Glucose fluctuation Impact on Delayed Cerebral Infarction and 30 Days Mortality in Aneurysm SAH: A Retrospective Study in Neurocritical Care Unit

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Research Article

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Abstract

Background Hyperglycemia was associated with delayed cerebral infraction (DCI) and poor outcomes in aneurysmal subarachnoid hemorrhage (aSAH) patients. However, the influence of glucose fluctuation on DCI and mortality in aSAH patients was still unclear.

Objective This study aimed to clarify the relationship of glucose fluctuation and DCI occurrence or 30 days mortality in aSAH patients who were admitted in Neurocritical Unit (NCU).

Methods A total of 341 patients with aSAH were retrospectively recruited and studied. Continuous 14-day fasting blood glucose was collected and divided into four groups: stable, unstable, well-controlled, bad-controlled. Risk factors that were associated with glucose fluctuation, DCI occurrence and 30 days mortality was analyzed.

Results Many risk factors, such as Age (59.09±11.95), Diabetes history, SBP (162.91±20.85), BUN (5.50±1.80), HA1c (7.12±1.65), BGV (0.32±0.11), Hunt-Hess Score (2.59±0.97), GCS Score (10.68±4.23), Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricles, are associated with glucose fluctuation. Bad controlled group has the highest mortality (15.91%), then unstable (13.04%), well-controlled (6.45%), and stable group (1.42%). The unstable group has the highest incidence of DCI (39.13%), then bad-controlled (29.55%), the stable (17.92%) and well-controlled (17.74%).

Conclusions Unstable and bad-controlled glucose during NCU admission was associated with DCI and 30 days mortality of aSAH patients.

1. Introduction

Subarachnoid hemorrhage (SAH), a life-threatened disease, is often caused by rupture of cerebrovascular aneurysm. Cumulative case fatality rates in the natural history of SAH over time are as follows: first day, 25–30%; first week, 40–45%; first month, 50–60%; sixth month, 55–60%; first year: 65% and fifth year, 65–70%. Approximately 12% of patients die before reaching medical attention. Many risk factors, such as early brain injury, delayed cerebral ischemia (DCI), increasing sympathetic activity, hyperglycemia, hypoglycemia and dysnatremia are associated with poor outcomes after SAH[1]. As glucose is metabolic substrate of central nervous system, both hypoglycemia and hyperglycemia would have equally worse outcomes[2], such as DCI and increased risk of pneumonia, which could lead to increased length of stay of ICU-days or hospital-days, even high mortality of aSAH in-hospital[2, 3]. Thus, several studies focused on how to control glucose level in neurological diseases, including stroke, traumatic brain injury (TBI), SAH, and even severe sepsis in Neurocritical Care Unit (NCU). The European Stroke Organization guidelines recommend that hyperglycemia with blood glucose > 10 mmol/L (180 mg/dL) should be treated [4]. However, a strict glucose control regimen seemed failed to improve time trend-adjusted neurological outcomes or reduce mortality after SAH [1]. Meanwhile, extensive changes in blood glucose concentrations, which is to say, big glucose variability was also associated with cerebral metabolic distress [5], energy metabolic crisis, and an elevated lactate/pyruvate ratio [6], which would finally result in unfavorable outcomes [5, 6]. Thus, moderate glucose control and minimizing glucose variability are important concepts in glycemic management in SAH patients, but the optimal target range remains unknown. Meanwhile, no consensus has been reached on the suitable glycemic level after SAH, and few studies have addressed this topic in terms of glucose, glucose variability and mortality in SAH.

DCI was a serious complication that gave rise to poor recovery and clinical outcomes, such as hemiparesis, confusion or drowsiness, persistent cognitive impairment, social and emotional disorders, in survivors of aneurysmal subarachnoid hemorrhage (aSAH) [7]. DCI was mainly believed associated with early brain injury, impaired cerebral metabolism, regional or global hypoperfusion in brain, and cerebral arterial vasospasm [8]. Besides, more clinical and radiological features were also involved in DCI incidence. Smoking was the strongest risk factor of DCI. Other possible factors included diabetes mellitus (DM), hyperglycemia on admission, acute hydrocephalus, early systemic inflammatory response syndrome, female, hypertension, CT Fisher grade and age [9]. DCI occurred after aSAH seemed have a complicated regulatory mechanism.

