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Glycemic Control in Hospitalized Stroke Patients: A Review

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Abstract

Purpose of Review The purpose of this review is to discuss clinical trials involving glycemic control in hospitalized stroke patients and to review oral medications used in glycemic control. GLP-1 agonists, which have some preliminary studies in ischemic stroke, will also be reviewed.

Recent Findings Until recently, glycemic control targets in hospitalized stroke patients remained unclear. The SHINE (Stroke Hyperglycemia Insulin Network Effort) trial demonstrated no significant difference between aggressive versus standard of care glycemic control in the acute ischemic stroke patient.

Summary Although SHINE demonstrated a lack of statistical difference in glycemic control targets, many questions remain including glycemic control in patients with other stroke types (SAH, ICH). The role of non–insulin-based medications in glycemic control for hospitalized stroke patients remains unclear and presents an opportunity for further research. Finally, GLP-1 agonists present an interesting area of research for acute ischemic stroke.

Keywords Stroke · Glycemic control · GLP-1 agonists · SHINE trial

Introduction

Stroke is a leading cause of mortality and morbidity in the USA [1]. Recent advances in endovascular therapy have significantly improved functional outcome in patients with large vessel occlusion. Further optimization of general medical care, specifically glycemic control in the hospitalized stroke patient, may lead to better outcomes.

Hyperglycemia is prevalent in up to 50% of acute stroke patients on admission and has been associated with poor outcome independent of age, stroke severity, and subtype. Moreover, hyperglycemia is known to worsen outcomes in patients with recanalization through TPA [1, 2]. Animal studies suggest that hyperglycemia is most harmful to reperfused tissue through delivery of glucose to ischemic tissue [1, 3]. Hyperglycemia worsens intracellular acidosis, accumulation of extracellular glutamate, worsening of brain edema, and an increased tendency for hemorrhagic transformation [1, 4].

Conversely, hypoglycemia is a common and frequent complicating factor. Studies estimate that 49–68% of patients undergoing continuous glycemic monitoring develop hypoglycemia (blood glucose < 60 mg/dL). In addition, hypoglycemia, both prolonged and repeated, has been linked to factors altering thrombosis and hemostasis [5]. Hypoglycemia can also exacerbate cerebral ischemia as cerebral tissue is heavily reliant on glucose metabolism.

Data-guided management of glycemic control in hospitalized stroke patients has been limited primarily to acute ischemic stroke patients. It is unknown if these data-driven studies apply to other stroke types including intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (aSAH). General surgical and critical care trials likely included a small percentage of such patients, but would not necessarily be generalizable to the variety of hospitalized stroke patients.

Of the 800,000 stroke patients/year in the USA, 87% are acute ischemic stroke, 10% ICH, and 3% aSAH; as such, this review will focus primarily on hospitalized acute ischemic stroke patients.

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Glycemic Control in Acute Ischemic Stroke Patients

Historically, several trials have been completed in the management of glycemic control in the hospitalized stroke patient and in the general critical care setting. We will review some of the key studies in the management of glycemic control in the acute ischemic stroke patient.

Post-stroke hyperglycemia is prevalent in up to 20–50% of acute stroke patients. This represents a combination of patients with diabetes (known and new diagnosis) and those with stress-induced hyperglycemia [1, 6]. There is strong evidence that persistent post-stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. MR spectroscopy has correlated hyperglycemia and increased lactate production in penumbral tissue, thereby increasing infarct volume [1, 7].

Based on observational studies that hyperglycemia worsens clinical outcome and infarct volume in the acute setting for ischemic stroke, investigators have examined aggressive glycemic control (IV insulin drip) versus standard of care (bolus insulin with corrective sliding scale). There have been a few randomized controlled trials of continuous insulin versus placebo and standard of care, with general target range for aggressive control considered blood glucose levels 80–130 mg/dL and standard of care blood glucose levels < 180 mg/dL.

