Persistent perioperative hyperglycemia as an independent predictor of poor outcome after aneurysmal subarachnoid hemorrhage

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Object. The authors of previous studies have shown that admission hyperglycemia or perioperative hyperglycemic events may predispose a patient to poor outcome after aneurysmal subarachnoid hemorrhage (SAH). The results of experimental evidence have suggested that hyperglycemia may exacerbate ischemic central nervous system injury. It remains to be clarified whether a single hyperglycemic event or persistent hyperglycemia is predictive of poor outcome after aneurysmal SAH.

Methods. Ninety-seven patients undergoing treatment for aneurysmal SAH were observed, and all perioperative variables were entered into a database of prospectively recorded data. Daily serum glucose values were retrospectively added. Patients were examined at hospital discharge (14–21 days after SAH onset), and Glasgow Outcome Scale (GOS) scores were prospectively documented. The GOS score at last follow-up was retrospectively determined. Serum glucose greater than 200 mg/dl for 2 or more consecutive days was defined as persistent hyperglycemia. Outcome was categorized as “poor” (dependent function [GOS Score 1–3]) or “good” (independent function [GOS Score 4 or 5]) at discharge. The independent association of 2-week and final follow-up outcome (GOS score) with the daily serum glucose levels was assessed using a multivariate analysis.

Results. In the univariate analysis, increasing age, increasing Hunt and Hess grade, hypertension, ventriculomegaly on admission computed tomography scan, Caucasian race, and higher mean daily glucose levels were associated with poor (dependent) 2-week outcome after aneurysmal SAH. In the multivariate analysis, older age, the occurrence of symptomatic cerebral vasospasm, increasing admission Hunt and Hess grade, and persistent hyperglycemia were independent predictors of poor (dependent) outcome 2 weeks after aneurysmal SAH. Admission Hunt and Hess grade and persistent hyperglycemia were independent predictors of poor outcome at last follow-up examination a mean 10 ± 3 months after aneurysmal SAH. Isolated hyperglycemic events did not predict poor outcome. Patients with persistent hyperglycemia were 10-fold more likely to have a poor (dependent) 2-week outcome and sevenfold more likely to have a poor outcome a mean 10 months after aneurysmal SAH independent of admission Hunt and Hess grade, occurrence of cerebral vasospasm, or all comorbidities.

Conclusions. Patients with persistent hyperglycemia were seven times more likely to have a poor outcome at a mean of 10 months after aneurysmal SAH. Isolated hyperglycemic events were not predictive of poor outcome. Serum glucose levels in the acute setting of aneurysmal SAH may help predict outcomes months after surgery.

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KEY WORDS • glucose • hyperglycemia • outcome • subarachnoid hemorrhage

Abbreviations used in this paper: CI = confidence interval; CT = computed tomography; DM = diabetes mellitus; GOS = Glasgow Outcome Scale; IQR = interquartile range; SAH = subarachnoid hemorrhage.

Morbidities and deaths are often caused by cerebral ischemia secondary to the initial hemorrhage or secondary effects of elevated intracranial pressure, cerebral vasospasm, and hydrocephalus. Previously described predictors of poor outcome after aneurysmal SAH include age, essential hypertension, DM, elevated body mass index, Fisher grade, Hunt and Hess grade, Glasgow Coma Scale score, and duration of temporary arterial occlusion during surgery.2,6,8,37,40,41,49

Recently, interest in the role of hyperglycemia after SAH has grown as a result of numerous authors having shown a strong association between elevated glucose level and morbidity in the critical care setting.2,6,8,37,40,41,49

After stroke,6,15,16 and after brain and spinal cord trauma,10,27,30,38,39,49 and after aneurysmal SAH,13,14,23,31 It remains to be clarified whether
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admission hyperglycemia, a solitary hyperglycemic event, or persistent hyperglycemia is predictive of poor outcome after aneurysmal SAH. Clinical and experimental evidence suggests that hyperglycemia affects arterial remodeling, lowers the neuronal ischemic threshold, lowers infarct volume after focal ischemia,7,17 Preservation of vascular endothelium and cerebral autoregulation is critical to reducing vasospasm-associated morbidity, and acutely elevated blood glucose alters endothelial function9,33 and increases free radical production39 and inflammatory cell migration27,28 after cerebral ischemia.

We investigated whether persistent perioperative hyperglycemia or isolated admission hyperglycemia that was subsequently corrected would negatively affect neurological outcome in patients undergoing the placement of aneurysm clips after aneurysmal SAH.

