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Effect of Admission Hyperglycemia on 6-Month Functional Outcome in Patients with Spontaneous Cerebellar Hemorrhage

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Cerebellar hemorrhage (CH) has a quite different treatment strategy and prognostic factors compared with supratentorial intracerebral hemorrhage (ICH). The prognostic role of hyperglycemia has been discussed mainly in cases of supratentorial hemorrhage; it remains to be elucidated following CH. We aimed to determine the association of hyperglycemia on admission with 6-month functional outcome in CH patients.

Material/Methods: We retrospectively analyzed 77 patients with acute CH between September 2010 and April 2015 in West China Hospital. Blood glucose level was measured when the patients were admitted. Primary outcome was 6-month functional outcome, which could comprehensively reflect the patient's recovery of physical and social ability after stroke and was assessed by the modified Rankin scale (mRS). Association of hyperglycemia with functional outcome was identified in logistic regression models.

Results: There were 50 (64.9%) patients with poor functional outcomes. Patients with poor outcome were much older (P<0.001) and had a significantly higher glucose level on admission (P<0.001), a lower Glasgow Coma Scale score (P<0.001), a larger hematoma (P=0.003), and a higher incidence of intraventricular extension (P=0.002), brainstem compression (P=0.013), and hydrocephalus (P=0.023). Multivariate analysis showed that hyperglycemia (OR 1.50, 95% CI 1.07–2.08, P=0.017 when glucose level was analyzed as a continuous variable; OR 7.46, 95% CI 1.41–39.51, P=0.018 when glucose level was dichotomized by the critical threshold of 6.78 mmol/L) emerged as an independent predictor for adverse functional outcome at 6 months.

Conclusions: To the best of our knowledge, this is the first study focusing on the relationship between hyperglycemia and long-term functional outcome after CH. The study combined with previous pertinent reports definitely indicates the poor effect of hyperglycemia on both supra- and infratentorial ICH independent of hemorrhage site. Therefore, further controlled trials are urgently needed to evaluate the benefits of glucose-lowing treatment.

MeSH Keywords: Cerebellar Diseases • Hyperglycemia • Intracranial Hemorrhage, Hypertensive • Prognosis

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Background

Cerebellar hemorrhage (CH) can become a critical condition due to direct brainstem compression and acute obstructive hydrocephalus, although it only accounts for fewer than 10% of all intracerebral hemorrhages (ICHs) [1]. The mortality rate within 6 months can reach 50%, and more than 60% of surviving patients had moderate or severe disability [2].

Compared with supratentorial ICH, most commonly basal ganglia hemorrhage, there are some differences in CH. First, the treatment strategy is quite distinctive. It has been recommended that patients with severe cerebellar hemorrhage (brainstem compression, obstructive hydrocephalus, deteriorating symptoms) should undergo hematoma evacuation as soon as possible, while the value of surgery for supratentorial hemorrhage is still uncertain [3]. Moreover, there are some clinical phenomena indicating that the pathophysiological mechanism may vary between supra- and infratentorial hemorrhage. For instance, elevated plasma homocysteine levels were associated with larger hematoma volume only in patients with thalamoganglionic ICH, not with infratentorial ICH [4]; Warfarin-related ICH has a predilection in the infratentorial region [5]. Additionally, preclinical studies also revealed that supra- and infratentorial neuronal and endothelia cell reaction to stroke differed markedly [6,7]. Therefore, findings from basal ganglia hemorrhage may not directly apply in CH, and CH should be discussed separately regarding the risk factors predicting prognosis, as has already been done in the literature [8,9].

Hyperglycemia is a common phenomenon after ICH, and the elevated level of blood glucose varied markedly between anterior and posterior circulation strokes [10]. Although there were conflicting results about the association of early hyperglycemia with prognosis after ICH, most researchers agreed that hyperglycemia had an deleterious effect on short-term survival and functional outcome [11–13]. Long-term mortality and outcome over 3-month follow-up were also affected in some recent reports [14,15]. A recent meta-analysis assessing the impact of hyperglycemia on mortality risk included 17 studies with a total of 6527 ICH patients and concluded that hyperglycemia significantly increases risk of both short-term mortality and long-term mortality [16]. However, these studies mostly focused on supratentorial ICH, with CH partly included or even excluded. Single analysis of the relevance of blood glucose levels in CH was seldom stated.

