Lower Extracellular Glucose Level Prolonged in Elderly Patients With Severe Traumatic Brain Injury: A Microdialysis Study

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Abstract

Age may be an independent predictor of outcomes in traumatic brain injury (TBI), but the causes of the poor outcomes in elderly patients remain unclear. To clarify the differences between elderly and young patients with TBI, brain metabolism parameters were monitored with the microdialysis method in 30 patients with severe TBI (Glasgow Coma Scale scores 3–8). The microdialysis probe was inserted in the penumbra area of the brain and extracellular levels of glucose, glutamate, glycerol, lactate, and pyruvate were measured hourly for the initial 168 hours (7 days) after operation. The lactate/pyruvate ratio, which is considered to be a good indicator of neuronal ischemia, was also calculated. The patients were divided into the elderly group aged 65 years or older and the young group aged less than 65 years, and the biochemical markers were compared daily between these two groups. The value of extracellular glucose concentration was significantly lower in the elderly group than in the young group, and continued until the 7th day after injury. Moreover, the lactate/pyruvate ratio peaked on the 5th day after injury in the elderly group, later than in the young group. We concluded that neural vulnerability persisted longer in elderly patients than in young patients with TBI, and this should be considered to prevent the occurrence of additional secondary brain injury.

Key words: geriatric head injury, glucose, microdialysis, traumatic brain injury, hypoperfusion

Introduction

Traumatic brain injury (TBI) is very significant problem in the elderly population. TBI is responsible for more than 80,000 emergency department visits by persons aged 65 years or older each year in the United States, and this group has the highest rates of TBI-related hospitalization and death.²⁹⁾ The Japan Neurotrauma Data Bank found significant differences in mortality rates between patients aged 65–69 years and patients aged 70–74 years.³¹⁾ Elderly individuals, 65 years of age or older, account for a disproportionate number of TBI cases and have a staggering incidence of morbidity and mortality. Older age is known to negatively influence outcome after TBI and the age may be the most important predictor of patient prognosis.^{10,14,18,21,22,26)} However, predicting outcomes and providing care in the older

adult population with TBI remains problematic without good clinical data.

Geriatric and neurotrauma investigators have identified many prognostic factors, but these variables remain understudied in older adults with TBI. Intracranial pressure (ICP), cerebral perfusion pressure (CPP), and jugular oxygen saturation (SjO₂) have been used in neurointensive care, and for decision making in neurotrauma treatment. In addition, cerebral microdialysis has been introduced as a neurochemical monitoring tool,²⁷⁾ and is now routinely used in several neurointensive care units for bedside monitoring of small molecules related to brain perfusion and metabolism in neurotrauma patients.³⁾ However, any differences between elderly and young head injury patients in brain perfusion and metabolism measured with microdialysis remain unclear.

The present study investigated the differences between elderly and young TBI patients by monitoring of brain micro-metabolism with the microdialy-

sis technique.

Materials and Methods

Ethical approval for the study was granted by the Ethical Committee of the Nippon Medical School Hospital. Patients were enrolled in the study in the emergency department and consented by proxy. The study involved 42 patients with severe TBI (Glasgow Coma Scale [GCS] scores 3–8) associated with acute subdural hematoma (ASDH) or diffuse brain injury (DBI) who were admitted to our emergency trauma center from January 1, 2009 to June 30, 2010. Consent from the families or proxy was not given for 9 patients. Three patients with epidural hematoma were excluded because of different clinical course and injury severity. Therefore, 30 patients (20 ASDH and 10 DBI) were finally enrolled in this study. No patient had additional injury including the trunk and extremities, and no history of serious preinjury use of anticoagulant and antiplatelet drugs, cardiovascular disease, diabetes mellitus, etc.

The initial management and operative procedures of the patients were performed with the protocols described in the Japanese Guidelines for the Treatment and Management of Severe Traumatic Brain Injury second edition,¹⁶⁾ and the Guidelines for the Management of Severe Traumatic Brain Injury third edition.⁵⁾ The patients remained in the neurointensive care unit for 7 days after surgery according to the above protocols.

