Glycemic control in acute stroke: ‘balancing the risks’
Kruyt, N.D.

Citation for published version (APA):
Chapter 10

GENERAL DISCUSSION

Kruyt ND
INTRODUCTION

At the time the Glucose Lowering in Acute Stroke Study project was designed in a collaborative research proposal of the departments of neurology of the Academic Medical Center in Amsterdam and the University Medical Center of Utrecht, in 2003, the primary objective was to perform a randomized clinical trial (RCT) to investigate the clinical benefit of glucose-lowering treatment in acute (ischemic) stroke patients. This was driven by the observations that hyperglycemia after stroke is a strong predictor of poor clinical outcome, that several pathophysiological mechanisms could account for this, and that glucose-lowering treatment reduced poor clinical outcome in other groups of critically ill patients. Seven years later, the concept of glucose-lowering treatment in critically ill patients has changed considerably. Most notably, the clinical evidence that critically ill patients benefit from glucose-lowering treatment appears to be less convincing. This has posed some important questions: should we still treat hyperglycemia after stroke, and if so decided, how can this be done safely and efficiently?

In this final chapter we will briefly discuss these questions. First we outline the developments that have sparked the debate on glucose-lowering treatment in critically ill patients and describe the current situation for stroke patients. Finally we will provide some indications for the design of a trial to investigate the clinical effect of glucose-lowering treatment in stroke patients.

HYPERGlyCEMIA, “TO tREAT OR NOT TO tREAT”?

One of the most important trials that investigated glucose-lowering treatment, also called “the Leuven trial” demonstrated that by targeting blood glucose levels between 4.4 to 6.1 mmol/L on the intensive care unit (ICU), case fatality could be reduced by a relative 43%. Several trials followed that could not always reproduce these positive findings, thus sparking the debate on the applicability of glucose-lowering treatment. The factor considered to be the most important in explaining the differential results between the positive findings in the Leuven trial and the subsequent negative findings in some other trials, was a lack of power to detect a reasonable case fatality difference in the negative studies. To address this, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial was designed to randomize over 6000 patients. Contrary to the expectations, NICE-SUGAR revealed that glycemic control was associated with a relative increase in mortality. Several methodological differences between the Leuven trial and the NICE-SUGAR trial have been put forward to account for this. Probably the most important explanation can be found in the differences in glycemic control. By the time the NICE-SUGAR trial was initiated, usual care concerning glycemic control had changed considerably. Therefore, instead of tolerating hyperglycemia, a policy of insulin therapy to target intermediate blood glucose levels was chosen for the control group, in line with what had been widely adopted in clinical practice. As a consequence, the NICE-SUGAR trial was executed in the “flatter” part of the J-shaped admission glucose-clinical outcome curve (figure) compared to the Leuven trial. Therefore, the control group in the NICE-SUGAR trial already could have benefited from reducing blood glucose other than the control group in the Leuven trial, thereby rendering the contrast in clinical benefit less pronounced. Furthermore, the degree of success in maintaining glucose levels in the target range in the intervention group as well as the degree of overlap with the
control group, varied greatly. In the Leuven trial, 70% of the patients in the intervention group were on average on target, whereas this was less than 50% in the NICE-SUGAR trial. Moreover, the mean glucose levels in the intervention groups of the trials (both targeting glucose levels between 4.4 to 6.1 mmol/L) fell within the target range in the Leuven trial (5.7 mmol/L), while in the NICE-SUGAR trial this fell outside the target range (6.4 mmol/L). The importance of this difference was demonstrated in a recent meta-analysis. The pooled studies that actually managed to achieve blood glucose within target levels showed a reduced case fatality, whereas the pooled studies that did not succeed in this did not. Another important point is the increased occurrence of serious hypoglycemic episodes (glucose level below 2.2 mmol/L) in the NICE-SUGAR trial. With a 13-fold higher rate in the intervention than in the control group this was much more pronounced than in the Leuven trial (6-fold higher in the intervention than in the control group). Finally, recent studies in patients treated with glucose-lowering treatment have revealed that fluctuating glucose levels (also called glucose variability) are an even stronger predictor of poor clinical outcome than mean glucose levels. Post-hoc analysis that investigated if glucose variability could indeed (partly) explain the differential outcomes

