Severity of Intraventricular Extension Correlates With Level of Admission Glucose After Intracerebral Hemorrhage

Geoffrey Appelboom, MD*; Matthew A. Piazza, BA*; Brian Y. Hwang, MD; Amanda Carpenter, BA; Samuel S. Bruce, BA; Stephan Mayer, MD; E. Sander Connolly, Jr, MD

Background and Purpose—Hyperglycemia after spontaneous intracerebral hemorrhage (ICH) is associated with poor outcome, but the pathophysiology of ICH-induced glucose dysregulation remains unclear. We sought to identify clinical and radiographic parameters of ICH that are associated with admission hyperglycemia.

Methods—Patients admitted to the Columbia University Medical Center Neurological Intensive Care Unit with spontaneous ICH between January 2009 and September 2010 were prospectively enrolled in the ICH Outcomes Project. Clinical, radiographic, and laboratory data were collected prospectively. Receiver operating characteristic analysis was used to identify the glucose level with optimal sensitivity and specificity for in-hospital mortality. Logistic and linear regression analyses were used to identify independent predictors of outcome measures where appropriate.

Results—One hundred four patients admitted during the study period were included in the analysis. Mean admission glucose level was 8.23±3.15 mmol/L (3.83 to 18.89 mmol/L) and 23.2% had a history of diabetes mellitus. Admission glucose was significantly associated with discharge (P=0.003) and 3-month mortality (P=0.002). Critical hyperglycemia defined at 10 mmol/L independently predicted discharge mortality (P=0.027; OR, 4.381; 95% CI, 1.186 to 16.174) and 3-month mortality (P=0.011; OR, 10.95; 95% CI, 1.886 to 62.41). Admission intraventricular extension score (P=0.038; OR, 1.117; 95% CI, 1.043 to 1.197) and diabetes mellitus (P=0.002; OR, 5.530; 95% CI, 1.833 to 16.689) were independent predictors of critical hyperglycemia. The intraventricular extension score (B=0.115, P=0.001) linearly correlated with admission glucose level (R=0.612, P=0.001) after adjusting for other clinical variables.

Conclusions—Admission hyperglycemia after spontaneous ICH is associated with poor outcome and potentially related to the presence and severity of intraventricular extension. (Stroke. 2011;42:1883-1888.)

Key Words: admission hyperglycemia ■ glucose ■ intracerebral hemorrhage ■ intraventricular extension ■ intraventricular hemorrhage

Admission hyperglycemia is frequently observed after spontaneous intracerebral hemorrhage (ICH), affecting 43% to 59% of patients, and is an independent predictor of poor outcome.¹⁻⁵ ICH is thought to cause hyperglycemia through an indirect, neuroendocrine stress-mediated mechanism.⁶ Excessive systemic and local glucose levels exacerbate secondary cerebral injuries through metabolic dysregulation, cytotoxicity, and neuronal death.⁷⁻⁸ Hemorrhage characteristics such as hematoma size and the presence of intraventricular extension (IVH) have been associated with acute hyperglycemia, suggesting that acute hyperglycemia is an indicator of disease severity.⁹⁻¹⁰ Nevertheless, the pathophysiology and risk factors of ICH-associated hyperglycemia remain largely undefined. An improved understanding of ICH variables that are associated with admission hyperglycemia may help further elucidate the pathophysiology and lead to more effective management. The purpose of this study was to determine the critical threshold of systemic glucose level predictive of mortality and identify radiographic predictors of admission hyperglycemia in a prospective cohort of patients with spontaneous ICH.

Methods

Study Population
Between February 2009 and September 2010, patients with spontaneous ICH diagnosed by admission CT scan were admitted to the Columbia University Medical Center Neurological Intensive Care Unit and prospectively enrolled in the Intracerebral Hemorrhage Outcomes Project (ICHOP). The study was approved by the Institutional Review Board and written consent was obtained for participation in the study either by the patient or the appropriate surrogate representative when the patient lacked capacity. Patients <18 years; patients with ICH due to malignancy, trauma, hemorrhagic conver-
Clinical Variables
Demographic, radiographic, and clinical course data were prospectively collected for patients presenting with spontaneous nontraumatic ICH as part of ICHOP. Admission blood glucose was defined as the first intravenous blood glucose level drawn at the time of the initial emergency department or in-hospital evaluation for ICH. Admission CT scan was evaluated for hematoma volume and location, presence and severity of IVH as assessed by the IVH score,11 degree of midline shift, and presence of hydrocephalus. Early do-not-resuscitate/do-not-intubate status was defined as do-not-resuscitate/do-not-intubate instituted on or before postbleed Day 1.12 Outcome was assessed at discharge using the modified Rankin Scale.

