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Brief Communication

Acute Hyperglycemia and In-Hospital Mortality in Spontaneous Intracerebral Hemorrhage

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ABSTRACT: Hyperglycemia is reported to predict worse outcome in patients with stroke, including intracerebral hemorrhage (ICH). In 83 consecutive cases of ICH at a tertiary stroke center, hyperglycemia (serum glucose >7 mmol/L) compared to normoglycemia at presentation was associated with higher rates of in-hospital mortality (51.2% vs. 26.2%, OR 2.3, CI 1.2–7.6, $p = 0.02$). The association with in-hospital mortality withstood adjustment for age, ICH volume, intraventricular hemorrhage, and infratentorial ICH location, but not baseline Glasgow Coma Scale. Acute hyperglycemia is associated with in-hospital mortality in spontaneous ICH patients, though this may be an indirect, rather than a causal relationship.

RÉSUMÉ : L'hyperglycémie aiguë et la mortalité hospitalière dans les hémorragies cérébrales spontanées. Selon différents rapports, l'hyperglycémie serait un indicateur prévisionnel sombre de l'issue chez les patients ayant subi un accident vasculaire cérébral (AVC), y compris une hémorragie cérébrale (HC). Ainsi, l'hyperglycémie (glucose sérique : > 7 mmol/l) à l'arrivée a été associée à un taux plus élevé de mortalité hospitalière (51,2 % contre 26,2 %; risque relatif approché : 2,3; IC : 1,2–7,6; $p = 0,02$) que la normoglycémie, dans une série de 83 cas consécutifs d'HC pris en charge dans un centre de soins tertiaires, spécialisé dans le traitement des AVC. L'association avec la mortalité hospitalière s'est montrée sensible aux rajustements pour tenir compte de l'âge, du volume des HC, des hémorragies intraventriculaires et du siège sous-tentoriel des HC, mais pas à la valeur initiale sur l'échelle de Glasgow. L'hyperglycémie aiguë est associée à la mortalité hospitalière chez les patients ayant subi une HC spontanée, mais il peut s'agir là d'une relation indirecte plutôt que d'une relation causale directe.

Keywords: Intracerebral hemorrhage; Hyperglycemia; Glucose; Prognosis; Mortality

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Intracerebral hemorrhage (ICH) accounts for 15–20% of all stroke and has the greatest rate of mortality amongst all stroke subtypes.[1] Hyperglycemia is prevalent amongst patients who experience cardiovascular and cerebrovascular events, even in the absence of preexisting diabetes mellitus.[2] In these settings, hyperglycemia has been associated with worse outcomes.[2,3] The association between hyperglycemia and worse ICH-related outcomes has been less consistent.[4,5]

We sought to further characterize the relationship between hyperglycemia and outcomes in ICH. We hypothesized that hyperglycemic patients with ICH would have higher in-hospital mortality rates. We further explored the association between hyperglycemia, ICH volumes, hematoma expansion, and perihematomal edema.

We performed a retrospective observational chart review at a single tertiary care center (Hamilton Health Sciences [HHS], Hamilton, Ontario, Canada). Approval of the study was obtained from the Hamilton Integrated Research Ethics Board.

Consecutive adult (≥18 years old) patients admitted to HHS with spontaneous intraparenchymal hemorrhages between March 2015 and June 2016 were reviewed ($n = 99$). Excluded were those determined to have secondary causes ($n = 8$; two cavernomas, two aneurysms, one developmental venous anomaly, two due to sympathomimetic agents, and one reversible cerebral vasoconstriction syndrome) or hemorrhagic transformation of an infarct misclassified as ICH ($n = 8$).

Hospital admission records were reviewed for demographic information and vascular risk factors. Variables of interest included age, sex, self-reported history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, myocardial infarction, prior stroke, atrial fibrillation, and congestive heart failure, baseline Glasgow Coma Scale (GCS) score, admission blood

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pressure, serum glucose, and time from last known well to computed tomography (CT). Admission hyperglycemia was defined as a serum glucose >7 mmol/L upon presentation to the emergency department (ED). Glucose levels for the first 24 hours of admission, whether serum or via point-of-care testing, were also collected. We also recorded whether patients had a change in their medical scope of treatment to comfort care within the first 2 days of admission.