Clinical outcome assessed with the modified Rankin scale; Adapted from Ntaios et al; Stroke 2010 PMID: 20724712. Glucose in mmol/L.
between the Leuven and NICE-SUGAR trials have to be awaited. Meanwhile, glucose-lowering treatment is still recommended on ICUs, although in general more lenient treatment regimes than in the Leuven trial are used.

To date, glucose-lowering treatment specifically for stroke patients has been investigated in only one large RCT. This trial, which included 633 patients, did not favor insulin treatment, but was hampered by several important shortcomings. The design was pragmatic and a heterogeneous group of stroke patients was included. For example, 22% of the patients had lacunar infarcts and 13% had a primary intracerebral hemorrhage. This heterogeneity might have diluted a treatment effect, because the association between hyperglycemia and clinical outcome differs according to stroke subtype, and might be absent or even reversed in lacunar stroke as we confirmed in the study presented in chapter 3. Moreover, treatment lasted for just 24 hours. It is conceivable that a substantial portion of the patients remained fasting during this period. Glucose levels tend to rise after these first 24 hours, and as we noted in chapter 4, especially postprandial glucose surges contribute to hyperglycemia. Therefore, increased levels of glucose after the intervention period could have offset a possible treatment effect. Finally, only a small contrast in mean blood glucose levels (0.57 mmol/l) relative to the regular care group was established with the intervention, which casts doubts on the expected clinical effect when projected to the admission glucose-clinical outcome curve shown in the figure. In addition to this trial, some smaller trials and retrospective studies have been published both in acute ischemic stroke and in acute aneurysmal subarachnoid hemorrhage (SAH) patients, but no definite conclusions can be drawn due to lack of statistical power (chapters 2 and 9).

It appears from the currently available data that blood glucose is not just an innocent bystander after stroke since altering its levels has been shown to affect clinical outcome in both directions. This has led to the statement in stroke guidelines that hyperglycemia (defined as glucose >7.8 mmol/l) should be actively treated. In practice, stroke physicians manage hyperglycemia with a high degree of variability. Often hyperglycemia is accepted initially and if persistent, a sliding scale insulin regime is used to lower blood glucose levels. These sliding scale regimes, however, are not associated with improved control, and increase the risk of hypoglycemia and glucose variability. In view of this, it is doubtful whether recommendations on glycemic control are met in clinical practice. Against this background, a clinical trial to investigate if adequate and safe glucose-lowering treatment is beneficial for clinical outcome in stroke patients could still be of clinical value. In fact, from an investigators’ point of view, stroke patients constitute an interesting patient group as the possible contrast in mean blood glucose levels that can be established between the intervention group and controls is relatively large. However, it is important to first optimize glycemic control in terms of safety and efficiency. This appears particularly true for patients with acute ischemic stroke other than patients aneurysmal SAH who are often admitted to an intensive care unit with considerably more expertise and facilities for glycemic control.

Insight into the mechanisms that lead to increased blood glucose levels in stroke patients can potentially facilitate glycemic control in future studies. In patients with acute ischemic stroke and in patients with acute aneurysmal SAH, several common factors appear to contribute to hyperglycemia (chapters 5 and 9). Most notably, an increased stress response and possibly an increased inflammatory response contribute to hyperglycemia in both patient groups.
However, there are also some important differences concerning glucose metabolism between these patient groups. In acute ischemic stroke (undiscovered) insulin resistance prior to the ictus contributes substantially to hyperglycemia, whereas in aneurysmal SAH abnormalities of glucose metabolism are transient. Interestingly, in the latter group primary pancreatic β-cell dysfunction rather than insulin resistance appears to be an important cause of hyperglycemia (chapter 9).

