Glycemic control in acute stroke: ‘balancing the risks’
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GENERAL INTRODUCTION
INTRODUCTION

Acute ischemic stroke and acute aneurysmal subarachnoid hemorrhage (SAH) are both classified as a “cerebrovascular accident (CVA)”. Indeed, both diseases result from a cerebrovascular accident in the brain, but apart from this there are substantial differences in terms of etiology, epidemiology, clinical presentation and treatment.

In acute ischemic stroke there is an acute lack of blood flow (ischemia) to brain tissue caused by blockage of a feeding artery with resultant damage or dysfunction of tissue. The typical patient admitted for acute ischemic stroke (about 80% of all strokes) has multiple cardiovascular risk factors including diabetes mellitus (DM), is more often male and older than 65 years. On presentation there is a sudden onset of a focal neurologic deficit only sometimes accompanied by headache. Prognosis is relatively favorable (about 20% case fatality).

In aneurysmal SAH there is a bleeding into the subarachnoid space—the area between the membranes that cover the brain. The typical patient admitted with acute aneurysmal SAH, accounting for about 5% of all strokes, is a previously healthy female and around 55 years. Clinical presentation is dominated by a sudden onset of severe headache, with or without a focal neurological deficit. Prognosis is relatively poor (about 50% case fatality).

ACUTE ISCHEMIC STROKE

Stroke ranks second after ischemic heart disease as a cause of lost disability-adjusted life-years with thirty-day case fatality rates ranging between 10 and 17%. The most important risk factors for ischemic stroke include age, hypertension, hypercholesterolemia, diabetes mellitus (DM) and smoking. Atherosclerosis and cardio-embolism causing arterial occlusion are the most important pathophysiological mechanisms of ischemic stroke. The onset is typically sudden with focal neurological deficits such as weakness, sensory loss, aphasia or hemianopia. It is generally believed that in the acute phase a central core of infarcted tissue is surrounded by a rim of ischemic tissue with preserved structural integrity but at risk of (irreversible) infarction. This rim of tissue is referred to as the ischemic penumbra. In the sequence of events that occur after the stroke onset, various factors decide on the fate of the ischemic penumbra: recovery or conversion to definite infarction. Of these, excess of extracellular excitatory amino acids, free-radical formation, inflammation and edema formation appear to be the most important. The prognosis of ischemic stroke also depends on various factors such as age and the coexistence of diseases such as ischemic heart disease or DM. Acute management of ischemic stroke focuses on recanalization of the occluded artery, preventing expansion of the ischemic tissue volume and preventing secondary complications such as pneumonia and deep venous thrombosis.

ACUTE ANEURYSMAL SUBARACHNOID HEMORRHAGE

Only one in every 20 strokes is caused by aneurysmal SAH. This devastating disease has high morbidity and fatality rates. Although these rates have decreased in the last decades, still 35% of acute aneurysmal SAH patients die within the first month after the event. Risk factors include age -although half of the patients are younger than 55 years at the time of the event-hypertension, smoking and moderate to heavy alcohol consumption. Factors that precipitate rupture of an aneurysm are complex, though a sudden increase in arterial pressure appears an important factor in at least a proportion of patients. Sudden headache is the most characteristic symptom of aneurysmal SAH classically described as the “worst headache of my life.” On
admission, two-thirds of the patients have depressed consciousness, while focal neurological deficits are relatively less common in the acute stage. In patients surviving the initial event, the most urgent danger is rebleeding of the aneurysm. In surviving patients, the cumulative risk of risk of rebleeding in the next 4 weeks is about 40% without intervention. Thereafter, delayed cerebral ischemia (DCI), which occurs in 20-30% of patients and is clinically often accompanied by focal neurological deficits, is the most feared complication. In the acute phase, treatment is focused on securing of the ruptured aneurysm, treatment of (systemic) complications and prevention of DCI. After the aneurysm is secured, late rebleeding can occur but is rare. In the long term, surviving patients often experience complications such as anosmia, epilepsy and cognitive deficits.³

**HYPERGLYCEMIA**

The assessment of blood glucose is probably one of the most frequently performed medical laboratory tests. There is, however, no consensus on the cut-off levels to define which glucose levels are too high (hyperglycemia) or too low (hypoglycemia). Hence, it is important to realize that definitions of these terms can vary between time epochs, institutions, departments, physicians and even patients. Nonetheless, regardless of the cut-off levels used to define hyperglycemia, it is described as a very common finding in hospitalized patients, especially in the critically ill patient: so called “stress hyperglycemia”.⁴