ICH topography was categorized as either lobar, deep, cerebellar, or brainstem. Associated intraventricular hemorrhage is either present or absent. ICH volume was calculated on baseline CT ($n = 73$) and repeat CT within 72 hours (where available; $n = 40$) using a modified ABC/2 formula that accounts for hemorrhage shape.[6] In cases with multiple repeat CTs during the initial 72 hours, the closest scan to 24 hours post-baseline imaging was selected. Perihematomal edema volume was determined by calculating the combined volume of edema and hematoma using the margins of edema via the ABC/2 method, and then subtracting the hematoma volume from this sum, as previously described.[7]

The primary outcome was in-hospital mortality. Secondary outcomes included disability at discharge according to the modified Rankin Scale (mRS), ICH volume, hematoma expansion (defined as either at least an absolute 6 mL or 33% increase from baseline), and perihematomal edema volume.

Descriptive statistics were used to compare characteristics between patients with hyperglycemia and those without. Dichotomous variables are presented as count (%) and continuous variables as mean (SD) or median (interquartile range [IQR]), as appropriate. Categorical variables were analyzed using the Pearson's chi-square or Fisher's exact test, and continuous variables using the two-sample t-test (for normal distributions) or the Mann–Whitney U-test (for non-normal distributions). Multivariate logistic regression analyses were performed, adjusting individually for age, ICH volume, GCS, infratentorial ICH (brainstem or cerebellum), intraventricular hemorrhage, and ordinal ICH score. These variables were selected a priori due to their association with mortality post-ICH.[8] Probability (p) values at the ≤ 0.05 level were deemed to be of statistical significance.

A total of 83 patients with spontaneous ICH were included in this study. The average age of patients was 73.5 years and 56.6% were male. Diabetes was prevalent (30.1%) and the median admission glucose for the cohort was 7.0 mmol/L (IQR 6.1–9.9 mmol/L). Median time to CT from time last known well was 2.9 hours and length of hospitalization was 7 (IQR 3–15) days. The majority of patients were admitted from home ($n = 77$, 92.8%), whereas only a minority were admitted from a long-term care facility ($n = 6$, 7.2%). Of the 73 patients admitted from home, 10 patients were transferred from a peripheral hospital.

ICH were non-lobar in 61 cases (73.5%) and lobar in 22 cases (26.5%). Of the 28 patients who underwent brain magnetic resonance imaging (MRI) during their hospitalization, 7 patients fulfilled clinico-radiographic modified Boston criteria for probable cerebral amyloid angiopathy (CAA), and an additional 2 patients had CAA proven on biopsy, for a total of 9 patients with probable CAA. Seven patients were on anticoagulation at the time of their ICH. There was no significant difference in the proportion of ICH that were non-lobar and lobar between hyperglycemic and non-hyperglycemic patients ($p = 0.75$).

Admission hyperglycemia was present in 49.4% ($n = 41$) of patients. Hyperglycemic patients were more often diabetic (41.5% vs. 19.0%, $p = 0.047$; Table 1), had poorer glycemic control as measured by the HbA1c (6.8% vs. 5.5%, $p = 0.02$), had greater proportion of prior stroke (17.1% vs. 2.4%, $p = 0.03$) and cerebellar ICH at presentation (22.0% vs. 2.4%, $p = 0.02$), and lower median baseline GCS (13 [7–14.8] vs. 15 [11.5–15], $p = 0.04$), but otherwise did not differ from non-hyperglycemic patients. Median time from admission to measurement of glucose was 1.6 hours, and this did not vary between the two groups ($p = 0.28$). Among the 24 patients with diabetes, hyperglycemic patients had a higher HbA1c compared to non-hyperglycemic patients (8.6% vs. 5.9%, $p = 0.01$). We also noted that the glucose trend during the first 24 hours of admission was more variable in hyperglycemic patients compared to non-hyperglycemic patients (Figure 1).