Both DM and hyperglycemia were considered as predictors and risk factors of DCI occurrence in aSAH. A two-center retrospective cohort study indicated that maximum glucose level (8.6-11.8 mmol/L) within the first 24 hours after admission may be as a consequence of increased adrenergic stress and as independent factor of higher DCI suffering in critically aSAH patients[10]. Moreover, glucose, as a direct precursor of lactate, its rise will increase the circulating levels of lactate which was an independent predictor of poor outcome of aSAH[10]. Additionally, Hyperglycemia was proven to be associated with vasospasm by inhibition of vasodilatation and enhancement of vasoconstriction, with thrombin formation by increase of coagulation and decrease of fibrinolysis, with increase of proinflammatory transcription factors and proinflammatory cytokines, all of which are possibly the pathophysiological causes of DCI[2]. Furthermore, Hyperglycemia can also facilitate the conversion of ischemia to irreversible infarction[11]. Hence, glucose management was obviously important to avoid occurrence of DCI and ameliorate clinical outcome after aSAH. Nowadays, most evidence focused on acute glucose level and its relationship to DCI incidence. However, for critically ill patients, due to stress response to disease itself or surgery, glucose level might be persistently high or fluctuated strongly after aSAH for several days, or even weeks without intervention. Persistent hyperglycemia, other than a single hyperglycemia event, was proven to be independent predictors of postoperative outcomes, which is 10-fold more likely to have a poor 2-week outcome and sevenfold more likely to have a poor outcome 7 to 13 months after aSAH[12]. Nevertheless, little evidence had shown that whether persistent hyperglycemia or glucose fluctuation might predict DCI occurrence and how to modulate glucose level might prevent critically ill patients with aSAH from suffering DCI.

Here, we hypothesized that persistent hyperglycemia or abnormal glucose fluctuation might be associated with occurrence of DCI and 30 days mortality in aSAH patients. Our study retrospectively recruited aSAH patients in NCU, collected their 14 days continuous glucose level from their first day on admission and focused on the impact of glucose variation on DCI incidence and 30 days mortality.

2. Methods

2.1 Subjects

Patients were recruited from a retrospectively collected database of all patients with SAH who were admitted to Tiantan Hospital in Beijing, China from January 2015 and December 2017. All patients suffered f

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have two experts to evaluate the occurrence of DCI, the Kappa value was 0.91 between the two experts. This retrospective study was approved by the Ethics Committee at the Tiantan Hospital in Beijing, in accordance with the Declaration of Helsinki. Our study was approved to collect data without requiring patient informed consent under the Waived Consent from the Ethics Committee at the Tiantan Hospital in Beijing (Ethics Approval Number: KY2019-060).

2.2 Clinical information

The following baseline characteristics were analyzed based on the data collected during the period of admission: sex, age, diabetes mellitus (DM), hypertension, glucose level, initial Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, treatment, surgery, mortality information and dates of death. Several indexes were collected as follows: AST, ALT, BUN, creatinine (Cr), D-dimer, BNP, EF, hemoglobin A1c (HA1c), blood glycemic variability (BGV), Hunt Hess, CT Fisher, hydrocephalus (Fourth ventricle, Third ventricle, Lateral ventricle, Quadrigeminal cistern, Ambiens cisterna, Suprasellar cistern, Sylvian fissure, Basilar cistern). The first day blood glucose level was taken immediately before any glucose management when admission. Then the other 13 days blood sample was taken around 6:00 am every morning as fasting blood glucose. These 14 days glucose value after SAH were collected and was divided into four groups - stable, unstable, well-controlled and bad controlled (Table 1). BGV was measured as glycated albumin/glycosylated hemoglobin ratio[13].

Table 1. Four groups of different glucose levels

Group	Glucose Level (mmol/L)	
	1^{st} day	2^{nd}-14^{th} day
Stable	< 7	Always < 10
Unstable	< 7	More than once ≥ 10
Well-controlled	≥ 7	Always < 10
Bad-controlled	≥ 7	More than once ≥ 10

2.3 Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 21.0 for Windows, SPSS, Chicago). Categorical variables were compared using Pearson Chi-square analysis or Fisher's exact test. Continuous variables were compared using the ANOVA test or the Kruskal-Wallis rank-sum test. Multivariate logistic regression analysis was performed to determine the effects of the variables on 30 days mortality or DCI. All statistical tests were two-tailed, and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1 Basic data, Biochemistry tests, Neuroimages, 30 days mortality and DCI occurrence (Table 2)

For biochemistry tests, the patients whose average 14-day glucose were bad-controlled have some commons, such as higher Age (59.09±11.95), Diabetes history, higher SBP (162.91±20.85) when admission, relatively higher BUN (5.50±1.80), higher HA1c (7.12±1.65), BGV (0.32±0.11), higher Hunt-Hess Score (2.59±0.97), lower GCS Score (10.68±4.23), Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricles. Bad controlled group has the highest mortality (15.91%), then unstable (13.04%), well-controlled (6.45%), and stable group (1.42%). The unstable group has the highest incidence of DCI (39.13%), then bad-controlled (29.55%), the stable (17.92%) and well-controlled (17.74%).

