neurocritical care society Neurocrit Care (2010) 12:181–187
DOI 10.1007/s12028-009-9311-z

ORIGINAL ARTICLE

Moderate Hypoglycemia is Associated With Vasospasm, Cerebral Infarction, and 3-Month Disability After Subarachnoid Hemorrhage

Andrew M. Naidech · Kimberly Levasseur · Storm Liebling · Rajeev K. Garg · Michael Shapiro · Michael L. Ault · Sherif Afifi · H. Hunt Batjer

Published online: 5 December 2009

Abstract
Background Many ICUs have implemented protocols for tight glucose control, but there are few data on hypoglycemia and neurologic outcomes in patients with subarachnoid hemorrhage (SAH).
Methods We prospectively ascertained 172 patients with SAH, who were treated according to a standard protocol for target glucose 80–110 mg/dl. Outcomes were assessed with the modified Rankin scale (mRS) at 14 days, 28 days, and 3 months.
Results Worse neurologic injury at admission ($P < 0.001$) and a history of diabetes ($P = 0.002$) were associated with increased glucose variance. There was lower nadir glucose in patients with radiographic cerebral infarction (81 ± 15 vs. 87 ± 16 mg/dl, $P = 0.02$), symptomatic vasospasm (78 ± 12 vs. 84 ± 16 mg/dl, $P = 0.04$) and angiographic vasospasm (79 ± 14 vs. 86 ± 16 mg/dl, $P = 0.01$), but maximum and mean glucose values were not different. Glucose < 80 mg/dl was earlier and more frequent in patients with worse functional outcome at 3 months ($P < 0.001$). Progressive reductions in nadir glucose were associated with increasing functional disability at 3 months ($P = 0.001$) after accounting for neurologic grade and mean glucose. Severe hypoglycemia (<40 mg/dl) occurred in one patient.
Conclusions In patients with SAH, nadir glucose < 80 mg/dl is associated with cerebral infarction, vasospasm, and worse functional outcomes in multivariate models. Protocols for target glucose 80–110 mg/dl effectively control hyperglycemia, but may place patients with SAH at risk for vasospasm, cerebral infarction, and poor outcome even when severe hypoglycemia does not occur.

Keywords Subarachnoid hemorrhage · Insulin · Glucose · Outcomes

A. M. Naidech (✉) · S. Liebling · R. K. Garg
Department of Neurology, School of Medicine, Northwestern University, 710 N Lake Shore Drive, 11th floor, Chicago, IL 60611, USA
e-mail: a-naidech@northwestern.edu

K. Levasseur
Northwestern Memorial Hospital, 251 E Huron, Chicago, IL 60611, USA

M. Shapiro
Department of Surgery, 676 St Clair Ave, Chicago, IL 60611, USA

M. L. Ault · S. Afifi
Department of Anesthesiology, 251 E Huron, Chicago, IL 60611, USA

H. H. Batjer
Department of Neurological Surgery, 676 St Clair Ave, Chicago, IL 60611, USA

Introduction

Insulin infusions to achieve tight glucose control (TGC, serum glucose 80–110 mg/dl) are commonly used in intensive care units in patients with subarachnoid hemorrhage (SAH). Data linking hyperglycemia to vasospasm [1] and mortality [2, 3] have led to all but mandatory implementation. Patients with more severe neurologic injury are more likely to need insulin infusion [4]. TGC after SAH seems to be well tolerated [5], decreases the risk of infection [6], and may improve outcome when it is successful in controlling glucose [7] in selected patients. TGC also increases the risk of hypoglycemia [8], however, and

the effect of hypoglycemia may annul the potential benefits of TGC [9, 10].

Increased glucose variability increases the odds of both hyper- and hypoglycemia. Both severe hyperglycemia and severe hypoglycemia are both harmful; whether 80–110 mg/dl is the optimal range for all patient populations is less clear. Increased glucose variability alone is associated with worse outcomes [11, 12], and minimizing glucose variance may be as important as minimizing hyperglycemia.

