Glycemic control in acute stroke: ‘balancing the risks’

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Chapter 2

HYPERGLYCEMIA IN ACUTE ISCHEMIC STROKE: PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT

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ABSTRACT

Patients with acute ischemic stroke frequently test positive for hyperglycemia, which is associated with a poor clinical outcome. This association between poor glycemic control and an unfavorable prognosis is particularly evident in patients with persistent hyperglycemia, patients without a known history of diabetes mellitus, and patients with cortical infarction. To date, however, only one large clinical trial has specifically investigated the effect of glycemic control on stroke outcome. This trial failed to show a clinical benefit, but had several limitations. Despite a lack of clinical evidence supporting the use of glycemic control in the treatment of patients with stroke, international guidelines recommend treating this subset of critically ill patients for hyperglycemia in the hospital setting. This treatment regime is, however, particularly challenging in patients with stroke, and is associated with an increased risk of the patient developing hypoglycemia. Here we review the available evidence linking hyperglycemia to a poor clinical outcome in patients with ischemic stroke. We highlight the pathophysiological mechanisms that might underlie the deleterious effects of hyperglycemia on acute stroke prognosis and systematically review the literature concerning tight glycemic control after stroke. Finally, we provide directions on the use of insulin treatment strategies to control hyperglycemia in this patient group.
INTRODUCTION

Many studies have shown that elevated levels of blood glucose are frequently observed in patients admitted to hospital for acute ischemic stroke, and can last for several days beyond the acute phase.\(^9\)\(^-\)\(^{17}\) High glucose levels predict a larger infarct size, poor clinical outcome and a higher risk of mortality, and are independent from other predictors of a poor prognosis such as age, diabetic status and stroke severity.\(^{11}\)\(^-\)\(^{23}\) Several mechanisms seem to account for the high frequency of hyperglycemia observed in patients with acute ischemic stroke, and various pathophysiological mechanisms have been proposed to account for the detrimental effect of hyperglycemia on the ischemic brain.

In critically ill patients with conditions other than stroke, tight glycemic control (TGC) has been shown to have a beneficial effect on clinical outcome,\(^6\)\(^-\)\(^{24}\)\(^-\)\(^{30}\) although recent trials investigating TGC on the intensive care unit (ICU) could not confirm these earlier positive findings.\(^8\)\(^-\)\(^{24}\) In fact, in the later trials TGC was shown to increase the risk of patients developing hypoglycemia, and a poor clinical outcome was documented to be associated with TGC treatment. Perhaps not surprisingly, these latest results have initiated a debate on the efficacy and safety of TGC.

In patients with ischemic stroke and concomitant hyperglycemia, TGC remains a potential treatment that could improve a patient’s clinical prognosis; however, successful and safe provision of TGC treatment to patients who are critically ill seems to be a challenging task. This review provides an overview of the potential causes and consequences of post-stroke hyperglycemia and specifically addresses the pathophysiological mechanisms that might link post-stroke hyperglycemia to increased infarct size and poor clinical outcome. Furthermore, we systematically review studies that investigate the feasibility and efficacy of TGC in patients with ischemic stroke. Finally, for the benefit of caregivers involved in caring for patients with acute ischemic stroke, we provide directions about different insulin strategies that might control hyperglycemia in this patient group.

HYPERGLYCEMIA AFTER ISCHEMIC STROKE

FREQUENCY, TIME COURSE AND MECHANISMS

A high frequency of admission hyperglycemia has long been recognized in patients with acute stroke.\(^{11}\)\(^-\)\(^{15}\) Irrespective of the time between stroke onset and glucose assessment or the conditions under which blood glucose levels are assessed (for example, random sampling versus fasting sampling), admission hyperglycemia is a frequent finding in patients admitted to hospital for acute ischemic stroke.\(^{11}\) A systematic review of 33 studies reported that 8 to 63% of non-diabetic and 39 to 83% of diabetic patients with ischemic stroke had admission hyperglycemia (definition of hyperglycemia used in these studies was blood glucose values >6.1 mmol/L).\(^{11}\) Blood glucose levels seem to decline within the first 24 hours after stroke onset,\(^{31}\)\(^-\)\(^{32}\) but they rise again after 24 to 88 hours, regardless of whether the patient has diabetes mellitus (DM).\(^9\) This late hyperglycemic phase is probably the result of impaired glucose metabolism that only becomes evident once the patient resumes feeding after an initial fasting period.\(^{33}\)\(^-\)\(^{34}\)