Statistical Analysis
Univariate analyses of pertinent clinical variables with respect to discharge and 3-month mortality was conducted using $\chi^2$ Test, Fisher exact test, independent $t$ test, and Mann-Whitney $U$ test where appropriate. Receiver operating characteristic analysis was undertaken to calculate Youden indices to determine the threshold for critical hyperglycemia that optimized sensitivity and specificity for discharge mortality. Multiple logistic regression was used to identify independent predictors of discharge mortality and 3-month mortality using the following variables: age, sex, history of diabetes, admission Glasgow Coma Scale score, arteriovenous malformation–ICH, admission hematoma volume (mL), admission IVH score, admission midline shift (mm), infratentorial location, critical hyperglycemia, external ventricular drainage, intrathecal tissue plasminogen activator administration, surgical hematoma evacuation, ventriculoperitoneal shunt requirement, early do-not-resuscitate/do-not-intubate status, and length of hospitalization. Significant predictors were used in a final model to calculate adjusted ORs. Univariable comparisons were performed between patients whose admission glucose level exceeded the critical value versus those who did not with respect to clinical variables using $\chi^2$ test, Fisher exact test, independent $t$ test, and Mann-Whitney $U$ test where appropriate. Multiple logistic regression analysis was used to evaluate predictors of admission critical hyperglycemia as a function of age, arteriovenous malformation–ICH, hematoma size, infratentorial hematoma location, presence of IVH, hydrocephalus, IVH score, degree of midline shift, and history of diabetes. Adjusted ORs were calculated in a final multivariate logistic regression model that contained only significant predictors. Linear regression analysis was used to determine if the IVH score is related to level of admission glucose after controlling for the following clinical and stroke severity variables: patient age, sex, history of diabetes, arteriovenous malformation–ICH, hematoma size, degree of midline shift, and infratentorial ICH location. All analyses were performed with SPSS Version 18 (Chicago, IL).

Results
One hundred twenty patients admitted with spontaneous ICH during the study period were enrolled in ICHOP. Sixteen patients were excluded because of missing data regarding admission radiographic characteristics or glucose measurements and the resulting 104 patients were included in the analysis. Demographic and clinical variables are detailed in Table 1. Forty-five percent were female and the median age was 63 years. Mean admission glucose was $8.23\pm3.15$.
Mortality rates at discharge and at 3 months were 23.2% and 29.5%, respectively. Admission glucose level was significantly associated with discharge mortality (P=0.003) and 3-month mortality (P=0.002). Receiver operating characteristics yielded a threshold for admission critical hyperglycemia level with a maximum Youden index for predicting mortality at 10 mmol/L. Multivariate logistic regression analysis with regard to the discharge mortality identified admission Glasgow Coma Scale score (P=0.002) and critical admission hyperglycemia (P=0.009) as significant independent predictors of discharge mortality with adjusted ORs of 0.658 (95% CI, 0.547 to 0.792) and 4.381 (95% CI, 1.186 to 16.174), respectively (Table 2). Multivariate logistic regression analysis with regard to the 3-month mortality identified age (P=0.045), admission Glasgow Coma Scale score (P=0.002), critical admission hyperglycemia (P=0.011), and intrathecal tissue plasminogen activator administration (P=0.045) as significant independent predictors with adjusted ORs of 1.107 (95% CI, 1.036 to 1.182), 0.579 (P<0.001; 95% CI, 0.454 to 0.738), 10.85 (P=0.008; 95% CI, 1.886 to 62.41), and 0.016 (P=0.011; 95% CI, 0.001 to 0.384), respectively (Table 2).

Twenty-two patients had critical admission hyperglycemia (Table 3). History of diabetes (P=0.001), presence of IVH at admission (P=0.007), presence of hydrocephalus at admission (P=0.004), and admission IVH score (P=0.001) were associated with admission critical hyperglycemia. Multivariate logistic regression identified history of diabetes (P=0.002) and admission IVH score (P=0.038) as independent predictors of admission critical hyperglycemia with adjusted ORs of 5.53 (95% CI, 1.83 to 16.7) and 1.117 (95% CI, 1.043 to 1.197), respectively. Additionally, linear regression of admission glucose level (P<0.001, R=0.612) identified admission IVH score as a positive linear predictor of admission glucose level (P=0.001, B=0.115) after controlling for other variables (Table 4). Mean admission glucose levels were 7.35±2.66 mmol/L, 8.54±3.11 mmol/L, 9.32±3.74 mmol/L, and 10.58 mmol/L for IVH score quartiles 0 to 5, 6 to 11, 12 to 17, and 18 to 23, respectively (P=0.004). The Figure shows a plot of mean admission glucose levels by IVH score quartiles.