Serum glucose measurements do not always directly translate into information about cellular energy metabolism. In patients with neurologic injury who are monitored with microdialysis catheters (allowing for inferences about neuronal function), cerebral hyperglycemia does not always correspond to serum hyperglycemia [13, 14], and parameters characteristic of neuronal energy failure may be seen with insulin therapy [15]. We tested the hypothesis that lower serum glucose is associated with more cerebral infarction, more vasospasm, and worse functional outcomes in a prospectively ascertained cohort of patients with SAH, all of whom had TGC.

Materials and Methods

Study Population

We enrolled 172 consecutive patients with SAH from May 2006, through March 2009. SAH was diagnosed by the admission CT scan or by xanthochromia of the cerebrospinal fluid if the CT was non-diagnostic. SAH due to trauma, arteriovenous malformation rupture, vasculitis, and other structural lesions was excluded.

Clinical Management

Body mass index was measured on admission. We measured physiologic derangement with the SAH-physiologic derangement scale [16], score from 0 (no derangement) to 8 (most derangement in alveolar-arterial gradient, blood pressure, glucose, and acid–base status). Diagnostic catheter or CT angiography and aneurysm obliteration with surgical clipping or endovascular coiling were performed as soon as possible. Enteral nimodipine was given unless the systolic blood pressure was <120 mmHg. All patients received pravastatin 40 mg daily as part of routine care [17]. Transcranial Doppler (TCD) sonography was performed daily. We prospectively recorded the presence of vasospasm, defined as mean transcranial Doppler >120 or >200 cm/s, clinically (new focal neurologic deficit or depressed mental status without other explanation), or arterial stenosis on angiography. Patients with clinical vasospasm were treated with hyperdynamic therapy [18]. Diagnostic angiography was performed with balloon angioplasty of vasospastic arteries and/or intra-arterial vasodilators if clinically appropriate. We transfused packed red blood cells for hemoglobin $<$ 10 g/dl [19]. Feeding tubes were placed on admission and all patients received enteral nutrition as soon as feasible, guided by the nutrition consultation service.

All ICU patents with hyperglycemia were treated with a hospital wide protocol including insulin infusion to target glucose 80–110 mg/dl. Insulin was started when the blood glucose was >110 mg/dl. The initial infusion rate was based on the initial blood glucose level (2 units/h for glucose 110–180 mg/dl, 3 units/h for glucose 181–240 mg/dl, and so on). Further changes in insulin infusion dose were based on a sliding scale depending on how the blood glucose changed on an hourly basis. Patients requiring insulin at ICU discharge or during enteral feedings were evaluated by a specialized team to adjust insulin requirements.

Clinical variables were prospectively collected. We prospectively recorded baseline demographic and past medical history data onto standardized forms. Neurological status on admission was assessed with the World Federation of Neurological Surgeons (WFNS) scale. The WFNS is graded as 1 (best, GCS 15), 2 (GCS 13-14, no motor deficit), 3 (GCS 13-14, motor deficit present), 4 (GCS 7-12), and 5 (worst, GCS 3-6). A history of diabetes was recorded when the patient had a characteristic medical history or known hypoglycemic medication prior to admission. Bacteremia was prospectively defined as positive blood cultures with the exception of one bottle consistent with a contaminant. Pneumonia was prospectively defined by study staff according to US Centers for Disease Control criteria.

Data Acquisition

We retrospectively obtained glucose measurements with an electronic query from the hospital's comprehensive electronic medical record. In this report, we describe the analysis of glucose measurements from the hospital's clinical laboratory. (We repeated the analysis with all available bedside glucose measurements and found similar results.) To evaluate the possibility of confounding by the use of dexamethasone we electronically retrieved data on all administered doses.

Outcomes

Cerebral infarction was prospectively recorded during the hospital stay by study staff as a new hypodensity on computed tomography (CT) not present on admission or due to post-operative changes or resolving edema, or on magnetic resonance imaging (MRI) of the brain as a new

area of increased intensity on B1000 with decreased intensity on apparent diffusion coefficient maps. Number and location were classified as previously described [20]. Functional outcomes were obtained at 14 days, 28 days, and 3 months with the modified Rankin scale (mRS). The mRS [21] is scored as 0 (no symptoms), 1 (no disability), 2 (mild disability), 3 (moderate disability, independent with a device), 4 (moderately severe disability, not independent), 5 (severe disability, bed bound), or 6 (dead). Results were similar 14 days, 28 days, and 3 months, so we present 3-month data throughout. We used a validated questionnaire [22] to ascertain the mRS after discharge, usually by telephone.