Several mechanisms have been proposed to account for hyperglycemia in patients with acute stroke (Figure 1), and in reality multiple mechanisms are probably involved. The high incidence of hyperglycemia after ischemic stroke could be partly explained by pre-existing abnormalities
in glucose metabolism. A substantial proportion of patients with ischemic stroke without a documented history of DM have insulin resistance or DM at follow-up. Furthermore, 27 to 37% of patients admitted to hospital with stroke and concurrent hyperglycemia and no history of DM were shown to have impaired glucose tolerance three months after the initial stroke, and approximately one-third of these cases had developed DM by this time point. Serious illnesses, including stroke, are accompanied by a generalized stress reaction that involves the activation of the hypothalamic–pituitary–adrenal axis. Activation of this complex neuronal circuit leads to increased levels of serum glucocorticoids, including cortisol, and activation of the sympathetic autonomic nervous system, resulting in increased catecholamine release. The acute phase of ischemic stroke and the first week after stroke are, therefore, accompanied by high levels of humoral cortisol and catecholamines. Increased levels of stress hormones such as cortisol enhance glycogenolysis, gluconeogenesis, proteolysis and lipolysis, which all result in excessive glucose production. In addition, epinephrine inhibits glucose transport into cells by inhibiting the binding of insulin to its receptor; thus, increased levels of circulating epinephrine can result in insulin resistance with hyperinsulinemia. The hypothesis that the stress reaction itself contributes to hyperglycemia after ischemic stroke is further supported by the observation that increased stroke severity is accompanied by a corresponding increase in the levels of stress hormones, with a concomitant increase in hyperglycemia. The exact mechanism that results in the activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system remains to be clarified, but it probably originates at the suprachiasmatic hypothalamic level. Animal studies have supported this hypothesis regarding the origin of the hypothalamic–pituitary–adrenal axis activation by the observation that stroke involving the insular cortex, a brain area with efferent projections to the autonomic nervous system, is associated with higher serum blood glucose levels and higher levels of circulating catecholamines than are seen in non-insular stroke.

Stroke is also associated with an increased inflammatory response with a subsequent release of a whole host of cytokines. Certain cytokines, such as tumor necrosis factor, have been shown to activate the hypothalamic–pituitary–adrenal axis and the activity of these cytokines has also been associated with the development of insulin resistance. Therefore, it seems...
that stroke can potentially induce hyperglycemia indirectly via activation of the inflammatory response.

**CLINICAL OUTCOME**

Over 30 years ago, Melamed and co-workers were the first group to identify the relationship between hyperglycemia and poor clinical outcome after stroke. Many studies have since confirmed these findings and have also demonstrated that this association is independent from other predictors of poor clinical outcome such as age, stroke severity, infarct size or diabetic status. The association between hyperglycemia and poor clinical outcome is even more pronounced when hyperglycemia persists during the first few days after acute stroke onset. A meta-analysis has revealed that patients with ischemic stroke who are non-diabetic have an increased risk of mortality at early time points after acute stroke onset if their blood glucose levels are exceed 6.1 mmol/L. By contrast, no association between high blood glucose levels and short-term mortality has been observed in ischemic stroke patients with a known history of DM. Furthermore, little evidence exists to support an association between high blood glucose and short-term mortality in patients who have not experienced a stroke, indicating that the deleterious effects of hyperglycemia are somehow restricted to non-diabetic patients with ischemic stroke. For example, patients with acute ischemic stroke who were admitted to a general hospital ward without a diagnosis of DM but were shown on admission to have hyperglycemia had an 18-fold increased risk of in-hospital mortality compared with normoglycemic patients. Hyperglycemic patients with known DM, however, only had a threefold increased risk of in-hospital mortality compared with normoglycemic patients. Thus, in non-diabetic patients with acute ischemic stroke, hyperglycemia resulting from stroke seems to be associated with a high in-hospital mortality risk. By contrast, hyperglycemia that relates to a diagnosis of DM is not associated with a high in-hospital mortality risk in patients with ischemic stroke.

The relationship between hyperglycemia and stroke outcome also seems to differ between ischemic stroke subtypes. Two studies have indicated that an association between hyperglycemia and poor stroke outcome exists in patients with cortical stroke, but not in patients with lacunar stroke. Moreover, post-hoc analysis of three large clinical trials revealed that high levels of blood glucose were associated with good rather than poor clinical outcome after lacunar infarction.

