Review Paper

Hyperglycemia Treatment with Intravenous Insulin in Acute Stroke Patients: A Scoping Review

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Abstract

Background: Hyperglycemia has been shown to be associated with worse outcomes for ischemic stroke patients, including those undergoing reperfusion therapies. However current guidelines do not exclude hyperglycemic patients from reperfusion therapy, nor do they advocate for early glycemic control. This scoping review examines what is known about the safety, feasibility, and efficacy of intravenous insulin treatment for acute ischemic stroke (AIS) patients.

Methods: PubMed, EBSCOhost, the Cochrane Database of Systemic Reviews, Embase, and Google Scholar were searched from inception to March 25, 2024. Titles, abstracts, and full texts were reviewed. Studies qualified for inclusion if they were peer-reviewed, published in English, full-text, human experimental studies using intravenous insulin for hyperglycemia treatment for hyperacute or acute stroke patients that measured serious adverse events, feasibility, disability, and/or functional outcomes.

Results: Ten studies were included (n=6 safety/feasibility; n=4 efficacy). Intravenous insulin infusion treatments were feasible with targets ranging from 70-200 mg/dL (3.9-11.1 mmol/L), maximum symptom onset to treatment times of 6-24 hours, but carried no clear signal of efficacy.

Conclusions: There are limited clinical trials evaluating intravenous insulin treatment for hyperglycemic AIS patients. Although safe and feasible, the hyperglycemic treatment in these trials was initiated well beyond the window for intravenous thrombolysis with some patients enrolled and treated at 24 hours from symptom onset. It remains unknown whether initiating hyperglycemic control prior to or at the time of reperfusion treatment could improve disability and functional outcomes in AIS patients.

Keywords: ischemic stroke; hyperglycemia; intravenous insulin; reperfusion therapy; outcomes.

Introduction

Roughly every 40 seconds, a stroke occurs in the United States, and every 3 minutes and 35 seconds, a stroke-related death occurs.[1] Ischemic mechanisms make up the majority of acute stroke cases,[1] and reperfusion treatment with thrombolytics or thrombectomy in these patients is known to significantly improve outcomes.[2] Diabetes is considered one of the most important risk factors for stroke. While the number of stroke patients with diabetes admitted to the

emergency department each year has not been reported, the likelihood of significantly elevated blood glucose in this population is high.

Hyperglycemia in patients with ischemic stroke is associated with poor outcomes due to an increase in brain injury and increased risk for hemorrhage following reperfusion therapy.[3,4] The pathophysiologic effects of hyperglycemia and cellular injury are thought to involve the ischemic penumbra, where there is still some perfusion and abundant availability of glucose.[3] The penumbra has less availability for energy, leading to activation of anaerobic pathways, which is further potentiated by excess glucose via glycolysis pathways.[5] The overactivation of glycolysis creates accumulation of harmful anaerobic byproducts that leads to excitotoxicity, oxidative stress, neuroinflammation, and ultimately cellular death within viable penumbral tissue.

The American Association of Clinical Endocrinologists defines hyperglycemia as a blood glucose concentration >140 mg/dl (>7.8 mmol/l). While hyperglycemia is common in those with premorbid diabetes, stress response with stroke onset may worsen glycemic levels.[6] In patients treated with thrombolytics or thrombectomy who do not suffer a symptomatic intracerebral hemorrhage (sICH), hyperglycemia is associated with worse disability and functional outcomes compared to normoglycemic patients.[7,8] Current guidelines do not exclude hyperglycemic patients from reperfusion therapy, nor do they recommend correction of hyperglycemia prior to or concurrent with provision of reperfusion.[2]

The management of hyperglycemia in acute ischemic stroke patients remains controversial. The emphasis on door-to-needle and door-to-puncture times may discourage hyperacute interprofessional clinicians from recognizing its significance beyond potentially altering the neurological presentation. This scoping review examines what is known about the safety, feasibility, and efficacy of intravenous insulin treatment for hyperacute and acute ischemic stroke patients, illustrating critical knowledge gaps requiring future investigation.

Methods

A review of the literature was undertaken to identify relevant peer-reviewed clinical trial articles related to hyperglycemia treatment in acute ischemic stroke patients. Included studies were limited to clinical trials using intravenous insulin for hyperglycemia treatment (independent variable) with endpoints ranging from safety to feasibility, disability, or functional outcomes (dependent variables) in acute ischemic stroke patients. No limits were set on year of publication to ensure a reasonable search return. Articles for which the full text was unavailable, animal studies, and articles not published in English were excluded. Search engines included PubMed, EBSCOhost, the Cochrane Database of Systemic Reviews, Embase, and Google Scholar. The following MeSH search terms were included: “stroke, “hyperglycemia,” and “insulin,” with the last search completed on March 25, 2024.