**Discussion**

We confirmed the relationship between admission glucose and mortality in a prospective cohort of patients with spon-
taneous ICH.4,5,9 We also identified 10 mmol/L as a critical threshold glucose level that is associated with the optimal Youden index for predicting mortality. The definition of hyperglycemia varies considerably among studies in hemorrhagic and ischemic stroke that examine the relationship between glucose level and outcome with reported cutoff points ranging between 6.0 mmol/L and 10.0 mmol/L.2,4,5,9,13,14 Our critical threshold for glucose level falls within the ranges used in previous ICH studies.

On a molecular level, disruption of the blood–brain barrier after ICH and exposure of brain tissue to excessive levels of glucose result in anaerobic glycolysis, accumulation of lactate, tissue acidosis, generation of free radicals, release of excitatory amino acids, and a massive influx of calcium.7,8 Furthermore, poorly controlled hyperglycemia is associated with reduced cerebral blood flow and tissue oxygenation, elevations in intracranial pressure,3 greater degrees of cerebral edema, and perihematomal neuronal death,15 which may explain the relationship between glucose levels and mortality. Although larger, prospective studies are required to identify the critical level of hyperglycemia after ICH and its consequences on brain tissue at the cellular and molecular level, this finding may serve as a threshold to initiate intensive insulin therapy to prevent the damaging consequences of hyperglycemia on central neurons.

Additionally, we identified initial radiographic hemorrhage characteristics that are associated with admission hyperglycemia. In particular, of the radiographic variables examined, only IVH severity as assessed by the IVH score was an independent predictor of hyperglycemia. More importantly, we identified a positive linear relationship between the IVH score and admission glucose level, suggesting that severity of intraventricular extension of ICH is directly related to the degree of hyperglycemia. Although previous studies have demonstrated an association between IVH and hyperglycemia,5,9 to our knowledge, this is the first time that IVH severity is shown to correlate with admission glucose level independent of other ICH severity markers.

The pathophysiological relationship between IVH and hyperglycemia is not well understood. In this study, other known outcome predictors of ICH such as hematoma volume, patient age, ICH location, and admission Glasgow Coma Scale score failed to independently show the same relationship.

Table 3. Baseline and Admission Radiographic Characteristics of Patients With and Without Critical Hyperglycemia (Blood Glucose >10 mmol/L) at Admission

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Admission Glucose &lt;10 mmol/L (N = 82)</th>
<th>Admission Glucose &gt;10 mmol/L (N = 22)</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>Adjusted ORs 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.7 ± 19.3</td>
<td>61.7 ± 13.0</td>
<td>0.810</td>
<td>0.177</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (17.1%)</td>
<td>12 (54.5%)</td>
<td>0.001</td>
<td>0.002</td>
<td>5.530 1.833–16.689</td>
</tr>
<tr>
<td>Hematoma volume, mL</td>
<td>23.4 ± 27.3</td>
<td>27.5 ± 25.6</td>
<td>0.525</td>
<td>0.534</td>
<td>...</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>15 (18.3%)</td>
<td>4 (18.2%)</td>
<td>1.000</td>
<td>0.389</td>
<td>...</td>
</tr>
<tr>
<td>Presence of IVH</td>
<td>37 (45.1%)</td>
<td>17 (77.3%)</td>
<td>0.007</td>
<td>0.640</td>
<td>...</td>
</tr>
<tr>
<td>Presence of HCP</td>
<td>25 (30.5%)</td>
<td>14 (63.6%)</td>
<td>0.004</td>
<td>0.605</td>
<td>...</td>
</tr>
<tr>
<td>IVH score</td>
<td>5.2 ± 6.9</td>
<td>12.0 ± 8.0</td>
<td>0.001</td>
<td>0.038</td>
<td>1.117 1.043–1.197</td>
</tr>
<tr>
<td>Midline shift, mm</td>
<td>2.3 ± 3.8</td>
<td>3.5 ± 3.6</td>
<td>0.176</td>
<td>0.803</td>
<td>...</td>
</tr>
<tr>
<td>AVM-ICH</td>
<td>15 (18.3%)</td>
<td>2 (9.1%)</td>
<td>0.516</td>
<td>0.196</td>
<td>...</td>
</tr>
</tbody>
</table>

IVH indicates intraventricular hemorrhage; AVM-ICH, arteriovenous malformation–intracerebral hemorrhage; OR, odds ratio; CI, confidence interval; ... not significant.

Table 4. Multiple Linear Regression of Admission Glucose of Baseline and Admission Variables

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Significance</th>
<th>Standardized Coefficient</th>
<th>Unstandardized Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.281</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.001</td>
<td>0.477</td>
<td>5.716</td>
<td>2.253–4.651</td>
</tr>
<tr>
<td>Admission hematoma volume, mL</td>
<td>0.281</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Admission IVH score</td>
<td>0.001</td>
<td>0.279</td>
<td>0.115</td>
<td>0.047–0.183</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>0.308</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>AVM-ICH</td>
<td>0.763</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

IVH indicates intraventricular hemorrhage; AVM-ICH, arteriovenous malformation–intracerebral hemorrhage; CI, confidence interval; ... not significant.