Table 2. Basic data, Biochemistry tests, Neuroimages, 30-days mortality and DCI occurrence

	stable (n=212)	unstable (n=23)	Well-controlled (n=62)	Bad-controlled (n=44)	F/x^2	P
Age	53.70±12.50	56.65±11.69	59.19±12.19	59.09±11.95	4.673	0.003
Sex					7.812	0.050
Male	103(48.58)	9(39.13)	18(29.03)	18(40.91)		
Female	109(51.42)	14(60.87)	44(70.97)	26(59.09)		
Diabetes	12(5.66)	3(13.04)	8(12.90)	29(65.91)	102.808	<0.001
Hypertension	119(56.13)	17(73.91)	40(64.52)	32(72.73)	6.589	0.086
SBP-adm.	148.03±21.26	155.83±17.07	153.81±24.91	162.91±20.85	6.412	<0.001
DBP-adm	86.84±13.63	87.74±12.90	85.90±16.06	86.89±15.27	0.114	0.952
Temp.-adm	36.76±0.79	36.81±0.52	36.91±0.56	36.95±0.42	1.384	0.248
Lab tests						
AST	25.39±17.11	26.97±13.18	26.30±15.08	25.48±12.38	0.107	0.956
ALT	25.56±17.34	26.47±14.42	25.00±14.49	23.43±10.41	0.270	0.847
BUN	4.72±1.43	5.33±1.62	5.11±1.54	5.50±1.80	4.215	0.006
Cr	56.11±16.09	53.62±18.79	54.10±18.24	60.56±19.13	1.443	0.230
D-dimer	2.99±4.00	3.80±3.48	4.71±7.37	3.25±4.13	2.075	0.103
BNP	156.84±305.31	131.62±147.94	177.76±312.28	123.59±154.63	0.325	0.807
EF	64.52±5.96	64.26±4.39	64.50±3.68	65.79±4.84	0.591	0.622
HA1c	5.44±0.40	5.55±0.37	5.76±0.68	7.12±1.65	57.543	<0.001
BGV	0.13±0.06	0.32±0.11	0.15±0.06	0.23±0.10	56.862	<0.001
Hunt-Hess	2.01±0.88	2.30±1.02	2.52±0.97	2.59±0.97	8.225	<0.001
CT-Fisher	2.24±0.83	2.39±0.72	2.34±0.85	2.55±0.70	1.936	0.124
GCS	13.57±2.72	12.43±3.59	11.34±4.04	10.68±4.23	14.144	<0.001
Hydrocephalus	68(32.08)	11(47.83)	26(41.94)	19(43.18)	4.706	0.195
Forth ventricle	47(22.17)	12(52.17)	20(32.26)	12(27.27)	10.839	0.013
Third ventricle	17(8.02)	8(34.78)	14(22.58)	10(22.73)	20.633	<0.001
Lateral ventricles	103(48.58)	18(78.26)	40(64.52)	30(68.18)	13.832	0.003
Quadrigeminal cistern	17(8.02)	2(8.70)	7(11.29)	7(15.91)	2.832	0.418
Cisterna amibiens	65(30.66)	7(30.43)	19(30.65)	22(50.00)	6.483	0.090

Suprasellar cistern	115(54.25)	13(56.52)	43(69.35)	31(70.45)	7.179	0.066
Basilar cistern	130(61.32)	14(60.87)	45(72.58)	34(77.27)	5.921	0.116
Lateral fissure cistern	164(77.36)	17(73.91)	47(75.81)	40(90.91)	4.744	0.191
30 d mortality	3(1.42)	3(13.04)	4(6.45)	7(15.91)	20.224	<0.001
DCI	38(17.92)	9(39.13)	11(17.74)	13(29.55)	8.144	0.043

3.2 Multivariate logistic regression analysis, 30 days Mortality and DCI

Taking the 30 days Mortality or DCI occurrence during hospitalization as the dependent variable respectively, and age, gender, SBP at admission, history of Diabetes Mellitus, BUN, HA1c, BGV, Hunt-Hess GCS, Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricles as independent variable, multivariate Logistic regression analysis showed that unstable and bad-controlled group have higher 30 days Mortality and DCI incidence (Table 3.)