Regarding acute treatment of glucose, only one patient with admission glucose of 29.2 mmol/L was treated by the ED physician with insulin. In our cohort, no other patients received antihyperglycemic treatment either by paramedics or ED physicians. As expected, hyperglycemic patients were more likely to be receiving oral antihyperglycemic medications than non-hyperglycemic patients (29.3% vs. 2.4%, $p < 0.001$). Otherwise, there were no statistical differences between hyperglycemic and non-hyperglycemic patients in terms of the treatments they received, including blood pressure control, use of in-hospital insulin sliding scale and/or long-acting insulin, and external ventricular drain placement (Table 1). Although a numerical trend suggested a greater need for neurosurgical evacuation in patients with presenting hyperglycemia, this was not statistically significant ($p = 0.08$).

In univariate analysis, the rate of in-hospital mortality was significantly higher in hyperglycemic patients compared to their non-hyperglycemic counterparts (51.2% vs. 26.2%, OR 2.3, 95% CI 1.2–7.6, $p = 0.02$). Hyperglycemic patients also had greater disability quantified by the discharge mRS (6 [IQR 4–6] vs. 4 [IQR 3–6], $p = 0.02$), and larger ICH (median 13.0 mL [IQR 7.8–37.0] vs. 7.3 mL [IQR 3.0–23.6], $p = 0.03$) and perihematomal edema volumes at baseline (median 9.3 mL [IQR 3.7–25.4] vs. 4.2 mL [IQR 1.3–10.6], $p = 0.01$) but were not at increased risk for hematoma expansion (Table 2). Moreover, hyperglycemia burden, defined as the average glucose level over the first 48 hours of admission, was not found to be significantly associated with in-hospital mortality (OR 1.13, 95% CI 0.98–1.31, $p = 0.10$).

The association between admission hyperglycemia and in-hospital mortality withstood individual adjustment for age (OR 3.4, 95% CI 1.3–9.1, $p = 0.01$), ICH volume (3.1, 1.1–10.3, $p = 0.04$), intraventricular hemorrhage (OR 3.0, 1.2–7.8, $p = 0.02$), infratentorial location (OR 2.8, 95% CI 1.1–7.5, $p = 0.03$) and comfort care orders during their admission (OR 3.3, 95% CI 3.2–27.2, $p = 0.03$), but not adjustment for GCS (OR 1.2, 95% CI 0.3–4.5, $p = 0.77$) or the ICH score as an ordinal variable (OR 1.9, 95% CI 0.6–5.9, $p = 0.27$).

Our findings suggest that hyperglycemia is common in acute spontaneous ICH and is associated with greater in-hospital mortality, ICH-related disability, and larger ICH and perihematomal edema volumes, but not hematoma expansion.

A recent systematic review and meta-analysis of 16 studies found that there were significant associations between hyperglycemia and functional outcome following ICH, both in the short and long term.[9] The relationship between hyperglycemia and mortality is less clear, with some studies showing reduced survival[4] and others suggesting no significant association once adjusted for confounding variables.[5] There are even fewer studies that have explored the relationship between neuroimaging findings, such as ICH volume and perihematomal

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Table 1: Baseline characteristics

