Management of blood glucose in patients with stroke

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Abstract
Stroke is a leading cause of death worldwide and the most common cause of long-term disability amongst adults, more particularly in patients with diabetes mellitus and arterial hypertension. Increasing evidence suggests that disordered physiological variables following acute ischaemic stroke, especially hyperglycaemia, adversely affect outcomes. Post-stroke hyperglycaemia is common (up to 50% of patients) and may be rather prolonged, regardless of diabetes status. A substantial body of evidence has demonstrated that hyperglycaemia has a deleterious effect upon clinical and morphological stroke outcomes. Therefore, hyperglycaemia represents an attractive physiological target for acute stroke therapies. However, whether intensive glycaemic manipulation positively influences the fate of ischaemic tissue remains unknown. One major adverse event of management of hyperglycaemia with insulin (either glucose-potassium-insulin infusions or intensive insulin therapy) is the occurrence of hypoglycaemia, which can also induce cerebral damage. Novel insights into post-stroke hyperglycaemia management have been derived from continuous glucose monitoring systems (CGMS). This article aims: 1) to describe the adverse effects of hyperglycaemia following acute ischaemic stroke and the risk associated with iatrogenic hypoglycaemia; 2) to summarise the evidence from current glucose-lowering treatment trials; and 3) to show the usefulness of CGMS in both non-diabetic and diabetic patients with acute stroke.

Keywords: Stroke; Diabetes; Hyperglycaemia; Hypoglycaemia; Insulin therapy; CGMS; Review

Résumé
Contrôle de la glycémie chez les patients présentant un accident vasculaire cérébral
Les accidents vasculaires cérébraux (AVC) sont une cause fréquente de mortalité et d’invalidité au long cours dans la population adulte, en particulier parmi les patients atteints de diabète sucré et/ou d’hypertension artérielle. De nombreuses observations ont montré que les perturbations des fonctions physiologiques secondaires à l’AVC, et tout spécialement l’hyperglycémie, affectent défavorablement le pronostic. L’hyperglycémie post-AVC est fréquente (touchant jusqu’à 50 % des patients) et peut être relativement prolongée, que le sujet soit diabétique ou non. Il a été démontré que l’hyperglycémie exerçait des effets délétères à la fois sur la récupération clinique et sur l’évolution des lésions cérébrales évaluées par l’imagerie médicale. Dès lors, l’hyperglycémie représente une cible physiologique intéressante dans la prise en charge des AVC. Cependant, il reste à apporter les preuves qu’une manipulation intensive de la glycémie influence positivement le pronostic cérébral. En effet, un événement indésirable sérieux de la correction de l’hyperglycémie par l’insuline (que ce soit par une perfusion combinée « glucose-potassium-insuline » ou par une insulinothérapie intraveineuse intensive) est la survenue d’une hypoglycémie qui, elle-même, peut entraîner des dommages cérébraux graves. Aussi, la détection et le traitement de l’hyperglycémie post-AVC pourraient bénéficier du recours à un système d’enregistrement continu des concentrations de glucose (CGMS). Cet article a pour but de rappeler brièvement les conséquences d’une hyperglycémie aiguë post-AVC et les risques associés à une hypoglycémie iatrogène, de résumer les principales données des essais cliniques qui ont tenté de contrôler l’hyperglycémie post-AVC et de décrire l’utilité des systèmes CGMS chez les patients avec ou sans diabète exposés à un AVC.

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Mots clés: Accident vasculaire cérébral ; Diabète ; Hyperglycémie ; Hypoglycémie ; Insulinothérapie ; CGMS ; Revue

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1. Introduction

Stroke is one of the most prevalent disabling disorders in western countries and shares many similarities with myocardial infarction [1]. Several aspects of physiology, notably blood pressure, body temperature, blood oxygen saturation, and blood glucose, may be altered after an ischaemic stroke or intracerebral haemorrhage. Patients with acute ischaemic stroke frequently test positive for hyperglycaemia, which is associated with a poor clinical outcome [2-4]. Most studies show the deleterious effect of early hyperglycaemia, especially in patients with non-lacunar focal or global ischaemia [5]. This association between poor glycaemic control and a poor prognosis is particularly evident in patients with persistent hyperglycaemia, patients without a known history of diabetes mellitus, and patients with cortical infarction [6]. It is well established that management of patients in the stroke care unit improves outcomes. How this is achieved, however, remains unclear. It may be hypothesized that closed monitoring and maintenance of physiological homeostasis, including glucose levels, could contribute to this benefit [7].