We note that many studies investigating an association between hyperglycemia and clinical outcome following stroke were performed before thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) became standard practice in acute ischemic stroke care. An increasing number of studies, however, are demonstrating that hyperglycemia on admission to hospital also predicts poor outcome in patients with acute ischemic stroke treated with rtPA. This association between poor clinical outcome and hyperglycemia is more pronounced in patients treated with thrombolytic therapy than in non-rtPA-treated patients.

**AGGRAVATED CEREBRAL DAMAGE**

The nature of the association between hyperglycemia and aggravated cerebral damage in ischemic stroke has been investigated in animal models of stroke as well as in clinical imaging studies. This section addresses the potential effects of hyperglycemia on the biological events...
Impaired recanalization
†Thrombin–antithrombin complexes
†Tissue factor pathway → †coagulation
†Plasminogen activator inhibitor
↓Recombinant tissue plasminogen activator activity → †fibrinolysis

Decreased reperfusion
↓Nitric oxide → ↑vasodilatation
↑Prostaglandins → vasoconstriction

Increased reperfusion injury
↑Oxidative stress → tissue damage, edema, and impaired blood–brain barrier
↑Inflammatory response
↑Cytokines → tissue damage

Direct tissue injury
Mitochondrial dysfunction
Anaerobic glycolysis → lactic acidosis
Hemorrhagic conversion
that occur after a cerebral artery becomes occluded (Figure 2). How hyperglycemia affects the salvage of the ischemic penumbra —ischemic tissue surrounding the infarct core that consists of potentially salvageable tissue at risk of infarction—is likely to be a key factor that directly affects the clinical prognosis of patients with acute ischemic stroke.

**IMPAIRED RECANALIZATION**

In human studies, hyperglycemia has been shown to stimulate coagulation by increasing the production of thrombin-antithrombin complexes and by stimulating the tissue factor pathway, whereas hyperinsulinemia decreases fibrinolytic activity by increasing the production of plasminogen activator inhibitor. In addition, both hyperglycemia and hyperinsulinemia have been shown to decrease the activity of rtPA in animal models. These observations support the hypothesis that altered glucose metabolism impairs recanalization through increased coagulation and decreased fibrinolytic activity. Furthermore, in clinical practice, transcranial Doppler imaging has confirmed this finding by demonstrating that hyperglycemia is associated with persistent occlusion in patients with ischemic stroke treated with rtPA.

**DECREASED REPERFUSION**

Studies using animal models of stroke have shown that hyperglycemia is associated with decreased reperfusion to the ischemic tissue and increased infarct volumes compared with normoglycemic controls. Hemispheric cerebral blood flow has been shown to be reduced by as much as 37% in hyperglycemic compared with normoglycemic rats. Furthermore, after recanalization, penumbral blood flow was shown to be 60% of pre-ischemic values in hyperglycemic rats, compared with 89% of pre-ischemic values in rats with normal blood glucose levels.

Inhibition of vasodilatation is an important mechanism by which hyperglycemia seems to reduce cerebral blood flow. Acute glucose infusion has been shown to reduce endothelium-dependent vasodilatation in healthy humans. Vasodilatation is predominantly mediated by endothelium-derived nitric oxide, which is synthesized by endothelial nitric oxide synthase. In vitro cell culture studies have demonstrated that reduced NOS3 gene expression is associated with a hyperglycemic environment. This reduction in gene expression is probably mediated via activation of protein kinase C. Moreover, hyperglycemia in cell culture studies has been shown to reduce the production of nitric oxide by increasing the activity of nicotinamide adenine dinucleotide phosphate oxidase, which seems to be mediated through the activation of protein kinase C. In addition, nicotinamide adenine dinucleotide phosphate oxidase increases the production of superoxide, which neutralizes nitric oxide, resulting in the production of peroxynitrite.

Further cell culture experiments have indicated that hyperglycemia also affects numerous other signaling pathways involved in vascular function. For example, hyperglycemia stimulates the lipooxygenase and cyclooxygenase pathways, leading to enhanced formation of vasoconstrictive prostaglandins such as thromboxane A2. In addition, hyperglycemia can increase eicosanoid production, which can affect vascular tone and result in vasoconstriction.