Statistical Analysis

Data are presented as mean ± SD (for normally distributed variables) or median [Q1–Q3] for non-normally distributed variables. Means were compared with ANOVA and multiple comparisons were corrected with the least significant differences technique. Non-normally distributed variables were compared with Mann–Whitney U (2 groups) or Kruskal–Wallis H (>2 groups) as appropriate. Categorial data were compared with chi-squared. Variability was defined as the variance (the square of the standard deviation) of glucose readings for each patient and was compared with non-parametric statistics. Time-related data were compared with Kaplan–Meier statistics (log-rank test). For multivariate analyses of outcomes, we used ordinal regression (with mRS, an ordinal variable, as the outcome) and logistic regression (with poor outcome defined as mRS 4 through 6) to ensure the results were consistent. $P \leq 0.05$ was considered significant. Statistical calculations were made with standard commercial software (PASW v. 17, SPSS Inc., Chicago, IL).

The study was approved by the Institutional Review Board (IRB). Written informed consent was obtained from the patient or a legally authorized representative (LAR) except when the patient died in hospital, in which case the IRB approved collection of data in a registry without consent.

Results

Demographics are shown in Table 1. Body mass index was not related to glucose measurements.

Glucose Readings

Each patient had a mean of 41 glucose measurements. Descriptive statistics regarding glucose measurements are shown in Table 2. Only one patient had nadir glucose $<$ 40 mg/dl (severe hypoglycemia). This patient had a history of diabetes and presented with a WFNS grade 5 SAH complicated by cerebral infarction, a NIH-stroke scale of 22 at 14 days, and was bed bound (mRS 5) at 14 days, 28 days, and 3 months.

Table 1 Demographics

Age (years)	54.8 ± 14.4
WFNS 1, GCS 15	92 (54)
2, GCS 13–14, no motor deficit	30 (17)
3, GCS 13–14, motor deficit	4 (2)
4, GCS 7–12	25 (15)
5, GCS 3–6	21 (12)
Ethnicity	
Caucasian	92 (54)
Hispanic	32 (19)
African-American	30 (17)
East Asian/Oceania	8 (5)
Middle Eastern	3 (2)
South Asian	2 (1)
Other	5 (3)
Thick subarachnoid clot (Columbia CT grades 3 or 4)	126 (72)
Diabetes prior to SAH	16 (9)
Women	115 (67)
Body mass index (kg/m^2)	28.8 ± 7.7
SAH-physiologic derangement scale	3 [0–4]
Bacteremia	7 (4)
Pneumonia	18 (11)
Clipped–coiled–no repair	99–46–27

Data are mean ± SD, median [Q1–Q3], or N(%) as appropriate

Table 2 Summary of glucose measurements

First measured glucose (mg/dl)	161 ± 123
Mean glucose (mg/dl)	123 ± 14
Nadir glucose (mg/dl)	84 ± 16
Maximum glucose (mg/dl)	203 ± 66
Days to nadir glucose	8.5 ± 6.3

Data are mean ± SD

Severity of Injury and Glucose

More severe neurologic injury (increasing WFNS grade) was related to higher maximum glucose ($P < 0.001$), higher mean glucose ($P < 0.001$), and lower nadir glucose ($P = 0.03$). The presence of both higher maximum and lower nadir glucose reflected progressively increasing variance of glucose across WFNS grades ($P < 0.001$). Patients with higher WFNS scores had a nadir glucose of $<$80 mg/dl more often ($P < 0.001$) and earlier ($P < 0.001$) than patients with lower WFNS scores.

Physiologic Derangement and Infection

Higher SAH-physiologic derangement score was related to progressively increasing mean ($P = 0.001$), maximum ($P < 0.001$), and first measured glucose ($P < 0.001$), but not to nadir glucose or number of glucose measurements. The seven patients with bacteremia had a lower nadir glucose (69 ± 15 vs. 82 ± 15 mg/dl, $P = 0.02$), but similar mean and maximum glucose. The 18 (10.5%) patients with pneumonia had a lower nadir glucose (72 ± 14 vs. 85 ± 15 mg/dl, $P = 0.001$), but similar mean and maximum glucose.