Clinical Material and Methods

Data obtained in 710 consecutive patients with aneurysmal SAH presenting to The Johns Hopkins Hospital between 1992 and 2005 were included in an institutional prospectively maintained database. Data pertaining to demographics; comorbidities; admission Hunt and Hess grade; number, location, and characteristics of aneurysms; selection of clip or coil therapy; presence of hydrocephalus on admission CT scan; operative variations (temporary clip, circulatory arrest, or intraoperative rupture); and occurrence of symptomatic cerebral vasospasm were prospectively assessed and recorded during each patient’s hospitalization. Patients were examined at hospital discharge (14–21 days after SAH onset), and GOS score was prospectively documented. The clinic notes at last follow-up were retrospectively assessed to establish the GOS score.

One hundred patients in this SAH database were randomly identified and their charts were reviewed. A 2-week GOS score was available for review in all patients. The clinical follow-up GOS score was available for 51 patients (52%) at a mean of 10 ± 3 months after aneurysmal SAH. Daily serum glucose values were retrospectively established and added to the database of prospectively collected data. Laboratory values were not available for three patients, whose data were subsequently excluded from analysis. Serum glucose greater than 200 mg/dl for 2 or more consecutive days was defined as persistent hyperglycemia. Outcome was categorized as “poor (dependent function [GOS 1–3]) versus “good” (independent function [GOS 4–5]) at discharge. The independent association of 2-week and last follow-up outcome with average daily serum glucose levels was assessed using multivariate analysis.

During the study period, standardized care in the neurointensive care unit included administration of 4 mg Decadron every 6 hours before surgery, nimodipine therapy, gastritis prophylaxis, and positive fluid balance. Decadron was routinely discontinued 24 hours after surgery. Coil or clip placement was performed within 48 hours in all reviewed patients. Patients exhibiting delayed neurological deficits not associated with rebleeding, hydrocephalus, or epileptic activity underwent hypervolemia–hypertensive therapy and cerebral angiography. Patients in whom there was angiographic evidence of cerebral vasospasm were classified as having symptomatic vasospasm and underwent papaverine injection or angioplasty. Glucose levels were obtained every 6 hours, and subcutaneous administration of sliding-scale insulin was performed in all patients. When serum glucose was persistently more than 200 mg/dl, patients in the intensive care unit were started on an insulin drip, whereas those not in the intensive care unit received an increased sliding-scale insulin protocol with increasing long-acting (isophane) insulin.

For intergroup comparison, continuous data were compared using two-way analysis of variance for parametric data and the Mann–Whitney U-test for nonparametric data. Percentages were compared using chi-square tests. All variables were assessed as univariate risk factors for “poor,” dependent outcome (GOS Score 1–3) with a logistic regression analysis (Statview, SAS). All variables significant or trending toward significance in univariate analysis were included in multivariate logistic regression analysis (Statview, SAS).

Patient Population

Ninety-seven patients with aneurysmal SAH were included in the study. Their mean age was 51 ± 16 years. Twenty-five individuals (26%) were men, and 32 (33%) were African-American. Thirty patients (31%) had chronic hypertension and six (6%) had coronary artery disease. Only two patients (2%) had a previous diagnosis of DM. Left-sided aneurysm rupture occurred in 43 cases (44%), and the hemorrhage was demonstrated in the posterior circulation in 17 (18%). Multiple aneurysms were present in 13 cases (13%). Craniotomy was performed in 91 cases (94%), whereas coils were used in six (6%) cases. Temporary clips were used in 13 patients (13%).

The median admission Hunt and Hess grade was II (IQR Scores I–III). Eighteen patients (19%) had a poor grade (Hunt and Hess Grade IV or V). Ventriculomegaly was present on admission CT scans obtained in 47 patients (48%). Nineteen (20%) patients developed symptomatic cerebral vasospasm 3 to 14 days after SAH onset. In 35 patients (36%), a single hyperglycemic event (>200 mg/dl) occurred, whereas in 26 patients (27%), persistent hyperglycemia (>200 mg/dl for ≥2 consecutive days) was observed. In the majority of cases (69% or 18 of 26) in which persistent hyperglycemia developed, the patients responded immediately to intensive insulin therapy, whereas eight (31%) experienced at least one additional serum glucose value greater than 200 mg/dl despite intensive insulin therapy. In these eight patients, the disorder was classified as stress-induced hyperglycemia. Infection, sepsis, active myocardial infarction, or any other clear cause of hyperglycemia was not evident in any of these eight patients.

The median length of hospital stay was 14 days (IQR 8–24 days). Median [IQR] 2-week GOS score was 4 (IQR Score 2–5). At a mean of 10 ± 3 months after aneurysmal SAH, the median GOS score was 3 (IQR Score 1–5). Fifty-six patients (58%) experienced good outcomes (independent function; GOS Score 4 to 5) 2 weeks after SAH onset. Of the 51 patients with long-term follow-up data, 25 (49%) experienced good outcomes (independent function) 10 ± 3 months after aneurysmal SAH.