In a broader context, hyperglycaemia in critically ill patients has been shown to be associated with increased morbidity and mortality. An astounding 42% relative risk reduction in mortality in surgical intensive care unit (ICU) patients was reported in a single centre study when blood glucose was tightly controlled between 4.5 and 6.1 mmol/L with insulin infusions [8]. In a subsequent study, the same group reported the absence of mortality benefit of intensive insulin therapy in medical ICU patients, except in a subgroup of patients requiring critical care for 3 or more days [9]. While the importance of glucose control in this ICU population is well recognized, many questions remain, including the external validity of these single centre trials, the feasibility and safety of intensive insulin therapy outside the setting of a clinical trial, and the most appropriate target for glycaemic control in such critically ill patients. Indeed, two other trials of intensive insulin therapy reported unacceptably high rates of severe hypoglycaemia, leading to the premature interruption of one of them [10,11]. This was confirmed by the recent observations of the multi-national NICE-SUGAR, a large study that randomized 6104 ICU patients to tight glycaemic control (4.5-6.0 mmol/L) or conventional control (8.0-10.0 mmol/L). An increase in mortality at 90 days was observed with intensive versus conventional glucose control (27.5 vs. 24.9%; odds ratio 1.14; P = 0.02) [12]. There is thus growing debate over the value of intensive insulin therapy in critically ill patients. Indeed, two other trials of intensive insulin therapy reported unacceptably high rates of severe hypoglycaemia, leading to the premature interruption of one of them [10,11]. This was confirmed by the recent observations of the multi-national NICE-SUGAR, a large study that randomized 6104 ICU patients to tight glycaemic control (4.5-6.0 mmol/L) or conventional control (8.0-10.0 mmol/L). An increase in mortality at 90 days was observed with intensive versus conventional glucose control (27.5 vs. 24.9%; odds ratio 1.14; P = 0.02) [12]. There is thus growing debate over the value of intensive insulin therapy in critically ill patients. Available trials have been performed in general medical and surgical ICUs, and these results may not be directly applicable to individuals with severe acute brain disease. Indeed, patients with acute stroke may have heightened susceptibility to hyperglycaemia and hypoglycaemia [13]. Therefore, considering the well-known susceptibility of cerebral tissue to glucose changes [14,15], the influence of acute variations of plasma glucose levels in patients with brain injuries certainly deserves careful investigation [7]. If there is evidence that hyperglycaemia can increase the likelihood of poor outcomes after stroke, including in patients receiving tissue plasminogen activator [16], the role of diabetes and hyperglycaemia is difficult to investigate due to the heterogeneous nature of diabetes/hyperglycaemia in regard to the site of ischaemia, the degree of vasculopathy, and the state of reperfusion.

The main aims of the present review are: a) to analyze the relationship between hyperglycaemia and stroke outcomes; b) to describe the potential risk of iatrogenic hypoglycaemia in stroke patients; c) to consider the possible contribution of continuous glucose monitoring system (CGMS) in a stroke unit; and d) to conclude with some clinical recommendations.