Wu et al. first demonstrated that hyperglycemia on arrival proved to be a strong predictive factor of poor outcome at discharge in patients with acute spontaneous CH [17]. Thereafter, they further investigated the prognostic factors of long-term mortality, finding that admission blood glucose level was significantly associated only in univariate analysis [9]. However, long-term functional outcome, which is more important for making the rehabilitation plan and predicting the ability to make a final social return, was not evaluated. In this study, we aimed to determine the prognostic influence of admission hyperglycemia on 6-month functional outcome.

Material and Methods

Study population

Seventy-seven patients with acute spontaneous CH who were admitted within 24 hours after onset were included in this study. The patients were consecutively admitted to our institution between September 2010 and April 2015. We excluded patients with head trauma, coagulopathy, warfarin therapy, cerebral venous thrombosis, hemorrhagic transformation from ischemic stroke, arteriovenous malformation, cavernous malformation, aneurysm, and tumor apoplexy. The Ethics Committee of West China Hospital approved the study protocol and all patients' guardians gave their informed consent.

Data collection

All patients' clinical data were retrospectively reviewed, including age, sex, hypertension (defined as pre-documented systolic blood pressure [SBP] >140 mm Hg or diastolic blood pressure [DBP] >90 mm Hg, or the use of an anti-hypertensive agent), diabetes mellitus (DM) based on previous diagnoses of diabetes or the current use of insulin or an oral hypoglycemic agent [18], drinking (>300 g of alcohol/week), smoking (>10 cigarettes/day), initial SBP and DBP, blood glucose level on admission, level of consciousness quantified by the Glasgow Coma Scale (GCS) score immediately after admission, radiological features, treatments (surgical hematoma evacuation or medical management), and outcome.

The location and size of hematoma, intraventricular hemorrhage (IVH), accompanying subarachnoid hemorrhage (SAH), the presence of hydrocephalus, brainstem compression, and fourth ventricle compression were evaluated on initial head computed tomography (CT). CHs were categorized as hemorrhage in the right hemisphere, left hemisphere, right hemisphere plus vermis, left hemisphere plus vermis, and left and right hemispheres plus vermis according to the location. The size of the hematoma was represented by the maximal diameter of the lesion as described previously [8,9].

The treatment algorithm was based on the recommendations of the ICH guideline [3]. Direct surgical evacuation rather than initial ventricular drainage was performed in CH patients with obstructive hydrocephalus, as suggested. Outcome was assessed by the modified Rankin scale (mRS) score. According

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to the outcomes at 6 months after CH, patients were divided into two groups: one group with poor functional outcome (mRS >2) and the other with a favorable outcome (mRS ≤2).

Statistics

All statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, New York, USA). Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ±SD or median with interquartile range (IQR) (25^{th}–75^{th} percentile). Univariate analyses of related clinical variables with respect to 6-month functional outcome were conducted using the χ^2 test, Fisher exact test, independent t test, and Mann-Whitney U test where appropriate. Receiver operating characteristic (ROC) analysis was undertaken to determine the threshold of critical hyperglycemia for 6-month outcome. Spearman's correlation analysis and multiple linear regression model were used to analyze the factors correlated with hyperglycemia. A logistic regression model was used to determine the effect of glucose level (either as a continuous variable or a categorical variable defined by the critical value) on 6-month functional outcome. Only variables with P<0.1 on univariate analysis were incorporated into the multivariate logistic regression model. A P value of <0.05 was considered clinically significant.

Results

Patients

Of the 77 eligible patients with CH included in this study, 50 (64.9%) were men and the mean age was 64.7±13.6 years with a range of 31 to 95 years. There were 9 patients (11.7%) with DM. The median glucose level on admission was 9.0 mmol/L (IQR 7.2–11.5 mmol/L) and the median initial GCS score was 12 (IQR 9–14). The average size of hematoma was 3.3±1.2 cm. IVH and SAH were presented in 36 (46.8%) and 26 (33.8%) of patients, respectively. The incidence of poor outcome at 6 months was 64.9%. The detailed information on demographics and clinical variables is listed in Table 1.

