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ARTICLE

Effects of glucose level on early and long-term mortality after intracerebral haemorrhage: the Acute Brain Bleeding Analysis Study

S.-H. Lee · B. J. Kim · H.-J. Bae · J. S. Lee · J. Lee · B.-J. Park · B.-W. Yoon

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Abstract
Aims/hypothesis Admission hyperglycaemia is associated with a poor outcome in patients with ischaemic stroke. However, its prognostic effects after intracerebral haemorrhage (ICH) are still unclear.
Methods We prospectively enrolled patients with ICH at 33 centres in Korea between October 2002 and March 2004. A total of 1,387 patients who had ICH and underwent brain computed tomography within 48 h of symptom onset were included in the study (n=1,387). Clinical information and radiological findings were collected at admission. Glucose levels were examined in relation to early (up to 30 days after ictus) and long-term (after 30 days) mortality rates using Cox regression analysis. To eliminate short-term effects, long-term mortality rate analysis was performed on surviving patients for more than 30 days.
Results The long-term mortality rate was 21.1% after a mean follow-up of 434.3±223.2 days and was found to increase significantly with glucose quartile (p<0.001). Admission glucose level was an independent risk factor for early mortality (per mmol/l; adjusted HR 1.10 [95% CI 1.01–1.19]), but not for long-term mortality. Moreover, when analysis was restricted to patients without diabetes, glucose level was found to be an independent risk factor for post-ICH mortality (n=1,119; adjusted HR 1.10 [95% CI 1.03–1.17]) and had marginal significance for early (p=0.053) and long-term mortality (p=0.09).
Conclusions/interpretation We found that admission glucose levels were associated with early mortality after ICH. In patients without diabetes, admission glucose levels were associated with long-term mortality. We therefore suggest that intensive lowering of glucose level should be further investigated in ICH patients.

Keywords Glucose · Intracerebral haemorrhage · Mortality

Abbreviations
CT Computed tomography
GCS Glasgow coma scale
ICH Intracerebral haemorrhage

Introduction

Diabetes is an important risk factor for myocardial infarction and stroke, and has an unfavourable influence

S.-H. Lee and B. J. Kim contributed equally to this work.

S.-H. Lee · B. J. Kim · B.-W. Yoon (✉)
Department of Neurology, Seoul National University Hospital,
28 Yeongun-dong, Jongro-gu,
Seoul 110-744, Republic of Korea
e-mail: bwyoon@snu.ac.kr

S.-H. Lee · B. J. Kim · B.-W. Yoon
Clinical Research Centre for Stroke, Clinical Research Institute,
Seoul National University Hospital,
Seoul, Republic of Korea

H.-J. Bae
Department of Neurology,
Seoul National University Bundang Hospital,
Seongnam-si,
Kyunggi-do, Republic of Korea

J. S. Lee · J. Lee
Department of Biostatistics, College of Medicine,
Korea University,
Seoul, Republic of Korea

B.-J. Park
Department of Preventive Medicine, College of Medicine,
Seoul National University,
Seoul, Republic of Korea

on recovery after stroke [1]. Even in patients without diabetes, admission hyperglycaemia in cases of acute ischaemic stroke is associated with a worse functional outcome, longer hospital stay and higher risk of death within 30 days according to a recent systematic review [2]. In addition, it has been suggested that intensive insulin therapy reduces morbidity and mortality rates in critically ill patients [3]. However, few studies have addressed this topic with regard to haemorrhagic stroke and no consensus has been established on the associated risks. A prospective study conducted in a single Italian centre indicated that hyperglycaemia is an independent predictor of 3 day and 3 month mortality in non-diabetic, non-comatose patients after supratentorial intracerebral haemorrhage (ICH) [4]. In contrast, a population-based retrospective study conducted in Finland suggested that high admission blood glucose is the result of serious ICH [5].

To determine whether admission glucose levels are associated with poor outcome in acute ICH patients, a study based on a larger ICH population and longer follow-up was necessary. The purpose of this study was to examine whether admission glucose level is associated with early and long-term mortality rates in ICH patients.