Variable	All patients ($n = 83$)	Hyperglycemic ($n = 41$)	Non-hyperglycemic ($n = 42$)	p-Value
Demographics				
Age (mean, SD)	73.5 (12.6)	72.8 (12.4)	74.1 (12.8)	0.64
Male (n, %)	47 (56.6%)	23 (56.1%)	24 (57.1%)	0.99
Admission from home (n, %)	77 (92.8%)	37 (90.2%)	40 (95.2%)	0.43
Vascular risk factors (n, %)				
Previous stroke	8 (9.6%)	7 (17.1%)	1 (2.4%)	0.03
Hypertension	69 (83.1%)	31 (75.6%)	38 (90.5%)	0.13
Diabetes	25 (30.1%)	17 (41.5%)	8 (19.0%)	0.047
Atrial fibrillation/flutter	18 (21.7%)	9 (22.0%)	9 (21.4%)	0.99
Dyslipidemia	31 (37.3%)	14 (34.1%)	17 (40.5%)	0.71
CAD/MI	14 (16.9%)	9 (22.0%)	5 (11.9%)	0.35
CHF	4 (4.8%)	3 (7.3%)	1 (2.4%)	0.36
Baseline measurements				
LKWT to baseline CT, hours (median, IQR)	2.9 (1.6–8.5)	3.3 (1.8–12.4)	8.6 (1.3–6.6)	0.41
GCS (median, IQR)	14 (7–15)	13 (7–14.8)	15 (11.5–15)	0.04
Admission SBP, mm Hg (mean, SD)	177 (34)	178 (33)	176 (35)	0.88
Admission DBP, mm Hg (mean, SD)	94 (23)	93 (21)	95 (24)	0.55
Admission serum glucose, mmol/L (median, IQR)	7.0 (6.1–9.9)	10.0 (8.3–13.8)	6.1 (5.6–6.6)	<0.001
Time from admission to serum glucose, hours (median, IQR)	1.6 (0.9–4.6)	2.1 (1.0–5.3)	1.3 (0.9–3.7)	0.28
HbA1c, % (median, IQR)*	5.6 (5.3–6.4)	6.8 (5.5–9.0)	5.5 (5.3–5.7)	0.02
Treatments (n, %)				
SBP target ≤ 160 mmHg	49 (59.0%)	22 (53.7%)	27 (64.3%)	0.45
Insulin	14 (16.9%)	9 (22.0%)	5 (11.9%)	0.39
Oral antihyperglycemic medication(s)	13 (15.7%)	12 (29.3%)	1 (2.4%)	<0.001
EVD insertion	12 (14.4%)	8 (19.5%)	4 (9.5%)	0.33
Neurosurgical evacuation	10 (12.0%)	8 (19.5%)	2 (4.8%)	0.08
Neuroimaging (n, %)				
Lobar ICH	22 (26.5%)	12 (29.3%)	10 (23.8%)	0.75
Deep ICH	27 (32.5%)	9 (22.0%)	18 (42.8%)	0.07
Brainstem ICH	4 (4.8%)	2 (4.9%)	2 (4.8%)	0.99
Cerebellar ICH	10 (12.0%)	9 (22.0%)	1 (2.4%)	0.02
Intraventricular hemorrhage	45 (54.2%)	23 (56.1%)	22 (52.4%)	0.90

CAD, coronary artery disease; MI, myocardial infarction; CHF, congestive heart failure; EVD, external ventricular drain; LKWT, last known well time; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; IQR, interquartile range.
Values expressed as mean (SD), n(%) or median (IQR).
*Forty-eight patients did not have an available HbA1c (26 hyperglycemic and 22 non-hyperglyercemic).

edema, and hyperglycemia in ICH, though some studies have reported an association between larger hematoma volumes and hyperglycemia.[4]

The direction of association between hyperglycemia and worse ICH-related outcomes is uncertain. It is possible that larger hematoma volumes elicit a greater stress response, and therefore trigger a stress-induced hyperglycemic state, which may destabilize the blood–brain barrier/endothelium, resulting in greater perihematomal edema formation, and/or impair hemostasis resulting in larger ICH volumes.[10] A recent report suggests that admission blood glucose predicts the spot sign, which can predict hematoma expansion.[11] Our findings, however, did not demonstrate an association between hyperglycemia and hematoma expansion. Further, the association between hyperglycemia and in-hospital mortality did not withstand adjustment for baseline GCS or the ICH score as an ordinal scale. Accordingly, our results are not compelling for a causal relationship between acute hyperglycemia and worse outcomes but favor the notion that hyperglycemia is a stress-induced epiphenomenon of more severe ICH. The association between hyperglycemia and cerebellar ICH is interesting and could suggest the potential for greater baseline systemic stress response resulting from ICH in this location. Whether this is due to mass effect onto the adjacent ventricular system and/or brainstem structures or alternatively from the severe vertigo and nausea/vomiting that

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Table 2: Univariate analyses assessing admission hyperglycemia and outcomes