Table 3. Multivariate Logistic Regression Analysis for 30 days Mortality and DCI

Mortality					
		Crude Results		Adjusted Results†	
Group	N(%)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Stable	3(1.4)	1.000		1.000	
Unstable	3(13.0)	7.541(1.507-37.729)	0.014	14.033(1.971-99.921)	0.008
Well-controlled	4(6.5)	4.939(1.105-22.076)	0.037	4.881(0.780-30.534)	0.090
Bad-controlled	7(15.9)	10.487(2.694-40.818)	0.001	19.723(3.597-108.143)	0.001
DCI					
		Crude Results		Adjusted Results†	
Group	N(%)	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Stable	38(17.9)	1.000		1.000	
Unstable	9(39.1)	2.944(1.187-7.298)	0.020	6.032(1.941-18.747)	0.002
Well-controlled	11(17.7)	0.988(0.471-2.070)	0.974	1.115(0.497-2.502)	0.792
Bad-controlled	13(29.53)	1.920(0.919-4.011)	0.083	2.889(1.247-6.691)	0.013

† Adjusted for age, gender, SBP at admission, history of Diabetes Mellitus, BUN, HA1c, BGV, Hunt-Hess GCS, Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricles

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4. Discussion

In this retrospective study, several risk factors were found to result in bad-controlled or unstable glucose during admission in NCU, such as older age, history of Diabetes Mellitus, higher SBP, BUN, HA1c, BGV and Hunt-Hess Score, lower GCS score, and Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricles. Subsequently, multivariate logistic regression analysis also showed that these factors have direct association with higher 30 days mortality and DCI incidence in patients with bad-controlled and unstable glucose level during NCU.

Hyperglycemia after SAH onset was induced by multiple responsive system, such as the activation of hypothalamic-pituitary-adrenal axis (HPA), the activation of sympathetic autonomic nervous system[14], the release of HPA related cytokines after increased inflammatory response[15], and the reduction of hepatic gluconeogenesis and increase of insulin sensitivity regulated by hypothalamus[16]. Clinically, mean glucose of patients admitted within 72 hours after aSAH is around 9 mmol/L, and still exceeding 7-8 mmol/L 1-2 weeks later[2]. Several researches revealed that hyperglycemia on admission or persistent hyperglycemia, occurred in 30-100% SAH patients, was involved in DCI and short- or long-term poor outcomes[17]. Similarly, our study found that average glucose and BGV was higher in patients who suffered DCI or had high mortality. In addition, HA1c, used as an evaluation of average blood sugar levels over a period of 2-3 months, was proven being associated with DCI and poor outcome in the present study. Different from what we found, collecting HA1c of 87 aSAH patients within 72h of admission, Beseoglu et al. showed that HA1c had little significant correlation with DCI occurrence or DCI related infarction by using correlation analysis[18]. However, the number of cases recruited was low in the study which could negatively influence statistical power. Therefore, although HA1c was proven having no association with rupture of aneurysms[19], whether HA1c could be a predictor of DCI and unfavorable outcome in aSAH still requires more evidence.

Intensive insulin therapy (IIT) was used worldwide in both surgical and general ICU, even though it was associated with severe hypoglycemia and subsequent poor clinical outcome. However, the value of IIT used in NCU patients was still controversial because those people, due to brain injury, were always highly susceptible to either hyperglycemia or hypoglycemia. Especially, acute injured brain required constant glucose supply in order to satisfy brain metabolism while hypoglycemia induced by IIT might lead to energy failure[20]. Different from in general ward, patients in NCU with critical brain injuries whose glucose level should have been monitored regularly and frequently, hence, rigorous and fine-tuning glucose management can be realized and be benefit to clinical outcome. Up to now, most research mainly discussed about optimal glycemia control in SAH patients in order to obtain favorable outcome. However, both the optimal pending value of hyperglycemia or the optimal cutoff value of hypoglycemia was still inconclusive. Two glucose control regimens from two single center before-after studies, 5.0 - 6.7 mmol/L and 4.4 – 7.8 mmol/L, failed to improve clinical outcome or reduce mortality of SAH, but was associated with incidence of hypoglycemia [21, 22]. Similarly, another control regimen (4.4 – 6.7) from a single center RCT study was proven to reduce infection rate but still no influence on postoperative vasospasm, neurological outcomes and mortality rates [23]. These evidences showed that narrowing glucose fluctuation doesn't seem favorable to SAH outcomes. In this retrospective study, we divided glucose level into four groups and find that DCI incidence was higher in those patients whose glucose level was greater than 10 mmol/L at least once during 14 consecutive days, no matter whether glucose at the first day was more than 7 mmol/L or not. Thus, 10 mmol/L seemed as an important upper limit that was associated with incidence of DCI in SAH patients, while 7 mmol/L was not for sure to be optimal lower limit because we tended to stop insulin treatment to avoid hypoglycemia when every two-hour fasting glucose level was tested lower than 5 mmol/L in NCU.

