hypoxia, and concluded that the high extracellular concentration of zinc is thought to be neuroprotective by blocking the receptors[14].

Alteration of zinc levels in the brain may influence neurotransmission in zinc-containing glutaminergic synapses. Therefore, dietary zinc deficiency may influence zinc homeostasis in the brain, resulting in brain dysfunction such as stroke. Study conducted by Aquilani et al, documented that patients in whom daily zinc intake was normalized had better recovery of neurological deficits than subjects given a placebo.[15] In their study, patients whose diet was supplemented with 10 milligrams of zinc per day showed superior recovery to those who were given placebo. Mutsushita et al, suggested in their study that transfer of exogenous zinc into the intracellular space is required for neuroprotection, presumably via the anti-endonuclease activity.[16] Various studies have demonstrated neuroprotective benefits following the administration of various zinc compounds. Yamasaki and colleagues, for example, examined the effectiveness of zinc protoprophryrin (ZnPP) in mediating post-ischemic brain edema by selectively blocking the cytokine, interleukin-I. The topical application of ZnPP was found to reduce ischemic brain edema significantly by blocking IL-I activity[17]. Zhao and colleagues suggested that zinc ions, in comparison to protoporphyrin, provide neuroprotection by mechanisms other than reducing brain edema[18]. Recently, Kitamura and colleagues have found that reduction in zinc levels following intracerebroventricular injection of Ca-EDTA prior to focal ischemia accelerated the early development of infarct suggests the need for minimum level of zinc to maintain cellular viability, even during cerebral ischemia[19]. Clinical studies have also shown an association between low zinc levels (<70mcg/dl) and high mortality in elderly patients with pneumonia[20], and higher incidence of opportunistic infections in AIDS patients with zinc levels <65mcg/dl[21]. It has also been shown that zinc levels tend to fall in myocardial infarction, but the effect on outcomes after myocardial infarction has not been determined[22] Zinc supplementation has been shown to improve cancer survival[23] and promote wound healing.

Pakistan lacks the data regarding the impact of nutritional factors on the treatment and prevention of cerebral infarction. This study conducted in department of Medicine Nishtar Hospital Multan identified the zinc-deficient population among the patients with ischemic stroke and found it to be quite significant. The present study also shows that zinc deficiency among the people suffering from cerebral infarction is much similar to that of advanced western countries. Taking into consideration data exclusively from the only other study carried out in this regard in USA, our findings in cerebral infarction population agree with those of Bhatt et al[9].

## RECOMMENDATIOS

This study, for the first time in Pakistan, indicates that quite a significant proportion of people with cerebral infarction suffer from zinc deficiency. The results of this study recommend that public health measures are mandatory to introduce risk factor intervention and appropriate primary and secondary preventive measures in the form of zinc supplementation at general population level. To combat zinc deficiency, following intervention strategies can be used:

- Supplementation using medicines
- Food fortification through the incorporation of zinc additives in food
- Dietary modification/diversification

- Agronomic bio-fortification through zinc fertilization

These interventional strategies may be used individually or in combination, depending on the setting, target group and degree of zinc deficiency. A study published in 2008 determined that zinc glycinate is the best absorbed of the four dietary supplements type available.

A program of continuing education covering the mechanisms of neuroprotective role of zinc should be established for doctors caring for patients of cerebral infarction. Appropriate information in this regard should also be given to non clinical staff, caregivers and the whole community. A National Stroke Prevention Program should be established which should initiate and coordinate public awareness campaigns, and develop guidelines and research related to the therapeutic effect of zinc in the treatment and prevention of stroke due to cerebral infarction. It is worth re-emphasizing that the nutritional therapeutic efforts to prevent and treat cerebral infarction in the form of zinc supplementation should be applied early since this problem accounts for considerable morbidity and mortality.

## CONCLUSION

The results of this study show that zinc is found to be deficient in a significant proportion of patients with cerebral infarction. The development of new treatment and preventive strategies for the CNS insults need to take into account the role of zinc in neuronal function, damage and repair.

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