The Glucose Paradox of Cerebral Ischaemia

The issue of hyperglycaemia in patients with acute stress continues to generate a lot of debate. Up to 50% of patients with stroke are reported to have hyperglycaemia at admission to the hospital and up to 25% of those admitted to the hospital with stroke may report history of diabetes mellitus.\textsuperscript{1,2} This increased incidence of hyperglycaemia in patients with stroke could partly be explained on the basis of increased prevalence of diabetes mellitus in the society. It is also well known that blood glucose levels are increased in the first 12 hours after the onset of acute stroke (as in any other stressful situation including myocardial infarction). This magnitude of the rise in blood glucose level is supposedly related to the severity of the stroke.\textsuperscript{3} This could be another reason for hyperglycaemia noticed in patients with stroke. Although there is no unanimity amongst researchers, several studies, both animal and human, report that hyperglycaemia occurring at the onset of stroke is associated with a worse prognosis, irrespective of patient’s age, severity of the condition, or stroke sub-type.\textsuperscript{1} It exacerbates the ischaemic lesions and is associated with an increase in the brain oedema and augmentation in the size of the infarct. It is also associated with a decrease in cerebral blood flow.\textsuperscript{1} Positive association has been shown between the blood glucose level at admission and stroke volume with higher glucose levels associated with larger stroke volumes. Patients with transient hyperglycaemia have been reported to have larger ischaemic lesions on computerized tomographic scans and a higher 30-day mortality than that in normoglycaemic individuals. The worse outcome manifests itself in terms of longer hospital stay, higher inpatient hospital charges and increased short-term and long-term mortality.\textsuperscript{1,5}

Researchers have invoked several mechanisms to explain the phenomenon of worsening of prognosis with hyperglycaemia. They point out that hyperglycaemia whether resulting form acute stress, poor glycaemic control in diabetic patients or both, worsens the prognosis through augmentation of acute brain injury and precipitation of intra-cerebral haemorrhage (ICH). Possible mechanisms responsible for augmenting acute ischaemic brain injury include increased brain tissue acidosis, accumulation of extra-cellular glutamate, increased blood–brain barrier permeability, cerebral oedema formation, decreased vascular reactivity or a combination of these. Hyperglycaemia-related increase in the size of infarction in animal studies has been blamed on impairment of mitochondrial function and facilitation of acidosis. Hyperglycaemia with reperfusion may augment ischaemic tissue acidosis, but it may not be detrimental in the absence of reperfusion.\textsuperscript{6} Residual blood flow to the ischaemic area is a requisite for glucose-mediated injury. The association between hyperglycaemia and poorer outcome is more consistently seen in the non-lacunar strokes. Glucose levels do not affect outcomes after lacunar infarcts as they involve end arteries. Hyperglycaemia also appears to increase the risk of symptomatic ICH. Hyperglycaemia during acute brain ischaemia increases the rate and extent of haemorrhage into the infarct; this may be related to increased blood–brain barrier permeability, though some trials have not shown such an association. Both diabetes and admission hyperglycaemia in non-diabetic patients are predictors of poor outcome after supra-tentorial ICH.\textsuperscript{7} Hyperglycaemia reportedly results in more profound brain oedema and peri-haematomal cell death in experimental animals.

Although an association between hyperglycaemia and poorer stroke outcome has been noted, it is not clear if this represents a causal relationship. It has been argued that acute hyperglycaemia could simply reflect a more severe stroke. In reversible ischaemia models, hyperglycaemia is associated with lactic acidosis and conversion of penumbral tissue to infarction. However, in humans, the relationship of hyperglycaemia and lactic acidosis with stroke outcome has not been proven. In one study\textsuperscript{8} involving serial diffusion-weighted and perfusion-weighted magnetic resonance imaging, in two-thirds of patients with acute perfusion-diffusion mismatch, acute hyperglycaemia was correlated with reduced salvage of mismatch tissue from infarction, greater final infarct size, and worse functional outcome. These correlations were independent of baseline stroke severity, lesion size, and diabetic status. Furthermore, higher acute blood glucose levels in patients with perfusion-diffusion mismatch were associated with greater acute-subacute lactate production and conversion of hypoperfused at-risk tissue into infarction, which may adversely affect stroke outcome.