Univariate analysis of factors related to outcome

Univariate analysis revealed that patients with poor outcomes at 6 months were significantly older (P<0.001), had lower GCS scores (P<0.001), higher initial glucose levels (P<0.001), larger hematomas (P=0.003), and a higher incidence of IVH (P=0.002), brainstem compression (P=0.013), and hydrocephalus (P=0.023) (Table 1). However, the presence of DM, hemorrhage location, and surgery were not associated with poor 6-month outcome (Table 1). After excluding data of patients with DM, we gained similar results in univariate analysis (Table 2).

Multivariate analysis of factors associated with outcome

Multivariate logistic regression analysis of all CH patients determined that age (OR 1.13, 95% CI 1.05–1.22, P=0.001; or OR 1.12, 95% CI 1.04–1.19, P=0.001), admission GCS score (OR 0.58, 95% CI 0.39-0.86, P=0.007; or OR 0.57, 95% CI 0.39–0.82, P=0.003), and admission hyperglycemia (OR 1.50, 95% CI 1.07–2.08, P=0.017; or OR 7.46, 95% CI 1.41–39.51, P=0.018) were significant independent predictors whether the glucose level was defined as a continuous or a categorical variable (Table 3). When only non-diabetic patients were included, these three factors were still associated (Table 4).

Factors correlated with blood glucose level

A ROC curve showed that an admission blood glucose level of >6.78 mmol/L predicted 6-month poor functional outcome of CH patients with 92% sensitivity, 48.1% specificity, and area under the curve 0.775. Spearman correlation analyses demonstrated that glucose concentration was correlated with the presence of DM (r=0.641, P<0.001), hematoma diameter of ≥3 cm (r=0.371, P=0.001), and GCS score (r=–0.437, P<0.001). Patients with hydrocephalus tended to have higher glucose levels than those without hydrocephalus (P=0.081) (Table 5). In addition, multiple regression of glucose level on admission indicated that presence of DM (P<0.001), hematoma size (P=0.020), and GCS score (P=0.030) were independent predictors of glucose on admission (Table 6).

Discussion

The current study reveals that admission glucose level can negatively affect the long-term functional outcome after acute spontaneous CH, which has never been reported to the best of our knowledge. Moreover, a critical threshold glucose level of 6.78 mmol/L was identified to be best at predicting the outcome. Another important finding was the factors (including the presence of DM, hematoma size, and admission GCS) that were relevant to the level of glucose at admission, suggesting that early hyperglycemia following CH may be a mixed reflection of premorbid diabetic glucose metabolism and a stress reaction.

The prognostic effect of hyperglycemia after ICH has attracted a great amount of interest for more than a decade because hyperglycemia is a modifiable risk factor that can be controlled by oral antidiabetics or insulin intensive treatment. Numerous studies concluded that hyperglycemia during the prestroke period [19], in the emergency department [20], on admission [13,18], or within the initial three days after admission [14,21,22] negatively affected the survival and good functional outcome in patients with ICH. However, most studies concentrated on supratentorial hemorrhage, and few investigations

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Table 1. Baseline characteristics and variables related to 6-month outcome in patients with CH.