**INCREASED REPERFUSION INJURY**

Although restoration of the blood flow to the ischemic tissue is essential for penumbral salvage, reperfusion itself can also induce injury, and hyperglycemia is associated with...
increased reperfusion injury. The mediators of reperfusion injury are oxidative stress and inflammation, and these processes both seem to be influenced by hyperglycemia. Oxidative stress occurs as a result of an imbalance between the production and neutralization of reactive oxygen species (ROS), such as superoxide and peroxides. In neuronal cultures, glucose functions as the electron donor during reperfusion-induced superoxide production. ROS have been shown to damage various cell components, including proteins, lipids and DNA, which can lead to impairments in blood–brain barrier function, as well as edema formation and increased infarct volume. Hyperglycemia increases the production of ROS through a protein kinase C-mediated pathway, and by increasing the production of nicotinamide adenine dinucleotide phosphate. By increasing the production of ROS hyperglycemia can increase oxidative stress, which can ultimately lead to neuron death. In fact, increased oxidative stress caused by the formation of superoxide is considered to be one of the major pathways that lead to hyperglycemic complications. Another important factor in reperfusion injury is the inflammatory response. During ischemia in humans, the inflammatory response develops through the production of pro-inflammatory cytokines (including tumor necrosis factor, as well as various interleukins and cell signaling molecules), and by infiltration of the tissue by inflammatory cells (such as leukocytes and macrophages). The inflammatory response leads to breakdown of the blood brain barrier, diapedesis of inflammatory cells out of the circulation into the interstitium, and edema formation resulting in tissue injury and increased infarct size. In addition, inflammation is a prominent source of oxidative stress. Hyperglycemia is known to be associated with increased expression of several pro-inflammatory transcription factors, such as nuclear factor κB. These factors have key roles in the regulation of the inflammatory responses by increasing the production of pro-inflammatory cytokines and promoting the adhesion of inflammatory cells to other inflammatory cells and the vascular endothelium.

OTHER MECHANISMS
A controversial mechanism has been suggested, that links anaerobic glycolysis under hyperglycemic conditions to the accumulation of lactic acid and dysfunctional pH homeostasis, which have been proposed to contribute to increased brain injury. In humans, this hypothesis is supported by the observation that hyperglycemia correlates positively with increased cerebral lactate concentration and reduced penumbral salvage after infarction. Hyperglycemia might also directly affect mitochondrial function in the ischemic penumbra, thereby causing substantial intracellular acidosis. Hyperglycemia has also been associated with an increased rate of hemorrhagic complications after rtPA treatment. One study in particular showed that hyperglycemia (blood glucose exceeding 11.1 mmol/L in this study) is associated with a 25% symptomatic hemorrhage rate in patients with acute ischemic stroke treated with rtPA. In these studies, however, DM was also associated with an increased rate of hemorrhage or the association between hyperglycemia and hemorrhagic complications disappeared after multivariate assessment. Hyperglycemia might, therefore, merely be a marker of DM, and evidence exists that DM is associated with impairments of the blood–brain barrier and microvasculature. Such impairments might result in an increased bleeding risk for patients with acute ischemic stroke.
TIGHT GLYCEMIC CONTROL

CONDITIONS OTHER THAN ISCHEMIC STROKE

One of the most important indications that patients with ischemic stroke might benefit from TGC came from clinical trials that investigated the effects of TGC treatment in other critically ill patient groups.

The landmark Leuven clinical trials showed that patients admitted to ICUs who received TGC treatment, which was designed to keep blood glucose values in the lower physiological range (<6.1 mmol/L), had better clinical outcomes than patients who did not receive TGC treatment. These results led to the worldwide implementation of TGC in ICU facilities. The clinical benefit of TGC, however, has recently become the subject of debate and the use of TGC in the ICU has to be regarded with caution. In contrast to earlier trials, recent trials have failed to demonstrate a clinical benefit from TGC treatment, and some trials have even showed that the implementation of TGC might be associated with increased mortality rates. TGC inevitably increases the risk of severe hypoglycemia (blood glucose levels <2.2 mmol/L), which might be a contributory factor towards poor clinical outcomes in patients treated with TGC. Why the different TGC trials have conflicting results remains unclear, and further post-hoc analyses that closely examine patient subgroups, as well as further analysis of blood glucose dynamics (in particular, the role of severe hypoglycemia), must be conducted to resolve this ambiguity. In the meantime, TGC is still recommended for patients admitted to the ICU. For a clinical benefit from TGC to become apparent, a substantial contrast in blood glucose levels between patients treated with TGC and control patients should be established. The diabetes and insulin–glucose infusion in acute myocardial infarction (DIGAMI) trials illustrate this point well. In the DIGAMI I trial, a substantial reduction in mean blood glucose of 2.1 mmol/L resulted in a 29% reduction in the 1 year mortality rate. In a subsequent trial, DIGAMI II, which did not achieve a substantial contrast in mean blood glucose levels between patients receiving TGC and untreated controls, no clinical benefit was seen. In addition, numerous trials conducted both in other critically ill patient groups and in patients with acute stroke have demonstrated that when TGC does not achieve a substantial lowering of blood glucose levels compared with standard ICU therapy, subsequent insulin treatment is not accompanied by a clinically beneficial outcome.