The data retrieved from each search were uploaded into Zotero Citation Manager (Zotero, Fairfax, Virginia, USA) and Microsoft Excel (Microsoft, Redmond, Washington, USA), where duplicates were removed. A single researcher reviewed the titles and abstracts of the studies, subsequently performing an independent analysis of full-text articles. Details of each

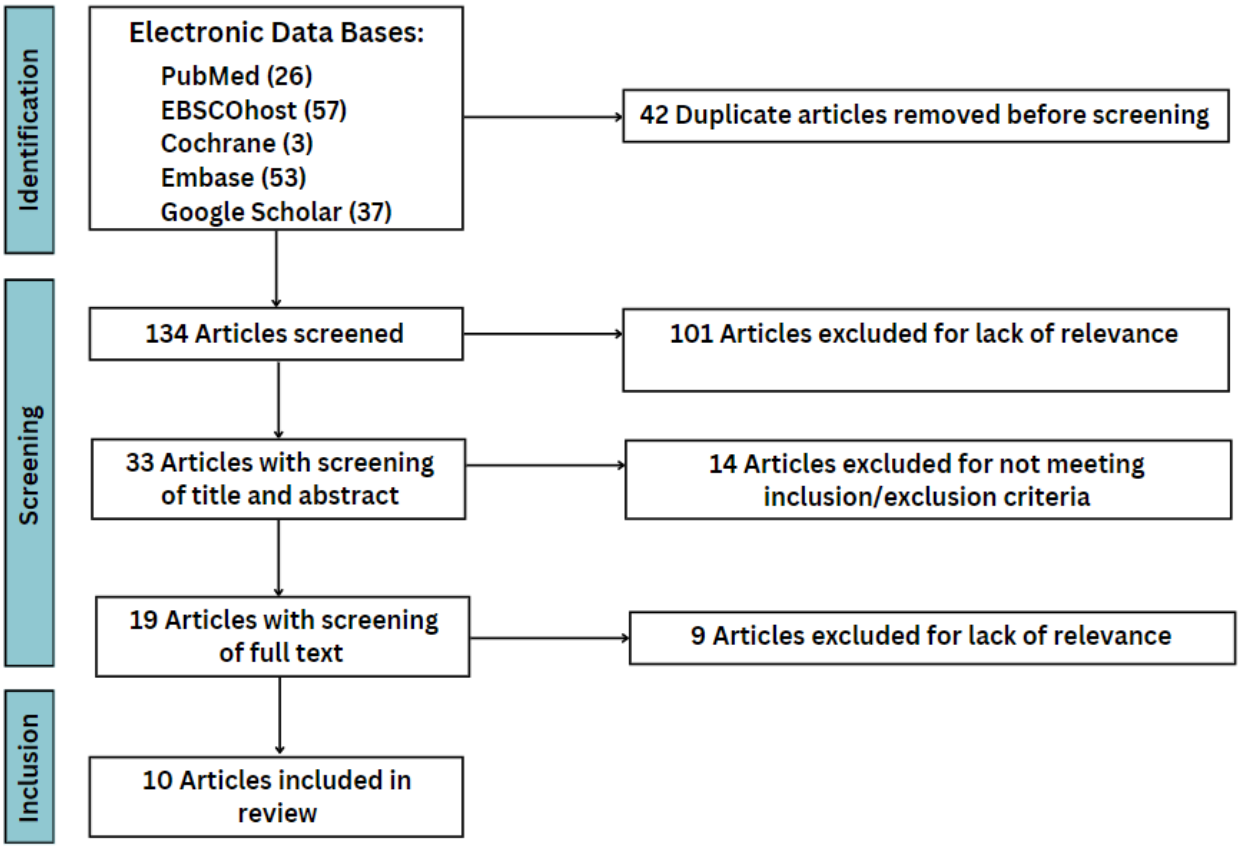

Figure 1: Flow diagram of Clinical Trials Article Selection; adapted from PRISMA Flowchart (Moher et al., 2009).

study were systematically extracted, including authors, year of publication, study methodology, type of insulin intervention, principal findings, and conclusions. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews was utilized to present findings from the review.

Results

A total of 176 articles were retrieved from initial database searches, with 42 duplicates removed before initiating the screening process. The titles and abstracts were screened of the 134 remaining articles for relevance to the research question leading to exclusion of another 101 articles. Next, the titles and abstracts for the remaining 33 articles were screened for inclusion and exclusion eligibility; 14 additional articles were removed that failed to meet eligibility. Nineteen articles had a full-text review for inclusion and exclusion eligibility, and of these 9 articles were excluded for lack of relevance, leaving 10 articles that met inclusion criteria. The reference lists for the 10 included refereed journal publications were then examined to identify additional relevant papers; however, none were found. Figure 1 illustrates the retrieval volume and the inclusion and exclusion of publications on hyperglycemia clinical trials in hyperacute and acute ischemic stroke patients, while Table 1 details study findings for each retained article.