Variable	Total (n=77)	6-month outcome		
		Good (n=27)	Poor (n=50)	*P*
Demographic data				
Age*, y	64.7±13.6	56.7±13.2	69.0±11.9	<0.001
Men**	50 (64.9)	19 (70.4)	31 (62.0)	0.463
Clinical data				
Hypertension**	40 (51.9)	13 (48.1)	27 (54.0)	0.624
Diabetes mellitus**	9 (11.7)	2 (7.4)	7 (14.0)	0.481
Drinking**	14 (18.2)	4 (14.8)	10 (20)	0.759
Smoking**	19 (24.7)	7 (25.9)	12 (24.0)	0.852
SBP*, mmHg	177±33	177±33	177±34	0.991
DBP*, mmHg	102±20	105±20	100±21	0.280
GCS score***	12 (9, 14)	14 (13, 15)	11 (8, 12)	<0.001
Radiological data				
Hemorrhage location**				0.482
LH	34 (44.2)	11 (40.7)	23 (46.0)	
RH	19 (24.7)	9 (33.3)	10 (20.0)	
Vermis	6 (7.8)	1 (3.7)	5 (10.0)	
LH+vermis	8 (10.4)	2 (7.4)	6 (12.0)	
RH+vermis	8 (10.4)	4 (14.8)	4 (8.0)	
LH+RH+vermis	2 (2.6)	0 (0)	2 (4.0)	
Presence of SAH**	26 (33.8)	8 (29.6)	18 (36.0)	0.573
Presence of IVH**	36 (46.8)	6 (22.2)	30 (60.0)	0.002
FVC	32 (41.6)	9 (33.3)	23 (46.0)	0.282
BSC	22 (28.6)	3 (11.1)	19 (38.0)	0.013
Hydrocephalus	24 (31.2)	4 (14.8)	20 (40.0)	0.023
Hematoma size(cm)	3.3±1.2	2.8±1.1	3.6±1.2	0.003
Glucose***, mmol/l	9.0(7.2, 11.5)	7.3(6.0, 9.1)	10.0(7.9, 12.9)	<0.001
Surgery**	21 (27.3)	7 (25.9)	14 (28.0)	0.845

CH – cerebellar hemorrhage; SBP – systolic blood pressure; DBP – diastolic blood pressure; GCS – Glasgow Coma Scale; LH – left hemisphere; RH – right hemisphere; SAH – subarachnoid hemorrhage; IVH – intraventricular hemorrhage; FVC – fourth ventricle compression; BSC – brainstem compression. * Mean ±SD; ** n (%);*** median (25^{th}–75^{th} percentiles).

have addressed this topic specifically concerning CH. Wu et al. were the pioneers who identified that admission hyperglycemia at 7.8 mmol/L, determined in a previous report, was an independent predictor of early poor outcome [8,17]. Our study further confirmed that hyperglycemia was also associated with long-term poor functional outcome, strongly suggesting that glucose-lowing management may improve prognosis, although the optimal glucose control is still unknown. Moreover, as we determined that the risk of poor outcome in those with glucose levels of >6.78mmol/L was more than seven-fold compared with those who had glucose levels of ≤6.78 mmol/L, glucose control lower than 6.78 mmol/L might be reasonable.

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Table 2. Baseline characteristics and variables related to 6-month outcome in non-diabetic patients with CH.

Variable	Total (n=68)	6-month outcome		
		Good (n=25)	Poor (n=43)	*P*
Demographic data				
Age*, y	64.8±13.8	57.1±13.3	69.3±12.2	<0.001
Men**	47 (69.1)	18 (72.0)	29 (67.4)	0.695
Clinical data				
Hypertension**	34 (50.0)	12 (48.0)	22 (51.2)	0.801
Drinking**	12 (17.6)	3 (12.0)	9 (20.9)	0.513
Smoking**	18 (26.5)	6 (24.0)	12 (27.9)	0.725
SBP*, mmHg	178±34	177±34	178±34	0.891
DBP*, mmHg	102±21	105±21	100±22	0.378
GCS score***	12 (10, 14)	14 (13, 15)	11 (8, 13)	<0.001
Radiological data				
Hemorrhage location**				0.178
LH	30 (44.1)	11 (44.0)	19 (44.2)	
RH	17 (25.0)	9 (36.0)	8 (18.6)	
Vermis	5 (7.4)	0 (0)	5 (11.6)	
LH+vermis	6 (8.8)	1 (4.0)	5 (11.6)	
RH+vermis	8 (11.8)	4 (16.0)	4 (9.3)	
LH+RH+vermis	2 (2.9)	0 (0)	2 (4.7)	
Presence of SAH**	20 (29.4)	6 (24.0)	14 (32.6)	0.455
Presence of IVH**	31 (45.6)	6 (24.0)	25 (58.1)	0.006
FVC	27 (39.7)	7 (28.0)	20 (46.5)	0.133
BSC	20 (29.4)	3 (12.0)	17 (39.5)	0.016
Hydrocephalus	21 (30.9)	4 (16.0)	17 (39.5)	0.043
Hematoma size (cm)	3.3±1.3	2.7±1.1	3.7±1.3	0.002
Glucose***, mmol/l	8.6(6.8, 10.2)	6.8(5.9, 8.8)	9.4(7.7, 11.8)	<0.001
Surgery**	17 (25.0)	6 (24.0)	11 (25.6)	0.885

