Original Research Article

International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 26-02-2020; Accepted: 21-03-2020; Published: 28-03-2020
www.medicalsciencejournal.com
Volume 6; Issue 3; 2020; Page No. 142-147

Study of levels of the glycated hemoglobin (HbA1C) in patients suffered from acute ischemic stroke

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Abstract
Co-morbid risk factors associated with stroke are predictors of poor outcomes in stroke patients. Various risk factors including hypertension, cardiac diseases, diabetes mellitus (DM), smoking, alcohol consumption, stress, and depression could account for 90% of stroke risk as suggested by an international multicenter study. DM is regarded as an independent risk factor for ischemic stroke, with an estimated prevalence of 21%-44.4% among patients who experience acute ischemic stroke. Several studies have suggested poor functional outcomes for stroke patients with increased blood glucose levels. Recent studies have found poor outcomes in prediabetic and denovo diabetes patients in acute ischemic stroke. Hence based on above findings the present study was planned for Study of Levels of the Glycated Hemoglobin (HbA1C) in Patients Suffered from acute ischemic stroke.

The present study was planned in Department of General Medicine, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. In the present study 200 cases suffered from the strokes were enrolled. The CT scan was performed in all the cases within 3 days of onset of symptoms to confirm the diagnosis and to ascertain the type of stroke (ischaemic/haemorrhagic) and size of stroke (small, medium, or large).

The data generated from the present study concludes that Hyperglycaemia in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. Management of hyperglycaemia in patients with diabetes and non-diabetes is an important aspect of the emergency management of stroke. Further studies with a larger sample and long-term outcomes measurements would be desirous to establish a definite relation of in hospital admission hyperglycemia and stroke short- and long-term outcomes.

Keywords: glycated hemoglobin, HbA1C, acute ischemic stroke, etc

Introduction

A stroke is a medical condition in which poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. Both result in parts of the brain not functioning properly. Signs and symptoms of a stroke may include an inability to move or feel on one side of the body, problems understanding or speaking, dizziness, or loss of vision to one side. Signs and symptoms often appear soon after the stroke has occurred. If symptoms last less than one or two hours it is known as a transient ischemic attack (TIA) or mini-stroke. A hemorrhagic stroke may also be associated with a severe headache. The symptoms of a stroke can be permanent. Long-term complications may include pneumonia or loss of bladder control [1].

The main risk factor for stroke is high blood pressure. Other risk factors include tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, a previous TIA, and atrial fibrillation. An ischemic stroke is typically caused by blockage of a blood vessel, though there are also less common causes. A hemorrhagic stroke is caused by either bleeding directly into the brain or into the space between the brain's membranes. Bleeding may occur due to a ruptured brain aneurysm. Diagnosis is typically based on a physical exam and supported by medical imaging such as a CT scan or MRI scan. A CT scan can rule out bleeding, but may not necessarily rule out ischemia, which early on typically does not show up on a CT scan. Other tests such as an electrocardiogram (ECG) and blood tests are done to determine risk factors and rule out other possible causes. Low blood sugar may cause similar symptoms [2].

Prevention includes decreasing risk factors, as well as possibly aspirin, statins, surgery to open up the arteries to the brain in those with problematic narrowing, and warfarin in those with atrial fibrillation. A stroke or TIA often requires emergency care. An ischemic stroke, if detected within three to four and half hours, may be treatable with a medication that can break down the clot. Aspirin should be used. Some hemorrhagic strokes benefit from surgery. Treatment to try to recover lost function is called stroke rehabilitation and ideally takes place in a stroke unit; however, these are not available in much of the world [3].

In 2013 approximately 6.9 million people had an ischemic stroke and 3.4 million people had a hemorrhagic stroke. In 2015 there were about 2.4 million people who had previously had a stroke and were still alive. Between 1990 and 2010 the number of strokes which occurred each year decreased by approximately 10% in the developed world and increased by 10% in the developing world. In 2015, stroke was the second most frequent cause of death after coronary artery disease, accounting for 6.3 million deaths

(11% of the total). About 3.0 million deaths resulted from ischemic stroke while 3.3 million deaths resulted from hemorrhagic stroke. About half of people who have had a stroke live less than one year. Overall, two thirds of strokes occurred in those over 65 years old [4].