The GLIAS study group (Glycemia in Acute Stroke, 2009), a multicenter prospective observational study, reported hyperglycemia (blood glucose > 155 mg/dL) during any time during the first 48 h is associated with poor outcome, independent of stroke severity, infarct volume, presence of diabetes, or age. This level was associated with a 2.7-fold increase in the odds of poor outcome and threefold risk of death at 3 months [1, 6].

The GIST-UK (Glucose Insulin in Stroke—UK, 2007) trial enrolled 933 patients. This was a prospective multicenter randomized controlled trial that found no benefit in mortality at 90 days (primary outcome) or clinical benefit in the treatment group, despite lowering blood glucose, 10 mg/dL on average. However, the authors admit that the trial was stopped short of its goal enrollment of 2355 patients secondary to slow recruitment. This may have underpowered the study to detect a significant difference in clinical outcome [1, 8].

The Treatment of Hyperglycemia in Ischemic Stroke (THIS, 2007) trial was a prospective multicenter randomized controlled blinded trial which was a safety and feasibility trial to examine aggressive control of hyperglycemia (treatment to maintain blood glucose less than 130 mg/dL) versus standard insulin sliding scale (treatment to maintain blood glucose less than 200 mg/dL). A total of 46 patients were enrolled; this study demonstrated that the intravenous insulin protocol corrected hyperglycemia significantly better, 133 vs. 190 mg/dL. Only the continuous insulin group had documented hypoglycemia (< 60 mg/dL) in 11 of the 31 patients; 1 with reversible neurologic deficits. Although the study was not powered to assess for improvement in clinical outcomes, the aggressive treatment group did have slightly better modified Rankin scale at 3 months, but not statistically significant in comparison to the standard treatment group [1, 9]. The modified Rankin scale (mRS) is a commonly used neurological disability scale from 0 to 6 with 0 considered asymptomatic and 6 death, and generally mRS > 4 is considered as severe disability.

The Glucose Regulation In Acute Stroke Patients (GRASP) trial, a prospective multicenter three-armed trial, included 74 patients who were randomized to receive insulin infusion to tight glucose control (target range 70–110 mg/dL), loose glucose control (70–200 mg/dL), and standard therapy (insulin sliding scale to maintain range 70–300 mg/dL). The tight group had a 30% rate of asymptomatic hypoglycemia (blood glucose < 55 mg/dL), while the other two groups had a 4% rate. There was one case of symptomatic hypoglycemia in the loose group. Glucose values were controlled 97% of the time with the infusion protocols (111 and 151 mg/dL, respectively, for the tight and loose groups) and only 88% with standard of care (151 mg/dL). Using an infusion to maintain a blood glucose in the 70–200 mg/dL change does not appear to differ from the control group with sliding scale, and in fact can be more burdensome and increase the risk of hypoglycemia without necessarily achieving a clinical target. Although the study was not powered to assess for clinical benefit, exploratory efficacy analysis did not reveal any statistically significant clinical benefit between groups [1, 10].

Understanding the SHINE Trial

The recently completed SHINE (Stroke Hyperglycemia Insulin Network Effort, 2019) helped to clarify conflicting smaller studies. SHINE was a large prospective multicentered NIH-sponsored randomized controlled double-blinded trial enrolling 1151 patients with acute ischemic stroke within the first 12 h of symptom onset. A total of 581 patients were enrolled in the intensive arm (blood glucose target 80–130 mg/dL) with continuous infusion of insulin with target range controlled via a computerized patient-specific learning algorithm. A total of 570 patients were enrolled in the control arm using sliding scale insulin treatment every 6 h, but checked every 3 h (blood glucose target 80–179 mg/dL). Patients were enrolled within 12 h of symptom onset and maintained at either goal for the first 72 h of hospital admission [11].

The trial was halted at 1151 patients due to hypoglycemia and adverse events in the intensive group (11.2% vs. 3.2% in the control group). Both groups remained remarkably well within their randomized groups in terms of glycemic target: the intensive group had an average of 118 mg/dL (95% CI 115–121), while the standard group had an average blood glucose of 179 mg/dL (85% CI 175–182). The average difference between the intensive and control groups was 61 mg/dL [11].

