Original Article

Frequency of Hyperthermia and Poor Outcome in Patients with Ischemic Stroke

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Objective: To determine the frequency of hyperthermia in patients with ischemic stroke and compare the frequency of poor outcome in patients with and without hyperthermia along with ischemic stroke.

Methods: This descriptive cross-sectional study was carried out in Medical Unit III, Postgraduate Medical Institute/Lahore General Hospital, Lahore over six months period six month from March 18, 2015 to September 17, 2015.Two hundred patients of both gender, aged 18-60 years, reaching within 24 hours of onset of symptoms and signs of ischemic stroke with Glasgow Coma scale (GCS) ≤ 10/15 were enrolled in the study. Axillary temperature was recorded by placing the thermometer in axilla for two minutes at interval of four hours from the time of admission to till 3rd day of stay in hospital. GCS was recorded at baseline and after three days of hospital stay and poor outcome was noted.

Results: In this study a total of 200 cases were enrolled, of which 143 (71.5%) were male. mean age of the patients was 43.11±6.97. it was noted that in 71 (35.5%) cases hyperthermia was present while in 129 (64.5%) cases hyperthermia was not present. poor outcome in 92 (46%) of cases and was absent in 108 (54%) p-value<0.05.

Conclusions: Hyperthermia can result in poor outcome in ischemic stroke patients

Keywords: Stroke, hyperthermia, mortality, poor outcome.

Introduction

Ischemia stroke is a cerebrovascular disease due to cerebral ischemia, resulting in neurological signs and symptoms that persist for more than 24 hours.[1] The neurological deficit depends on site and size of area of brain damage and presents most commonly as hemiplegia with or without signs of focal higher cerebral dysfunction such as aphasia, hemisensory loss, visual field defects for brain stem defects.[2] CT scan brain is the investigation of choice for this.[1]

Ischemic stroke is the leading cause of death,[3] standing at number three after cancer and ischemic heart disease2. It is a poly etiologic disease and many factors are responsible for poor outcome.[4,7] One of these factors is hyperthermia that occurs almost in one third of patients with ischemic stroke.[8]

Hyperthermia in patients with ischemic stroke occurs due to many treatable conditions like aspiration pneumonia, urinary tract infection, respiratory tract infection, infectious endocarditis andmeningoencephalitis.[9] It is related to poor outcome in patients with ischemic stroke8. So by treating hyperthermia one can play an important role in improving the outcome of patients with ischemic stroke.[10] A study was done in United States that included cases of ischemic stroke. The study was undertaken on 1361 patients with ischemic stroke and frequency of hyperthermia and relationship of hyperthermia burden to outcome of patient was noted. It was found that 483 (35%) patients had hyperthermia and a high hyperthermia burden was associated with 6-fold increased risk of death or discharge to hospital.[8] Another study was done in Edinburgh which included 44 case of ischemic stroke and relationship of hyperthermia to outcome of patents was noted. it was found that out of 44 patients of ischemic stroke, 16 patients (36%) developed hyperthermia. 25 patients (56.81) had poor outcome. A higher proportion of patients with hyperthermia 12/16 (75%) had poor outcome than patients without hyperthermia 13/28(46%).[11]

There is high prevalence of patients who develop post-stroke hyperthermia in our population but there is paucity of local studiesabout the relationship between post-stroke hyperthermia and outcome.We planned this study in our local population to determine the frequency of hyperthermia in patients with ischemic stroke and compare frequency of poor outcome in such patients with and without hyperthermia. If hyperthermia occurs in patients of ischemic stroke and it is related to poor outcome in

ischemic stroke's patients then we can reduce mortality, morbidity and economic burden of ischemic stroke by treating hyperthermia.