We are not aware of any clinical trials that have specifically investigated for how long TGC must be maintained to achieve an optimal effect on clinical outcome. The combined subgroup analysis of the Leuven trials showed that the TGC-related benefits experienced by patients with myocardial infarction increased when the treatment was continued for a minimum of three days when compared with treatment lasting less than three days. The trial was not, however, designed to test the effects of different treatment durations, so this positive outcome of TGC treatment can only be regarded as circumstantial evidence for the potential benefit of prolonged TGC treatment. Moreover, the detrimental effects of hyperglycemia and the putative beneficial effects of TGC on secondary complications occurring during the clinical course such as nosocomial infections, acute renal failure, liver dysfunction and critical illness polyneuropathy also extend beyond the acute phase of the disorder.

Although the clinical benefits of TGC for all patients admitted to the ICU are debatable, TGC still has the potential to improve clinical outcome in various patient subgroups. A prospective
sub-analysis of the first Leuven trial demonstrated that TGC during intensive care reduced the incidence of critical illness polyneuropathy in the ICU setting, thereby reducing the need for mechanical ventilation. In addition, post-hoc analysis revealed that patients with isolated brain injury who received TGC treatment in the ICU setting were more likely to show clinical improvement than were patients with brain injury who were not subjected to TGC.

In patients with aneurysmal subarachnoid hemorrhage, hyperglycemia is associated with delayed cerebral ischemia and poor clinical outcome. A sequential comparison study demonstrated that the introduction of TGC on the ICU was associated with improved clinical outcome in patients with this neurological condition.

**CURRENT PRACTICE ON THE STROKE UNIT**

Current guidelines from the American Heart Association and the European Stroke Organization state that following an ischemic stroke, blood glucose concentrations exceeding 7.8 mmol/L warrant the administration of insulin. However, the means by which glucose levels should be established and maintained throughout the clinical course of a patient’s stay in hospital is unclear. A survey of stroke physicians revealed a high degree of variability in the aggressiveness of glucose management in patients with stroke. In most hospital wards, sliding-scale insulin regimens are used to manage hyperglycemia. Although we could not find any published data that specifically stated this fact in relation to glucose management in stroke units, in our experience this is the method that is most often used to control blood glucose concentrations in patients with stroke. The extensive use of sliding-scale insulin regimens is probably due to convenience, simplicity, and the promptness with which treatment can be initiated. The use of such regimens, does not consistently improve glycemic control, however, and it is associated with an increased risk of hypoglycemia. The main limitation of these protocols is that they require a reactive rather than a proactive approach, requiring the modification of insulin dosage in response to changes in blood glucose concentrations. By contrast, oral glucose lowering agents reduce blood glucose levels effectively, but these agents act substantially more slowly than insulin. Subcutaneous meal-related or intravenous insulin regimens, therefore, seem to be most appropriate for establishing glycemic control on stroke units.