Table 1 Summary of Main Characteristics of Included Clinical Trial Studies

Citation	Design	Objective/ Study Aims	Subjects	Results	Conclusion
Trials Studying Safety and Feasibility of Intravenous Insulin in Acute Stroke					
Glucose Potassium Insulin Infusions in the Treatment of Acute Stroke Patients with Mild to Moderate Hyperglycemia: The Glucose Insulin in Stroke Trial (GIST) Scott, et al., 1999	Single center, open-label randomized control pilot study	To evaluate safety and practicality of GKI infusion treatment at 100 mL/hr. for 24 hours with target range 4 to 7 mmol/L.	A total of 53 patients with acute stroke (excluding SAH & SDH) with mild to moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmol/L) within 24 hours of stroke symptom onset, receiving 24-hour infusion of 0.9% saline (25) or GKI infusion (28) at 100mL/hr.	There were no cardiovascular adverse events in either group. Four (16%) GKI patients required 10mL 50% glucose IV for asymptomatic hypoglycemia and 4% (n=1) for symptomatic hypoglycemia. Two (8%) deaths occurred in the GKI group and one (4%) in control within 72 hours of infusion initiation. The GKI group had seven (28%) deaths at 4 weeks, and eight (n=32%) in the control group. There were no significant differences between groups in the European Stroke Scale or Barthel Index scores at each assessment interval.	The investigators concluded that GKI infusions can be safely administered to acute stroke patients with mild to moderate hyperglycemia.
A Randomised, Controlled Pilot Study to Investigate the Potential Benefit of Intervention with Insulin in Hyperglycaemic Acute Ischaemic Stroke Patients Walters, Weir, & Lees, 2006	Single center, open label randomized control pilot study	To evaluate safety of dosage adjusted insulin combined with 0.9% saline or 5% glucose infusion according to sliding scale for 48 hours comparing the treatment [TG]) and standard treatment (ST) groups.	A total of 25 AIS patients [13 TG and 12 ST] with moderate hyperglycemia (8-20 mmol/L) within 24 hours of stroke symptom onset.	One death occurred in the TG, none in the ST group at one month. The treated group's glucose concentration fell significantly lower within 4 hrs. A significant reduction in mean area under the glucose/time curve was seen in the TG (324±15 h*mmol/L) versus ST group (385±28 h*mmol/L). Mean baseline NIHSS score in the TG was 7.6 (range 2–28), ST 8.3 (range 4–17), 1 month scores TG 4 (range 0–17), and ST 6.5 (range 2–13). One symptomatic hypoglycemic episode occurred in TG, which was treated with oral glucose administration.	Glycemic control with sliding scale insulin for 48 hrs. is feasible and well-tolerated after AIS for patients with moderate hyperglycemia.
Glucose Regulation in Acute Stroke Patients (GRASP) Trial: A Randomized Pilot Trial	Multicenter randomized clinical trial	To evaluate safety and feasibility of tight [target 70 to 110 mg/dL (3.9-6.1mmol/L)] and loose (target 70 to 200 mg/dL (3.9-11.1 mmol/L)	74 patients with AIS receiving tight, loose, or standard care within 24 hours of stroke	Of the 23 patients in the tight control group, 44% achieved target glucose at 24 hours and had a 30% rate of at least one hypoglycemic event (<55 mg/dL). Deaths (13%) in the tight control group were not significantly different than the usual care group. In the loose control group (n=24 patients), 92% achieved target at 24 hours and had a 4% rate of at	The data demonstrated safety and feasibility in both tight and loose glucose control groups. The loose