There were no significant differences in the primary outcome prespecified as functional outcome at 90 days as measured by the mRS based on admission NIH Stroke Scale (NIHSS). Additional functional outcome scores including 90-day NIHSS, Barthel Index, or Stroke Specific Quality of Life score did not demonstrate a benefit to the intensive arm. These data do not support the use of intensive glucose control in acute ischemic stroke patients due to lack of improvement in functional outcome and a significantly higher rate of adverse events including hypoglycemia [11]. Although a 90-day functional outcome assessment may seem prolonged for a short-term glycemic target, it is a relatively standard timeline for functional outcomes in the neuroscience literature.

Limitations of the trial include that 42% of the patients were enrolled at six centers, potentially creating a bias in the overall results. Patients with type 1 diabetes or known insulin dependence were excluded from the trial for study and safety reasons for concern that randomization to the control arm, which only included insulin sliding scale, would result in higher blood sugars and potentially have a higher risk for requiring insulin infusion. Another limitation is the potential for confounding treatment variables: although the study's aim was to assess a specific range of glycemic control, the modes of insulin delivery varied, insulin infusion versus subcutaneous sliding scale insulin. Moreover, many hospitals do not have computer program–based insulin infusions that are able to learn individual patient sensitivity and adjust, as opposed to standard insulin infusions [11].

Strengths of the SHINE trial include the excellent patient enrollment and a large sample size, and the difference between glycemic target ranges that was achieved, on average 61 mg/dL. Previous smaller trials had not achieved that degree of difference between intervention and control arms [11].

The SHINE trial raises some additional areas for research. As 80% of patients in the SHINE trial had type 2 diabetes, the anticipated difference in outcome between patients presenting with stress-induced hyperglycemia versus hyperglycemia from diabetes may be negligible, but does merit further investigation. Management of glycemic control in patients undergoing postoperative cardiothoracic surgery have benefited from tight glycemic control in the postoperative period; it is unknown if similar stress-induced hyperglycemia in the acute ischemic stroke setting may benefit in a similar fashion.

Additional areas of ongoing research in glycemic control in hospitalized stroke patients need to be initiated in other stroke diseases: to date, most glycemic control trials have focused on ischemic stroke patients. However, hyperglycemia is quite common in patients with aneurysmal SAH as well as intra-parenchymal hemorrhages. It is unknown if data and conclusions from glycemic control in ischemic stroke patients can be extrapolated to include other stroke types. A current AHA/ASA recommendation for acute ischemic stroke patients is to target blood glucose 140–180 mg/dL [12].

Non–Insulin-Based Drugs in Glycemic Control

Many patients with acute ischemic stroke are often admitted to Critical Care Units; the natural tendency to aggressively manage blood sugars in the ICU setting generally leads to insulin drip infusions to target blood glucose levels < 180 mg/dL. Bolus insulin dosing with correction is also commonly used in patients who take oral medications at home, but are unable to continue those in the hospital. There is a paucity of data regarding the use of non–insulin-based antihyperglycemic agents in the hospitalized stroke patient. The often longer half-lives, unfamiliarity with safety profiles, concern for deteriorating mental status and dysphagia, and lack of literature have left many neurologists hesitant to initiate these medications in the hospital.

Recent promising studies in cardiovascular outcome trials have demonstrated a benefit in reduction of non-fatal stroke [13, 14]. In addition, there is emerging basic science research on potential benefits of GLP-1 agonists in the blood–brain barrier in patients with acute ischemic stroke [15].

In this section, we review non-insulin agents in the management of glycemic control and potential for use in the hospitalized stroke patient. It should, however, be noted that current guidelines from the ADA recommend insulin as first-line therapy for the management of hyperglycemia for both critically ill and non-critically ill hospitalized patients [16, 17].