After surgery for hematoma removal, a microdialysis probe (CMA70; CMA Microdialysis, Stockholm, Sweden), with a 10-mm membrane and 20,000-dalton molecular weight cut-off, and ICP monitor (Codman Microsensor; Codman & Shurtleff, Inc., Raynham, Massachusetts, USA) were inserted into the white matter to 1–2 cm depth (so-called “brain penumbra area”) from the brain surface with removed hematoma.³⁾ A CMA 103 perfusion pump (CMA Microdialysis) was connected in the operating theater, and normal saline was perfused through the catheter at a rate of 0.3 μ l/min, and the microdialysate was collected and frozen in 60-minute samples for the initial 168 hours (7 days) after neurointensive care unit admission. The initial 60-minute sample was not used for analysis because this was the time allowed for stabilization of the probe.

Microdialysis was not interrupted for transport or bedside testing. The bedside nurse maintained a detailed patient event log to identify important events and to record times of vial sampling and all physiological monitoring data. The following data was recorded hourly: ICP, CPP, mean arterial pressure,

heart rate, arterial oxygen saturation, core temperature (temperature in the rectal colon), and GCS score. In addition, doses of sedatives, mannitol, and other neurologically active medications were recorded hourly.

Frozen samples were briefly centrifuged and then analyzed on the ISCUS microdialysis analyzer (CMA Microdialysis) by batch analysis using standard ISCUS reagents. Extracellular levels of glucose, glutamate, glycerol, lactate, and pyruvate were measured, and the lactate/pyruvate ratio, which is considered to be a good indicator of neuronal ischemia, was also calculated in all samples.

The 30 patients were divided into the elderly group aged 65 years or older and the young group aged less than 65 years, and the biochemical markers were compared daily between these groups. Each case was treated with same target value of ICP and CPP. Statistical analysis was performed using Stat View software (SAS Institute Inc., Cary, North Carolina, USA). Differences in physiological parameters and biomarkers during the 7 days were analyzed by the Fisher exact test, Student's *t*-test, and one-factor analysis of variance. The analysis of significance between each day in every parameter used Scheffe's *F* test. The parameters are expressed as mean $\pm$ standard deviation. The daily values of ICP, CPP, and chemical biomarkers were compared using the mean $\pm$ standard error of the mean. The level of significance was taken as $p < 0.05$.

Results

The characteristics of the patient groups are shown in Table 1. The mean age was 74.0 ± 7.0 years in the elderly group and 42.5 ± 15.9 years in the young group ($p < 0.0001$). The numbers of ASDH and DBI patients were the same in each group. Initial GCS score, blood pressure, body temperature, arterial blood gas examinations, and blood sugar showed no significant difference between the two groups. Good outcome (good recovery and moderate disability by the Glasgow Outcome Scale) was achieved in 4 of 15 patients in the elderly group and 9 of 15 patients in the young group, without significant difference ($p = 0.0281$).

The biochemical parameters are compared in the elderly and young groups in Table 2. A total of 3,507 microdialysate samples (1,560 from the elderly group and 1,947 from the young group) were collected and analyzed. The overall mean glucose level was higher in the young group (19.0 ± 17.3 mmol/l in the young group, 15.3 ± 20.0 mmol/l in the elderly group, $p < 0.0001$). The concentrations of glycerol, which indicate the degree of cell damage, were

Table 1 Patient characteristics in the elderly and young groups

	Elderly group	Young group	p Value
No. of patients	15	15	
Sex			
male	11	12	
female	4	3	
Age (years)	74.0 ± 7.0	42.5 ± 15.9	< 0.0001
Diagnosis			
ASDH	10	10	
DBI	5	5	
Consciousness			
initial GCS score	5.9 ± 3.3	5.5 ± 2.1	0.6972
E	1.5 ± 0.9	1.0 ± 0.0	0.0583
V	1.4 ± 1.1	1.3 ± 0.5	0.8259
M	2.9 ± 1.8	3.1 ± 1.9	0.7703
Vital signs and general conditions			
initial SBP (mmHg)	154.2 ± 34.8	145.3 ± 31.5	0.4670
initial DBP (mmHg)	85.0 ± 23.6	85.1 ± 21.1	0.9871
initial heart rate (/min)	98.2 ± 16.1	83.6 ± 21.9	0.0464
initial respiratory rate (/min)	17.0 ± 8.0	19.4 ± 6.4	0.3691
initial body temperature (°C)	35.7 ± 1.1	35.6 ± 0.7	0.8561
initial pH on arterial blood gas	7.410 ± 0.061	7.370 ± 0.087	0.3461
initial PaO ₂ (mmHg)	218.5 ± 103.0	309.4 ± 189.7	0.1139
initial PaCO ₂ (mmHg)	36.5 ± 5.6	37.9 ± 8.6	0.5938
initial blood sugar (mg/dl)	196.3 ± 40.5	169.4 ± 40.0	0.0775
Outcome			
GR	1	3	
MD	3	6	
SD	1	1	
PVS	3	4	
dead	7	1	
good outcomes (GR, MD)	4	9	0.0281

ASDH: acute subdural hematoma, DBI: diffuse brain injury, DBP: diastolic blood pressure, GCS: Glasgow Coma Scale, GR: good recovery, MD: moderate disability, PVS: persistent vegetative state, SBP: systolic blood pressure, SD: severe disability.