Methods

Participants The Acute Brain Bleeding Analysis Study is a multicentre project designed to produce a nationwide, large, prospective and reliable haemorrhagic stroke registry in Korea [6]. Between October 2002 and March 2004, a consecutive series of patients with haemorrhagic stroke (ICH, n=1,604; subarachnoid haemorrhage, n=1,106) were registered in 33 medical centres. Because of variable intervals between symptom onset and hospital admission or time to brain computed tomography (CT), patients who visited during the acute stage were selected. In this context, we excluded patients who underwent brain CT>48 h after symptom onset. As a result, a total of 1,387 participants were included in the study population. The protocol used in this study was approved by the Institutional Review Board of our hospital, and the participants or their next of kin gave informed consent.

Clinical information and mortality data The following baseline patient characteristics were collected from the database: sex, age, hypertension, diabetes, admission systolic and diastolic blood pressures, body temperature, glucose level, initial Glasgow Coma Scale (GCS) score, presence of intraventricular haemorrhage and the use of surgical treatment (evacuation or stereotactic aspiration). Hypertension was defined as a prior history of hypertension, current antihypertensive medication or a systolic and diastolic blood pressure of ≥140 and ≥90 mmHg respectively at discharge. Diabetes was considered to be present if a patient had a history of diabetes and glucose-lowering medication before admission, and also if the fasting glucose level was ≥7.0 mmol/l (126 mg/dl) during hospitalisation [7]. ICH volumes were measured using an image analyser (Image-Pro Plus; Media Cybernetics, Silver Spring, MD, USA). Admission glucose levels were measured during the morning of the day following admission after a fast of at least 8 h (overnight). Mortality information and dates of death were obtained from Korean National Death Certificates, which allowed the dates of death from all cases to be traced using a unique 13-digit identification code containing the date of birth. Data from 2002 to 2004 were collected as of 31 December 2004. In Korea, the law requires that the family or guardians report a death to the village office when a person dies. Death information is collected and managed exclusively by Korean National Death Certificates. We therefore do not believe that there are any errors in our mortality data. However, to confirm the validity of fatality information, we chose three hospitals (Eulji Hospital, Nowon Eulji Hospital and Seoul National University Bundang Hospital) and verified the mortality information of the relevant patients at these hospitals by telephone. As no misclassifications were found, we concluded that there were no erroneous data on mortality.

Statistical analysis In this analysis, glucose levels were classified into quartiles, i.e. first quartile (<6.25 mmol/l), second (6.25–7.50 mmol/l), third (7.50–9.30 mmol/l) and fourth (>9.30 mmol/l). Survival probabilities after ICH were estimated using the Kaplan–Meier product-limit method and survival probabilities of patients by glucose quartile were compared using logrank tests. To examine the effects of admission glucose level on early or long-term mortality rates, Cox proportional hazard regression analyses were used to calculate the crude and adjusted HRs with 95% CIs. Second, third and fourth quartiles were compared separately with the first quartile. Cox models were used to assess the effect of glucose level at admission on mortality. Two different models were fitted: model 1 using glucose level as a categorical variable, and model 2 using glucose level (mmol/l) as a linear variable. These models incorporated variables found to be associated with mortality by univariate analyses (p<0.10). The presence of significant interaction between diabetes and glucose level was tested, but with negative results. We included an indicator for time after 30 days as time-dependent variable in the Cox model. The interaction between this and glucose level was used to assess the differences in the effect of glucose level on early (up to 30 days after ictus) and long-term mortality (>30 days after ictus; censored on 31 December 2004) rates. The hypothesis of equal effect of glucose level on early and