2. Stroke-associated hyperglycaemia

The phenomenon of increased glucose levels after acute stroke was already described in 1976 [17]. A neuroendocrine stress response and an inflammatory response may play a role in generating hyperglycaemia, which may be attributed to several underlying mechanisms: a non-specific reaction to acute stress and tissue injury with the associated autonomic, hormonal and metabolic alterations; uncovering of underlying latent diabetes by the acute stroke; increased secretion of growth hormone due to stroke-induced hypothalamic dysfunction; and irritation of the glucose regulatory centres in the hypothalamus and brain stem by blood-laden cerebrospinal fluid or local ischaemia [17]. One study involving non-diabetic patients demonstrated a rise in median blood glucose level from 5.9 mmol/L at 2.5 h to 6.2 mmol/L at 6 h post-stroke [18]. Indeed, post-stroke hyperglycaemia is a frequent phenomenon, with up to 50% of the patients having an initial blood glucose of over 6.0-7.0 mmol/L [19]; notably, such glucose levels, while fasting, would be consistent with a pre-diabetic state [20]. Hyperglycaemia appears to be associated with more severe stroke, as assessed either with a clinical stroke scale or by brain lesion volume measurement. Post-stroke hyperglycaemia has been associated with poor outcomes [21] but seems to particularly affect outcomes in patients without diabetes. In a meta-analysis, the relative risk of in-hospital 30-day mortality in patients with admission hyperglycaemia (> 6.1-7.0 mmol/L) was 3.28 (95% CI 2.32 to 4.64) in ischaemic stroke patients without diabetes, but it was not significantly increased in patients with diabetes [22]. This observation may suggest that hyperglycaemia per se is a marker of the severity of the stroke rather than a real risk factor. Consequently, the poor outcomes in patients with hyperglycaemia may in part reflect the seriousness of the vascular event itself. Alternatively, diabetes is associated with microcirculatory abnormalities in the brain, including arteriovenous shunting and a reduction in glucose transport across the blood-brain barrier. These processes would reduce the delivery of glucose from the blood to the brain of a patient with diabetes, thus possibly protecting cerebral tissue from high glucose levels after acute stroke. Nevertheless, hyperglycaemia has a particularly potent adverse effect after thrombolysis, also in patients with diabetes [23]. Hyperglycaemic patients develop intracerebral
haemorrhage after thrombolysis more often and have overall poorer clinical and radiological outcomes [24]. Hyperglycaemic patients are also less likely to experience recanalisation with thrombolysis. Even if it does occur, hyperglycaemic patients are more likely to deteriorate, particularly if hyperglycaemia appears early after recanalisation. So even if the mechanisms of cerebral glucotoxicity remain unclear, it seems logical to provide early management of hyperglycaemia in patients presenting with acute stroke.

Unfortunately, there are no relevant scientific data proving clear-cut efficacy of managing hyperglycaemia in acute stroke. A few exploratory randomised trials showed that glucose-potassium-insulin (GKI) infusions can be safely administered to acute stroke patients with mild to moderate hyperglycaemia producing a physiological but attenuated glucose response to acute stroke, the effectiveness of which remains to be elucidated [25,26]. The large multicentre GIST-UK trial (Glucose Insulin in Stroke Trial) aimed to demonstrate that treatment with GKI infusions to maintain euglycaemia immediately after the acute event reduces death at 90 days [27]. The trial was stopped due to slow enrolment after 933 patients were recruited. For the intention-to-treat data, there was no significant reduction in mortality at 90 days (GKI vs. control: odds ratio 1.14; 95% CI 0.86-1.51; \( p = 0.37 \)). There were no significant differences for secondary outcomes either. In the GKI group, the overall mean plasma glucose and mean systolic blood pressure were significantly lower than in the control group (mean difference in glucose 0.57 mmol/L, \( p < 0.001 \); mean difference in blood pressure 9.0 mmHg, \( p < 0.0001 \)). This neutral result does not prove inefficacy of acute glucose control for several reasons: acute blood pressure changes may be a confounding factor; the study was underpowered; glucose-lowering therapy was administered relatively late after the stroke event; and perhaps more importantly, GKI infusions achieved only modest decrements in glucose levels. A recent randomised, placebo-controlled trial of GKI infusion in patients with blood glucose > 7 mmol/L within 24 hours of ischaemic stroke measured infarct growth assessed by magnetic resonance imaging (MRI) between baseline and day 7 as the primary endpoint, and brain lactate concentrations with magnetic resonance spectroscopy [28]. GKI infusions lowered blood glucose (approximately 5.6 mmol/L \textit{versus} 7.0 mmol/L in control subjects from 6 to 12 hours post-intervention) and attenuated an increase in brain lactate; they did not affect infarct growth in patients with persistent arterial occlusion, and with a high incidence of asymptomatic hyperglycaemia (< 4 mmol/L in 76% of patients; almost 50% of GKI patients required intravenous dextrose infusion).