Johnston et al., 2009		glucose control by 24 hours with glucose/insulin/potassium infusions in patients with acute ischemic stroke.	symptom onset.	least one hypoglycemic event. This group had a significantly greater proportion of deaths (25%) compared to the usual care group (4%). There was only one *symptomatic* hypoglycemic patient in the study (loose control group). Of the serious adverse events in all groups (n=74), only one was found to be definitely related to treatment, and four were considered "probably" related to treatment.	control group had similar glucose concentrations and hypoglycemic episodes compared to tight control, suggesting this approach had no benefit.
Treatment of Hyperglycemia in Ischemic Stroke (THIS): A Randomized Pilot Trial Bruno et al., 2008	Multicenter randomized blinded clinical trial	To evaluate safety, feasibility, and effectiveness of aggressive treatment using insulin infusion with target glucose levels of <7.2 mmol/L (<130 mg/dL) for 72 hours in patients with cerebral infarction.	46 (31 aggressive treatment vs 15 standard care) patients with cerebral infarction who had symptom onset within 12 hrs., and baseline glucose ≥8.3 mmol/L (≥150 mg/dL), and NIHSS score 3-22	The aggressive treatment group corrected hyperglycemia significantly better (p<0.001), unadjusted mean 7.4±0.9mmol/L (133±16mg/dL) compared to usual care 10.5±3.6mmol/L (190±64 mg/dL); removing confounding factors, mean glucose levels for the aggressive group were 3.7mmol/L (66 mg/dL; 9.7 vs 6.0 mmol/L, or 174 vs 108 mg/dL; P<0.001). 35% (n=11) of the aggressive treatment group developed hypoglycemia (<3.3mmol/L or <60 mg/dL), of those 64% (n=7) being asymptomatic. 3% (n=1) symptomatic hypoglycemia requiring IV dextrose, and 10% (n=3) symptomatic patients did not require IV dextrose. Functional outcomes were not significantly different (all p values ≥0.35) and after adjusting for confounding factors (all p values ≥0.09).	Aggressive insulin infusion therapy is safe and effective. The aggressive group had non-significantly better outcomes. The aggressive therapy was significantly better at correcting hyperglycemia during acute cerebral infarction.
Pragmatic Management of Hyperglycaemia in Acute Ischaemic Stroke: Safety and Feasibility of Intensive Intravenous Insulin Treatment Kreisel et al., 2009	Single center, open-label randomized control study	To evaluate safety and feasibility of intensive insulin infusion with target glucose levels of [4.44mmol/l (80mg/dL) and 6.11 mmol/l (110mg/dL)] for 5 days in patients with acute ischemic stroke.	40 (20 intensive insulin treatment vs 20 subcutaneous insulin treatment) patients with AIS with onset <24h.	The average blood glucose for entire study period was significantly lower in the intensive treated group (6.49± 2.19 mmol/l) compared to the subcutaneous treated group (8.0 ±3.06 mmol/l; 95% CI = –1.78 to –1.28, p< 0.0005). Protocol violations were frequent in the intensive treatment group (n=1,215) with 67% (8 of 12) of the specified ranges in non-diabetic and diabetic groups being significant with a p≤0.05. The subcutaneous treated group had statistically nonsignificant differences in protocol violations (n= 475). There were 25 hypoglycemic episodes (<3.33 mmol/l), associated with the intensive treatment group (IRR=5.3, 95% CI=1.2-22.4, p<0.05; n=7, compared to n=1 for subcutaneous treated patients), and 13 severe hyperglycemic episodes (>16.65 mmol/l). 6 patients died (4 intensive vs 2 subcutaneous treated; OR =2.1, 95% CI =0.3-13.4, p=ns).	Intensive insulin infusion treatment effectively lowers blood glucose levels with an increased risk of hypoglycemic events. However, protocol violations limit feasibility outside of specialty care settings.
Intravenous Insulin Therapy in the Maintenance	Single center, open-label randomized	To evaluate safety and effectiveness of insulin infusion with target glucose [4.5-7.0 mmol/L	50 (26 insulin infusion group and 24 subcutaneous insulin group)	Mean glucose levels were significantly different at 8, 16, and 24 hours (p value for all being <0.01). There were 2 events (8%) of hypoglycemia in the infusion treated group, 100% of those being symptomatic	The intensive insulin infusion treatment for 24-hours in nondiabetic