Outcomes	Hyperglycemic ($n = 41$)	Non-Hyperglycemic ($n = 42$)	p-Value
In-hospital mortality (n, %)	21 (51.2%)	11 (26.2%)	0.02
Secondary outcomes			
mRS (median, IQR)	6 (4–6)	4 (3–6)	0.02
ICH volume, mL (median, IQR)	13.0 (7.8–37.0)	7.3 (3.0–23.6)	0.03
Perihematomal edema volume, mL (median, IQR)	9.3 (3.7–25.4)	4.2 (1.3–10.6)	0.01
Hematoma expansion (n, %)*	5 (35.7%)	9 (34.6%)	0.94

mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; IQR, interquartile range.
*Forty-three patients did not have a repeat CT scan to assess hematoma expansion (27 hyperglycemic and 16 non-hyperglycemic).

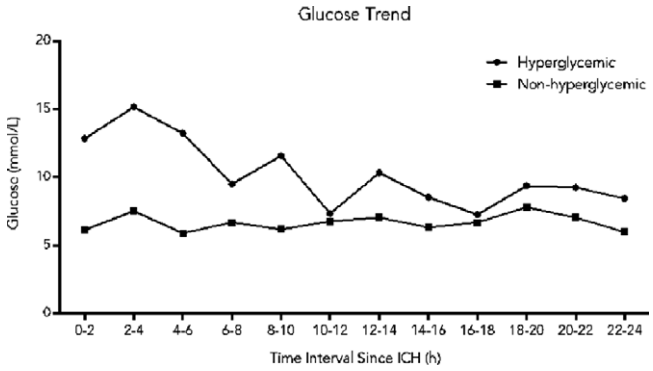

Figure 1: Glucose trend over first 24 hours of hospital admission. Trend of glucose over the first 24 hours since the ICH, with glucose measurements averaged in 2-hour intervals.

often accompanies cerebellar ICH is uncertain. The lack of an association between hyperglycemia and IVH or brainstem ICH in our cohort lends more support to the latter hypothesis.

Our study is largely limited by its observational design and small sample size. As stated, we cannot infer the directionality of the relationship between hyperglycemia and mortality in ICH due to these limitations. The single-center nature of our cohort further limits the generalizability of our results. We do not have long-term functional outcome data given the retrospective nature of the study. Baseline CT scans and repeat scan images were only available in a subset of our cohort, which may have introduced selection bias in analyses of neuroimaging findings. Although we did observe that patients with an acute hyperglycemic response had poorer long-term glycemic control as measured by the HbA1c compared to non-hyperglycemic patients, data for HbA1c were limited by missing data as it is not routinely measured in patients with ICH. Furthermore, the use of ABC/2 method for measuring ICH and perihematomal edema volumes is imprecise and may have limited our ability to fully assess the relationship between hyperglycemia and these measures.

Acute hyperglycemia is common in ICH patients and is a marker of in-hospital mortality. Our results would suggest however that hyperglycemia is most likely a stress-induced epiphenomenon of more severe ICH, rather than an independent contributor to mortality.

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References

1. Poon MTC, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85:660–7.
2. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–32.
3. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology 2002;59:669–74.
4. Saxena A, Anderson CS, Wang X, et al. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: the INTERACT2 study. Stroke. 2016;47:682–8.
5. Kongwad LI, Hegde A, Menon G, Nair R. Influence of admission blood glucose in predicting outcome in patients with spontaneous intracerebral hematoma. Front Neurol. 2018;9:725.
6. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke. 1996;27:1304–5.
7. Shulman JG, Jara H, Qureshi MM, et al. Perihematomal edema surrounding spontaneous intracerebral hemorrhage by CT: ellipsoidal versus morphometric volumetry. Medicine. 2020;99:e20951.
8. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891–7.
9. Zheng J, Yu Z, Ma L, et al. Association between blood glucose and functional outcome in intracerebral hemorrhage: a systematic review and meta-analysis. World Neurosurg. 2018;114:e756–65.
10. Song E-C, Chu K, Jeong S-W, et al. Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. Stroke. 2003;34:2215–20.
11. Zhang F, Zhang S, Tao C, et al. Association between serum glucose level and spot sign in intracerebral hemorrhage. Medicine. 2019;98:e14748.

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