

Glycemia in spontaneous intracerebral hemorrhage: clinical implications

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Abstract

Spontaneous cerebral hemorrhage or intracranial hemorrhage accounts for 10-15% of all strokes. Intracranial hemorrhage is much less common than ischemic stroke, but has higher mortality and morbidity, one of the leading causes of severe disability. Various alterations, among these the endocrine were identified when an intracerebral hemorrhage, these stress-mediated mechanisms exacerbate secondary injury. Deep knowledge of the injuries which are directly involved alterations of glucose, offers insight as cytotoxicity, neuronal death and metabolic dysregulations alter the prognosis of patients with spontaneous intracerebral hemorrhage.

Key words: intracranial hemorrhage, Glycemia, stroke, neurosurgery

Introduction

Spontaneous intracerebral hemorrhage (sICH) is a devastating and disabling disease (1, 2). Is the second most common form of stroke, representing 10-30% of first-ever strokes (3). Overall incidence sICH worldwide

is 24.6 per 100,000 person-years with approximately 40,000 to 67,000 cases per year in the United States (4-7), approximately half of this mortality occurs within the first 24 hours, highlighting the critical importance of early and effective treatment in EDs (8).

Deleterious effect of metabolic derangements like hyperglycemia has been studied since Claude Bernard described the relationship between hyperglycemia and cerebral injury (9). The occurrence of hyperglycemia is a known phenomenon in various types of acute cerebral injury. When measured at arrival to ED, hyperglycemia is associated with worse outcome in both diabetic and nondiabetic patients (10-13).

A high proportion of patients (about 60%) might develop hyperglycemia even in the absence of a previous history of diabetes after sICH (14). Increased blood glucose in the acute setting of sICH is probably a response to stress and severity of sICH (15) and can persist for up to 72 h after sICH (14). Declining glucose values after sICH are associated with a decreased risk of hematoma expansion and poor outcome, suggesting that early glucose

control may improve outcomes (16). Many studies have shown that increased serum glucose on admission is associated with larger haematoma size, expansion, perihematomal oedema, cell death, intraventricular extension (17), and increased risk of poor outcome (10, 11, 14, 18, 19), furthermore is a potent predictor of 30 day mortality in both diabetic and non-diabetic patients with sICH as well as an independent predictor of early mortality and worse functional outcome in non-diabetic patients with sICH (11, 19, 20).

Glucose and brain physiology (21-48)

The brain is an expensive energy organ. Brain function requires the 15% of the cardiac output, consumes 20% of the oxygen and the 25% of the total organism glucose; has a high tolerance to the temporal fuel deficit, because it only consumes approximately 33% of the available oxygen and a 10% of the total glucose. The cerebral blood flow (CBF) is the supply of energetic sources, in a mean of 50mL/100g/min, with a brain oxygen consumption of 50cm³/min, and a similar carbon dioxide production, with a respiratory quotient near to 1, indicating that carbohydrates are the main substrates for the brain oxidative metabolism (49).

All the different cells types in the central nervous system (i.e., neurons, glia and vascular cells) show a different metabolic glucose consumption rate. Virtually, the only metabolic fuel of the brain is glucose; under aerobic conditions this molecule undergoes glycolysis to adenosine triphosphate (ATP) and pyruvate. Pyruvate is converted to acetyl-CoA via the Krebs' cycle to generate ATP and reducing equivalents, this is the aerobic way,

renders 30 moles of ATP; exists another way to convert glucose to ATP, the anaerobic way, but it is inefficient, just renders 2 moles of ATP through production of lactic acid.

Glucose enters to the brain through GLUT family of hexose transporters; astrocytes express GLUT1, GLUT2, and GLUT4, neurons express GLUT3, GLUT4, and GLUT8 (50). If neurons, preferentially access to glucose directly from the brain interstitial fluid or if the metabolism of glucose to lactate by astrocytes is a required step, is still in debate (51, 52).