For acute ischemic stroke patients, we are currently performing a small trial to further address glycemic control. Elaborating on the study presented in chapter 5 which showed that continuous tube feeding and a computerized treatment algorithm can improve glycemic control,134 we aim to improve this therapy in terms of safety and feasibility. Patients are randomized for treatment with vildagliptin, (Galvus®) or placebo in a double blind fashion. Vildagliptin has been shown to reduce the number of hypoglycemic episodes as an add-on therapy to insulin.343 In addition to this, patients are also randomized for continuous tube feeding- or regular feeding as we want confirm the previous observation that continuous tube feeding is indeed essential for reaching preset glycemic targets. In addition, we use a continuous glucose monitoring device with the aim of decreasing the number of fingerpicks needed to monitor blood glucose levels.

**GLUCOSE LOWERING IN STROKE, “INDICATIONS FOR A FUTURE TRIAL”**

Provided that glucose control can be established efficiently and safely, a RCT has to resolve the question whether stroke patients will benefit from glucose-lowering treatment. We will attempt to provide some indications for the design of such a trial in acute ischemic stroke patients. With regard to patients with aneurysmal SAH, the potential benefit that can be achieved with glycemic control is probably smaller since the majority of these patients are admitted to ICU’s and therefore already subjected to (tight) glycemic control. Still, a substantial portion of these patients will not be subjected to glycemic control, and as we highlighted in chapter 9, glycemic control in these patients is challenging leaving room for glycemic control improvement. We will, however, focus on the design of a RCT to investigate the clinical benefit of glucose-lowering treatment in acute ischemic stroke patients.

**PATIENT ELIGIBILITY**

Ischemic stroke is a heterogeneous disorder and hyperglycemia relates differently to clinical outcome in various subtypes of ischemic stroke. Hence, the effect of glucose-lowering treatment is likely to be differential for these subtypes. Although ideally it would be desirable for treatment efficacy to be proven in all patient groups, inclusion of patients for whom less clinical benefit is expected would dilute the number of end points reached, necessitating a much larger sample size. Besides this, such dilution would mean that more patients than otherwise are exposed to an as yet unproven therapy.

Patients with cortical (vs. lacunar) infarction and non-diabetic patients (vs. diabetic) appear to be much more adversely affected by high levels of blood glucose. Moreover, for patients with a very poor or more favorable prognosis (e.g. patients in a coma or with rapidly resolving deficits, respectively) the anticipated treatment effect would be much smaller. Therefore, it is more reasonable to select patients with moderate to severe cortical stroke (e.g. National Institutes of Health Stroke Scale (NIHSS) score 2-20) without a previous history of DM. Distinguishing patients with cortical infarcts from those with lacunar strokes on the basis of clinical signs alone
could be difficult in clinical practice, but standard criteria lists have been shown to distinguish between different stroke subtypes in the acute phase with reasonable accuracy.  

Another important factor to be considered is the cut-off level of admission glucose that should be used to select patients for inclusion. The admission glucose-clinical outcome curve from the figure shows that glucose levels exceeding 7.3 mmol/L are associated with unfavorable outcome. The curve, however, was derived from a heterogeneous group of more than 1400 acute ischemic stroke patients, including patients with DM or lacunar infarction. It would be interesting to construct this curve for patients with ischemic cortical stroke only and for patients with-or without a previous history of DM separately. Currently we intend to combine databases to obtain a more accurate estimate of the cut-off admission glucose levels that predict poor outcome for specific subsets of acute ischemic stroke patients.