Ideally, protocols designed to achieve glycemic control should be straightforward, with a minimal risk of hypoglycemia. Various computer-guided treatment protocols designed to control hyperglycemia in patients admitted to the ICU have now been published. In our view, however, several limitations must be overcome before these protocols can be successfully implemented in stroke facilities. First, in many stroke units, the circumstances are different from those in the ICU. Fewer nursing personnel are assigned to each patient, and direct venous or arterial access for frequent blood glucose monitoring might be lacking. Second, the relative unfamiliarity of stroke specialists with blood glucose management and a perceived general lack of communication between diabetes specialists and stroke specialists could impede the proposed implementation of computer-guided protocols for glycemic control. Third, oral intake of nutrients is often resumed in patients with stroke after an initial fasting period, and unpredictable nutritional absorption is typically seen in this post-fasting period. In fact, postprandial glucose surges substantially contribute to recurrent hyperglycemia in patients with ischemic stroke. Last, the warning symptoms of hypoglycemia might be less clear in patients with stroke than in other patients, as these symptoms are similar to some stroke comorbidities.
Table 1 | Studies investigating different glucose-lowering protocols in patients with stroke.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Admission blood glucose (mmol/L)*</th>
<th>Target blood glucose (mmol/L)</th>
<th>Intervention and time of treatment</th>
<th>Mean blood glucose during treatment (mmol/l)</th>
<th>Difference in mean blood glucose with therapy</th>
<th>Hypoglycemia Cut-off (mmol/l)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno¹³</td>
<td>Ischemic stroke &lt;12 h, all DM (24)</td>
<td>14.7 ± 4.9</td>
<td>3.9–7.2</td>
<td>intravenous insulin + Meal-related subcutaneous insulin (72 h)</td>
<td>7.3 ± 1.1</td>
<td>Not reported</td>
<td>&lt;3.0</td>
<td>46</td>
</tr>
<tr>
<td>Walters¹⁴⁻¹⁵</td>
<td>Ischemic stroke &lt;24 h (13)</td>
<td>10.6 ± 1.9</td>
<td>5.0–7.9</td>
<td>intravenous insulin (48 h)</td>
<td>6.9 ± 1.9</td>
<td>1.2‡</td>
<td>&lt;3.5‡ (one symptomatic)</td>
<td>23‡</td>
</tr>
<tr>
<td>Gray³¹</td>
<td>All stroke (460)</td>
<td>7.8 [6.8–9.2]</td>
<td>4.0–7.0</td>
<td>intravenous GKI (24 h)</td>
<td>NR</td>
<td>0.57</td>
<td>&lt;4</td>
<td>16</td>
</tr>
<tr>
<td>Kreisel¹⁴⁻¹⁵</td>
<td>Ischemic stroke &lt;24 h (20)</td>
<td>7.6 ± 4.7</td>
<td>4.4–6.1</td>
<td>intravenous insulin (5 days)</td>
<td>6.5 ± 2.1</td>
<td>1.52</td>
<td>&lt;3.3</td>
<td>35</td>
</tr>
<tr>
<td>Kruyt¹³⁻¹⁴</td>
<td>Ischemic stroke &lt;24 h (10 insulin and tube feeding; 13 insulin only)</td>
<td>9.1 ± 2.4</td>
<td>4.4–6.1</td>
<td>intravenous insulin + Continuous tube feeding (5 days)</td>
<td>5.8 ± 0.3</td>
<td>Not applicable</td>
<td>&lt;3.5</td>
<td>20</td>
</tr>
<tr>
<td>Johnston¹³⁻¹⁴</td>
<td>Ischemic stroke &lt;24 h (25 loose control and 24 tight control)</td>
<td>9.3 [7.0–12.7]</td>
<td>3.9–6.1</td>
<td>intravenous insulin (5 days)</td>
<td>8.4 [range not reported]</td>
<td>Not reported</td>
<td>&lt;3.1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.3 [7.0–12.7]</td>
<td>3.9–6.1</td>
<td>intravenous insulin (5 days)</td>
<td>6.2 [range not reported]</td>
<td>Not reported</td>
<td>&lt;3.1</td>
<td>30</td>
</tr>
</tbody>
</table>

*: mean ± SE, median [inter quartile range]; ‡: Personal communication with the study authors. Abbreviations: DM, diabetes mellitus; GKI, glucose–potassium–insulin infusion; N, number of patients subjected to glucose lowering therapy.
Table 2 | Ongoing studies investigating different glucose lowering protocols in stroke.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study name</th>
<th>Patient type (target number)</th>
<th>Therapy</th>
<th>Target blood glucose concentration (mmol/L) (therapy duration)</th>
<th>Primary outcome</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samson et al.</td>
<td>Efficacy and Safety of Continuous Intravenous Versus Usual Subcutaneous Insulin in Acute Ischemic Stroke (INSULINFARCT)</td>
<td>Ischemic stroke &lt;6 h (180)</td>
<td>Intravenous insulin versus subcutaneous sliding-scale</td>
<td>&lt;7.0 (24 h)</td>
<td>Proportion of patients in target range at 24 h</td>
<td>92* patients included</td>
</tr>
<tr>
<td>Gentile et al.</td>
<td>The Effect of Insulin on Infarct Size and Neurologic Outcome After Acute Stroke</td>
<td>Ischemic stroke &lt;24 h (133)</td>
<td>Intravenous insulin IV</td>
<td>4.4–6.1 (48 h)</td>
<td>Infarct volume change at 7 days.</td>
<td>On hold due to lack of funding*</td>
</tr>
<tr>
<td>Muir et al.</td>
<td>Trial of Insulin to Control Blood Sugar After Acute Stroke Using Magnetic Resonance Imaging (MRI) End-Points (SELESTIAL)</td>
<td>Ischemic stroke &lt;24 h (45)</td>
<td>Intravenous insulin: 24 versus 72 h.</td>
<td>Not reported</td>
<td>Infarct expansion at 7 days.</td>
<td>40* patients; inclusion ended.</td>
</tr>
<tr>
<td>Azevedo et al.</td>
<td>Comparison of Two Strategies for Glycemic Control in Acute Ischemic Stroke</td>
<td>Acute ischemic stroke (70)</td>
<td>Intravenous insulin versus subcutaneous sliding-scale</td>
<td>&lt;8.3§ and &lt;10.0§ (Not reported)</td>
<td>4 month clinical outcome</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kruyt et al.</td>
<td>Glucose regulation by continuous tube feeding and Vildagliptin in addition to insulin in hyperglycemic acute stroke patients (GLUCOVAS)</td>
<td>Ischemic stroke &lt;24 h (30)</td>
<td>Intravenous insulin + continuous tube feeding +/- vildagliptin/placebo</td>
<td>4.4–6.1 (5 days)</td>
<td>Mean percentage of time in target</td>
<td>To start</td>
</tr>
</tbody>
</table>