Until the end of the last century high levels of blood glucose were considered to be a harmless epiphenomenon to a generalized stress reaction and it was even conceived of as advantageous for the patient. It was reasoned that increased blood glucose levels were a physiological response to support the increased energy demands of glucose dependent tissue such as the brain. Several studies, however, have revealed that patients with high levels of blood glucose fare worse than patients with normal blood glucose levels, irrespective of disease (severity) or other predictors of poor clinical outcome.⁵ In addition to this, experimental studies have revealed that high blood glucose levels enhance various pathophysiological mechanisms, as such suggesting a causal link between hyperglycemia and poor clinical outcome. Therefore the initiation of a randomized controlled trial to investigate the clinical benefit of glucose-lowering treatment appeared logical. Indeed, in 2001 a landmark trial revealed that in critically ill patients admitted to the intensive care unit (ICU), intensive insulin therapy (IIT) was associated with an impressive 43% relative reduction in case mortality.⁶ Moreover, post-hoc analysis of the trial data revealed improved case morbidity for various subgroups of patients, including patients with traumatic brain injury.⁷ These impressive results, together with the widespread availability of insulin to lower blood glucose levels soon resulted in the worldwide implementation of IIT on ICU’s. The landmark trial, however, was performed in a single dedicated center, and included predominantly surgical patients. Therefore caution has to be taken in extrapolating these results to other centers and patient groups. Moreover, more recent trials have tempered the enthusiasm for glucose-lowering treatment as earlier positive findings could not be confirmed in subsequent trials, and IIT was even documented to be associated with worse clinical outcome.⁸

Although the clinical benefits of glucose-lowering treatment have become the subject of debate, it still has the potential to improve clinical outcome in various subgroups of patients, including patients with acute ischemic stroke or acute aneurysmal SAH.
At the time we started this dissertation project, which is part of the Glucose Lowering in Acute Stroke Study (GLASS) project, the primary objective was to set up a trial to investigate the clinical benefit of glucose-lowering treatment in stroke patients. However, before initiating such a trial, this therapy first had to be optimized in terms of safety and efficacy. This appeared to be much more challenging than we anticipated. This thesis therefore consists of studies into the association between glucose metabolism and various measures of clinical outcome, the improvement of glycemic control in terms of safety and efficacy and assessment of the current evidence on glucose-lowering treatment in stroke patients.

**THE GLUCOSE LOWERING IN ACUTE STROKE STUDY**

The research presented in this thesis is funded by the board of directors of the Academic Medical Center (AMC) in Amsterdam and the University Medical Center in Utrecht (UMCU). Both neurology departments of these centers have a special interest in ischemic stroke and in aneurysmal SAH. In the AMC the department of internal medicine has a special interest in research concerning the in-hospital regulation of increased blood glucose levels. Collaboration between these departments resulted in The Glucose Lowering in Acute Stroke Study (GLASS)-project.
AIMS AND OUTLINE OF THE THESIS

AIMS
This thesis consists of two main parts. PART ONE deals with hyperglycemia and its treatment control in patients with acute ischemic stroke, PART TWO addresses hyperglycemia in patients with aneurysmal SAH.

PART ONE 'GLYCEMIC CONTROL IN PATIENTS WITH ACUTE ISCHEMIC STROKE'
Chapter 2 of this thesis provides a review of the available evidence linking hyperglycemia to poor clinical outcome in patients with acute ischemic stroke and highlights the pathophysiological mechanisms that might underlie the deleterious effects of hyperglycemia on acute stroke prognosis and systematically reviews the literature concerning the effects of tight glycemic control after acute ischemic stroke. Chapter 3 describes a cohort study that investigates if cognitive outcome may be different in acute ischemic stroke patients with high or with normal glucose levels on admission. This study was performed to investigate if cognitive outcome could serve as a surrogate marker for clinical outcome in a future randomized clinical trial. Chapters 4 and 5 describe two small multicenter studies, one small trial and a cohort study, that investigated different treatment regimes to control hyperglycemia in patients admitted with acute ischemic stroke.

PART TWO ‘HYPERGLYCEMIA IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE’
Chapter 6 of the thesis describes a systematic review and meta-analysis that investigates the association between admission hyperglycemia and clinical outcome after acute aneurysmal SAH. Chapter 7 describes a cohort study that aimed to assess the association between abnormalities of glucose metabolism with delayed cerebral ischemia and with clinical outcome in acute aneurysmal SAH patients. Chapter 8 contains a laboratory study aimed to characterize glucose metabolism in acute aneurysmal SAH patients. Chapter 9 reviews and highlights the mechanisms that may cause hyperglycemia after acute aneurysmal SAH, and discusses how hyperglycemia may contribute to poor clinical outcome in these patients and systematically reviews the literature on insulin therapy in acute aneurysmal SAH patients.

In chapter 10, the general discussion and summary, future directions for research are discussed and the findings of this thesis are summarized.