Methods

This descriptive cross-sectional study was conducted in medical unit III, Postgraduate Medical Institute/Lahore General Hospital, Lahore during six-month period from March,2015 to September, 2015. A study sample of 200 cases was calculated at margin of error 6% and confidence level by 95% and taking expected percentage of hyperthermia i.e. 35% in patients of ischemic stroke. Non-probability consecutive sampling technique was used to enroll patients. Inclusion criteria of the study were patients reaching in tertiary care hospital within 24 hours of onset of symptoms and signs of ischemic stroke (presence of weakness of one or more limbs for more than 24 hours and confirmed by CT scan brain as hypodense area),belonging to either gender, aged 18-60 year, with Glasgow coma score (GCS) ≤ 10/15. Patients with recurrent ischemic stroke on history, those with history of hyperthermia before the onset of ischemic stroke or those with hemorrhagic stroke (shown by hyperdense area on CT scan brain) were excluded from the study.

After fulfilling the inclusion and exclusion criteria 200 patients were enrolled in the study. Informed consent was obtained from patient or his / her guardian if patient was unable to do so. Demographic information including name, age, sex and address was noted. Axillary temperature was taken by placing the thermometer in axilla for two minutes at interval of 4hour from the time of admission to till 3rd day of his/her stay in hospital and was evaluated for hyperthermia as per operational definition. All the patients were managed as per hospital routine. GCS was recorded as baseline and after three days of hospital stay and poor outcome was labeled. Hyperthermia was defined to be present if axillary temperature recorded within three days during hospital exceeded 37.8°C for at least four hours. Similarly, if the patient's GCS remained same or reduced on assessment on third day, it was graded as poor outcome.

Data wereanalyzed using SPSS version 20.0. Continuous variable like age was presented by mean and standard deviation. Categorical variable such as gender, hyperthermia and poor outcome were described as frequency and percentage. chi square test was used to determine the significant difference of outcome in patients with and without hyperthermia. A p value of less than 0.05 was considered significant. Data was stratified for age, gender, history of diabetes mellitus, hypertension, and GCS at baseline to deal with effect modifier. Post stratification chi-square test was used. P-Value ≤ 0.05 was considered significant.

Results

Of 200 cases, 143 (71.5%) were male and 57 (28.5%) were female. Mean age of the patients was 43.11 ± 6.97 years with age range of 19to 52 years.

It was noted that 71 (35.5%) were suffering from hyperthermia while 129 (64.5%) hadnormal temperature.92 (46%) of cases developed poor outcome **(Table 1)**.

Table-1: Comparison of poor outcome in cases with and without hyperthermia (n=200).

Hyperthermia	Poor Outcome		p-value
	Yes	No	
Present	55 (77.5)	16 (22.5)*	P=000
Absent	37 (28.7)	92 (71.3)	

Table-2: Hyperthermia in different factors (n=200).

Factors		Hyperthermia		P-Value
		Present	Absent	
Age (Years)	<30	7 (9.9%)	4 (3.1%)	0.045
	>30	64 (90.1%)	125 (96.4%)	-
Gender	Male	52 (73.2%)	91 (70.5%)	-
	Female	19 (26.8%)	38 (29.5%)	0.686
Diabetes Mellitus	Yes	49 (69%)	38 (29.5%)	0.485
	No	22 (31%)	34 (26.4%)	-
Hypertesnsion	Yes	64 (90.1%)	116 (89.9%)	-
	No	7 (9.9%)	13 (10.1%)	-
GCS Scale Score	<7	42 (59.2%)	69 (53.5%)	0.440
	>7	29 (40.8%)	60 (45.5%)	-

It was noted that there were more 55 (77.5%) cases who had developed poor outcome and were having hyperthermia while 16 (22.5%) cases had not developed poor outcome but were having hyperthermia with a significant difference pvalue 0.000 **(Table 1)**. Data of hyperthermia and poor outcome were stratified for age, gender, diabetes mellitus, hypertension and GCS as shown in **Table 2** and **3**. Hyperthermia was more frequent in patients

years and poor outcome was higher in patients with GCS <7 (p<0.05).

Table-3: Stratification with respect to poor outcome (n=200).