of Strict Glycemic Control in Nondiabetic Acute Stroke Patients with Mild Hyperglycemia Staszewski et al., 2011	control pilot study	(81-126mg/dL)] for 24 hours in nondiabetic AIS patients with mild hyperglycemia [≥7.0-10.0 mmol/L (≥126-180mg/dL)]	nondiabetics, 50 to 80-year-old patients recruited with AIS, confirmed by CT imaging, within 12h symptom onset	compared to 0 events reported in the subcutaneous group. At baseline there was no difference in NIHSS between groups. At 30 days there was a significant difference with infusion group NIHSS 4 versus 7 in subcutaneous group (p=0.04). There was 1 death (3.8%) in the infusion group and 2 (8.3%) in the subcutaneous group, with nonsignificant difference (p=0.5). There was no significant difference (p=0.22) in 30-day non-dependence (mRS ≤2) between infusion group [12(46%)] and subcutaneous group [7(29%)].	patients with mild hyperglycemia is feasible and safe. There was less neurologic disability demonstrated at 30 days, but no statistically significant difference in functional outcome and mortality between the groups.
Trials Studying Efficacy of Intravenous Insulin in Acute Stroke					
Glucose-Potassium-Insulin Infusions in the Management of Post-Stroke Hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK) Gray et al., 2007	Multicenter randomized control clinical trial with blinded outcome assessments	To evaluate if GKI infusions with target glucose 72–126mg/dL (4-7mmol/L) for 24 hours in acute stroke patients with admission glucose 108-203mg/dL (6-17 mmol/L) influence favorable outcomes.	933 patients with clinical diagnosis of acute stroke (excluding SAH) causing physical disability, and previous mRS ≤3, within 24h of symptom onset were recruited.	96.4% (n=899) surviving patients who received some or all treatment analyzed as safety dataset, 80.8% (n=754) surviving patients who had complete treatment analyzed as per-protocol dataset. 15.7% (n=73) of GKI treated patients experienced hypoglycemia (≤4mmol/L). ITT analysis, death at 90 days for GKI group 30%(n=139) and control 27.3%(n=128), no significant difference (p=0.37) with OR 1.14 (95% CI 0.86-1.51). Time to event of death analysis, no significant difference between groups (p=0.59). For avoidance of severe disability (mRS score >3) or severe functional impairment (Barthel index <9) no significant difference at 90 days (OR 0.96, 95% CI 0.70-1.32 and OR 0.84, 95% CI 0.59-1.20). No significance with neurological impairment at 90 days between groups [(ESS scores, mean 73.4 (SD 24.6) vs 74.5 (SD 23.8), n=626; p=0.6].	They found no significant differences in death, severe disability, functional dependance, or neurological impairment at 90 days between the groups. No benefit seen with the use of GKI infusion for this population.
Randomized, Controlled Trial of Insulin for Acute Poststroke Hyperglycemia McCormick et al., 2010	Single center randomized control trial with blinded imaging assessments	To evaluate if there is a relationship with GKI infusion in patients with target glucose 72–126mg/dl (4 – 7mmol/l) for 24 hours in AIS with admission glucose >126mg/dl (7mmol/l) and infarct growth and brain lactate concentrations.	40 patients (10 pilot phase, 25 to GKI infusion [5 on protocol for 48 hours, 10 for 72 hours, 10 for 24 hours] and 15 to saline infusion) with AIS confirmed on MRI with DWI lesion within <24h of symptom onset were recruited.	30% (n=12) of patients had preadmission diabetes. 33% (n=13) received IV alteplase. 76% (n=19) patients in GKI group had at least one episode of hypoglycemia, with 42 episodes occurring in total and 2.4% were symptomatic (n=1). 12 patients received IV dextrose. Mean blood glucose lower than control from 6 hours (97.2mg/dL [5.4mmol/L] vs 124.2mg/dL[6.9mmol/L] p<0.001) and at 12 hours (104.42mg/dL [5.8mmol/L] vs 126.0mg/dL[7.0mmol/L] p<0.008). Between the three GKI duration groups, blood glucose was maintained lower than placebo in 48-hr group, but not 24-hr and 72-hr groups. SBP was significantly lower in GKI group (p<0.0001). No significant difference in median lesion volume between GKI and saline groups at	No difference in incidence in infarct growth for hyperglycemic patients in GKI compared to saline-treated groups. There was a high rate of asymptomatic hypoglycemia. Hypoglycemia or duration of hypoglycemia in the different groups of GKI

