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High glucose variability increases cerebral infarction in patients with spontaneous subarachnoid hemorrhage☆

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Abstract

Purpose: High glucose variability is a significant marker for poor outcome in critically ill patients. We evaluated the impact of high glucose variability on cerebral infarction following spontaneous subarachnoid hemorrhage (SAH).

Materials and Methods: Consecutive adult patients with spontaneous SAH and Hunt Hess score of at least 3 were retrospectively identified. Patients were excluded if their intensive care unit length of stay was less than 24 hours or if there were less than 5 glucose assessments. Glucose values from the first 7 days of intensive care unit admission were assessed. Variability was calculated as the average change in glucose over time for each patient. Classification and regression tree analysis was used to determine high vs low glucose variability, and the incidence of cerebral infarction was compared. Multivariate analysis was used to control for confounding variables.

Results: There were 42 patients. Classification and regression tree analysis revealed a change in glucose greater than 9.52 mg/dL/h as the determinant for high variability. The incidence of cerebral infarction was 64% when glucose variability was high vs 20% when it was low ($P = .006$). Multivariate analysis identified high glucose variability (odds ratio [95% confidence interval] = 11.4 [1.9-70.2], $P = .008$) and female sex (odds ratio [95% confidence interval] = 5.2 [1-26.8], $P = .047$) as independent predictors for cerebral infarction.

Conclusion: Glucose variability is a significant predictor of cerebral infarction in patients with severe spontaneous SAH.

The value of tight glycemic control has been heavily debated with the publication of the NICE-SUGAR trial [1]. In this study, 90-day mortality was higher using intensive insulin therapy targeting a goal of 81 to 108 mg/dL compared to a more liberal strategy (< 180 mg/dL), a finding conflicting with the widely referenced Leuven study in surgical intensive care unit (ICU) patients [2]. Other studies have evaluated intensive insulin therapy; and benefits on mortality have not been demonstrated, illustrating the limitations of extrapolating these results across different ICU populations

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[3,4]. The issue of glycemic control in neurosurgical patients is even more unknown. The detrimental effects of hyperglycemia have been extensively documented, but the role of insulin therapy remains unclear [5]. One study of patients with severe brain injury, which used microdialysis to assess cerebral glucose levels, noted tight glycemic control to be associated with reduced cerebral glucose availability and increased prevalence of brain energy crisis [6]. A second study of patients with subarachnoid hemorrhage (SAH) reported higher mean glucose values to be associated with an increased incidence of vasospasm [7]. As such, recently published guidelines do not recommend tight glycemic control in patients following SAH [8].

Recent evidence has illustrated glucose variability (as opposed to absolute glucose values) to be an important indicator for clinical outcome in critically ill patients. One study of 858 surgical ICU patients noted glucose variability (defined using multiple methods) to be significantly higher among nonsurvivors, whereas mean glucose values were similar [9]. In fact, it has been recently suggested that all previously published interventional studies of glycemic control be reinterpreted using the metric of glucose variability to assess the overall impact of tight glycemic control [10].

Data reporting the influence of glucose variability in patients with intracranial pathology remain sparse, and this concept has not been adequately evaluated in patients with SAH. The objective of this study was to determine the impact of glucose variability on cerebral infarction in patients following spontaneous SAH.

1. Methods

This study was approved by the Institutional Review Board. Consecutive patients aged at least 18 years with spontaneous SAH and a Hunt Hess score of at least 3 were retrospectively identified using an institutional database. The Hunt Hess classification system is a method for classifying the severity of spontaneous (ie, nontraumatic) SAH and serves as a predictor of patient prognosis/outcome. Hunt Hess scores range from 1 to 5, with higher scores being indicative of worse outcome. Patients were excluded if they had less than 5 glucose assessments over the course of their ICU admission, an ICU length of stay less than 24 hours, or insufficient data from the medical record. Selected patients were reviewed for their demographics, location, and severity of hemorrhage (defined using Hunt Hess and Fisher scores), surgical intervention (clipping vs coiling), glucose values, and presence of cerebral ischemia.

All patients were managed in an ICU using a standardized protocol which included routine administration of nimodipine and pravastatin. Goal mean arterial pressures were 70 to 110 mm Hg. To assess for vasospasm, transcranial Doppler was performed daily; and all patients received an angiogram on day 7 or sooner if there was clinical suspicion for vasospasm (eg, mental status changes). Interventions for clinically significant vasospasm (eg, intraarterial verapamil) were administered as needed as determined by a neuroradiologist. Insulin was administered at the discretion of a board-certified intensivist and titrated using an institutional protocol. As per the protocol, glucose assessments occur every 30 minutes to 1 hour initially but become less frequent with stabilization. The target glucose range was 100 to 150 mg/dL.

Glucose values were obtained for the first 7 days of hospital admission; and glucose variability, average glucose, and incidence of hypoglycemia (defined as glucose <60 mg/dL) were determined. Only glucose values obtained from the point-of-care device were used. Glucose variability was determined by using the average change in glucose over time for each patient and reported in milligrams per deciliter per hour. To calculate the average variability for each patient, the following formula was used: [(Δ glucose 1-2/Δ time 1-2) + (Δ glucose 2-3/Δ time 2-3) + (Δ glucose 3-4/Δ time 3-4) + …] divided by the number of data sets. For example, given the following glucose values and times [140 mg/dL (0800), 120 mg/dL (0900), 160 mg/dL (1000)], the calculated average variability would be 30 mg/dL/h. Glucose values were assumed to be static for this calculation. Classification

Table 1 Demographics

Age (y)	55 ± 11
Sex (% male)	50% (21/42)
Diabetes	7% (3/42)
Fisher score	
1	2.4% (1/42)
3	21.4% (9/42)
4	76.2% (32/42)
Hunt Hess score	
3	40.5% (17/42)
4	47.6% (20/42)
5	11.9% (5/42)
Location	
Anterior	42.9% (18/42)
Posterior	33.3% (14/42)
Unidentified	23.8% (10/42)
Treatment	
Clip	31% (13/42)
Coil	45% (19/42)
None	24% (10/42)
Glucose assessments per patient	51 (7-115)
Duration of evaluation (d)	5.9 ± 1.5
Intravenous insulin (%)	74% (31/42)
Dextrose 50% in water (%)	26% (11/42)
Average glucose (mg/dL)	126 ± 15
Variability glucose (mg/dL/h)	9.6 (1.8-30)
% Glucose within 100-150 mg/dL	65 ± 15
% Glucose <100 mg/dL	19 ± 13
Any glucose <60 mg/dL	21% (9/42)
Cerebral infarction	43% (18/42)