Diabetes

Diabetes prior to SAH was present in 16 (9%) patients. The first measured glucose was not significantly higher in patients with diabetes, 195 ± 80 vs. 157 ± 126 mg/dl ($P > 0.1$). Patients with a history of diabetes had higher maximum (241 ± 70 vs. 199 ± 64 mg/dl, $P = 0.01$) and lower nadir (72 ± 22 vs. 85 ± 14 mg/dl $P = 0.04$), but similar mean (128 ± 14 vs. 122 ± 14.6 mg/dl) glucose, reflecting greater variance ($P = 0.002$). The time to nadir glucose < 80 mg/dl was not related to diabetes.

Dexamethasone Use

Dexamethasone was given in 83 (48%) patients. The most common maximum dose was 2 mg [2–4], and the median administered dose was 2 mg for a median of 4 days [2–7]. There were no associations between dexamethasone, glucose measurements, and outcomes ($P > 0.1$).

Vasospasm and Cerebral Infarction

Cerebral infarction was detected in 91 (53%) patients. Patients with a cerebral infarction had lower nadir glucose than those without (81 ± 15 vs. 87 ± 16 mg/dl, $P = 0.02$), but mean, first, and maximum glucose values were not different ($P > 0.1$). Glucose was not related to the number or location of cerebral infarction.

Symptomatic vasospasm occurred in 30 (17%) patients. Patients with symptomatic vasospasm had lower nadir glucose (78 ± 12 vs. 84 ± 16 mg/dl, $P = 0.04$), but mean, first, and maximum glucose were not different. Angiographic vasospasm occurred in 56 (33%) patients. Patients with angiographic vasospasm has lower nadir glucose (79 ± 14 vs. 86 ± 16 mg/dl, $P = 0.01$), but mean, first, and maximum glucose were not different. There were no associations between measured glucose and vasospasm as defined by TCD.

Functional Outcomes

In univariate analysis, progressively worse functional outcomes were related to higher first measured ($P = 0.04$), higher mean ($P < 0.001$), higher maximum ($P < 0.001$), and lower nadir glucose ($P < 0.001$). Lower nadir glucose was associated with worse functional outcomes, with the exception of patients who died and were usually hyperglycemic (Fig. 1). Patients with more functional disability at 3 months were more likely to be have a nadir glucose < 80 mg/dl, and had such a measurement earlier than patients with better outcomes ($P < 0.001$, Fig. 2). Patients who were dependent at 3 months had a higher percentage of glucose measurements < 80 mg/dl on most days (Fig. 3).

In ordinal regression, mRS at 3 months was related to admission WFNS grade ($P = 0.001$), mean glucose ($P < 0.001$) and nadir glucose ($P = 0.001$, Nagelkerke $R^2 = 0.38$). Diabetes, maximum glucose, and age did not add to this model. There were similar results for logistic regression (Nagelkerke $R^2 = 0.36$) when mRS at 3 months was dichotomized as functional independence (mRS 0 through 3) or not (mRS 4–6).

Discussion

These data show that glucose below the target range of 80–110 mg/dl, but not low enough to be considered severe,

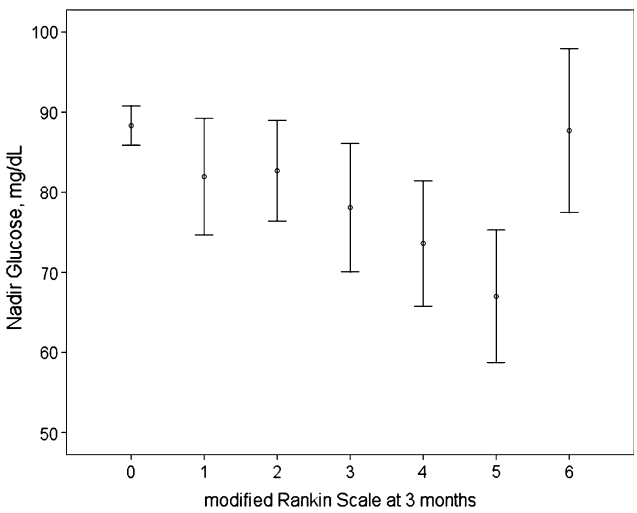

Fig. 1 Nadir glucose and 3-month mRS. With the exception of patients who died, progressively decreasing nadir glucose was associated with progressively worse functional outcome at 3 months. $P < 0.001$ for the overall comparison. After correction for multiple comparisons, mRS 0 is different than mRS 3–5 ($P \leq 0.02$ for all), mRS 3 and 5 are different ($P = 0.04$), mRS 4 is different than mRS 6 ($P = 0.003$), and mRS 5 is different than mRS 6 ($P < 0.001$)