CH – cerebellar hemorrhage; SBP – systolic blood pressure; DBP – diastolic blood pressure; GCS – Glasgow Coma Scale; LH – left hemisphere; RH – right hemisphere; SAH – subarachnoid hemorrhage; IVH – intraventricular hemorrhage; FVC – fourth ventricle compression; BSC – brainstem compression. * Mean ±SD; ** n (%);*** median (25^{th}–75^{th} percentiles).

The possible explanations with regard to the role hyperglycemia plays in poor outcome after ICH were stated in several previous reports [13–15,17,20], but the definite molecular mechanism remains to be elucidated [23,24]. Experimental studies showed that diffuse brain edema, perihematomal increased neuronal apoptosis, and reduced autophagy, as well as larger hematoma formation, were caused by hyperglycemia after ICH [25–27]. The speculations about hyperglycemia-induced brain injury mechanisms involved the direct toxic role, free-radical formation, bradykinin release, and cytosolic free calcium elevation [11]. Nevertheless, the animal model only partially mimics the clinical condition because hyperglycemia

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Table 3. Predictors of 6-month functional outcome in patients with CH in multiple logistic regression model.

Variable	Glu as continuous variable			Glu as categorical variable (> 6.78 mmol/L)		
	OR	95%CI	P	OR	95%CI	P
Age	1.13	1.05–1.22	0.001	1.12	1.04–1.19	0.001
GCS	0.58	0.39–0.86	0.007	0.57	0.39–0.82	0.003
Presence of IVH	2.53	0.50–12.7	0.261	2.79	0.58–13.37	0.200
BSC	2.88	0.42–19.86	0.283	2.10	0.30–14.55	0.452
hydrocephalus	1.26	0.19–8.24	0.810	1.45	0.25–8.46	0.677
Diameter ≥3 cm	0.76	0.12–4.93	0.772	1.01	0.17–5.91	0.992
Glu	1.50	1.07–2.08	0.017	7.46	1.41–39.51	0.018

CH – cerebellar hemorrhage; Glu – glucose; OR – odd ratio; CI – confidence interval; GCS – Glasgow Coma Scale; IVH – intraventricular hemorrhage; BSC – brainstem compression.

Table 4. Predictors of 6-month functional outcome in non-diabetic patients with CH in multiple logistic regression model.

Variable	Glu as continuous variable			Glu as categorical variable (>6.78 mmol/L)		
	OR	95%CI	P	OR	95%CI	P
Age	1.14	1.05–1.24	0.002	1.12	1.04–1.21	0.003
GCS	0.56	0.36–0.89	0.015	0.55	0.36–0.84	0.006
Presence of IVH	2.18	0.36–13.15	0.395	2.42	0.48–12.24	0.284
BSC	2.30	0.35–15.32	0.388	1.06	0.12–9.73	0.960
hydrocephalus	0.76	0.09–6.72	0.808	1.08	0.15–7.84	0.573
Diameter ≥3 cm	1.27	0.18–8.82	0.809	1.58	0.32–7.75	0.617
Glu	1.85	1.13–3.03	0.015	8.49	1.51–47.64	0.015

CH – cerebellar hemorrhage; Glu – glucose; OR – odd ratio; CI – confidence interval; GCS – Glasgow Coma Scale; IVH – intraventricular hemorrhage; BSC – brainstem compression.

was not spontaneously produced following ICH, but was induced by intraperitoneal injection of exogenous streptozotocin or glucose. Furthermore, neither increased brain edema nor hematoma expansion was observed in hyperglycemic patients following ICH [15,22]. Alternatively, it was suggested that a higher incidence of cerebral and infectious complications may be related to poor outcome in ICH patients with admission hyperglycemia [28].