				any time (p=0.770). There was significant interaction with vessel patency and infarct growth in the treatment group in patients with large vessel occlusions (p=0.011). For spectroscopy there was a significant treatment group-time interaction (p=0.037); for the 19 patients where mRS was available, post hoc analysis indicated significance between GKI and control only at day 3. (p=0.05). mRS scores were not significant at 30 days between groups (GKI: 16% independent, 76% functional dependence, 8% dead vs saline: 13%, 87% and 0%).	infusion durations was not associated with infarct growth or difference in outcome. No effect was seen on MRI markers with hyperglycemia with insulin treatment.
Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients with Acute Ischemic Stroke: The SHINE Randomized Clinical Trial Johnston et al., 2019	Multicenter randomized control trial with blinded outcome assessments	To evaluate if intensive glucose control (target blood glucose concentration of 80-130 mg/dL [4.4-7.2 mmol/L]) improved functional outcomes in patients with AIS and hyperglycemia glucose concentration of >110 mg/dL (>6.1 mmol/L) if diagnosed with diabetes, or ≥150 mg/dL (≥8.3 mmol/L) if not diagnosed with diabetes)	1151 patients (581 intensive group vs 570 standard treatment group) with AIS within 12 hours from stroke onset, NIHSS 3-22, pre-stroke mRS 0-1 were recruited.	97% (n=1118) of patients completed the trial. 80% (n=923) of patients had preadmission diabetes. Reperfusion therapies were used in 68% (63% tPA, 3% intra-arterial drug therapy, 13% mechanical thrombectomy). A total of 82% (n=943) patients completed treatment (74.5% [n=433] intensive treatment group and 89.5% [n=510] in standard treatment group). Treatment was stopped for hypoglycemia or adverse events in 11.2% (n=65) intensive group patients versus 3.2% (n=18) in standard group patients. Mean glucose concentration between groups: 118 mg/dL (95% CI, 115-121 mg/dL; 6.6 mmol/L [95% CI, 6.4-6.7 mmol/L]) intensive group vs. 179 mg/dL (95% CI, 175-182 mg/dL; 9.9 mmol/L [95% CI, 9.7-10.1 mmol/L]) standard group. 20.5% (n=119) favorable outcome seen in the intensive group, 21.6% (n=123) standard group (adjusted RR, 0.97 [95% CI, 0.87 to 1.08], p=0.55; unadjusted risk difference, −0.83% [95% CI, −5.72% to 4.06%]. 2.6% (n=15) patients experience severe hypoglycemia in the intensive group, 0 in the standard treatment group. Death occurred in 9.3% (n=54) in intensive group patients vs in the 11.4% (n=65) standard group. No neurological worsening events occurred due to hypoglycemia.	Among patients with acute ischemic stroke and hyperglycemia, treatment with intensive vs standard glucose control for up to 72 hours did not result in a significant difference in favorable functional outcome at 90 days. These findings do not support using intensive glucose control in this setting.
Intensive Versus Subcutaneous Insulin in Patients with Hyperacute Stroke: Results from the Randomized INSULINFA RCT Trial Rosso et al., 2012	Single center randomized unblinded control trial.	To evaluate if intensive insulin treatment (IIT) utilizing nomogram with hourly dose adaptation of carotid territory AIS patients reduced subsequent MRI infarct growth compared to	180 patients (90 IIT group, 90 SC) with carotid artery AIS confirmed by DWI, with initial MRI completed within 5h of symptom onset and treatment initiated within 1h of MRI, NIHSS 5-25,	Four (2.2%) patients excluded from glucose control analysis due to missing glucose data and 6 (3.3%) patients for protocol violations (IIT 87, SC 89). 98% of patients in IIT group received insulin (24-hour dose, 18.5 UI; IQR, 9 –24), where 55% in SC received insulin (dose, 2 UI; IQR, 0 – 4; p=<0.0001 between groups). Mean capillary glucose test <7 mmol/L in the first 24 hours was higher in the IIT group (95.4% [n=83] versus 67.4% [n=60]; p<0.0001). MRI analysis performed in 88.9% (n=160; 80 IIT, 80 SC) due to 3.3% (n=6) early death, 1.7% (n=3) coma, and 3.9% (n=7) MRIs performed after 3 days.	Among patients with carotid territory AIS receiving treatment within 6h of symptom onset, intensive insulin treatment regimen improved glucose control in the first 24

		standard care (SC).	and premorbid mRS ≤2.	Infarct growth median was significantly larger in IIT group (27.9cm3 vs. 10.8 cm3; p=0.04). The 3-month functional outcome (45.6% [41 of 90] versus 45.6% [41 of 90]), death (15.6% [14 of 90] versus 10% [9 of 90]), and serious adverse events (38.9% [35 of 90] versus 35.6% [32 of 90]) were similar in the subcutaneous insulin and IIT group.	hours but was associated with larger infarct growth. Thus, IIT cannot be recommended in hyperacute ischemic carotid artery strokes.
Abbreviations: GKI, glucose potassium insulin; SAH, subarachnoid hemorrhage; MRI, magnetic resonance imaging; SDH, subdural hematoma; NPO, nil per os; MI, myocardial infarction; LVF, left ventricular failure; ESS, European Stroke Scale; AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; CT, computer tomography; SBP, systolic blood pressure.					

Safety and Feasibility of Intravenous Insulin in Acute Stroke

Several studies have examined the safety and feasibility of different insulin infusions on various hyperglycemic control targets. Intervention treatment characteristics are summarized in Table 2 for both safety/feasibility trials and efficacy trials. A total of six clinical trials explored safety and feasibility. The pre-interventional treatment glucose level of the studies ranged from 80-360 mg/dL, with only the Intensive Versus Subcutaneous Insulin in Patients with Hyperacute Stroke: Results from the Randomized (INSULINFARCT) Trial[9] having no glycemic threshold for study enrollment. Treatment initiation times ranged from 6-24 hours from symptom onset across all retained studies. Many studies used insulin-only infusions, with three using glucose-potassium-insulin (GKI) infusions. Most studies demonstrated protocol safety, however, McCormick and colleagues[10] reported concern over high rates of asymptomatic hypoglycemia and a significant interaction between intracranial arterial patency for patients presenting with large vessel occlusions. Although not specified as a safety concern, Johnston and colleagues[11] reported a 24% proportion of death in their "loose control" group (Table 1) compared to the usual care group proportion of 4% (p=0.05, Fisher exact test) with no significant difference observed between the "tight control" group and usual care group (p=0.26, Fisher exact test). Overall, the feasibility of hyperglycemic treatment was demonstrated in 5 studies.[11–15] Kreisel and colleagues[16] reported 1,215 protocol violations in their intensive treatment group and 475 in the subcutaneous group; most violations reflected insufficient insulin administration based on the study protocol to maintain a target glucose of 80-110mg/dL (4.4-6.1 mmol/L), thus limiting the feasibility of their treatment protocol.