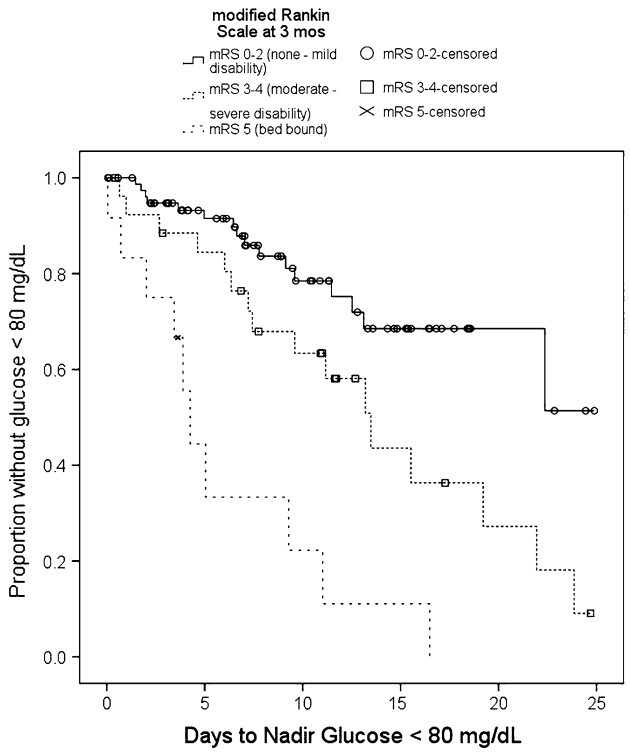

Fig. 2 Patients with more functional disability (higher modified Rankin Scale) at 3 months were more likely to have a nadir glucose $<$ 80 mg/dl, and had so earlier ($P < 0.001$). Disability is categorized as mRS 0–2 (none to mild disability), 3–4 (moderate–severe disability) or 5 (severe disability, bed bound). Censored cases had nadir glucose $\geq$80 mg/dl

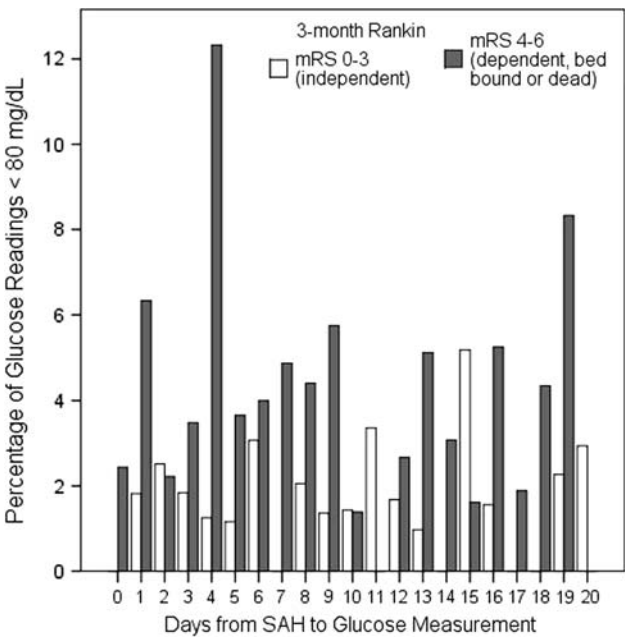

Fig. 3 Patients who were disabled at 3 months had a higher percentage of glucose measurements $<$80 mg/dl on any given day

was associated with more vasospasm, cerebral infarction, and worse functional outcomes. Severe hypoglycemia was rare and did not explain the impact of lower glucose. Hyperglycemia was associated with poor outcomes only in univariate analysis, but the impact was likely muted because of the mandatory implementation of the protocol.