More substantial reductions in plasma glucose concentrations can be achieved using intensive intravenous insulin, but perhaps at the expense of a higher risk of hypoglycaemia. In a single centre pilot study, 25 acute ischaemic stroke patients were randomised to an insulin sliding scale approach or standard management [29]. Sliding scale insulin therapy significantly reduced blood glucose throughout the 48-hour treatment. Stability of blood glucose within a pre-defined range was achieved with only one possible adverse event related to hypoglycaemia. Although not adequately powered to assess outcome, no significant differences in mortality or disability were observed between the two groups. In another study of 40 ischaemic stroke patients with onset less than 24 hours earlier, an intensive intravenous insulin infusion protocol with the aim of reaching and maintaining blood glucose levels between 4.44 mmol/L and 6.11 mmol/L effectively lowered blood glucose levels compared to subcutaneous insulin if concentrations were above 11.10 mmol/L [30]. Hypoglycaemic events were five times more common (but with few symptomatic events) in patients treated intensively, whereas severe hyperglycaemia was five times more frequently associated with conventional treatment. In addition to the increased risk of manageable hypoglycaemic events, the authors concluded that intensive insulin treatment imposes a considerable strain on both patients and caregivers. A highly motivated and trained staff seems essential, limiting feasibility outside of specialty care settings [30].

Despite the absence of clear evidence from interventional studies, current guidelines recommend management of hyperglycaemia in acute stroke. The main reason is that several reports provide reasonable evidence that persistent elevations of blood glucose levels are associated with neurological worsening. Nevertheless, most recommendations are prudent. Indeed even if experts concluded that the level of hyperglycaemia that previously mandated emergency treatment in the setting of stroke was too high, most of them considered that a reasonable approach would be to initiate insulin treatment among patients with a blood glucose level > 11.10 mmol/L, although this remain a matter of controversy (see below). However, close monitoring of glucose concentrations with adjustment of insulin doses to avoid hypoglycaemia is recommended. Simultaneous administration of glucose and potassium also may be appropriate [31].

3. Iatrogenic hypoglycaemia and stroke

Hypoglycaemia is a common complication of the use of glucose-lowering agents in diabetic patients, and its symptoms may mimic those of a stroke, which may cause problems regarding the clinical evaluation of patients admitted in stroke units. The reason that thresholds proposed in guidelines to initiate insulin therapy remain so “comfortable” is that severe hypoglycaemia may occur if the blood glucose targets are too strict. However, if glucose management is to be undertaken, this should be instituted while there is still salvageable tissue and the glucose reduction must be substantial. As already mentioned, intensive intravenous insulin may be more effective than GKI infusions. In either case, both interventions carry a risk of hypoglycaemia, and any proposed intervention must balance the efficacy/safety ratio as well as the convenience of glycaemic control. Indeed, in clinical practice, it is a real challenge to obtain
near normal glycaemic values using aggressive management of hyperglycaemia without experiencing any hypoglycaemic event. A pilot study assessed the feasibility of early intravenous insulin in patients with post-stroke hyperglycaemia (admission glucose concentration: 9.4-22.2 mmol/L). In 24 patients, there was a substantial decrease in glucose level (from 14.7 ± 4.9 mmol/L pre-intervention to 7.3 ± 1.1 mmol/L post-intervention), with a 21% incidence of symptomatic hypoglycaemia [29]. With no control group, it is difficult to know how much of this change can be attributed to the natural history of post-stroke hyperglycaemia rather than a specific intervention. Based on these pilot data, the latter group completed a larger randomised controlled trial. The recently published Treatment of Hyperglycaemia in Ischaemic Stroke (THIS) study randomised a predominantly diabetic cohort to intravenous insulin for 72 h or usual care (subcutaneous insulin) [32]. In this study, aggressive glucose management achieved better glycaemic control (mean difference in glucose concentration averaging 3.7 mmol/L). However, this was at the cost of an increased rate of hypoglycaemia (12 episodes versus 0 episodes). Clearly the limiting factor of intensive management of hyperglycaemia in acute stroke is the risk of hypoglycaemia, which may also be deleterious for the brain [14, 15]. Nevertheless, in available studies it is difficult to link poor outcome after stroke and the occurrence of treatment-induced hypoglycaemia.

