Original Article

Impact of Hyperglycemia on Cerebral Vasospasm and Delayed Cerebral Ischemia in Spontaneous Subarachnoid Hemorrhage

Ehab S. Belal[1], Husam S. Mourad[1], Sandra M. Ahmed[1,2], Islam I. Zaid[1]
Departments of Neurology[1], Neurosonology Unit (CUNU)[2], Cairo University; Egypt

ABSTRACT

Background: Subarachnoid hemorrhage (SAH) is a significant cause of morbidity and mortality. Hyperglycemia seems to play a role in predictive outcome. Aggressive hyperglycemic control is associated with better prognosis. **Objective:** Evaluate hyperglycemia following spontaneous subarachnoid hemorrhage and its impact on outcome. **Methods:** Twenty patients with spontaneous SAH were recruited at day one of hemorrhage and followed for 14 days. Transcranial Doppler examination using Lindegaard ratio (Lr) was used to assess vasospasm. CT scan was used to assess delayed cerebral ischemia (DCI). Average mean glucose burden (GB) was calculated all through the first 14 days. **Results:** At the day of admission the Mean GB was 150±76.4 mg/dl. Vasospasm occurred in 16 patients. DCI occurred in 9 patients. Mean GB was higher in patients with severe vasospasm (Lr>6) and those with DCI (P=0.02 and 0.03 respectively). **Conclusion:** Hyperglycaemia affects the course of the SAH critical illness through increasing the incidence of vasospasm and delayed cerebral ischemia. **[Egypt J Neurol Psychiat Neurosurg. 2014; 51(1): 7-11]**

Key Words: Subarachnoid hemorrhage (SAH), hyperglycemia, vasospasm, delayed cerebral ischemia (DCI)

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH), mostly from ruptured intracerebral aneurysm, is a significant cause of morbidity and mortality throughout the world. Mortality mean is around 25% and 50% are left with some persistent neurological deficit[1]. One of the most feared complications are symptomatic vasospasm and delayed cerebral ischemia, which occur in nearly 30% of patients 4-10 days following the initial hemorrhage[2].

Hyperglycemia was revealed to occur after aneurysmal subarachnoid hemorrhage, to be related to delayed cerebral ischemia (DCI) and hence poorer outcome[3]. Glucose level at admission seemed to be a predictive value for mortality even one year after primary event[4]. It was stated that aggressive hyperglycemic control (AHC) was associated with better outcome although not directly related to a decrease incidence of vasospasm and delayed cerebral ischemia[5].

Aim of this study is to evaluate hyperglycemia following aneurysmal subarachnoid hemorrhage and its impact on outcome through evaluation of cerebral vasospasm (VSP) and delayed cerebral ischemia (DCI).

Correspondence to Sandra M. Ahmed, Department of Neurology, Cairo University, Egypt.
Tel: +201005162225 Email: sandra.ahmed@kasralainy.edu.eg

SUBJECT AND METHODS

Twenty Egyptian patients presenting with spontaneous aneurysmal subarachnoid hemorrhage were recruited from the departments of neurology and neurosurgery, Faculty of Medicine, Cairo University. Both adult male and female patients above 18 years were included. We excluded patients presenting with traumatic SAH, arterio-venous malformation, mortality within the first two weeks (mortalities after the day 14 were included) and patients with bad temporal window.

Patients were followed from day 1 up to day 14 using clinical evaluation, laboratory and imaging studies. Trans-cranial Doppler examination was performed in Cairo University Neurosonology Unit (CUNU). Further observation of the outcome was performed till the end of the month.

Primary clinical evaluation was done using Glasgow coma scale (GCS), APACHE II score, Hunt and Hess criteria[6] and radiological assessment using Fisher criteria[7]. Detection of DCI was done clinically by detecting focal neurological deficit or global unexplained deterioration of consciousness supported by CT finding of cerebral infarct.