*: Personal communications with the study coordinating authors (June 2009); ‡: Target blood glucose concentration for intravenous insulin therapy; §: Target blood glucose concentration for subcutaneous sliding scale therapy.
The main disadvantage of TGC treatment is the increased risk of severe hypoglycemia to which patients with stroke are exposed when receiving this therapy. No universally accepted definition of hypoglycemia has been accepted for ischemic stroke, which is alarming considering that hypoglycemia might be even more detrimental to patients with stroke than to patients with other serious conditions. Furthermore, incidental hypoglycemia with concurrent ischemia has been hypothesized to substantially aggravate the brain damage caused by cerebral infarction. In rat studies, low blood glucose levels were associated with increased infarct size and a heightened risk of short-term mortality, and the benefit of reducing blood glucose levels was lost when blood glucose levels fell below 2 to 3 mmol/L.

**SYSTEMATIC REVIEW OF THE LITERATURE**

**GLUCOSE-LOWERING PROTOCOLS**

Various attempts have been made to achieve glycemic control after ischemic stroke. We have identified these studies through a systematic review of the literature (Tables 1 and 2). A PubMed search retrieved seven relevant articles that reported glucose levels in patients with acute stroke who were subjected to glucose lowering therapy (Table 1). Only one of these studies, however, managed to maintain mean blood glucose levels within a low physiological range (<6.1 mmol/L). This targeted lowering of patient blood glucose levels was achieved by subjecting the patients to continuous tube feeding in addition to a computerized intravenous insulin treatment protocol. One other study managed to maintain mean blood glucose levels within a more liberal predefined target range (5.0 to 8.0 mmol/L; mean glucose during treatment: 6.9 mmol/L). Our systematic review revealed that avoiding hypoglycemia in patients with ischemic stroke who are subjected to glycemic control is challenging. Hyperglycemic episodes were reported in all the studies that we identified. Furthermore, all the identified studies showed that at least 30% of patients subjected to glycemic control experienced one or more episodes of hypoglycemia (blood glucose <3.0 to 3.5 mmol/L). Although no serious adverse events were reported, these results raise concerns about the safety of TGC after acute ischemic stroke. A search of the trial registries yielded five ongoing trials investigating glucose control in patients with acute ischemic stroke (Table 2); however, to date no trial results are available.

**CLINICAL OUTCOMES OF GLYCEMIC CONTROL**

One retrospective study showed that patients with ischemic stroke who received glycemic control treatment (normalization of blood glucose to <7.2 mmol/L) had a 4.6-fold decrease in mortality risk compared with patients with persistent hyperglycemia. The UK Glucose Insulin in Stroke Trial (GISt-UK) is the only large-scale clinical trial to date that has prospectively investigated the influence of glycemic control on clinical outcome after stroke. The results of this trial did not favor treatment with insulin, although several limitations must be noted. First, the trial had to be stopped prematurely due to slow enrollment, so the data are underpowered to allow definite conclusions concerning clinical outcome to be drawn. Second, the trial included a heterogeneous group of patients with stroke; for example, 22% of the patients had lacunar infarcts and 12% had primary intracerebral hemorrhage. This heterogeneity might have diluted the treatment effect, because observational studies indicate that the relationship between hyperglycemia and clinical outcome differs according to stroke subtype, and might be
absent or even reversed in lacunar stroke. Last, insulin was administered for just 24 hours, and only a small contrast in mean blood glucose levels (0.57 mmol/L) was established between the stroke group and control group.