Table 1 Baseline characteristics

Variable	Death up to 30 days	Death after 30 days	Survived
n	130	163	1,094
Male sex, *n* (%)	67 (51.5)	81 (49.7)	605 (55.3)
Age (years)	64.1±15.2	70.1±11.9	58.6±12.1
Hypertension, *n* (%)	69 (53.1)	93 (57.1)	655 (59.9)
Diabetes, *n* (%)	23 (17.7)	30 (18.4)	108 (9.9)
Systolic BP (mmHg)	178.2±41.8	168.7±33.9	170.0±42.0
Diastolic BP (mmHg)	108.3±82.3	98.2±20.0	99.8±33.6
Body temperature (°C)	36.3±1.0	36.5±0.6	36.4±0.9
Glucose (mmol/l)	10.0±3.7	8.6±2.8	7.9±2.6
Location of haemorrhage, *n* (%)			
Lobar	33 (25.4)	26 (16.0)	183 (16.7)
Putaminal	51 (39.2)	68 (41.7)	474 (43.3)
Thalamic	36 (27.7)	53 (32.5)	296 (27.1)
Pontine	22 (16.9)	10 (6.1)	72 (6.6)
Cerebellar	8 (6.2)	12 (7.4)	77 (7.0)
Unspecified	7 (5.4)	9 (5.5)	52 (4.8)
ICH volume (ml)	37.3±32.5	24.1±24.5	17.2±19.9
Intravent. haemorrhage, *n* (%)	56 (43.1)	69 (42.3)	289 (26.4)
Initial GCS score	7.5±3.7	11.0±3.3	12.7±2.8

Unless otherwise indicated, values are presented as mean ± standard deviation

Intravent., intraventricular

long-term mortality was tested by a likelihood-ratio test. The proportionality assumption of the constructed multivariable model was test and not violated. Statistical analysis was conducted using SPSS for Windows (version 12.0; SPSS, Chicago, IL, USA), with statistical significance accepted at $p<0.05$.

Results

Of the 1,387 participants with ICH included in this study, 753 were men and 634 were women. The ages of the participants ranged from 15 to 97 years (mean 60.4± 13.0 years). Mean glucose level on admission was 8.1± 2.8 mmol/l and mean ICH volume was 19.9±22.7 ml. Intraventricular haemorrhage was observed in 414 patients (29.8%); the initial GCS score was 12.2±3.2. The early mortality rate was 9.4% (130 patients) at 1 month, with an overall mortality rate of 21.1% (293 patients) during the follow-up period (mean 434.3±223.2 days). Baseline characteristics are shown in Table 1.

After reclassifying glucose levels by quartile, early and long-term mortality rates were found to be positively correlated with glucose quartiles. In terms of early mortalities, ten patients (2.9%) were in the lowest quartile, 27 (7.7%) in the second quartile, 31 (8.8%) in the third quartile and 62 (18.1%) in the highest quartile ($p<0.001$). In terms of long-term mortalities, 30 patients (9.0%) were in the lowest quartile, 31 (9.6%) in the second quartile, 51 (15.9%) in the third quartile and 51 (18.2%) in the highest quartile ($p=0.001$). Survival curves are illustrated in Fig. 1. During follow-up, survival rates were found to differ significantly by quartile ($p<0.001$ logrank test).

Regarding early mortality, multivariate analysis showed that associations with age, systolic blood pressure, pontine location of haemorrhage, ICH volume and initial GCS score were significant. With regard to glucose level, five Cox proportional hazard regression analysis models were used, as described in Table 2. Model 1 identified the highest quartile

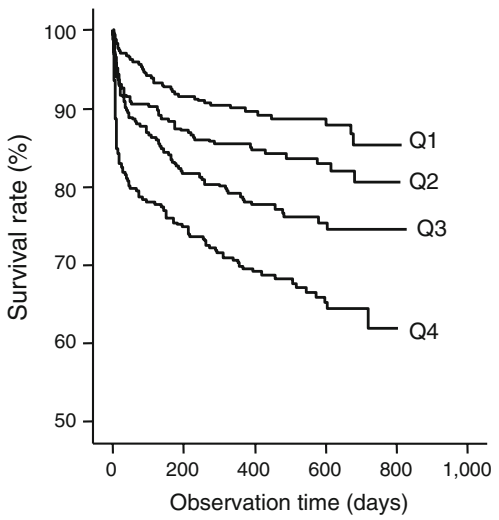

Fig. 1 Survival curves. Q1, first glucose level quartile; Q2, second glucose level quartile; Q3, third glucose level quartile; Q4, fourth glucose level quartile