The association of lower glucose with vasospasm and cerebral infarction implies that mild reductions in serum glucose contributed to worse outcomes, as seen in traumatic brain injury [15]. Our findings of lower glucose and increased vasospasm contrast with other published results [1], and the difference may be due to TGC in the entire cohort as opposed to part of the cohort. The difference in glucose measurements between cerebral infarction and vasospasm were statistically significant but clinically small. Infectious complications (pneumonia and bacteremia) were associated with lower nadir glucose, placing these patients at higher risk. Glucose $<$ 80 mg/dl, the lower range of the target, may be a threshold for adverse events.

Lower nadir glucose was independently associated with worse functional outcomes after correction for mean glucose and neurologic severity of injury without further contribution of diabetes. Nadir glucose was not associated with mortality, probably because patients who died were likely to be very hyperglycemic. Severe hypoglycemia markedly increases the risks of poor outcome [23] but only occurred in one patient in our series, so these results are unlikely to be confounded by poor implementation or an overly aggressive insulin protocol. Dexamethsaone was given in minimal doses and was not associated with outcomes, but higher doses of steroids for other conditions might.

Our results generally parallel data that show glycemic variability is associated with worse outcomes [24]. Diabetes and worse neurologic injury were associated with increased glucose variance [25], although we did not find more admission hyperglycemia in diabetic patients, which may be confounded by the acute stress response. We did not find that diabetes worsened functional outcomes in multivariate models, although the low percentage of patients with diabetes probably reduced our power to see such an effect; one would expect the increased glucose variance to increase the likelihood of poor outcomes. The association of more variability with worse neurologic grade implies that the patients who are most likely to need intensive care and TGC are likely to be the patients at highest risk for hyperglycemia, hypoglycemia, increased glucose variance, and poor outcome. Separate protocols for the sickest patients have intellectual appeal, but would be difficult to implement and might increase variability. We did not routinely measure glycosylated hemoglobin (HbA1c), so we cannot say if it was associated with

glucose control or outcomes. Patients with higher WFNS grade (worse neurologic injury) had more glucose measurements, although we corrected for WFNS in the multivariate model.

If relative hypoglycemia and glucose variability are potentially hazardous after SAH, protocols may need to be refined for different ICU settings. Instead of TGC, "pretty good glucose control" with a target of <140 mg/dl [26], while minimizing variability might lead to improved outcomes. Our results suggest that 80 mg/dl might be considered a threshold for "moderate" hypoglycemia, as opposed to the definition of glucose $<$ 40 mg/dl as "severe."

Our results have some limitations. This observational cohort study cannot establish causality, although it might lead to refinement of glucose control protocols. (Our institution is revising its insulin protocol, allowing for a future historically controlled analysis.) Patients with worse neurologic grade had increased hyperglycemia and insulin protocol use and might be a potential confounder, but results did not change once we corrected for this in multivariate analysis. We did not have data on invasive monitors such as brain oxygen tension or microdialysis parameters, so the mechanism of neuronal energy failure with normal serum glucose is speculative. It is unclear if real-time monitoring of neuronal markers would allow further refinements of insulin infusion protocols. All of the patients in this sample had SAH, so these data may not apply to intracerebral hemorrhage or cerebral infarction. We did not have data on nutrition administration electronically available, so we were unable to determine the amount and type of enteral feedings on glucose. Not every patient had MRI imaging, but cerebral infarction on neuroimaging had similar results to clinical and angiographic vasospasm. Many patients received dexamethasone postoperatively, but the low dose and brief duration were not associated with glucose or outcomes. Strengths of our data include prospective case ascertainment, recording of clinical events, and outcomes with validated scales after discharge, and automated retrieval of relevant data from the hospital laboratory and pharmacy.

In summary, we found that lower glucose was associated with more vasospasm, cerebral infarction, and worse outcome after SAH even though severe hypoglycemia was rare. While controlling hyperglycemia is important, patients with SAH and neurologic disease may benefit from protocols that have a higher and wider target to minimize mild to moderate hypoglycemia and glucose variability.