Metformin

Metformin historically has been first-line therapy for non-insulin agents for type 2 diabetes. Its postulated mechanism of action is decreasing gluconeogenesis and glycogenolysis in the liver, increasing anaerobic glucose metabolism in the intestine, and increasing insulin-mediated glucose uptake in the skeletal muscle. An additional benefit is the lack of associated hypoglycemia. The use of metformin in hospitalized patients has been associated with lactic acidosis and contrast-induced nephropathy (CIN) after receiving IV iodinated contrast [18]. Patients with acute ischemic stroke often undergo CT angiograms of the head and neck to assess

for large vessel occlusion as well as CT perfusion imaging to assess for potential reperfusion therapy. Some of these patients then require additional intra-arterial contrast for cerebral angiography. However, newer contrast agents are less often associated with CIN, and many patients tolerate CIN with a transient increase in Cr [19]. Generally, metformin is held for at least 48 h before/after the procedures and tests requiring contrast media for patients taking metformin. However, a meta-analysis that included 347 trials showed no fatal lactic acidosis (4.3 cases in the metformin per 100,000 patients years vs. 5.4 cases per 100,000 in the non-metformin group) [20]. Studies show that metformin may decrease insulin requirement in the outpatient setting, but there are little data to suggest similar data for the hospitalized patient. Another study has shown that adding metformin to standard care (long acting insulin + SSI) in the hospitalized patient reduced the total insulin requirement to maintain euglycemia (0.58 ± 0.28 vs. 0.28 ± 0.13 U/kg, $p < 0.01$) and lower bolus insulin doses (0.26 ± 0.18 vs. $0.11 \pm 0.0.8$ U/kg, $p < 0.01$) [21]. These patients were admitted to the hospital for 14 days for this specific study.

Patients included in this study were healthy without an active disease process. However, in the critically ill stroke patient, metformin should be held since there are no proven benefits of treating hyperglycemia with metformin.

Sulfonylureas

The sulfonylureas (glyburide, glimepiride, glipizide) are popular second-line oral agents. They stimulate insulin release from the beta cells of the pancreas, thereby ultimately increasing the risk of hypoglycemia. Additional side effects include significant drug-to-drug interactions, most often with anti-fungal agents with "azole" rings, as well as non-selective beta blockers. An increased risk of cardiovascular events was also reported; 19% of hospitalized patients who took sulfonylureas have developed at least one episode of hypoglycemia, especially with glyburide [22]. Our current practice is to not continue home sulfonylureas for hospitalized stroke patients secondary to unpredictable PO intake secondary to dysphagia and tolerance of TFs.

Thiazolidinediones

Thiazolidinediones (pioglitazone, rosiglitazone) activate the PPAR-gamma pathway and increase insulin sensitivity in the liver, adipose tissues, and skeletal muscles. It also has the added benefit of decreasing triglycerides and plasma fatty acid levels and increasing HDL levels. The known side effects include peripheral edema and worsening heart failure. These drugs tend to have effects lasting for a few weeks; as such, discontinuation in a hospitalized patient should have minimal effect on glycemic control. Our practice is not continuing these agents for the acute ischemic stroke hospitalized patient.