Strokes can be classified into two major categories: ischemic and hemorrhagic. Ischemic strokes are caused by interruption of the blood supply to the brain, while hemorrhagic strokes result from the rupture of a blood vessel or an abnormal vascular structure. About 87% of strokes are ischemic, the rest being hemorrhagic. Bleeding can develop inside areas of ischemia, a condition known as "hemorrhagic transformation." It is unknown how many hemorrhagic strokes actually start as ischemic strokes [3].

In the 1970s the World Health Organization defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours", although the word "stroke" is centuries old. This definition was supposed to reflect the reversibility of tissue damage and was devised for the purpose, with the time frame of 24 hours being chosen arbitrarily. The 24-hour limit divides stroke from transient ischemic attack, which is a related syndrome of stroke symptoms that resolve completely within 24 hours [3]. With the availability of treatments that can reduce stroke severity when given early, many now prefer alternative terminology, such as brain attack and acute ischemic cerebrovascular syndrome (modeled after heart attack and acute coronary syndrome, respectively), to reflect the urgency of stroke symptoms and the need to act swiftly [5].

There are two main types of hemorrhagic stroke: [6]

Intracerebral hemorrhage, which is basically bleeding within the brain itself (when an artery in the brain bursts, flooding the surrounding tissue with blood), due to either intraparenchymal hemorrhage (bleeding within the brain tissue) or intraventricular hemorrhage (bleeding within the brain's ventricular system).

Subarachnoid hemorrhage, which is basically bleeding that occurs outside of the brain tissue but still within the skull, and precisely between the arachnoid mater and pia mater (the delicate innermost layer of the three layers of the meninges that surround the brain).

The above two main types of hemorrhagic stroke are also two different forms of intracranial hemorrhage, which is the accumulation of blood anywhere within the cranial vault; but the other forms of intracranial hemorrhage, such as epidural hematoma (bleeding between the skull and the dura mater, which is the thick outermost layer of the meninges that surround the brain) and subdural hematoma (bleeding in the subdural space), are not considered "hemorrhagic strokes" [7].

Hemorrhagic strokes may occur on the background of alterations to the blood vessels in the brain, such as cerebral amyloid angiopathy, cerebral arteriovenous malformation and an intracranial aneurysm, which can cause intraparenchymal or subarachnoid hemorrhage.

Stroke symptoms typically start suddenly, over seconds to minutes, and in most cases do not progress further. The symptoms depend on the area of the brain affected. The more extensive the area of the brain affected, the more functions that are likely to be lost. Some forms of stroke can cause additional symptoms. For example, in intracranial hemorrhage, the affected area may compress other structures. Most forms of stroke are not associated with a headache, apart from subarachnoid hemorrhage and cerebral venous thrombosis and occasionally intracerebral hemorrhage.

Various systems have been proposed to increase recognition of stroke. Different findings are able to predict the presence or absence of stroke to different degrees. Sudden-onset face weakness, arm drift (i.e., if a person, when asked to raise both arms, involuntarily lets one arm drift downward) and abnormal speech are the findings most likely to lead to the correct identification of a case of stroke, increasing the likelihood by 5.5 when at least one of these is present. Similarly, when all three of these are absent, the likelihood of stroke is decreased (– likelihood ratio of 0.39) [8]. While these findings are not perfect for diagnosing stroke, the fact that they can be evaluated relatively rapidly and easily make them very valuable in the acute setting.