Acknowledgments This work was departmentally funded. The authors acknowledge the team at the Enterprise Data Warehouse who built the portal for electronic retrieval of laboratory and medication data. The Enterprise Data Warehouse is a joint project of Northwestern Memorial Hospital, Northwestern University, and the Northwestern Memorial Faculty Foundation. More information is available at www.edw.northwestern.edu.

Conflict of Interest Statement AMN has received past grant support from the Neurocritical Care Society, NovoNordisk, and the Northwestern Memorial Foundation, and current grant support from Gaymar Inc and Astellas Pharma US for unrelated work. AMN has received past speaker fees from EKR Therapeutics (ended 2008). It is unclear how these might relate to this manuscript.

References

1. Badjatia N, Topcuoglu MA, Buonanno FS, Smith EE, Nogueira RG, Rordorf GA, et al. Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. Crit Care Med. 2005;33:1603–9.
2. Frontera JA, Fernandez A, Claassen J, Schmidt M, Schumacher HC, Wartenberg K, et al. Hyperglycemia after SAH: predictors, associated complications and impact on outcome. Stroke. 2006; 37:199–203.
3. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B, Roos YB. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage. A meta-analysis. Stroke 2009; Epub ahead of print.
4. Schlenk F, Graetz D, Nagel A, Schmidt M, Sarrafzadeh A. Insulin-related decrease in cerebral glucose despite normoglycemia in aneurysmal subarachnoid hemorrhage. Crit Care. 2008;12:R9.
5. Bell DA, Strong AJ. Glucose/insulin infusions in the treatment of subarachnoid haemorrhage: a feasibility study. Br J Neurosurg. 2005;19:21–4.
6. Bilotta F, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol. 2007;19:156–60.
7. Latorre JG, Chou SH, Nogueira RG, Singhal AB, Carter BS, Ogilvy CS, et al. Effective glycemic control with aggressive hyperglycemia management is associated with improved outcome in aneurysmal subarachnoid hemorrhage. Stroke. 2009;40:1644–52.
8. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA. 2008;300:933–44.
9. Thiele RH, Pouratian N, Zuo Z, Scalzo DC, Dobba HA, Dumont AS, et al. Strict glucose control does not affect mortality after aneurysmal subarachnoid hemorrhage. Anesthesiology. 2009;110: 603–10.
10. The Nice-Sugar Study Investigators. Intensive versus conventional glucose control in critically patients. New Engl J Med 2009;360:1283–97.
11. Ali NA, O'Brien JMJ, Dungan K, Phillips G, Marsh CB, Lemeshow S, et al. Glucose variability and mortality in patients with sepsis. Crit Care Med. 2008;36:2316–21.
12. Egi M, Bellomo R, Stachowski E, French C, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105:244–52.
13. Schlenk F, Vajkoczy P, Sarrafzadeh A. Inpatient hyperglycemia following aneurysmal subarachnoid hemorrhage: Relation to cerebral metabolism and outcome. Neurocrit Care 2009; Epub ahead of print.
14. Schlenk F, Nagel A, Graetz D, Sarrafzadeh A. Hyperglycemia and cerebral glucose in aneurysmal subarachnoid hemorrhage. Intensive Care Med. 2008;34:1200–7.

15. Vespa P, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. Crit Care Med. 2006;34:850–6.
16. Classen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med. 2004;32:832–8.
17. Tseng M-Y, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase 2 randomized placebo-controlled trial. Stroke. 2005;36:1627–32.
18. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N. Triple-h therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol. 2003;2:614–21.
19. Naidech A, Jovanovic B, Wartenberg K, Parra A, Ostapkovich N, Connolly E, et al. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. Crit Care Med. 2008; 35:2383–9.
20. Rabinstein AA, Weigand S, Atkinson JLD, Wijdicks EFM. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke. 2005;36:992–7.
21. Banks J, Marotta C. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38:1091–6.
22. Wilson JTL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, et al. Improving the assess of outcomes in stroke. Use of a structured interview to assign grade on the modified Rankin scale. Stroke. 2002;33:2243–6.
23. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med. 2007;35: 2262–7.
24. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36: 3008–13.
25. Egi M, Bellomo R, Stachowski E, French C, Hart G, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36:2249–55.
26. Inzucchi SE, Siegel MD. Glucose control in the icu—how tight is tight enough? New Engl J Med. 2009;360:1346–8.