Table 2 Cox proportional hazard regression analyses

Models	Early mortality		Long-term mortality	
	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Model 1[a]				
Second vs first	2.93 (0.99–8.71)	0.05	0.96 (0.53–1.72)	0.88
Third vs first	1.68 (0.54–5.28)	0.37	1.46 (0.85–2.50)	0.17
Fourth vs first	3.34 (1.15–0.73)	0.03	1.45 (0.83–2.53)	0.19
Model 2[b]				
Glucose level (per mmol/l)	1.10 (1.01–1.19)	0.03	1.05 (0.98–1.11)	0.15

[a] Model 1: glucose level (quartiles) + age, diabetes, systolic and diastolic BP, pontine location of haemorrhage, ICH volume, intraventricular haemorrhage and GCS score (with $p<0.10$ in univariate analyses)

[b] Model 2: glucose level (continuous data, mmol/l) + age, diabetes, systolic and diastolic BP, pontine location of haemorrhage, ICH volume, intraventricular haemorrhage and GCS score (with $p<0.10$ in univariate analyses)

of glucose level as an independent risk factor of early mortality. The relationship between glucose level and early mortality was also found to be significant when glucose level was analysed as a continuous variable (mmol/l; Model 2).

In terms of long-term mortality, the highest glucose level quartile was not found to be significantly related with mortality by Models 1 and 2. However, when we reclassified patients according to presence of diabetes, glucose level was found to have significant associations with mortality in patients without diabetes (n=1,226; adjusted HR 1.10 [95% CI 1.03–1.17] for glucose level per mmol/l). When the timepoint of mortality was categorised as early and long-term, glucose level had marginal significance with early (adjusted HR 1.11 [95% CI 0.999–1.22], p=0.053) and long-term mortality (adjusted HR 1.07 [95% CI 0.99–1.16], p=0.09). However, in patients with diabetes (n=138), glucose level was not found to be associated with mortality over the total period (adjusted HR 1.03 [95% CI 0.95–1.13]), or with early (adjusted HR 1.01 [95% CI 0.85–1.19]) and long-term mortality (adjusted HR 1.01 [95% CI 0.91–1.11]).

Discussion

In this study, which was performed on 1,387 consecutive cases registered at 33 Korean centres, admission hyperglycaemia was found to be an independent risk factor for early mortality, but not for long-term mortality. However, when restricted to patients without diabetes, admission hyperglycaemia was found to be independently related to both early and long-term mortality. To the best of our knowledge, this is the first study to identify the deleterious effects of admission hyperglycaemia on early and long-term survival in ICH patients without diabetes.

Hyperglycaemia during the acute stroke period may be caused by premorbid glucose metabolism [8, 9] or a stress reaction induced by severe neurological injury [10, 11]. However, even in patients without diabetes, it is not understood why hyperglycaemia is directly related to brain damage. Experimental studies indicate that hyperglycaemia may increase brain oedema [12], inflammatory reaction [13], free radical injury [14] and excitotoxic or apoptotic cell death after stroke [15], but these results have not yet been demonstrated in humans to our knowledge. Although several studies have described possible effects of hyperglycaemia in ICH patients [4, 5, 16–21], these studies used either small populations [5, 16, 17, 19] or long enrolment periods [4]. Two small prospective studies [17, 22] showed that hyperglycaemia is independently associated with short-term mortality. Another hospital-based study conducted in Italy [4], which included a consecutive series of 764 ICH patients over a 19 year period, concluded that hyperglycaemia (≥130 mg/dl) is a strong predictor of 30-day and 3-month mortality in non-diabetic, non-comatose supratentorial ICH patients. However, a retrospective study in a Finnish population [5] found no difference between admission glucose levels in non-diabetic ICH patients who died and those in diabetic ICH patients who survived. This study therefore concluded that hyperglycaemia is probably a stress response to neurological injury. Moreover, a retrospective study in Taiwan [23] failed to reveal an independent relationship with 30-day mortality rates. The results in the present study show that admission hyperglycaemia is independently associated with early mortality. Interestingly, this result supports the hypothesis that hyperglycaemia after ICH may increase neurological damage. Indeed, it also suggests that hyperglycaemia caused by a stress reaction during acute-stage ICH might be associated with further neurological damage.