Because hypoglycaemia may produce neurological signs that mimic ischemic stroke and because hypoglycaemia itself may lead to brain injury, prompt measurement of the plasma glucose concentration and rapid correction of a low serum glucose level are important. Current guidelines point out that hypoglycaemia should be treated in patients with acute ischemic stroke (class I, level of evidence C) [31]. The goal is to restore normoglycaemia, but excessive post-hypoglycaemia elevation of blood glucose levels should be avoided.

4. Lessons from continuous glucose monitoring

Most of the actual data have been obtained by research groups that have used a single time point measurement of blood glucose to define glycaemic control. This method cannot precisely evaluate the severity and the duration of hyperglycaemia however [33]. The development of the continuous glucose monitoring system (CGMS) with a subcutaneous sensor device has provided a novel tool for recording interstitial glycaemic kinetics [33]. GGMS revealed that normoglycaemia was only achieved in 22% of the time in diabetic/non diabetic ICU patients [34] and that early and frequent hyperglycaemia occurred in non-diabetic patients with acute coronary syndromes [35]. Recent evidence suggests that continuous monitoring of glucose levels may help to signal glycaemic excursions and eventually to optimize insulin titration in the ICU [36].

Using this technology, Baird et al. performed a pilot study in which they aimed to directly address the relationship between stroke outcome and contemporaneous glycaemia [37]. This trial enrolled 25 subjects within 24 hours of ischaemic stroke symptoms. Multiple regression analysis indicated that both mean CGMS and blood glucose levels ≥7 mmol/L were independently associated with increased final infarct volume change. The conclusion was that there is an urgent need to study normalization of blood glucose after stroke. Later, Allport et al. [38] used CGMS devices in 59 patients with acute hemispheric ischaemic stroke. The patients were prospectively studied regardless of medication, admission plasma glucose value, and diabetes status. On admission 36% of patients had pre-existing diabetes. At the earliest analyzed time point of 8 h from stroke onset, 50% of non-diabetic subjects and 100% of diabetic patients were hyperglycaemic (≥7 mmol/L). This early-phase hyperglycaemia was followed by a decrease in glucose level 14-16 h post-stroke when only 11% of non-diabetic and 27% of diabetic patients were still hyperglycaemic. However, a late hyperglycaemic phase 48-88 h post-stroke was observed in 27% of non-diabetic and 78% of diabetic patients. Thirty-four percent of non-diabetic and 86% of diabetic patients were hyperglycaemic for at least a quarter of the monitoring period. Multivariate regression analysis demonstrated that diabetes, insular cortical ischaemia, and increasing age independently predicted higher glucose values. Thus post-stroke hyperglycaemia is common and rather prolonged despite treatment based on current guidelines. There are early and late hyperglycaemic phases in non-diabetic as well as diabetic patients. Treatment protocols with frequent glucose measurements and intensive glucose-lowering therapy for a minimum of 72 h post-stroke need to be evaluated. With the recent improvement of glucose monitoring systems [36], it will probably be easier to manage post-stroke hyperglycaemia in a more effective and safe manner in the near future [33].

5. Practical implications regarding glucose management during acute stroke

Stroke is the second most common cause of death and a major cause of disability worldwide. Advances have occurred in the prevention and treatment of stroke during the past decade [39]. However, the lack of high quality evidence on the effects of blood glucose manipulation in acute stroke is reflected by the wide variation in current clinical practices. Similarly, local and international guidelines differ in their recommendations for treatment of post-stroke hyperglycaemia. Comparing guidance from the American Stroke Association [31], the UK Royal College of Physicians [40] and the European Stroke Organisation (ESO) [41], all agree that post-stroke hyperglycaemia is associated with poorer outcomes, that (major) hyperglycaemia should be prevented/treated and that iatrogenic hypoglycaemia must be avoided or promptly treated (Fig. 1). However, there is no consensus on the frequency of glucose monitoring, thresholds for intervention or methods to achieve glucose control [42,43].