SGLT2 Inhibitors

Sodium-glucose cotransporter (SGLT2) inhibitors (canagliflozin, dapaglifozin, and empaglifozin) are newer oral agent medications for control of diabetes and hyperglycemia. As a result, there are currently little data to determine the risks and benefits of continuing SGLT2 inhibitors in the hospitalized or critically ill stroke patient. The mechanism of action of SGLT2 inhibitors is blocking glucose reabsorption in the proximal collecting duct of the kidney. The common side effects include increased risk of urinary and genital tract infection. These drugs tend to have low risk to develop hypoglycemia unless the patient is also being treated with insulin, canaglifozin (RR 1.49; 95% CI 1.14–1.95; $p = 0.004$), and dapaglifozin (RR 1.16; 95% CI 1.05–1.29; $p = 0.005$) [23]. In the EMPA-REG trial, empaglifozin and insulin did not cause significant hypoglycemic events; however, the percentage of insulin use reduction was not reported in this study [24]. In addition, diabetic ketoacidosis has been reported as a potential side effect for patients taking SLGT2 inhibitors. A plausible explanation is reduction of renal excretion of ketones [25] and an increase in ketone production [26]. A previous meta-analysis [27] reported no significant DKA events in the hospital setting for patients with type 2 diabetes; however, a more recent study showed an increased risk of DKA (38% vs. 2%, OR 37.4; 95% CI 8.0–175.9; $p < 0.0001$) [28]. The authors in the study have identified risk factors to develop SGLT2-associated DKA such as surgery and fasting. A recent meta-analysis of three randomized controlled trials along with smaller trials of SGLT2 inhibitors on cardiovascular events in patients with type 2 diabetes did not demonstrate a reduction in risk of ischemic stroke [29]. We do not recommend that these medications be continued in the inpatient acute ischemic stroke setting.

DPP4 Inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors (sitagliptin, linagliptin) are enzymes used to break down endogenous GLP-1. It is a second-line agent and does not cause weight gain or hypoglycemia.

A large prospective trial of sitagliptin and alogliptin did not show an increased risk of acute or chronic pancreatitis [30, 31]. It does, however, show a small increase in infection risk, such as urinary tract infection and nasopharyngitis [32]. There are not many studies that have evaluated the safety profile of using DPP4 in the critical care setting or hospitalized stroke patient. In the SITA-HOSPITAL trial, it is reported that the sitagliptin-treated group did not show a significant difference in the rate of hypoglycemia, treatment

failures, hospital length of stay, or complications compared with the insulin group. Nevertheless, the total daily insulin requirement was reduced (24.1 U vs. 34.0 U; $p < 0.0001$) [33]. Glucose variability was not reported in this study. Studies that have examined cardiovascular outcomes in DPP4 inhibitors have not demonstrated a clinical benefit for ischemic stroke reduction [33].

Overall, non–insulin-based medications, as discussed above, have shown minimal benefits of lowering insulin requirements or decreasing serum glucose variability in the hospitalized/critically ill patient. There are very little data on hospitalized stroke patients. In fact, many studies have shown conflicting results. Nevertheless, they have the potential to worsen heart failure, acidosis, and hypoglycemia, particularly in the setting of renal failure. It is reasonable to hold home non–insulin-based medications and achieve glycemic control with insulin in hospitalized stroke patients until further experience and data-driven studies provide more insight.

GLP-1 Agonists

In recent years, there has been a growing interest in using incretin-based medications. Glucagon-like peptide agonists/GLP-1 (exenatide, liraglutide, albiglutide, semaglutide, dulaglutide) are often a second-line add-on medication after metformin has been initiated. These drugs have the benefit of weight loss, increased satiety, and favorable metabolic changes including a decrease in triglycerides and an increase in HDL. As a convenience factor, some are injected once a week. The main effect of GLP-1 is to promote insulin secretion from pancreatic beta cells, decreased glucagon secretion, and glucose production in the liver, increased glucose uptake in the muscle, and decreased appetite and deceased gastric emptying. Overall, the incidence of hypoglycemia has remained low in the outpatient setting.

There is a growing interest of using GLP-1 agonists in the inpatient setting. These drugs carry a low risk of developing hypoglycemia and augment glucose dependent insulin secretion while a patient is receiving insulin therapy, thereby potentially decreasing overall insulin requirement. Intravenous GLP-1 is used with a fixed dose except for patients who are in renal failure who need a reduction in dosing. One study in the surgical ICU setting has demonstrated that GLP-1 is a safe and effective way to reduce the serum glucose variability (glucose coefficient of variation 18% in GLP-1 group vs. 30% in saline group, $p = 0.01$) [34]. In studies with patients undergoing CABG, there was a 45% less insulin requirement to achieve the same glycemic control [35]. One study included 40 patients with an initial glucose of 140 ~ 400 mg/dL admitted to cardiac ICU. Patients reached their target range (100 ~ 140 mg/dL) quicker with median time to steady state (2 h; 95% CI 1.5 ~ 5) in the exenatide group (12 h; 95% CI 7 ~ 15). No episode of severe hypoglycemia (< 50 mg/dL) was reported [36].