A small trial including 74 patients with acute ischemic stroke did not show a substantial effect of TGC on clinical outcome, but this trial was not powered to assess clinical efficacy. Nevertheless, a subgroup analysis from that study, which included patients with clinically more-severe stroke and admission blood glucose levels exceeding 8.3 mmol/L, indicated that TGC increased the odds of a favorable outcome in patients with acute ischemic stroke.

**CONCLUSIONS**

If future glucose-lowering protocols are to be effective on the stroke unit, some lessons can be learned from the implementation of glycemic control in the ICU setting. First, the awareness and readiness to control hyperglycemia by both stroke physicians and nursing personnel must be improved. Second, multidisciplinary teams, which include stroke and diabetes experts with expertise and knowledge of the day-to-day operations of a stroke unit, must be involved in the implementation of the glycemic control protocols. Last, blood glucose monitoring must be aggressive, and frequent insulin adjustments should be employed to successfully control fluctuations in blood sugar levels. Continuous glucose monitoring devices are now becoming available, and computerized treatment algorithms have the potential to greatly facilitate this aggressive monitoring strategy. Decreasing the rate of hypoglycemic events is also a priority.

Box 1 summarizes recommendations for the treatment of hyperglycemia in patients with acute ischemic stroke. These recommendations are based on the currently available evidence and expert opinion.

Ultimately, the question of whether patients with acute ischemic stroke will benefit from glycemic control must be resolved by a large-scale randomized controlled trial. Several factors need to be taken into account when initiating such a trial. Furthermore, the threshold glucose level that should be used to assess glucose-lowering treatment remains to be established. We suggest lowering blood glucose levels to the lower physiological range (4.4 to 7.0 mmol/L) to ensure that a substantial difference in mean glucose levels is observed between patients treated with glycemic control therapies and patients whose blood glucose is not controlled. This approach has proved to be beneficial in previous trials in other groups of critically ill patients. Moreover, caution is warranted when selecting patients with acute ischemic stroke to participate in such a trial. Patients with a known history of DM seem to benefit less from glycemic control than patients without such a history. In addition, patients with lacunar infarcts could actually benefit from hyperglycemia, and stroke clinicians should, therefore, consider withholding intensive glycemic control treatment from patients with this stroke subtype. Selecting non-diabetic patients with cortical ischemic stroke might improve the probability of finding a treatment effect associated with glycemic control. The clinical benefit of glucose-lowering therapy is probably maximized when treatment is continued for at least 2 to 3 days beyond the acute phase. Furthermore, adequate lowering of glucose levels of patients with acute ischemic stroke remains challenging because of postprandial glucose surges, and the risk of development of hypoglycemia during aggressive blood glucose monitoring. Standardized
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continuous tube feeding, even in patients without dysphagia has the potential to greatly improve glycemic control, but is still accompanied by hypoglycemia. Further studies that establish safe methods of improving glycemic control are awaited before a randomized controlled trial that assesses clinical outcome measures associated with glycemic control can be initiated.

BOX 1. MANAGEMENT OF POST STROKE HYPERGLYCEMIA.

Until further evidence indicates otherwise, recommendations are the same as those published by the American Heart Association and the European Stroke Organization. Both organizations state that blood glucose concentrations exceeding 10.0 mmol/L should trigger insulin administration. Blood glucose levels should then be continuously monitored throughout the clinical course for the following reasons:

- Glucose levels tend to rise after an initial decline
- Admission hyperglycemia after ischemic stroke could indicate underlying, previously unrecognized diabetes mellitus
- Treatment of hyperglycemia carries a substantial risk of hypoglycemia

Initiate intravenous insulin infusions according to a predefined treatment protocol, rather than subcutaneous sliding scale regimes (expert opinion).

Establish multidisciplinary collaboration between stroke physicians and diabetes experts (expert opinion).

Improve awareness and readiness to control hyperglycemia by both stroke physicians and nursing personnel (expert opinion).

BOX 2. REVIEW CRITERIA

PubMed was searched for papers covering the main topics in this review. The search terms blood glucose”, “stroke”, “cerebral infarction”, “insulin” and “hyperglycemia” were used to identify relevant papers written in English, German, French and Spanish published before October 2009. The same search terms and limits were used to perform a systematic review of the literature relating to tight glycemic control after stroke. In addition, we searched the stroke Trials Registry, ClinicalTrials.gov and abstract books from European and American stroke conferences held from January 2008 to October 2009. Only studies that reported blood glucose levels in patients with acute stroke treated with glucose-lowering therapy were included.