Ischemic stroke occurs because of a loss of blood supply to part of the brain, initiating the ischemic cascade [9]. Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 seconds [citation needed], and after approximately three hours will suffer irreversible injury possibly leading to the death of the tissue, i.e., infarction. (This is why fibrinolytics such as alteplase are given only until three hours since the onset of the stroke.) Atherosclerosis may disrupt the blood supply by narrowing the lumen of blood vessels leading to a reduction of blood flow, by causing the formation of blood clots within the vessel, or by releasing showers of small emboli through the disintegration of atherosclerotic plaques [10]. Embolic infarction occurs when emboli formed elsewhere in the circulatory system, typically in the heart as a consequence of atrial fibrillation, or in the carotid arteries, break off, enter the cerebral circulation, then lodge in and block brain blood vessels. Since blood vessels in the brain are now blocked, the brain becomes low in energy, and thus it resorts to using anaerobic metabolism within the region of brain tissue affected by ischemia. Anaerobic metabolism produces less adenosine triphosphate (ATP) but releases a by-product called lactic acid. Lactic acid is an irritant which could potentially destroy cells since it is an acid and disrupts the normal acid-base balance in the brain. The ischemia area is referred to as the "ischemic penumbra" [11].

As oxygen or glucose becomes depleted in ischemic brain tissue, the production of high energy phosphate compounds such as adenosine triphosphate (ATP) fails, leading to failure of energy-dependent processes (such as ion pumping) necessary for tissue cell survival. This sets off a series of interrelated events that result in cellular injury and death. A major cause of neuronal injury is the release of the excitatory neurotransmitter glutamate. The concentration of glutamate outside the cells of the nervous system is normally kept low by so-called uptake carriers, which are powered by the concentration gradients of ions (mainly Na+) across the cell membrane. However, stroke cuts off the supply of oxygen and glucose which powers the ion pumps maintaining these gradients. As a result, the transmembrane ion gradients run down, and glutamate transporters reverse their direction, releasing glutamate into the extracellular space. Glutamate acts on receptors in nerve cells (especially NMDA receptors), producing an influx of calcium which activates enzymes that digest the cells' proteins, lipids, and nuclear material. Calcium influx can also lead to the failure of mitochondria, which can lead further toward energy depletion and may trigger cell death due to programmed cell

death [12].
Ischemia also induces production of oxygen free radicals and other reactive oxygen species. These react with and damage a number of cellular and extracellular elements. Damage to the blood vessel lining or endothelium is particularly important. In fact, many antioxidant neuroprotectants such as uric acid and NXY-059 work at the level of the endothelium and not in the brain per se. Free radicals also directly initiate elements of the programmed cell death cascade by means of redox signalling [13].
These processes are the same for any type of ischemic tissue and are referred to collectively as the ischemic cascade. However, brain tissue is especially vulnerable to ischemia since it has little respiratory reserve and is completely dependent on aerobic metabolism, unlike most other organs.
In addition to damaging effects on brain cells, ischemia and infarction can result in loss of structural integrity of brain tissue and blood vessels, partly through the release of matrix metalloproteases, which are zinc- and calcium-dependent enzymes that break down collagen, hyaluronic acid, and other elements of connective tissue. Other proteases also contribute to this process. The loss of vascular structural integrity results in a breakdown of the protective blood brain barrier that contributes to cerebral edema, which can cause secondary progression of the brain injury.
Hemorrhagic strokes are classified based on their underlying pathology. Some causes of hemorrhagic stroke are hypertensive hemorrhage, ruptured aneurysm, ruptured AV fistula, transformation of prior ischemic infarction, and drug-induced bleeding [14]. They result in tissue injury by causing compression of tissue from an expanding hematoma or hematomas. In addition, the pressure may lead to a loss of blood supply to affected tissue with resulting infarction, and the blood released by brain hemorrhage appears to have direct toxic effects on brain tissue and vasculature. Inflammation contributes to the secondary brain injury after hemorrhage [15].
Co-morbid risk factors associated with stroke are predictors of poor outcomes in stroke patients. Various risk factors including hypertension, cardiac diseases, diabetes mellitus (DM), smoking, alcohol consumption, stress, and depression could account for 90% of stroke risk as suggested by an international multicenter study. DM is regarded as an independent risk factor for ischemic stroke, with an estimated prevalence of 21%-44.4% among patients who experience acute ischemic stroke [16]. Several studies have suggested poor functional outcomes for stroke patients with increased blood glucose levels [17]. Recent studies have found poor outcomes in prediabetic and denovo diabetes patients in acute ischemic stroke. [18].
Hence based on above findings the present study was planned for Study of Levels of the Glycated Hemoglobin (HbA1C) in Patients Suffered from acute ischemic stroke.