Brain needs glucose, but also controls the glucose levels when integrating information from peripheral receptors (53). Has been established that brain insulin plays a crucial role in the regulation of the metabolism, enhancing glucose uptake by astrocytes (54). Studies using SPECT technology have suggested that glucose transport and metabolism in human brain are dependent of blood supply. Has been demonstrated insulin-mediated increases in mean global rate of brain glucose utilization, suggesting that insulin may play some role in the regulation of cerebral glucose, especially in the cortex (55).

Alterations of the insulin actions in the brain are involved in metabolic diseases. The mechanisms by which glucose sensitive neurons detect changes in glycemia and alter their firing pattern are still being investigated. In the glucose sensing process participate the same proteins that control glucose signaling in pancreatic beta-cells (56), i.e., the GLUT2, the enzyme glucokinase and the ATP sensitive potassium channel. In the response to

hypoglycemia participate the AMP-activated protein kinase (57).

When an injury impaired the oxidative phosphorylation, either lower arterial oxygen tension, mitochondrial dysfunction or brain lesions, the glycolysis is deviated to the anaerobic way, producing lactic acid and hydrogen ions, generating tissue acidosis and reactive species of oxygen, respectively. When this takes place, trigger deleterious effects in the neuronal cells, product of the activation of calcium entry to the cells, the release of cytotoxic free fatty acids and excitotoxic neurotransmitters like glutamate. Although the intermediate metabolites of glucose breakdown, pyruvate and lactate, in some circumstances can sustain the energy demand of the neuronal activity, both lack the ability to cross the blood-brain barrier. In pathological states, also are used as metabolic substrates the ketonic bodies.

Brain glycogen is primarily located in the astrocytes (58). And its stores finishes in about 5 minutes, when needed. In an animal model of type 2 diabetes mellitus, glycogen metabolism has been demonstrated to be important for supporting glutamatergic and GABAergic homeostasis, maintaining a proper ratio between excitatory and inhibitory neurotransmitters (59). Different animal and human studies evidence a significantly compromised altered glucose metabolism in the setting of traumatic brain injury, cerebral ischemia and hemorrhages. Due to the mitochondrial membrane dysfunction during hypoxic and hyperglycemic insults, the cells in the perihemorrhagic area are unable to metabolise the excess of glucose, this happens

specifically in intracerebral hemorrhage, and are the main phenomena to comprehend why hypo/hyperglycemia are so deleterious in the setting of an acute brain lesion.

Hyperglycemia and the sICH

The hyperglycemic state results from metabolic derangements in the glucose metabolism (60). In the acute phase of sICH develops an unspecific, programmed and adaptive response to the stress that induce activation of the hypothalamic-hypophysis-adrenal axis and the subsequent releasing of hyperglycemic hormones (61-64), activation of the autonomous nervous system and changes in the behavior, everything as a part of the well described metabolic-hormonal response to stress and to the systemic inflammatory response syndrome (SIRS).

In the context of a lesion, irrespective of the nature, the mechanism that drives to a stress hyperglycemia are the increased gluconeogenesis and insulin resistance, the later, may be result from impaired insulin receptor binding and signal transduction, increased hepatic glucose production, and decreased peripheral glucose uptake (65).

The big final effect, a stress-induced hyperglycemic state, constitutes an aggravating factor of the lesion. Also has been demonstrated an independent relationship between the kind and the severity of the neurologic injury (66, 67). The surgical procedures also contribute to activate a neuroendocrine response that predispose the patient to develop hyperglycemia and ketoacidosis because its antagonizing action on the insulin activity (60, 63). Other well documented effects of stress-induced

hyperglycemia are the endothelial cell dysfunction, increased oxidative stress, cardiovascular effects and lesion in other specific brain areas (68-70).

When the hyperglycemic state is established, it plays a range of deleterious mechanisms on the injured brain, through the increase of oxidative stress, inflammatory cytokines, induction of excitotoxicity [e.g., stimulation of the N-methyl-D-aspartate (NMDA) receptor] potentiating the calcium entry to the cells, alters the brain metabolism and therefore the perfusion (71-73). Due to the above, glucose neurotoxicity

The excessive glucose concentration in the lesions microenvironment induces lipid peroxidation, protein carbonilation, and DNA damage. As the superoxide is being neutralizing the nitric oxide, the vasodilation is impaired (74, 75). As result of the productions of reactive species of oxygen (RSO), then is activated an inflammatory response that leads to immune cells attraction, and then increasing the production of EROs. Lactic acid is also concentrated, so is an easy way to turn acidotic the neuron cells, this acidosis alters mitochondrial function (76, 77).