According to the American Stroke Association [31], because evidence indicates that persistent hyperglycaemia
solution of predetermined concentrations of glucose, insulin, and potassium, with peripheral glucose monitoring to guide the rate of infusion. An alternative approach is that of a “sliding scale” insulin administration, wherein the infusion uses a rapidly acting insulin preparation. Proponents of GKI state that this approach is more “physiological” and less prone to dangerous extremes of blood sugar. However, the frequent changes of infusion required for maintaining glucose is time consuming. Alternatively, treating hyperglycaemia with intravenous insulin therapy only (without concomitant glucose infusion) requires frequent control of blood glucose concentrations to adapt rates of insulin in order to avoid hypoglycaemia. Ideally, clinicians should not infuse any glucose solution during the management of such patients (except to correct hypoglycaemia) in order to avoid acute hyperglycaemia, which may be deleterious for the injured brain [7]. Even if CGMS has only been used to carefully evaluate post-stroke hyperglycaemia up until now, this technology will probably be interesting in the future for managing hyperglycaemia in stroke units in a more effective and safer manner [33], as in other critically ill patients [34-36].

6. Conclusion

The danger of post-stroke hyperglycaemia is well established, with numerous data confirming an association between hyperglycaemia and poor outcomes, including in patients treated with thrombolysis. However, although there is compelling evidence that hyperglycaemia has an effect on stroke outcome, the debate continues as to whether the effect is independent of the influence of diabetes or initial stroke severity. The aetiology of hyperglycaemia and the pathophysiology that underlie its detrimental effects remain unclear. A distinction between unknown diabetes and non-diabetic hyperglycaemia seems important, as prognosis and effect of intervention have been shown to differ in these two groups. When attempts are made to treat hyperglycaemia, care should be taken to avoid rapid fluid shifts, electrolyte abnormalities, and hypoglycaemia, all of which can be detrimental to the brain. Patients with critical brain disease should have frequent glucose monitoring because (severe) hyperglycaemia and even modest hypoglycaemia may be detrimental. The safety and efficacy of intravenous insulin therapy in patients with critical brain disease have not been well studied. Careful use of insulin infusion protocols appears advisable, but maintenance of strict normoglycaemia cannot be recommended in this population because of a too high risk of hypoglycaemia. Rigorous studies must be conducted to assess the value of insulin therapy and to determine the optimal blood glucose targets in patients with the most common acute vascular insults. Finally, experts have to propose clear guidelines, which are feasible in clinical practice. One of the key successes will probably be the ability to check glucose continuously in order to adapt insulin therapy on time. This approach needs CGMS devices with good accuracy and a short lag time in order to minimize the risk of both stroke-induced hyperglycaemia and iatrogenic hypoglycaemia.

Figure 1. Illustration of the interrelationships between stroke and glucose control.
A: Deleterious effects of post-stroke hyperglycaemia.
B: Deleterious effects of iatrogenic hypoglycaemia.
C: Potential benefit of Continuous Glucose Monitoring System (CGMS) and Intensive Insulin Therapy (IIT) driven by CGMS. GKI: Glucose-Potassium-Insulin.

(> 7.8 mmol/L) during the first 24 hours after stroke is associated with poor outcomes, lower plasma glucose concentrations than the commonly accepted 10-11 mmol/L threshold (possibly > 7.8 to 10.3 mmol/L) should probably trigger administration of insulin. This approach is similar to the procedure in other acute situations accompanied by hyperglycaemia (recommendation class IIa, level of evidence C) [31]. However, the most recently revised guidelines of the European Stroke Organisation still suggest considering intervention if blood glucose concentration is greater than 10 mmol/L, provided that hypoglycaemia can be avoided [41].

In clinical practice the first step is to objectify hyperglycaemia on admission and in the post-stroke state in a sufficiently accurate manner in order to evaluate its severity and duration. Intravenous insulin therapy and frequent blood glucose control for adapting insulin delivery are required. A number of approaches to acute glycaemic control have been described, and there is presently no consensus as to the optimal intervention. Glucose-potassium-insulin (GKI) – based regimes infuse a solution of predetermined concentrations of glucose, insulin...
References