Methodology

The present study was planned in Department of General Medicine, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India.
In the present study 200 cases suffered from the strokes were enrolled. The CT scan was performed in all the cases within 3 days of onset of symptoms to confirm the diagnosis and to ascertain the type of stroke (ischaemic/haemorrhagic) and size of stroke (small, medium, or large).
All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.
Following was the inclusion and exclusion criteria for the present study.
Inclusion Criteria: All male and female cases of acute ischemic stroke. Patients of age more than 18 yrs.
Exclusion Criteria: Patients of age less than 18yrs, haemorrhagic stroke, cardiac disease.

Results & Discussion

Stroke remains the major cause of morbidity and mortality along with being the major cause of adult disability [19]. Stroke is defined as "Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin [20]. Despite the advancements in the diagnosis and pharmacotherapy, stroke remains one of the major neurological diseases often causing gross disability and death [21]. According to WHO, stroke is considered as second leading cause of death above the age of 60 y and fifth leading cause of death between the age group of 15 to 59 y old, it is estimated that 15 million people suffer from stroke annually worldwide, among which 5.5 million die and 5 million are left permanently disabled. [22]. The relative number of stroke deaths fell from 35.1% to 21. %, yet approximately 7,95,000 experience new or recurrent stroke, in 2011 stroke caused 1 of every 20 deaths in USA [23]. Developing countries like India are facing a huge burden of cardiovascular diseases, among which stroke remains one of a leading cause of disability and death. It is estimated that the adjusted prevalence rate of stroke is about 84-262/100,000 in rural and about 334-424/100,000 in urban areas of India. The incidence rate according to recent population-based studies is about 119- 145/100,000 [24]. Estimates indicated by Indian Council of Medical Research–ICMR states that among non-communicable diseases (NCD's), stroke contributes to about 41% deaths and 72% of Disability Adjusted Life Years (DALY) [25].

Table 1: ADA-2019: Criteria for screening and diagnosis of diabetes-

Diabetes			
	Normal	Pre-diabetes	Diabetes
HbA1C	<5.7	5.7-6.4	≥6.5
Symbol used	e	f	g

Among 200 patients of AIS, 66 (33%) patients presented within diabetic range (HbA1c ≥6.5%), 24 (12%) in prediabetic range (HbA1c 5.7-6.4 %) and 110 (55%) were in non-diabetic range (HbA1c <6.4) of HbA1c. History of diabetes were present in 36% patients of the total patients.

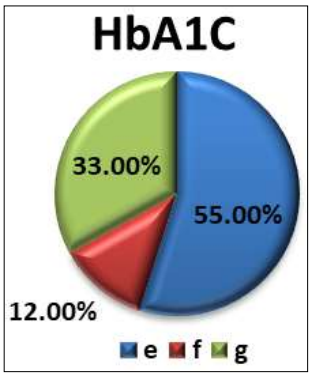

Fig 1

Hjalmarsson *et al*. study suggests that poor glycemic control (baseline HbA1c) prior to ischemic stroke is an independent risk factor for poor survival and a marker for increased stroke severity and unfavourable long-term functional outcome [26]. Johnston *et al*. noted that infarct volume significantly predicted NIHSS score on admission [27]. Kamouchi *et al*. who studied 3627 patients, the result showed that neurological improvement is lower relevant to age and sex and is higher relevant to the blood HbA1C levels on admission [28]. Toumilehto j *et al*. study proved that Diabetes mellitus was the strongest risk factor for death from stroke among both men and women.Men with diabetes at baseline appeared to be at a six fold increased risk of death from stroke [29].