**GLUCOSE-LOWERING TREATMENT**

It is unclear for how long blood glucose levels have to be lowered to be clinical effective. On the one hand, taking into account the pathophysiological perspective of the ischemic penumbra (chapter 5), a treatment duration of 24 to 48 hours after the ictus seems logical as beyond this time window the ischemic penumbra has most likely disappeared. On the other hand, from a clinical perspective, glucose levels often rise later in the clinical course and appear to be an even stronger predictor of poor outcome than single admission blood glucose levels. 10;56 In addition, previous trials revealed that the glucose lowering related benefits experienced by patients increased when the treatment was continued for a minimum of three days (when compared with treatment lasting less than three days). 121 Moreover, the putative beneficial effects of glucose lowering on secondary complications probably also extend beyond the acute phase of stroke.

Not only the duration, but also the target value of glucose-lowering treatment is unclear. Ideally, the target value of glucose-lowering treatment should be in the flat part of the admission glucose-clinical outcome curve depicted in the figure. It is possible that the nadir glucose in the figure (5.0 mmol/L) decreases for patients with cortical infarction without DM. For the time being, however, targeting these values with glucose-lowering treatment in stroke patients proved to be too difficult in terms of safety and efficacy.

**OUTCOME**

When the Glucose Lowering in Acute Stroke Study (GLASS) was initiated, we also studied surrogate endpoints for a future RCT. We regarded cognition as a possible surrogate endpoint in acute ischemic stroke. However, we rejected this as we could not find an apparent association between increased levels of admission blood glucose and cognitive outcome (chapter 2).61 Another potential surrogate endpoint for clinical outcome considered was (final) infarct size. High levels of blood glucose have been associated with increased infarct size in humans and in several experimental studies treatment with insulin reduced this expansion. However, in a recent trial, glucose-lowering therapy did not reduce infarct growth between baseline and day 7, although also in this glucose-lowering therapy did not accomplish lowering of blood glucose levels. 345 Further trials that use infarct expansion or final infarct size as a surrogate endpoint are currently under way and the results will have to be awaited. In patients with acute aneurysmal SAH, we found an association between high levels of fasting blood glucose in the first week
after the ictus and the occurrence of delayed cerebral ischemia (DCI). However, we could not pinpoint DCI as the key determinant in the association between high fasting glucose and poor clinical outcome which renders it less feasible as a surrogate marker for clinical outcome in a future trial that aims to investigate the clinical benefit of glucose-lowering therapy (chapter 7).

In conclusion, as currently there appears to be no valid surrogate endpoint for clinical outcome, the most reasonable endpoint for a future RCT remains overall clinical outcome, in term of the way the patient can function at home and socially.

**FINAL NOTE**

It is clear from the currently available data that blood glucose is not just an innocent bystander during critical illness because altering its levels has been shown to affect clinical outcome in both directions.

To the clinical neurologist and neurosurgeon it might perhaps seem somewhat surprising that even though we dispose of insulin therapy since a long time, still today it remains such a challenge to (safely) manage in-patient glucose levels. Perhaps a historical view can put this a little into perspective.

Already in 1869 a Berlin student, Langerhans, identified the pancreatic cells that produce insulin and that were later called after him. However, it took another halve century before the Canadian Banting managed to isolate insulin from dogs (1921) which eventually earned him the Nobel price. Although the first patient was treated already a year after this, it took another halve century before the first synthetic “human” insulin was produced in a laboratory in 1977 and the search for the optimal treatment for (ambulatory) patients with DM that started eight decades ago is still ongoing. Hence, it would be illusory to expect the definite answer from just a few studies on glucose-lowering treatment in the complex setting of critical illness.

For the time being, the question as to whether to actively treat or not to treat hyperglycemia in stroke patients remains elusive and is hampered by the fact that treatment has to be optimized first. Optimal glycemic control could perhaps be compared with the optimal course that was necessary when navigating through Homer’s Strait of Messina. In the Greek mythology this strait was sided on opposite sides by two sea monsters: Skylla and Charybdis. They were close enough to each other that they posed an inescapable threat to passing sailors; avoiding Skylla meant passing too closely to Charybdis and vice versa. In analogy, avoiding hyperglycemia could mean reaching too closely to hypoglycemia and vice versa.