TABLE 1
Univariate predictors of poor 2-week outcome in patients with aneurysmal SAH*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1.06 (1.03–1.10)</td>
<td>0.005</td>
</tr>
<tr>
<td>Caucasian</td>
<td>5.73 (2.08–15.80)</td>
<td>0.007</td>
</tr>
<tr>
<td>male</td>
<td>1.57 (0.60–3.78)</td>
<td>0.371</td>
</tr>
<tr>
<td>Hunt &amp; Hess grade</td>
<td>3.07 (1.95–3.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>DM</td>
<td>0.001 (0.00–19.2)</td>
<td>0.981</td>
</tr>
<tr>
<td>hypertension</td>
<td>2.52 (1.04–6.09)</td>
<td>0.040</td>
</tr>
<tr>
<td>coronary artery disease</td>
<td>2.67 (0.47–15.4)</td>
<td>0.271</td>
</tr>
<tr>
<td>lt-sided aneurysm</td>
<td>0.60 (0.26–1.34)</td>
<td>0.209</td>
</tr>
<tr>
<td>posterior circulation aneurysm</td>
<td>1.14 (0.40–3.26)</td>
<td>0.803</td>
</tr>
<tr>
<td>multiple aneurysms</td>
<td>1.56 (0.48–5.03)</td>
<td>0.461</td>
</tr>
<tr>
<td>intraop rupture</td>
<td>1.69 (0.67–4.29)</td>
<td>0.266</td>
</tr>
<tr>
<td>coil therapy</td>
<td>6.97 (0.78–68.1)</td>
<td>0.081</td>
</tr>
<tr>
<td>mean daily glucose</td>
<td>1.06 (1.03–1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>admission hyperglycemia†</td>
<td>6.88 (1.40–33.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>persistent hyperglycemia‡</td>
<td>18.67 (4.96–70.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>ventriculomegaly</td>
<td>4.14 (1.76–9.72)</td>
<td>0.011</td>
</tr>
<tr>
<td>cerebral vasospasm</td>
<td>1.97 (0.72–5.46)</td>
<td>0.181</td>
</tr>
</tbody>
</table>

* Poor outcome was defined as a GOS score of 1 to 3.
† Serum glucose greater than 200 mg/dl on admission day only.
‡ Serum glucose greater than 200 mg/dl for 2 or more days.

Outcome Predictors

In a univariate analysis of 2-week outcome, older age, higher Hunt and Hess grade, hypertension, ventriculomegaly on admission CT scan, Caucasian race, and higher mean daily glucose levels were associated with poor (dependent) 2-week outcome after aneurysmal SAH (Table 1). A previous diagnosis of DM was not associated with outcome. Each 10-point increase in the mean daily serum glucose level was associated with a 40% increase in the likelihood of poor outcome (Table 2). The 2-week outcome score in patients with post-SAH persistent hyperglycemia (median GOS Score 2, IQR 1–3) was significantly worse than that in patients with good glucose control (median GOS Score 4, IQR 3–5, p < 0.01). Patients with poor (dependent) 2-week outcomes had greater mean glucose levels on post-SAH Days 1, 2, 5 to 11, 13, and 14 (p < 0.05) (Fig. 1). There was no association of timing of persistent hyperglycemia and outcome.

In the univariate analysis of outcome at last follow-up examination performed a mean of 10 ± 3 months after aneurysmal SAH, older age, higher Hunt and Hess grade, Caucasian race, and greater mean daily glucose levels were associated with poor (dependent) outcome after aneurysmal SAH (Table 2). In patients with persistent hyperglycemia compared with those with good glucose control, a higher incidence of poor (dependent) outcome was observed at both 2 weeks (23 patients [88%] compared with 20 patients [28%], p < 0.01) and 10 ± 3 months (14 [88%] and 12 [33%], respectively, p < 0.01) after aneurysmal SAH.

In multivariate analysis of outcome 2 weeks after aneurysmal SAH, older age, the occurrence of symptomatic cerebral vasospasm, higher admission Hunt and Hess grade, and persistent hyperglycemia were independent predictors of poor (dependent) outcome (Table 3). Corrected admission hyperglycemia greater than 200 mg/dl did not independently predict poor outcome. Patients with persistent hyperglycemia were 10-fold more likely to have a poor (dependent) 2-week outcome independent of admission Hunt and Hess grade, occurrence of cerebral vasospasm, or all comorbidities (Table 3).