The exact mechanism how elevated glucose levels worsens the outcomes in stroke patients in not clearly understood. The proposed mechanisms explaining hypothesis of an impact of hyperglycemia on stroke includes increased acidosis at brain injury site [30], increased oxidative stress causing further damage at brain injury site [20], impaired thrombolysis, disturbing recanalisation and causing reperfusion injury [31].

A recent study, including 120 T2DM patients reported a mean HbA1c significantly higher in diabetic patients with silent myocardial ischemia. Glycemic disorder can be estimated as a whole from the determination of HbA1c level, which integrates both basal and postprandial hyperglycaemia. The measurement of HbA1c is well standardized, and the biologic variability is less and does not require fasting. In addition, it is relatively unaffected by acute changes in glucose levels [32].

Hyperglycemia is common in patients with acute stroke, occurring in upto 60% of patients and is believed to aggravate cerebral ischaemia [33]. It leads to intracellular acidosis, accumulation of extra cellular Glutamate, cerebral oedema, blood-brain barrier disruption, and tendency for haemorrhagic transformation. It is observed that between 20 - 40% of patients admitted with ischaemic stroke are hyperglycemic, often without a pre-existing diagnosis of diabetes, which can be due to stress hyperglycemia or undiagnosed diabetes exposed during an acute incident [34].

Diabetes remained an independent risk factor even after adjusting for age, hypertension, smoking and left ventricular hypertrophy [35]. In a meta-analysis of 13 prospective cohort studies, for every one-percentage point increase in glycosylated haemoglobin (HbA1c), the relative risk for any cardiovascular event was 1.18 [36]. Interventional studies have established that cardiovascular complications are mainly or partly dependent on sustained chronic hyperglycaemia and diabetic dyslipidemia.

Diabetes is considered a highly ‘vascular disease’ with both micro vascular and macro vascular complications. Macro vascular complications start taking place long before the patient has overt diabetes. Hyperglycemia is an independent risk factor for cardiovascular disease. Hyperglycemia accelerates the process of atherosclerosis by the formation of glycated proteins and advanced glycation end products, which act by increasing the endothelial dysfunction. HbA1c could be considered a good marker of glycated proteins and its assay has been used as a measure of glycemic control in several landmark trials. The Framingham study has shown that the cardiovascular mortality is twice in Diabetic men and four times in Diabetic women when compared to their Non-Diabetic counterparts. HbA1c levels of more than 7% are associated with a significant increase in the risk of cardiac events and deaths. Interestingly, this correlation between higher HbA1c levels and increased cardiovascular morbidity occurs even before the diagnosis of clinical diabetes.

Stroke is the second leading causes of death worldwide and one of the leading causes of disability. The most common cause of stroke is represented by cerebral ischemia and approximately 80% of strokes are due to ischemic cerebral infarction and 20% due to brain haemorrhage. Cerebrovascular disorders are increasing in prevalence and incidence in India due to rapid escalation of risk factors including Hypertension, Diabetes Mellitus, Smoking and obesity affecting considerable proportion of adult population. The combination stroke and Diabetes Mellitus is associated with worse stroke related outcome, high disability and stroke recurrence. Approximately 20% of patients with Diabetes die from stroke.

There are many patients in our society who are suffering from diabetes mellitus but are undiagnosed. Many of them are diagnosed to have diabetes at the time of acute cardiac emergency. Earlier diagnosis and treatment of diabetes mellitus could have prevented these emergencies. Hence regular screening for diabetes mellitus should be carried out in the general population especially in people above the age of forty having family history of diabetes mellitus. Patients with diabetes mellitus having higher glycosylated hemoglobin levels have higher incidence of acute coronary syndromes and have worse outcomes. Tight control of diabetes mellitus helps in prevention of the acute cardiac complications in diabetic patients.

Conclusion

The data generated from the present study concludes that Hyperglycaemia in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. Management of hyperglycaemia in patients with diabetes and non-diabetes is an important aspect of the emergency management of stroke. Further studies with a larger sample and long-term outcomes measurements would be desirous to establish a definite relation of in hospital admission hyperglycemia and stroke short- and long-term outcomes.

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