Vasospasm was evaluated and followed using transcranial Doppler (TCD) Lindegaard criteria[8]. The machine used for TCD was (DWL Ez-Dop, Compumedics) with a 2 MHZ probe. The patients were classified according to Lindegaard ratio (Lr)

into; no vasospasm (Lr<3) mild to moderate vasospasm (Lr 3-6) and severe vasospasm (Lr >6). Final evaluation was done at the end of the 2 weeks using Glasgow outcome scale[9].

Hyperglycemia was assessed using the glucose burden (GB). Glucose burden was calculated as the excess value above 105 mg/dl. If the daily maximum glucose value was below the reference (105 mg/dl) the GB was considered zero. A mean glucose burden (mGB) was obtained for each patient by averaging the GB all through the 14 days[10].

Patients who developed vasospasm were medically treated using the triple-H therapy. Definitive aneurysm repair was done either surgically or through endovascular procedure as decided by neurosurgeons.

Statistical Analysis

Variables were analysed using "Statistical Package of Social Science Software program" version 21 (SPSS). Data were summarized using mean and standard deviation (parametric variables) or median and interquartile range (non-parametric variables) for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample t-test or Mann Whitney test for quantitative variables and Chi square or Fissure's exact test for qualitative ones. Pearson or Spearman correlation coefficients were calculated to get the association between quantitative or ordinal variables respectively. P-values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

RESULTS

The twenty patients included 12 males (60%) and 8 females (40%). Their mean age was 51±9.9 years. Risk factors were distributed as follow; smoking 60%, positive family history of SAH 15%, hypertension 45%, diabetes mellitus 30%, ischemic heart diseases 25% and history of cerebrovascular diseases as previous strokes or TIA's 15%.

Patients who developed vasospasm received medical treatment in the form of triple-H therapy. Twelve patients (60%) underwent surgical aneurysm clipping within 14 days of onset while definitive aneurysm repair of the remaining was taken place later. Two of those eight patients were revealed as angiogram negative SAH (as resulted from CTA) and were managed conservatively.

None of the patients experienced re-bleeding while five patients developed hydrocephalus (25%), three ones suffered from hyponatremia (15%) and eight patients experienced seizures (40.0%) in the first 14 days of SAH.

Primary clinical assessment using different scales and scores showed the following results (Table 1):

At the day of admission the glucose burden ranged from 32 mg/dl to 387 mg/dl. Average glucose burden above 105 mg/dl along the first 14 days ranged from 33.9 to 247.0 mg/dl (mean was 150±76.4, 95% CI was 116.5 to 183.5).

Transcranial Doppler examination revealed the occurrence of vasospasm in 16 (80%) patients. Only four (20%) didn't have vasospasm. Lindegaard ratio median and iqr on right side was 3.4 (2.8-8.3) and on the left side 4.4 (2.7-7.8). Of the patients who experienced vasospasm (n=16/20), four (20%) had mild to moderate VSP (Lr 3-6) and 12 patients (60%) had severe VSP (Lr > 6). Delayed cerebral ischemia (DCI) was clinically detected and confirmed radiogically in 9/20 patients (45%). Glasgow outcome scale revealed four deaths (20%), two (10%) patients with persistent vegetative state, three (15%) with severe disability, 3 (15%) with mild to moderate disability and 8 (40%) with minimal disability.

Highest cut-off blood glucose >105mg/dl on the day of onset and average GB over the 14 days showed a statistically positive correlation with degree of severity of the detected TCD-VSP (Lindegaard ratio) (r=0.610, P=0.004 and r=0.590, P=0.006 respectively)

No correlation was found between both GCS and APACHE II score and at onset measurement of glucose burden. Hunt and Hess and Fisher score at initial presentation showed a statistically significant correlation with at-onset GB (r=0.466, P=0.038 and r=0.463, P=0.04 respectively) (Figure 1).

Statistically significant difference of mean glucose burden (mGB) was found in patients with and without severe vasospasm (Lr >6) and patients with and without DCI (Table 2).