Figure. Admission blood glucose by intraventricular hemorrhage (IVH) quartiles. The vertical axis depicts mean admission blood glucose with standard error (SE) bars as a function of IVH score quartiles (horizontal axis). Mean admission glucose levels are 7.35 ± 2.66 mmol/L, 8.54 ± 3.11 mmol/L, 9.32 ± 3.74 mmol/L, and 10.58 ± 2.96 mmol/L for IVH score quartiles 0 to 5, 6 to 11, 12 to 17, and 18 to 23, respectively (P = 0.004; analysis of variance test for linearity P < 0.001).
ship with glucose elevation, underscoring a more faithful interaction between the presence of IVH and admission glucose levels. Furthermore, we observed a linear relationship between admission glucose level and IVH severity. Although the mechanism of IVH-induced systemic hyperglycemia is unclear, it is possible that greater ventricular involvement leads to a stronger stress response, sympathetic activation, and the release of catecholamines, cortisol, and inflammatory cytokines. Moreover, intraventricular involvement may specifically trigger hyperglycemia through another mechanism independent of stroke severity. Specifically, IVH may lead to abnormal activation of the hypothalamic–pituitary–adrenal axis through extravasation of blood breakdown products and inflammatory markers into the ventricular system and subsequent irritation of hypothalamic structures. Experimental models have demonstrated that intraventricular injection inflammatory mediators result in increased levels of serum corticotropin-releasing hormone, adrenocorticotropin-releasing hormone, and cortisol, which lead to systemic insulin resistance, greater rates of gluconeogenesis, and increased circulating levels of glucose. Conversely, hyperglycemia itself may be a causative factor in the development and progression of IVH. Previous studies have identified hyperglycemia as a risk factor for parenchymal hemato growth after spontaneous ICH and hemorrhagic conversion after administration of intravenous tissue plasminogen activator for the treatment of ischemic stroke. Experimental models have demonstrated that acute hyperglycemia impairs the integrity of the blood–brain barrier, suggesting that elevated blood glucose may lead to a prohemorrhagic state after brain injury. Interestingly, hematoma size was not associated with either admission glucose or critical hyperglycemia in our cohort and may reflect the relatively small sample size compared with other studies. However, the effect of elevated blood glucose on hemostasis remains somewhat controversial, because there is ample evidence that suggests that both acute and chronic elevations of glucose promote a thrombotic state. Further experimental and clinical studies are necessary to confirm the relationship between IVH and the onset of hyperglycemia and to elucidate the mechanism behind the interactions of the 2 important ICH disease severity factors.

This study has several limitations. First, the relatively small sample size, when compared with other case series, may have been underpowered to detect significant associations between certain radiographic features of ICH that have been identified in previous studies. However, we demonstrated a relationship between IVH and hyperglycemia and, perhaps more importantly, that admission glucose and severity of IVH are linearly related. Second, history of diabetes was obtained by interviewing patients and their families. Given that diabetic patients may be asymptomatic for years before manifesting the sequelae of sustained chronic hyperglycemia, some patients identified as nondiabetics in our cohort may have indeed had undiagnosed diabetes. However, our study did not rely heavily on subgroup analysis of diabetic and nondiabetic patients. Moreover, the focus of this study was the relationship between admission radiographic variables and hyperglycemia, and history of diabetes was controlled for in the analyses related to this primary clinical question. Third, pre-emergency department treatments were not included in the design of this prospective study and were not included in these analyses. Finally, a significant fraction of patients admitted to our institution were transfers from outside hospitals. However, we used the first intravenous glucose gathered at the initial evaluation after the patient manifested ICH.

**Conclusions**

In this study, we confirmed the relationship between hyperglycemia and mortality after ICH and found that admission glucose increased with more severe IVH. Although the pathophysiological basis for this result still needs to be investigated, ventricular extension of ICH may trigger hyperglycemia either through a nonspecific stress response or through irritation of hypothalamic nuclei involved in hypothalamic–pituitary–adrenal axis. Further studies are needed to elucidate the relationship between hyperglycemia and IVH and to determine whether aggressive targeting of intraventricular bleeding reduces the risk of developing hyperglycemia and ultimately poor outcome.

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**Disclosures**

E.S.C. has submitted a grant application to the National Institutes of Health (1R01NS07263501) for a multicenter prospective database on spontaneous intracerebral hemorrhage that will include data presented in the current study.

**References**


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