Efficacy of Intravenous Insulin in Acute Stroke

Table 2 also presents treatment characteristics for the 4 efficacy endpoint clinical trials. The UK Glucose Insulin in Stroke Trial's (GIST-UK)[17] primary endpoint was death at 90 days, and the secondary endpoint was avoidance of death or severe disability. The study was terminated for slow enrollment after 754 patients completed the protocol. There was no significant difference in rates of death, severe disability, functional dependence, or neurological impairment at 90 days between the groups. McCormick and colleagues'[10] primary endpoint was infarct growth on MRI. There was no difference in infarct growth for those receiving the GKI infusion versus saline-treated controls. However, imaging analysis of those with intracranial vessel patency data (n= 31) demonstrated patients in the treatment group (n=17) compared to placebo group (n=10) had a significant interaction with vessel patency (p =0.011, 2-way ANOVA), with the GKI group having more infarct growth compared to the control group with complete vessel occlusions. The INSULINFARCT[9] Trial's primary objective was to assess the efficiency of glucose control to less than 126 mg/dL (7.0 mmol/L), and the secondary objective compared MRI infarct growth between groups. Investigators reported that intensive intravenous insulin treatment provided better control versus subcutaneous treatment. However, the intensive intravenous insulin treatment group experienced increased infarct growth in patients with persistent occlusions. In the Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients with Acute Ischemic Stroke (SHINE)[18] study, investigators did not find significant differences in functional outcome, disability on the National Institutes of Health Stroke Scale (NIHSS) score, Barthel Index, or Stroke Specific Quality of Life score

Table 2 Summary of Intervention Treatment Characteristics & Endpoints

Citation	Symptom Onset to Treatment Time Max	Pre-Intervention Glucose Level	Treatment	Duration of Treatment	Treatment Target Glucose
Trials of Safety and Feasibility of Intravenous Insulin in Acute Stroke					
Glucose Potassium Insulin Infusions in the Treatment of Acute Stroke Patients with Mild to Moderate Hyperglycemia: The Glucose Insulin in Stroke Trial (GIST) Scott, et al., 1999	24 hours	126-306 mg/dL	Glucose Potassium Insulin Infusion	24 hours	72-126 mg/dL
A Randomised, Controlled Pilot Study to Investigate the Potential Benefit of Intervention with Insulin in Hyperglycaemic Acute Ischaemic Stroke Patients Walters, Weir, & Lees, 2006	24 hours	144-360 mg/dL	Insulin Infusion	48 hours	90-144 mg/dL
Glucose Regulation in Acute Stroke Patients (GRASP) Trial: A Randomized Pilot Trial Johnston et al., 2009	24 hours	110-300 mg/dL	Insulin Infusion	5 days or Discharge (which ever came first)	Loose Control Group: 70-200 mg/dL; Tight Control Group: 70-110 mg/dL
Treatment of Hyperglycemia in Ischemic Stroke (THIS): A Randomized Pilot Trial Bruno et al., 2008	12 hours	≥150 mg/dL	Insulin Infusion	72 hours	<130 mg/dL
Pragmatic Management of Hyperglycaemia in Acute Ischaemic Stroke: Safety and Feasibility of Intensive Intravenous Insulin Treatment Kreisel et al., 2009	24 hours	>80 mg/dL	Insulin Infusion	5 days or Discharge (which ever came first)	80-110mg/dL
Intravenous Insulin Therapy in the Maintenance of Strict Glycemic Control in Nondiabetic Acute Stroke Patients with Mild Hyperglycemia Staszewski et al., 2011	12 hours	126-180 mg/dL	Insulin Infusion	24 hours	81-126 mg/dL
Trials of Efficacy of Intravenous Insulin in Acute Stroke					
Glucose-Potassium-Insulin Infusions in the Management of Post-Stroke Hyperglycaemia: The UK Glucose Insulin in Stroke Trial (GIST-UK) Gray et al., 2007	24 hours	108-306 mg/dL	Glucose Potassium Insulin Infusion	24 hours	72-126 mg/dL
Randomized, Controlled Trial of Insulin for Acute Poststroke Hyperglycemia McCormick et al., 2010	24 hours	> 126 mg/dL	Glucose Potassium Insulin Infusion	24 hours	72-126 mg/dL
Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients with Acute Ischemic Stroke: The SHINE Randomized Clinical Trial Johnston et al., 2019	12 hours	Diabetes: >110 mg/dL Without Diabetes: 150 mg/dL	Insulin Infusion	72 hours	80-130 mg/dL
Intensive Versus Subcutaneous Insulin in Patients with Hyperacute Stroke: Results from the Randomized INSULINFARCT Trial Rosso et al., 2012	6 hours	None	Insulin Infusion	24 hours	<100 mg/dL