No statistically significant correlation was detected between GB and the GOS of the patients after 30 days of onset.

Table 1. Primary assessment of SAH patients at admission.

Score/scale	Median (iqr)
Glasgow coma scale (GCS)	15.0 (10.8-15)
APACHE II score	11.0 (7.25-13.5)
Hunt and Hess score	3 (2-3)
Fischer score	3 (3-3.75)

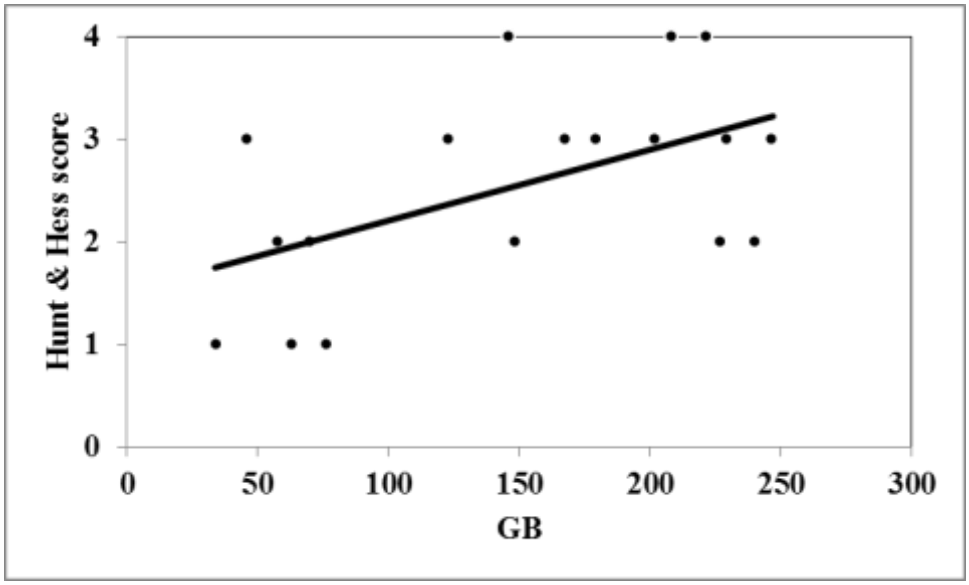

Figure 1. Positive correlation between Hunt and Hess score and GB.

Table 2. Glucose burden (GB) affects vasospasm (VSP) and delayed cerebral ischemia (DCI).

	GB		
	Mean±SD	**t value**	**P value**
Severe VSP (Lr >6)			
Yes (n=12)	182.3±53.9	2.7	0.02*
No (n=8)	101.6±82.6		
DCI			
Yes (n=9)	189.8±47.2	2.5	0.03*
No (n=11)	117.5±82.0		

* Significant at P<0.05

DISCUSSION

Twenty patients with spontaneous SAH were screened for hyperglycemia at admission and during the 14 days following initial presentation. Our study showed that hyperglycemia is a common finding in patients presenting with spontaneous aneurysmal subarachnoid hemorrhage. Hyperglycemia was shown to affect initial clinical presentation and to have a role in predicting outcome.

During the first 14 days following subarachnoid hemorrhage (SAH) onset, the mean glucose burden (mGB) above 105 mg% ranged from 33.9 mg% to 247.0 mg% with a mean of 150.0±76.4 mg%. This reference value (105 mg%) was chosen because of the available data indicating that tight glucose control to approximately this level is associated with improved survival in critically ill patients[11]. As many as 90.0% of the included sample (18 patients) had average mean GB higher than 50 mg% during the 14 days of observation, and 40.0% of the sample (8 patients) had average GB >200 mg%. This reflects the previously observed association between the incidence of SAH and the elevated serum glucose level[12]. Six out of the 20 patients (30.0%) were already diabetics. Five of them were among the 8 patients whose average GB was the highest (> 200 mg %). Yet, diabetes mellitus (DM) is not considered as a risk factor for SAH, on the contrary critical illness has a consequence on glycemic state[13].