		Poor outcome		P-Value
		Yes	No	
Age (Years)	<30	8 (8.7%)	3 (2.8%)	0.067
	>30	84 (91.3%)	105 (97.2%)	-
Gender	Male	68 (73.9%)	75 (69.4%)	0.067
	Female	24 (26.1%)	33 (30.5%)	
Diabetes Mellitus	Yes	62 (67.4%)	82 (75.9%)	0.180
	No	30 (32.6%)	26 (24.1%)	
Hypertesnsion	Yes	83 (90.2%)	97 (89.8%)	0.925
	No	9 (9.8%)	11 (10.2%)	
GCS Scale Score	<7	64 (69.6%)	47 (43.5%)	0.000
	>7	28 (30.4%)	61 (56.5%)	

Discussion

Hyperthermia following ischemic stroke is a common but undesirable event whose pathophysiology and clinical importance are not fully recognized. Hyperthermia is ischemic stroke may result from the brain infarct itself; however, the progress of biochemical and inflammatory mechanisms associated with cerebral ischemia is also relevant. Consequently, the presence of hyperthermia accentuates ischemic mechanisms within the penumbra, an area of reversibly impaired neuronal function surrounding the infarct, contributing to conversion of the penumbra in to an irreversible lesion.[12]

Hyperthermia in the neurocritical care setting is common and has a negative impact on outcome of all disease types. Meta-analyses have demonstrated that hyperthermia at onset and in the acute setting after ischemic brain injury, intracerebral hemorrhage, and cardiac arrest has a negative impact on morbidity and mortality. Recent advances focus on eliminating hyperthermia and maintaining normothermia.[13]

In this study we found that hyperthermia occurred in 35.5% of our ischemic stroke patients. These results are similar to those described by Phipps et al [8] and Bartosz et al,[11] while Przelomski et al[14] and Terent and Andersson[15] described a higher incidence of hyperthermia. However, comparison among various studies is difficult because of differences in the definition and measurement of hyperthermia. Considering no improvement in GCS as the main measure of poor outcome, we found that hyperthermia was significantly related to a poor outcome. It was not possible to determine a threshold above which hyperthermia seemed detrimental. Probably a range of cutoffs would have given significant results.

Our data did not provide information on underlying causes of hyperthermia in our patients. Thus, we could not exclude a priori that temperature of at least 37.8C° in the first 3 days after a stroke as a marker of poor prognosis might to some extent or entirely be an epiphenomenon of some common causes of hyperthermia (e.g. pulmonary or urinary tract infections, sepsis, or pulmonary embolism from deep venous thrombosis). However this was evident that hyperthermia of at least 37.8C° indicated poor prognosis even without a consideration of its underlying causes. Since the majority of the experimental studies documented the direct effects of temperature on neurological damage, our data suggest thathyperthermia could worsen prognosis through direct neurological damage.

Only two studies have investigated the prognostic significance of hyperthermia in stroke. Hindfelt[16] found that a mean body temperature above 37.5C° from any cause in the first 7 days was associated with poor prognosis at 2 months after the ischemic stroke. However, his study was retrospective, the sample excluded patients who died within 2 months, and the measurement of outcome was not validated, so that his conclusions are not easily generalized to the whole population of stroke patients.

In a prospective study of 281 patients with stroke, Terent and Andersson[15] found that in patients with mean body temperature of 38C° or more during the first week, chest x-ray films revealed bronchopneumonia in half. Hyperthermia as defined above indicated a significantly worse prognosis, but their data did not distinguish between the consequences of complete paresis and bodytemperature. We could not consider complete paresis because of its strong association with level of consciousness impairment, reported as having a superior prognostic value forearly mortality.

Przelomski et al[14]prospectively investigated the frequency and causes of hyperthermia in a sample of 104 consecutive stroke patients. In particular, these authors studied the possible association between hyperthermia, almost always secondary to infections, and the size of the lesion, comparison with our study is difficult because the authors excluded brain stem infarcts, condition in which "neurogenic >30 hyperthermia" is most likely, and they did not evaluate

the prognostic value of hyperthermia.