In rat models of intracerebral hemorrhage (78-80) have been demonstrated the mentioned physiopathological events, and higher size of hemorrhage in the hyperglycemic rat groups. In a recent experiment was observed that in response to the intracerebral hemorrhage lesion, significant increase of albumin was ubiquitously observed in the brains of normoglycemic rats but not in the brains of hyperglycemic rats. In the last group, more

significant neuronal apoptosis were found in the perihematomal regions of hyperglycemic rats, suggesting a protection role of albumin in acute stage of intracerebral hemorrhage, which may be dependent on different blood sugar levels (81).

Hypoglycemia and the sCHI

Defined as glucose plasma level <50mg/dL (<2.8mmol/L) with/without symptoms (49). Currently, there is a paucity of data on cerebral glucose metabolism in human subjects with spontaneous intracerebral hemorrhage, but have been demonstrated that hypoglycemia, the other side of the coin, also worsens the outcome of patients with critical illness. In the acute injured brain, hypoglycemia could be particularly harmful.

The “neurological injury glucose threshold” varies with some patient’s factors, i.e., history of diabetes mellitus, the speed of the glucose level drop, the duration of the hypoglycemia event and the cerebral blood flow, etc. In patients with poor-grade subarachnoid hemorrhage the acute reductions in serum glucose, even to levels within the normal range, could generate brain energy metabolic crisis and lactate/pyruvate ratio elevation (82). When the brain’s metabolism autoregulation is altered, there are parts of them specially more susceptible than others (83-86), when could be thoughtful glucose level as “sufficient” in a patient with acute brain lesion this might be insufficient and even deleterious. The brain’s compensation systems (release of counter-regulatory hormones, increase the cerebral blood flow, use of the glycogen storages) to the hypoglycemia are limited (87-89). The big problem with a

hypoglycemia state is that is associated with aberrant depolarization in the perilesional tissue that drives to a perpetuating glucose depletion, as has been demonstrated in traumatic brain injury (32, 90)

Mortality and other Outcomes

As stated in other items of this review, the hyperglycemia measured in peripheral blood is both a marker of injury severity and of poor outcome, a relationship that has captured the attention of clinicians over the past few years. Studies evaluating the association of glycemia derangements and sICH are scarce (10, 14), in comparison with other types of stroke, where later researches utilize multimodal neuromonitoring with intracerebral microdialysis catheters, brain oxygen monitors and measurements of both, peripheral and cerebral blood glucose.

Kimura and colleagues with a prospective observational study design and 100 patients with acute supratentorial Intracerebral hemorrhage, assessing clinical characteristics and plasma glucose. ICH volume was measured on admission CT (b24 h) and follow-up CT (b48 h) scans. Patients were divided into two groups: the death group, who died within 14 days of onset, and the survival group. Using receiver operating characteristic (ROC) curve, founded that cut-off values that predicted early death were 150 mg/dl for the glucose level and N20 ml for the initial IVH volume, they conclude that admission hyperglycemia may independently increase the risk of early death in acute spontaneous intracerebral hemorrhage (10).

Godoy and colleagues in a prospective study with 250 patients with a well-defined diagnosis

of sICH admitted into 24 h in three primary referred centers. Patients had extensive monitoring of BG values and those with BG values >8.29 mmol/l (150 mg/dl) received a variable intravenous insulin dose to maintain BG concentrations during the first 72 h after sICH between 3.32 and 8.29 mmol/l (60–150 mg/dl) using pre-specified insulin dosing schedule protocol, and using a cutoff value of >164mg/dL, they conclude that hyperglycemia is a common condition after sICH that could worsen prognosis and the very early insulin therapy does not improve prognosis, also show an increased risk of poor outcomes and death.