between groups. The Treatment of Hyperglycemia in Ischemic Stroke (THIS) trial[14] found there was no significant difference in functional outcomes between groups at the 3-month assessment, though the study was limited by safety and feasibility primary endpoints and therefore was not powered for an efficacy analysis.

Discussion

This scoping review found that hyperglycemic treatment is feasible, but may be tied to safety concerns, and that treatment efficacy remains unclear regardless of the endpoints examined. The prevalence of hyperglycemia has been well documented in acute stroke, both in diabetic and nondiabetic patients. A recent systematic review and meta-analysis found that the pooled incidence of hyperglycemia in non-diabetic stroke patients was 24% (95% CI: 21-27%).[19] Another recent meta-analysis and literature review found that the prevalence of diabetes in ischemic stroke patients was 33% (95% CI 28–38).[20] Additionally, outcome analysis for hyperglycemia has been shown to lead to unfavorable outcomes[7,21–30] irrespective of diabetes or reperfusion therapy status.[31]

The purpose of this scoping review was to identify studies that employed the use of intravenous insulin as a treatment for hyperglycemia in acute stroke patients since this is such a prevalent problem. Ten studies met the review criteria, of which six focused on safety and feasibility and four on treatment efficacy. The treatment duration of the safety and feasibility studies varied significantly, with one treating out to five days from initiation and requiring high resource utilization to achieve targeted glucose levels for this period of time.[16] Previous studies demonstrated that persistent hyperglycemia out to 72 hours from stroke onset is independently associated with increased infarct volume,[32,33] which may be why none of the efficacy trials reviewed had treatment durations greater than 72 hours. All studies reported that hyperglycemic treatment was safe, although Johnston and colleagues[11] reported higher death rates in the patients with loose control of glucose. Additionally, a duration of up to 72 hours appears to be the most feasible target duration, especially if tighter glucose control is used.

Overall, initiation of glucose control from the time of stroke onset and/or treatment was long in these studies, and while this may have increased protocol feasibility, it may also have reduced protocol efficacy. The INSULINFARCT trial [9] had the shortest time to treatment initiation (<6 hours), but while not all studies included data on time to treatment, those reporting these data achieved median times from symptom onset to randomization or treatment time ranging from 6 to 20.75 hours. The INSULINFARCT trial did not specify their time to treatment, however their reported time to initial MRI was 132 min, with initiation of insulin treatment within one hour of MRI per protocol, making their time to treatment the fastest of all the trials included.

Efficacy trials included in this review demonstrated that insulin infusions were efficacious at decreasing blood glucose levels and maintaining levels to less than 130 mg/dL (7.2 mmol/L). Although this scoping review is focused specifically on clinical trials, some observational studies suggest that blood glucose levels between 120-145 mg/dL (6.7-8.0 mmol/L) may lead to worse functional outcomes.[30,34–36] However, this was not demonstrated in the 4 efficacy trials reviewed here which showed no significant difference in functional outcomes, death at 90 days, or infarct growth.

This review has limitations. Importantly, stroke reperfusion treatment times in relation to the insulin infusion treatment start time is unclear in clinical trials. Although these clinical trials did not specify any significant differences in those patients treated with reperfusion therapies, multiple studies have shown that hyperglycemia impacts clinical outcomes, and late control of hyperglycemia may have influenced negative efficacy outcomes given the deleterious impact of hyperglycemia on the ischemic penumbra.[3] Secondly, because this is a scoping review, complete access to data was lacking, with only those data reported in publications available for inclusion. Therefore, it is entirely possible that other unknown findings may have contributed to the study outcomes reported.

In conclusion, while hyperglycemic insulin treatment protocols are feasible for at least 72 hours after symptom onset, safety is an important consideration and efficacy has yet to be demonstrated. Future studies should explore the impact of hyperglycemic treatment administered concurrent to intravenous thrombolysis in eligible patients or prior to thrombectomy in those ineligible for thrombolysis.

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