Our study shows that body temperature ≥37.8C° predicts poor outcome in patients with ischemic stroke. These results are in line with the well-established deleterious effect of hyperthermia in this neuronal pathology. It has been widely described the relationship between hyperthermia and poor functional outcome after ischemic stroke. However, the molecular mechanisms associated to the deleterious effects of hyperthermia in ischemic stroke have not yet been fully clarified.

It has been suggested that molecular processes such as inflammation, glutamate excitotoxicity and infections, which induces early pathophysiologic changes in the surrounding brain tissue such as breakdown of the brain-blood barrier (BBB) and development of vasogenic edema, considered relevant predictors of poor outcome, could be involved in the deleterious consequences of hyperthermia.

In our study, elderly patients (>30 years) developed hyperthermia more frequently (90.1%) than younger patients (9.9%) and patient with lower GCS level had poor outcome more frequently (69.6%) than patients with higher GCS level. It suggested that hyperthermia occurs more frequently in elderly patients and lower GCS level is an independent risk factor for poor outcome. No difference was found for the other clinical characteristics like gender or diabetes mellitus.

Hyperthermia is a robust protectant against brain ischemia. Early clinical studies have shown feasibility, but the potential for neurological improvement needs to be weighed against the higher occurrence of pneumonia and the potential for reduced thrombolytic efficacy. Combination of hypothermia with other neuroprotectants and modern reperfusion therapies should be explored.[17]

Conclusion

Our results indicated that patients with higher temperature have a worse prognosis. Future studies distinguishing between the causes of hyperthermia in ischemic stroke patients would be useful to evaluate the role of infections, and more studies are needed on larger scale to observe the actual effect of hyperthermia in cases who are presenting with ischemic stroke. This was a single centered study so has its limitations. But it showed the resemblance with the internationally published literature in context with the effect of hyperthermia in cases of ischemic stroke.

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Medical News

World's first vaccine developed against Toxic Shock Syndrome

TToxic Shock Syndrome (TSS) is a severe circulatory and organ failure caused by bacterial toxins, usually triggered by bacteria from the Staphylococcus group. Researchers from MedUni Vienna's Department of Clinical Pharmacology, in collaboration with the company BiomedizinischeForschungsgesells- chaftmbH in Vienna, have now developed the world's first safe and effective vaccine against this disease and successfully tested it in a Phase I trial. The promising results were recently published in the leading journal The Lancet Infectious Diseases.

This syndrome was first described in the 1980s. General symptoms of sepsis or blood poisoning occurred in young women who had used so-called "super tampons" during their periods. This is why the syndrome was also known as "tampon disease". This subsequently led to the absorption capacity of tampons being regulated.

Staphylococci colonize nearly all of us, especially on our skin and mucous membranes. They are totally harmless to most people. "However, for people with weakened immune systems, they can cause serious diseases such as Toxic Shocks Syndrome," explains Martha Eibl, director of Biomedizinische-ForschungsgesellscaftmbH and former university professor at the Institute for Immunology of the medical faculty of the University of Vienna. This affects dialysis patients, the chronically sick, people with liver diseases and people recovering after heart operations. "Nevertheless, in 50% of cases the disease is associated with menstruation in young women," says Bernd Jilma from MedUni Vienna's Department of Clinical Pharmacology.

The vaccine, which has now been found to be safe and effective - and to have practically no side effects - in a clinical Phase I trial, and has been tested on 46 young men and women, was developed from a detoxified Staphylococcus toxin. The vaccine is injected into the skin and its effect is similar to that of a tetanus vaccination, says Jilma. "Immunization with such vaccines lasts for five years or more." Once vaccinated, a person develops antibodies, which become active if the germs start to pose a threat. A blood test can show whether someone is short of antibodies. Risk groups could then be preventively vaccinated.

"We are well on the way to having a vaccine that prevents this series disease. However, it will still take some years before it is in clinical use," explains Eibl. A Phase II trial with a larger test population has now started, in order to check the initial, promising results. "We are still looking for more volunteers," says Jilma.

Courtesy: medicalnewstoday