Table 2 Comparison of biochemical parameters between the elderly and young groups

	Normal value or target value ²⁵⁾	Elderly group	Young group	p Value
Number of samples		1560	1947	
Glucose (mmol/l)	> 20	15.3 ± 20.0	19.0 ± 17.3	< 0.0001
Lactate (mmol/l)	< 2	6.7 ± 5.2	7.1 ± 6.5	0.0472
Pyruvate (mmol/l)	< 0.12	0.14 ± 0.10	0.15 ± 0.11	< 0.0001
Glycerol (μmol/l)	< 20–50	681.6 ± 755.8	445.1 ± 598.9	< 0.0001
Glutamate (μmol/l)	< 10	60.7 ± 107.4	64.3 ± 115.7	0.3415
LPR	< 15–20	115.6 ± 325.6	137.7 ± 688.0	0.2444

LPR: lactate/pyruvate ratio.

higher in the elderly group. However, the lactate/pyruvate ratio showed no significant difference between the two groups. The extracellular concentration of glucose was lower and the lactate/pyruvate ratio was higher than the normal range²⁵⁾ in

both groups.

Within the intensive care period of 7 days, the mean ICP remained in the range of < 20 mmHg (Fig. 1A), and CPP remained in the range of > 70 mmHg in both groups (Fig. 1B), showing good control wi-

Fig. 1 Time courses of extracellular concentrations of biochemical parameters comparing the daily values in the young (<65 years; squares) and elderly groups (≥65 years; circles) for 7 days after head injury. Daily values are expressed as mean ± standard error of mean. * $p < 0.05$, significant difference between elderly and young groups. CPP: cerebral perfusion pressure, ICP: intracranial pressure, LPR: lactate/pyruvate ratio.

thin the target limits of the treatment guidelines. The extracellular glucose concentration showed no significant difference between the elderly and young groups on the 1st hospital day, but was significantly lower in the elderly group than in the young group from the 2nd day until the 7th day after injury (Fig. 1C). On the other hand, the extracellular glucose concentration recovered within 7 days in the young group (Fig. 1C). The lactate/pyruvate ratio gradually increased from the 1st day and peaked on the 5th day after injury in the elderly group, but peaked on the 2nd day in the young group (Fig. 1D). The extracellular concentrations of glycerol, which indicate neural cell damage, were significantly higher in the elderly group than in the young group at 3 days after injury, and continued for the remaining period (Fig. 1E). The extracellular glutamate concentrations peaked on the 4th day in the young group, but no abrupt change was observed in the elderly group (Fig. 1F). The mean glycerol and glutamate concen-

trations gradually decreased in the young group, but significantly increased on the 7th day in the elderly group (Fig. 1E, F).

Discussion

Our results demonstrated that lower extracellular glucose concentration persisted longer in elderly patients than in young patients after suffering TBI, and higher lactate/pyruvate ratio was prolonged in the elderly group. Moreover, the extracellular glucose concentration recovered to the normal range within 7 days in the young group, but remained lower than the normal range for 7 days in the elderly group.

Lower cerebral extracellular glucose concentration may be the consequence of several mechanisms, such as impaired glucose uptake,⁴⁾ or, in combination with high lactate/pyruvate ratio, may be a marker of increased anaerobic metabolism with hypoperfusion.^{13,15)} Lower extracellular glucose concentration was associated with higher lactate/pyruvate ratio in our elderly patients, so cerebral hypoperfusion may have persisted in elderly patients with head injury longer than in younger patients.

In our study, the mean CPP was maintained within the target range recommended in the guidelines. The CPP value was higher almost throughout the treatment course in elderly patients compared to young patients. However, cerebral hypoperfusion might have occurred in elderly patients with TBI. Cerebral extracellular glucose is a good indicator of the prognosis,²⁴⁾ and levels of extracellular cerebral glucose are significantly less in patients with TBI who had poor outcome.³³⁾ These findings together suggest that persistent cerebral hypoperfusion may underlay the persistent lower glucose concentration and poor outcome in elderly patients.