The exact manner and mechanisms that lead to worsening of prognosis remain to be elucidated. Different researchers and investigators have blamed lactic acid production, heightened release of glucocorticoids, the beta-amyloid precursor proteins and the increased superoxide and nitric oxide production for hyperglycaemia-induced worsening. It is believed that increased lactic acid production is the detrimental factor responsible for aggravation of delayed neuronal damage by peri-ischaeic hyperglycaemia. However, there are constraints that limit our understanding. First, the glucose paradox of cerebral
ischaemia, namely, the aggravation of delayed neuronal damage by pre-ischaemic hyperglycaemia, cannot be reproduced in vitro. Second, in vitro elevated glucose levels protect against ischaemic (hypoxic) damage, an outcome that has seldom been reproduced in vivo. Recent studies, both in vitro and in vivo, have demonstrated that lactate is an excellent aerobic energy substrate in the brain, and aerobic lactate utilization is crucial for neuronal recovery in the immediate post-ischaemic period. An alternative explanation tends to incriminate glucocorticoids for the aggravating effect of pre-ischaemic hyperglycaemia. This hypothesis states that hyperglycaemia (or glucose loading) results in a transient elevation in the release of glucocorticoids, which is responsible for worse outcome. This notion derives support from an animal study in which blockade of corticosterone (CT) elevation with metyrapone (CT synthesis inhibitor) or the blockade of CT receptors in the brain with mifepristone negated the aggravating effect of pre-ischaemic hyperglycaemia on the post-ischaemic outcome. Thus, although elevated levels of brain lactate cannot explain the glucose paradox of cerebral ischaemia, hyperglycaemia-induced, short-lived elevation in CT blood levels could.9

Some experiments have shown that ischaemia under hyperglycaemic conditions leads to early intra-neuronal expression of beta-Amyloid Precursor Protein (beta-APP) within neuronal populations showing a heightened susceptibility to hyperglycaemia-induced accentuation of ischaemic injury. This observation has led many to believe that beta-APP or its metabolites might be involved in the injury process.10 Hyperglycaemia also results in an early and concomitant increase in both superoxide and nitric oxide production, which can lead to peroxynitrite formation that then nitrates tyrosine residues.11

It is debatable whether the effect of hyperglycaemia during acute stroke is independent of long-term glycaemic control. Studies have reported that the increased mortality seen in hyperglycemic stroke patients is not an effect of poor long-term glycaemic control and that hyperglycaemia was an independent predictor of poor clinical outcomes.12

Looking at the relationship between hyperglycaemia and prognosis following acute myocardial infarction (AMI) could be rewarding. Acute hyperglycaemia is a common feature and a predictor of mortality during the early hours after the onset of acute myocardial infarction. Prodromal angina occurring shortly before the onset of AMI has a cardio-protective effect in patients with AMI by the mechanism of ischaemic pre-conditioning. It has been shown that mitochondrial potassium adenosine triphosphate (K\textsubscript{ATP}) channels play an important role for the promotion of ischemic preconditioning and that acute hyperglycaemia in the presence or absence of diabetes mellitus impairs activation of mitochondrial K\textsubscript{ATP} channels and abolishes the cardio-protective effect of pre-conditioning.13 Since AMI and ischaemic stroke are both ischaemic events, similar mechanisms influencing the outcome are likely to operate.

It is worth remembering that better glycaemic control with insulin during the acute phase reduces morbidity and mortality from and improves clinical outcomes following myocardial infarction and post-surgical states in critically ill patients. Recent experimental studies have reported that insulin restores ischaemic pre-conditioning during prodromal angina. Insulin acts as a neuro-protective agent by decreasing blood glucose levels and through direct interaction with ischaemic tissue. In animals, treatment with insulin has been shown to reduce infarct size.14 Because acute treatment of hyperglycaemia is available in most acute care settings, hyperglycaemia is an attractive target for acute stroke therapy. It should, however be conceded that the clinical benefits of lowering plasma glucose levels in patients with acute stroke remain unknown. It is also not clear whether the beneficial effects are due to glycaemic control or direct actions of insulin. The time window of opportunity for hyperglycaemia control to minimize brain damage during acute stroke remains undetermined. Lowering hyperglycaemia during acute stroke as close to normal as possible while avoiding hypoglycaemia might be an optimal approach.

There are many limitations in the understanding the glucose paradox of cerebral ischaemia and the therapeutic implications of this phenomenon. There have been no prospective studies assessing the effects of treating hyperglycaemia on stroke outcome in humans. The effects of diabetes mellitus and admission-hyperglycemia on clinical course after intracerebral haemorrhage are largely unknown. There is also a need to determine the efficacy of rapid normalization of hyperglycaemia in acute ischaemic stroke. Magnesium and insulin together have been shown to be effective in experimental brain ischemia15 and human trials in this field need to be undertaken. Animal experiments showing the role of endogenous corticosteroids in aggravating the effect of perischemic hyperglycaemia on post-ischaemic outcome and role of corticosteroids inhibitors in neuroprotection have not been reproduced in humans. This could have important therapeutic implications as steroids tend to be used as cerebral decongestants in acute stroke syndromes. The wide range of ideas and lacunae in our knowledge should spur further research directed at resolving issues related to mechanisms of hyperglycaemia-related aggravation of neuronal injury and management of hyperglycaemic state in patients with stroke.
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References

Announcement
Golden Jubilee of Journal of Postgraduate Medicine

In the year 2004, the Journal of Postgraduate Medicine is entering into the 50th year of its existence and growth. During the Golden Jubilee of the journal a variety of programs and functions will be organised. This would include a program on medical writing editing and electronic publishing. This international conference will be organised in collaboration with the World Association of Medical Editors (WAME) and International Network for the Availability of Scientific Publications (INASP) between 23rd and 26th September 2004. For more details, check our forthcoming announcements. Details will also be available from our website www.jpgmonline.com.