DM is a potential confounder when discussing the adverse effect of blood glucose in CH. Although presence of DM was not related to outcome in our study, as it was in a larger Chinese population study [29], hyperglycemia was partly regarded as a manifestation of premorbid diabetic glucose metabolism [18] and diabetes status was found to independently influence the prognosis of patients after ICH in some reports [15]. Therefore, stratification statistical analysis was performed in our study. Although the number of patients with DM was too small for any meaningful statistical analysis, hyperglycemia remained an independent risk factor in patients without DM. This result was consistent with the previous studies [18,28].

ICH-induced hyperglycemia is considered a result of an indirect, neuroendocrine stress-mediated mechanism, and many clinical and radiological features were defined as risk factors for ICH-associated hyperglycemia. In a recent prospective report from the INTERACT 2 study, hyperglycemia occurred significantly more often in patients from outside of China, and patients with greater cortical hematomas, DM, higher SBP, greater clinical severity of stroke, and larger hematomas with intraventricular hemorrhage extension [15]. Of those indicators, severity of stroke including intraventricular hemorrhage was most important [30,31]. Appelboom et al. reported that IVH severity was shown to correlate with admission glucose

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Table 5. Spearman correlation analyses of the correlation of admission Glu level with clinical parameters in patients with CH.

Clinical parameter	Glu	
	r	p
Age, years	–0.020	0.865
Diabetes mellitus	0.641	<0.001
Location of CH	–0.037	0.750
IVH	0.125	0.278
Hematoma size	0.371	0.001
GCS score	–0.437	<0.001
FVC	0.137	0.234
BSC	0.144	0.211
Hydrocephalus	0.200	0.081

Glu – glucose; CH – cerebellar hemorrhage; IVH – intraventricular hemorrhage; GCS – Glasgow Coma Scale; FVC – fourth ventricle compression; BSC – brainstem compression.

level independent of other ICH severity markers [31]. To our knowledge, our study was the first one demonstrating that presence of DM, larger hematoma, and lower GCS score were the contributing factors in hyperglycemia after CH in a multiple linear regression model. The results were similar to those observed in patients with supratentorial hemorrhage.

Patients surviving the acute phase of CH often suffer significant residual disability, so predictors of long-term functional outcome are vital for developing a rehabilitation strategy. Predictors of long-term poor outcome following acute CH included age >75 years [32], initial GCS <13 [33], low level of consciousness [33,34], acute hydrocephalus [34,35], admission SBP >200 mm Hg [35], coagulopathy [8], hematoma size >3 cm [8,35], radiological brainstem compression [8,33–35], a tight posterior fossa [33], and intubation and surgical intervention [34]. Our results indicating that older age and lower GCS score on admission correlated with worse prognosis further confirmed these conclusions. Moreover, glucose level as an inexpensive and readily available biochemical marker might strengthen the predictive power when incorporated into conventional scoring models.

Table 6. Multiple linear regression of admission glucose and admission variables in patients with CH.

Variable	Standardized Coefficient	P value
Diabetes mellitus	6.433	<0.001
Hematoma size	0.634	0.020
GCS score	–0.228	0.030
Hydrocephalus	0.377	0.552

CH – cerebellar hemorrhage; GCS – Glasgow Coma Scale.

There were several limitations in the current study. First, the rarity of the entity determined the relatively small population size. Actually, to our knowledge, our case number is the second largest among published reports concerning the prognosis of CH [8,9]. Second, although all subjects were admitted within 24 hours of onset, the admission glucose level was affected by the postprandial increase. Besides, the diagnosis of DM was based on the past medical history without objective measurement of hemoglobin A1c, which indicates the average glucose level over a 2- to 3-month period [19], so the incidence of DM may be underestimated. Lastly, this study is retrospective with its innate limitations and unavoidable selection bias.

Conclusions

We found that admission hyperglycemia was an independent risk factor for poor functional outcome at 6 months in patients with acute spontaneous CH. Hyperglycemia correlated with the presence of DM, the GCS score on admission, and hematoma size. The present study with previous pertinent reports [9,17] implicates the poor effect of hyperglycemia on both supra- and infratentorial ICH independent of hemorrhage location. Further controlled trials are urgently required to define whether lowering of the glucose level during the acute phase after ICH leads to a better prognosis.

Conflict of interest

None.

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