In the multivariate analysis of outcome at last follow-up, higher admission Hunt and Hess grade (odds ratio 2.83 [95% CI 1.46–5.46], p < 0.01) and persistent hyperglycemia (odds ratio 6.97 [95% CI 1.09–44.7], p < 0.05) were independent predictors of poor (dependent) outcome 10 ± 3 months after aneurysmal SAH. Patients with persistent hyperglycemia were nearly sevenfold more likely to have a poor (dependent) outcome 10 ± 3 months after aneurysmal SAH independent of admission Hunt and Hess grade, occurrence of cerebral vasospasm, or all comorbidities.

Discussion

In this study, we reviewed and analyzed perioperative glucose levels in relation to postoperative outcomes in 97 patients who underwent surgical or endovascular treatment after aneurysmal SAH. Each 10-point increase in mean daily serum glucose level was associated with a 40% increase in the likelihood of poor outcome. Both 2-week and 10-month GOS scores obtained in patients with persistent hyperglycemia after SAH were significantly worse than those in patients with good glucose control. Conversely, admission hyperglycemia subsequently corrected (glucose > 200 mg/dl for 1 day only) was not associated with worse outcome. Independent of admission Hunt and Hess grade, occurrence of cerebral vasospasm, or all comorbidities, patients with persistent hyperglycemia (> 200 mg/dl) were nearly sevenfold more likely to suffer a poor 10-month outcome.

Few clinical studies have been conducted to investigate the effect of acute hyperglycemia on surgical outcomes after SAH. Lanzino et al. were one of the first groups to look at this association and found that elevated glucose levels (≥ 120 mg/dl) at admission and 1 week after SAH predicted poor 3-month outcome. Recently, Juvela et al. also ob-

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After acute stroke, hyperglycemia has consistently been shown to increase morbidity and mortality rates, increase length of hospital stay, reduce long-term functional recovery, and diminish ability to return to work, regardless of a patient’s prior diabetes status.1,2,4,6,8,12,15,25,32,40–42

With this study, there is now growing evidence that rigorous glucose control after SAH may also improve outcomes and limit mortality and morbidity rates. Given the retrospective design of this study, the mechanism or causality post-SAH of hyperglycemia-related morbidity cannot be determined. The observed relationship between hyperglycemia and poor outcome is one of association, not causality, potentially representing an epiphenomenon. It could be argued that persistent hyperglycemia is simply a surrogate marker of an underlying etiological factor for poor outcome. The rate of response to aggressive insulin therapy varied in patients with persistent hyperglycemia, highlighting the heterogeneity in the respective origins of their elevated glucose levels. Eight patients in our series experienced further hyperglycemia despite aggressive management, a phenomenon often observed with increasing systemic disease in the critical care setting. Serum glucose may be a surrogate marker in these patients. Furthermore, without glycosylated hemoglobin A1C levels in this study, we cannot determine whether acute ischemic threshold lowering or a more chronic augmentation of cerebral vasculopathy contributed to the observed increased hyperglycemia-related morbidity rate. Nevertheless, close perioperative glucose control may be an important modifier of SAH-related morbidity.

**Conclusions**

Independent of admission Hunt and Hess grade, the occurrence of cerebral vasospasm, or clinical comorbidities, patients with persistent hyperglycemia were significantly more likely to have a poor outcome after aneurysmal SAH. Serum glucose levels in the acute setting of SAH may help predict outcomes months after surgery.

**References**


**TABLE 3**

| Multivariate predictors of poor outcome 2 weeks after aneurysmal SAH* |
|-------------------------------|-----------------|-----------------|
| Variable                      | Odds Ratio (95% CI) | p Value |
| age                           | 1.04 (1.02–1.09)  | 0.040          |
| Hunt & Hess grade             | 2.52 (1.48–4.31)  | 0.006          |
| cerebral vasospasm            | 4.9 (1.17–21.2)   | 0.029          |
| admission hyperglycemia†      | 3.51 (0.56–22.1)  | 0.181          |
| persistent hyperglycemia‡     | 10.3 (2.2–48.21)  | 0.003          |

* Poor outcome was defined as a GOS score of 1 to 3. Patients developing cerebral vasospasm or persistent hyperglycemia were independently five- and 10-fold more likely to experience a poor outcome 2 weeks after SAH, respectively. Increasing age and decreasing Hunt & Hess grade were also associated with poor outcome.
† Serum glucose greater than 200 mg/dl on admission day only.
‡ Serum glucose greater than 200 mg/dl for 2 or more days.

**Fig. 1.** Graph showing the serum glucose levels (mean ± standard deviation) in patients with poor (GOS Score 1–3) and good (GOS Score 4 or 5) 2-week outcome. Patients with poor 2-week outcomes experienced greater mean glucose levels on SAH Day 1, 2, 5 to 11, 13, and 14 (p < 0.05).


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