Stress hyperglycaemia is a common finding in patients presenting with intracerebral haemorrhage. It is a marker of poor outcomes and higher mortality, more so in patients with no known history of diabetes (91). Over the years ICH has been reported to have a mortality rate between 35–52% and poor functional outcome of survivors, with only 10–20% living independently at 30 days (92-96) Literature has reported Glasgow Coma Scale (GCS) on arrival, blood pressure on presentation, volume of hemorrhage, concomitant intraventricular hemorrhage, previous ischemic stroke, and National Institutes of Health Stroke Scale (NIHSS) score as predictors of early mortality in patients with ICH (11).

For evaluating glycaemia derangements in unspecific medical conditions but in critically ill patients a study look for evaluate the compared risk adjusted mortality when those patients were admitted to a surgical intensive care over 4 years. Patients were divided into glyceimic groups: HYPER (≥ 1 episode > 180

mg/dL, any <60), HYPO (≥ 1 episode < 60 mg/dL, any >180), BOTH (≥ 1 episode < 60 and ≥ 1 episode > 180 mg/dL), NORMO (all episodes 60-180 mg/dL), HYPER-Only (≥ 1 episode > 180, none <60 mg/dL), and HYPO-Only (≥ 1 episode < 60, none >180 mg/dL). The mortality ratios (O/E) were studied using the expected Acute Physiology and Chronic Health Evaluation (APACHE) III. Number of adverse glycemic events was compared with mortality. Hypoglycemia and hyperglycemia occurred in 18 per cent and 50 per cent of patients. Mortality was 12.4 per cent (O/E = 0.88). BOTH had the highest O/E ratio (1.43) with HYPO the second highest (1.30). Groups excluding hypoglycemia (NORMO and HYPER-only) had the lowest O/E ratios: 0.56 and 0.88. Increasing number of hypoglycemic events were associated with increasing O/E ratio: 0.69 O/E for no events, 1.19 for 1-3 events, 1.35 for 4-6 events, 1.9 for 7-9 events, and 3.13 for ≥ 10 events. As result was observed that, ten or more hyperglycemic events were needed to significantly associate with worse mortality (O/E 1.53); and hyper/hypoglycemia increase mortality compared with APACHE III expected mortality, with highest mortality risk if both are present. In this study hypoglycemia was associated with worse risk, so the authors recommend that glucose control may need to be loosened to prevent hypoglycemia and reduce glucose variability (97).

In a study evaluating the prognosis and outcome of acute stroke in an University hospital in Nigeria, founded that age above 39 years, male gender, systemic hypertension, early onset of coma after stroke, and presence

of co-morbidities were associated with poor stroke outcome, the 78.8% of all stroke subtypes corresponded to intracerebral hemorrhage (98).

The effects of parameters as elevation of white blood cell count (WBC), C-reactive protein (CRP), and blood glucose (BG) concentration at presentation prognosticate poor outcome in sICH patients were investigated for Di Napoli and colleagues conclude that higher WBC, CRP, and BG are associated with increased mortality in sICH patients, and also founded that only CRP elevation portends higher risk of death independently of other indicators of sICH severity (99).

In the Acute Brain Bleeding Analysis Study, a Korean study for evaluate the effects of glucose level on early and long-term mortality after intracerebral haemorrhage was observed a long-term mortality rate of 21.1% after a mean follow-up of 434.3 +/- 223.2 days and was found to increase significantly with glucose quartile ($p < 0.001$). The admission glucose level was an independent risk factor for early mortality (adjusted HR 1.10 [95% CI 1.01-1.19]), but not for long-term mortality. Moreover, when analysis was restricted to patients without diabetes, glucose level was found to be an independent risk factor for post-ICH mortality ($n = 1,119$; adjusted HR 1.10 [95% CI 1.03-1.17]) and had marginal significance for early ($p = 0.053$) and long-term mortality ($p = 0.09$). From the above is conclusive that admission glucose levels are associated with early mortality after intracerebral hemorrhage. In patients without diabetes, admission glucose levels were

associated with long-term mortality (19).

Kimura and colleagues have founded an association between hyperglycemia at admission to EDs and an increased risk of early death (10). Other worry about the assessment of mortality in sICH is that in comparison with other cerebrovascular diseases, there are no grading prognostic scales routinely used in sICH around the world.

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