BGV refers to swing in blood glucose level and was highly suggested to be an important key determinant of vascular damage [24]. Several studies showed BGV was possibly associated with cerebral infarction, mortality and even clinical poor outcomes in central nervous system diseases. Using standard deviation (SD) as daily glycemic variability (GV), a retrospective study observed 28 patients with SAH and revealed that systematic GV was associated with cerebral metabolic distress and hospital mortality in SAH[5]. Although no reference to GV, another study showed that acute reduction of glucose level, in spite of being within normal range, was related to brain energy metabolic crisis in poor grade SAH patients [6]. Similarly, our present study found that BGV was associated with occurrence of DCI and high mortality within 30 days admission.

Up to now, there was still no consensus on the relationship of age and DCI incidence. Some studies showed that relatively young people have greater risk of occurring DCI. Using univariate analysis on 463 aSAH patients with an overall DCI incidence of 21%, Lee et al found that age between 40-59, higher modified Fisher grade and aneurysm rupture in anterior circulation could be more accurate predictors of DCI risk [25]. Another earlier study that included 3567 aSAH patients, using multivariate analysis, revealed that symptomatic vasospasm has significant association with age 40 to 59 years[26]. Most theory thought that, compared to younger ones, senescent intracranial arteries were so stiffer and less elastic, due to thicker vessel walls, higher thickness-to-radius ratio and more collagen fiber, that they are more resistant to vasospasm [25]. However, the mechanism is still unclear. Similarly, this present study showed older patients tend to have DCI and higher 30 days mortality. Contrarily, in a systematic review, 6 studies included showed that there was no difference with risk of DCI between young and old patients. Thus, different theories came from these results thought young people might have stronger resilient to ischemia and better autoregulation [25].

5. Conclusions

We showed that unstable or bad-controlled glucose fluctuation was associated with DCI incidence and high mortality in SAH patients who are critically ill and admitted in NCU. Several risk factors, such as age, history of Diabetes Mellitus, SBP, BUN, HA1c, BGV, Hunt-Hess Score, GCS score, and Hydrocephalus in Forth ventricle, Third ventricle and Lateral ventricle, probably led to unstable and bad-controlled glucose lever during admission, and eventually DCI and death.

6. List Of Abbreviations

DCI	delayed cerebral infraction
aSAH	aneurysmal subarachnoid hemorrhage
NCU	neurocritical unit
TBI	traumatic brain injury
DM	diabetes mellitus
GCS	glasgow coma scale
SBP	systolic blood pressure
DBP	diastolic blood pressure
Cr	creatinine
HA1c	hemoglobin A1c
BGV	blood glycemic variability
AST	glutamic oxaloacetic transaminase
ALT	glutamic pyruvic transaminase
BUN	urea nitrogen
EF	ejection fraction
HPA	hypothalamic-pituitary-adrenal axis
IIT	intensive insulin therapy
GV	glycemic variability

6. Declarations

Ethics approval and consent to participate: This retrospective study was approved by the Ethics Committee at the Tiantan Hospital in Beijing. Our study was approved to collect data without requiring patient informed consent under the Waived Consent from the Ethics Committee at the Tiantan Hospital in Beijing (Ethics Approval Number: KY2019-060). Patients privacy and data confidentiality were ensured.

Consent for publication:Not applicable.

Availability of data and material:The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Authors' contributions:

QW and LT:conceived and designed the study and drafted and revise the manuscript for important intellectual content.

LZ and LL:conceived and designed the study.

DM: given final approval of the version and financial support.

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