The benefits of GLP-1 agonists appear to be independent of a history of diabetes. In a smaller study of acute myocardial infarction (MI) patients in a cardiac ICU, left ventricular dysfunction improved in the GLP-1 agonist group (LVEF 29 ± 2% to 39 ± 2%, $p < 0.01$) whereas there was no improvement in the control group after a continuous 72-h infusion (1.5 pmol/kg/min) [37]. This may provide additional benefit when stress-induced cardiomyopathy is also present in patients with stroke, particularly in the critical care setting.

The authors are not aware of any specific prospective trials involving GLP-1 agonists in hospitalized acute ischemic stroke patients. However, some cardiovascular outcome trials do suggest a benefit for ischemic stroke reduction. All of these trials were randomized, placebo-controlled, double-blinded trials with the primary end points being either mortality from cardiovascular causes, MI, or stroke versus non-fatal MI, non-fatal stroke, and death from cardiovascular causes. Specifically, semaglutide was found to have significantly fewer (1.6% vs. 2.7%) non-fatal strokes in the clinical trial SUSTAIN-6 (2016) that enrolled 3297 patients. Albiglutide was studied in the Harmony outcomes trial (2018), enrolling 9463 patients; this trial demonstrated a significant combined reduction in mortality from cardiovascular causes, MI, and stroke (7% vs. 9%). Dulaglutide was studied in the REWIND trial (2019), enrolling 9901 patients. The trial demonstrated a significant reduction in non-fatal stroke (2.7% vs. 3.5%, $p = 0.017$) [38].

Overall, a meta-analysis study evaluating cardiovascular outcomes in patients using GLP-1 agonists found that there was a significant reduction in MI and ischemic stroke risk [39].

The most common side effects of GLP-1 agonists are nausea and vomiting. This may be potentially problematic in stroke patients in the Neuroscience Critical Care Unit with elevated intracranial pressure. It has been reported that GLP-1 agonists delay gastric emptying in over 50% of critically ill patients without prior history [40]. However, it does not appear to worsen gastroparesis if it is already a chronic pre-existing complication [41]. A meta-analysis concluded that the incidence of hypoglycemia was not significant (7.4% in the GLP-1 group and 6.8.% in the standard group; $p = 0.94$) [42].

Many studies have shown the benefits of using intravenous GLP-1 as an adjunct to the standard insulin treatment. It has been effective in treating stress hyperglycemia whether the patient is receiving parenteral or enteral feeding. The beneficial profile of GLT-1 agonists lowers serum glucose to the target faster and less glucose variability and insulin requirement. Besides nausea and vomiting, it carries a safe side effect profile and does not significantly affect hemodynamic stability. The potential neuroprotective benefits and

favorable glycemic control profile without significant hypoglycemia suggest further areas of research for this class of drugs, particularly for the hospitalized stroke patient.

Conclusion

Glycemic control in hospitalized stroke patients has made significant progress in the last few years. The SHINE trial was a prospective randomized controlled trial that helped to define targets for management of glycemic control in the acute ischemic stroke patient. We now know that intensive regimens for glycemic control in the acute stroke patient do not provide a clear long-term functional outcome benefit in a population with a large percentage of those with diabetes, and poses an increased risk of hypoglycemia. Many neurohospitalists in clinical practice pragmatically tend to prescribe insulin for management of glycemic control in stroke patients as opposed to the many of the oral agents. The GLP-1 agonists appear to be a promising target for stroke patients based on outpatient outcomes; their utilization in the hospitalized stroke patient remains to be studied.

Declarations

Ethics Statement All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards, including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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