In terms of early mortality rates, admission hyperglycaemia was found to be an independent risk factor in the whole population, but this was caused by a strong association in patients without diabetes. Moreover, admission hyperglycaemia was found to have a slight but

significant relationship with long-term mortality rates only in patients without diabetes. Accordingly, our findings show that admission hyperglycaemia is a predictor of mortality in patients without diabetes, and our post hoc analyses indicated that the influence of admission hyperglycaemia on post-ICH mortality diminished after the index stroke event. These results are consistent with the findings of previous systematic studies on ischaemic stroke [2] and suggest that the effect of diabetes on long-term mortality rates may be greater than that of hyperglycaemia in patients with diabetes. In this study, patients without diabetes amounted to about 90% of total population. Accordingly, the number of patients with diabetes was quite small (n= 161 for early mortality; n=131 for long-term mortality). For these reasons, the association between hyperglycaemia in patients with diabetes and mortality remains to be resolved.

Along with hyperglycaemia, ICH volume and initial GCS score were also independent risk factors for long-term mortality in this study. ICH volume and lower GCS score are poor prognostic factors and have generally been accepted as surgical indications on a case-by-case basis. However, the presence of intraventricular haemorrhage was not a risk factor for early mortality in this study. Although this study did not focus on intraventricular haemorrhage, it is not the first to report the lack of a prognostic effect [24]. The presence of intraventricular haemorrhage itself might affect outcome in patients with ICH, and the amount of intraventricular haemorrhage, the presence of hydrocephalus and subsequent systemic complications might be more direct prognostic factors. In addition, the possible statistical interaction with ICH volume or neurologic severity might be associated with the loss of significance for the effect of intraventricular haemorrhage.

Some important caveats in this study must be noted. First, mortality rate was the only outcome variable studied with respect to glucose level at admission, and no functional scale (e.g. the modified Rankin Scale) was used. Therefore, the effects of admission glucose level on neurological status could not be determined. In addition, details of vascular events that occurred during follow-up were not collected. Furthermore, the initial neurological severity was assessed only by the GCS score. If we had used other neurological scales, such as the National Institute of Health Stroke Scale (NIHSS), the present results would have improved.

Despite its limited power, the present study also has several strengths concerning the enrolled study population and study design. For example, 2,710 patients registered at 33 hospitals in Korea were analysed. Selection bias was thus minimised, because all of the ICH patients were entered consecutively for this study. Accordingly, this study analysed the largest population to date for an association between glucose level and ICH mortality.

Considering the present results, intensive lowering of blood glucose might be a therapeutic option during the acute period of ICH. Although not directly related to this issue, a randomised, controlled trial reported the effects of intensive insulin therapy on patients admitted to a surgical intensive care unit and receiving mechanical ventilation [3]. The intensive lowering of glucose to maintain euglycaemia reduced both morbidity and mortality rates. Based on experimental and clinical experience, glucose–potassium–insulin therapy has been tested with a view to improving neurological outcome in patients with acute stroke (GIST-UK trial) [25]. This trial, which involved 933 stroke patients, did not provide evidence for a favourable effect on 90-day mortality rates or on secondary endpoints. Because participants were acute ischaemic stroke patients, the efficacy of glucose control in ICH patients was not determined. The results of the present study, therefore, suggest that intensive lowering of glucose level in ICH patients should be further investigated.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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