What are the causes of the cerebral hypoperfusion? One of the causes of insufficiency of cerebral perfusion may be that cerebral vascular pressure autoregulation is more impaired in elderly patients than in young patients. Cerebrovascular autoregulation is said to decrease with aging, and age-related decline in cerebrovascular autoregulation is associated with a relative deterioration in outcome in elderly TBI patients.^{6,7)} Therefore, we supposed that pressure autoregulation might be impaired longer in elderly patients than in young patients, and inadequate cerebral blood flow might lead to progression of secondary brain damage, as reflected by higher extracellular concentration of glycerol.

Serum thrombomodulin and von Willebrand factor levels, which are thought to be biochemical mar-

kers reflecting injury of the cerebral vascular endothelium in TBI patients, were compared between elderly and young patient groups, and suggested that cerebral vascular endothelial injury would be more serious in elderly patients than in young patients.³⁴⁾ As in our elderly patients, such vulnerability might be one of the reasons for long-term impairment of autoregulation and subsequent persistent cerebral hypoperfusion. The level of endothelial damage was higher in elderly patients than in younger patients, so the impairment of autoregulation might persist longer in elderly patients in our study.

To prevent secondary brain injury and improve outcome, accurate estimation of pressure autoregulation and adequate cerebral perfusion might be needed, especially in elderly patients. Continuous cerebrovascular autoregulation has been measured in the neurointensive care unit as correlation coefficients between arterial blood pressure and ICP, or the transcranial Doppler systolic flow velocity and ICP.^{8,9)} The correlation between extracellular glutamate and CPP values was evaluated with the microdialysis method. Autoregulatory index, the correlation coefficient calculated by comparing glutamate concentration with CPP using Pearson's correlation, may be a good indicator for impaired or preserved autoregulation.²⁷⁾ These techniques or equipments especially might be needed in the treatment of elderly TBI patients, and the efficacy of autoregulation-oriented intensive care should be analyzed in elderly patients with head injury.

Other factors may be related to decreasing extracellular glucose concentrations and increasing lactate/pyruvate ratio with mitochondrial damage in elderly patients. Deterioration of mitochondrial function has been proposed as a contributor to the aging process^{19,23,30,32)} and has been well characterized in pathological conditions.¹²⁾ Age-related mitochondrial dysfunction also occurs in traumatic brain-injured patients.^{1,2,11,28)} Age-related oxidative mitochondrial damage could accumulate in proteins responsible for importing substrates inside the mitochondria, affecting the enzymes need to start the tricarboxylic acid cycle, such as pyruvate dehydrogenase.¹⁷⁾ Such mitochondrial dysfunction might impair glucose transporting mechanisms and aerobic metabolism, and also extracellular glucose concentration and lactate/pyruvate ratio might be affected as in our study. Lower glucose concentration might occur as one of the features of persistent cerebral vulnerability in elderly TBI patients. Therefore, we should prevent progression of secondary brain injury in neurointensive care. Hypotension and hypoxia should be avoided with delicate intensive treatment, especially in elderly TBI patients.

In our study, there are some limitations about the technical factors. First, the biochemical measurement with microdialysis was restricted to only regional areas of the brain, and additional global cerebral monitoring (SjO₂, etc.) might be helpful for accurate cerebral perfusion and metabolism. Second, two types of injury (ASDH and DBI) were present in each group. The ratio of injury type was the same, but the mechanism might be different between ASDH and DBI.²⁰⁾ More TBI cases should be analyzed with microdialysis in future investigations.

The main findings of this study are that the extracellular glucose concentration is lower in elderly patients than young patients with TBI and is associated with elevation of lactate/pyruvate ratio, which indicates progression of secondary brain injury, and with poor outcome in elderly TBI patients. Moreover, lower extracellular glucose persisted for 7 days after injury, and for longer in elderly patients than in young patients. Persistent low extracellular glucose level, associated with increasing lactate/pyruvate ratio and glutamate and glycerol levels, is considered to prolong secondary brain injury. We conclude that neural vulnerability persists for longer in elderly patients than in young patients with TBI, and we should consider these factors to prevent the occurrence of additional secondary injury.

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