Our study revealed that neither state of consciousness (Glasgow Coma Scale) on admission, nor severity of critical illness (APACHE II score) in the first 24 hours seemed to be predictors for the average GB. Increased GB was found to be associated with the severity of the neurological deficits caused by SAH (Hunt and Hess scale) as well as the amount of blood flooding the subarachnoid space (Fisher score). A statistically significant positive correlation was detected between GB and Hunt and Hess scale (rho 0.466, P value

0.038) and also Fisher score (rho 0.463, P value 0.04). Indeed, higher levels of admission glucose were reported to be associated with the severity of SAH[14].

Patients with severe vasospasm (Lr > 6) showed a statistically significant higher mGB when compared to patients with less severe vasospasm (Lr < 6) (P value = 0.02). One previous study has reported similar association between hyperglycaemia and an increased risk of vasospasm after SAH[15], while another one failed to confirm this association for reasons that were unclear to its investigators[10]. As vasodilatation was shown to be predominantly mediated by endothelium-derived nitric oxide[16] *in vitro* studies showed that hyperglycemia reduces the production of nitric oxide by increasing the activity of nicotinamide adenine dinucleotide phosphate (NADP) oxidase. Another explanation was also postulated; hyperglycemia is associated with the formation of vasoconstrictive prostaglandins and increased eicosanoid production, both resulting in vasoconstriction[17].

Average glucose burden showed statistically significant higher values in our nine patients who developed delayed cerebral ischemia (DCI) compared to the 11 patients without DCI (GB; 189.8±47.2 and 117.5±82.0 respectively P=0.03) matching with previous studies[2,18,19]. Four of the nine patients affected by DCI (44.4%) were among the six who were already diabetics before SAH event. Several theories linking DCI to hyperglycemia have been proposed; first through increasing incidence of vasospasm as previously mentioned[20]. This agrees with our findings since all of the nine patients affected by DCI were among the 12 ones with severe VSP. Secondly, hyperglycemia stimulates coagulation by increasing platelet activation through thrombin–antithrombin complexes and the tissue factor pathway[21]. Finally, hyperglycemia is associated with an increase in pro-inflammatory transcription factors and pro-inflammatory cytokines[21,22]. In SAH patients, several studies have linked markers of increased inflammation to the development of DCI[23,24].

Neither GCS nor GOS had any correlation with mGB. That is to say; effect of hyperglycaemia is more in relation to causing mild disability in the course of the disease within the 30 days rather than being related to or affecting clinical presentation or outcome through severe disabilities or mortalities. Hyperglycaemia was stated to be rather associated with disabling but nonfatal complications, such as signs of cerebral infarct, ICU neuropathy, nosocomial infections, and impaired wound healing[25,26].

Conclusion

Hyperglycaemia was found even in non-diabetic patients presenting with spontaneous SAH. Hyperglycaemia affects the course of the SAH critical illness through increasing the incidence of vasospasm and delayed cerebral ischemia. Hyperglycaemia does not affect severity of presentation and does not seem to be the sole factor affecting outcome.

Acknowledgment:

Special thanks to residents of Neurosurgery ER and Neurology department for their kind help and support throughout the study.

[Disclosure: Authors report no conflict of interest]

REFERENCES

1. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012; 43(6): 1711-37.
2. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry. 2000; 68(3): 337-41.
3. Kruyt ND, Biessels GJ, DeVries JH, Luitse MJ, Vermeulen M, Rinkel GJ, et al. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010; 30(9): 1577-87.
4. Bian L, Liu L, Wang C, Hussain M, Yuan Y, Liu G, et al. Hyperglycemia within day 14 of aneurysmal subarachnoid hemorrhage predicts 1-year mortality. Clin Neurol Neurosurg. 2013; 115(7): 959-64.
5. 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(5): 1644-52.
6. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968; 28(1): 14-20.
7. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980; 6(1): 1-9.
8. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir Suppl (Wien). 1988; 42: 81-4.
9. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975; 1(7905): 480-4.
10. 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(1): 199-203.

11. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
12. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke. 2009; 40(6): e424-30.
13. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773-80.
14. Kruyt ND, Roos YW, Dorhout Mees SM, van den Bergh WM, Algra A, Rinkel GJ, et al. High mean fasting glucose levels independently predict poor outcome and delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2008;79(12):1382-5.
15. 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(7):1603-9; quiz 23.
16. Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. Am J Physiol Regul Integr Comp Physiol. 2003;284(1):R1-12.
17. el-Kashef H. Hyperglycemia increased the responsiveness of isolated rabbit's pulmonary arterial rings to serotonin. Pharmacology. 1996; 53(3): 151-9.
18. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2007;38(8):2315-21.
19. Hijdra A, Van Gijn J, Stefanko S, Van Dongen KJ, Vermeulen M, Van Crevel H. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: clinicoanatomic correlations. Neurology. 1986; 36(3): 329-33.
20. Fergusen S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2007;60(4):658-67; discussion 67.
21. Gentile NT, Vaidyula VR, Kanamalla U, DeAngelis M, Gaughan J, Rao AK. Factor VIIa and tissue factor procoagulant activity in diabetes mellitus after acute ischemic stroke: impact of hyperglycemia. Thromb Haemost. 2007; 98(5): 1007-13.
22. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002;106(16):2067-72.
23. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A. Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res. 1997;22(10):1249-55.
24. Osuka K, Suzuki Y, Tanazawa T, Hattori K, Yamamoto N, Takayasu M, et al. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. Acta Neurochir (Wien). 1998;140(9):943-51.
25. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.
26. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992-1000.

الملخص العربى

يعتبر نزيف تحت العنكبوتية من الأمراض الخطيرة التى ينتج عنها نسبة وفيات مرتفعة وتعقيدات مرضية خطيرة. من أهم مضاعفات النزيف الانقباض الوعائى المخى ونقص التروية المخية المتأخرة. لوحظ تزامن المرض مع ارتفاع نسبة السكر/الجلوكوز بالدم وارتباطه بخطورة الحالة.

أجريت هذه الدراسة على عشرين مريض من المصريين المصابين بمرض النزيف تحت العنكبوتية لقياس تأثر الإصابة بارتفاع السكر بالدم, فى صورة متوسط حمل الجلوكوز, على كل من الانقباض الوعائى المخى ونقص التروية المخية المتأخرة.

تم التقييم الإكلنيكى للمرضى باستخدام مقياس هانت وهيس ومقياس أباتشى الثانى. كما تم تقييم التصوير الدماغى باستخدام معيار فيشر. قيس ارتفاع السكر بالدم باستخدام حمل الجلوكوز كمتوسط قياسى فوق ١٠٥ مجم/ديسيليتر خلال ال١٤ يوم الأولى. تم الكشف عن الانقباض الوعائى المخى من اليوم الرابع وحتى اليوم ال١٤ باستخدام الدوبلر عبر الجمجمة وقياس لينجارد كما تم الكشف عن نقص التروية المخية المتأخرة إكلينيكيا وبالأشعة التشخيصية.

تراوح ارتفاع حمل الجلوكوز عند أول المرض ما بين ٣٢مجم/ديسيلستر إلى ٣٨٧ مجم/ديسيلستر وكان فى خلال الأسبوعين يتراوح ما بين ٣٣,٩مجم/ديسيلستر إلى ٢٤٧ مجم/ديسيلستر. وقد تم الحصول على ارتباط موجب بين ارتفاع السكر بالدم والانقباض الوعائى المخى ونقص التروية المخية المتأخرة. لوحظ أن ارتفاع السكر أيضا أثر بشكل سلبى على الضرر العصبى (مقياس هانت وهيس) وكمية النزيف (مقياس فيشر).