Relation between extracellular Chemistry and Patient Outcome for Severe Traumatic Brain Injury within the First 24 hours: A Microdialysis Study

Yutaka Igarashi[1]   Shoji Yokobori[1]   Hidetaka Onda[1]   Tomohiko Masuno[1]   Hiroyuki Yokota[1]

[1]Department of Emergency and Critical Care Medicine,
 Nippon Medical School, Bunkyo-ku, Tokyo, Japan

Address for correspondence Yutaka Igarashi, MD, PhD,
Department of Emergency and Critical Care Medicine,
Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603,
Japan (e-mail: igarashiy@nms.ac.jp).

Abstract

Object   Many studies have reported that extracellular chemistry is related to the outcome of patients with traumatic brain injury (TBI). No study has reported that extracellular chemistry predicts outcome in less than 3 days. Moreover, in other studies, both focal brain and diffuse brain injuries have been often discussed. The authors focused on the relationship between extracellular chemistry in a shorter period and the outcome of patients with focal brain injury.

Methods   By using intracerebral microdialysis monitoring, extracellular fluid concentrations of glucose, lactate, glycerol, glutamate, lactate/pyruvate (L/P), and lactate/glucose (L/G) were determined in 30 patients with severe TBI for initial 24 hours. The results were analyzed between favorable and unfavorable, and between survival and mortality.

Results   The medians of glycerol and L/P in the favorable group were significantly lower than those in the unfavorable group (124 µmol/L vs. 808 µmol/L, $p = 0.002$; 31 vs. 48, $p = 0.021$, respectively). All parameters apart from glutamate differed significantly between the survival and mortality groups (glucose, 25 mmol/L vs. 77 mmol/L, $p = 0.035$; lactate, 38 mmol/L vs. 73 mmol/L, $p = 0.018$; glycerol, 168 µmol/L vs. 1462 µmol/L, $p = 0.002$; glutamate, 14 µmol/L vs. 95 µmol/L, $p = 0.019$; L/P, 32 vs. 124, $p < 0.001$; L/G, 1.46 vs. 4.52, $p = 0.004$).

Conclusion   Cerebral extracellular glycerol and L/P was the most reliable predictor of outcomes in patients with focal brain injury and can discriminate between favorable and unfavorable outcomes for the first 24 hours, using the threshold of 200 and 40, respectively.

Keywords
► microdialysis
► traumatic brain injury
► cerebral extracellular chemistry
► lactate/pyruvate
► glycerol

Introduction

Traumatic brain injury (TBI) is a major cause of mortality, morbidity, and long-term disability worldwide. In Japan, TBI is a leading cause of accidental death, but the outcome of patients with TBI has improved recently. Although the death rate from severe TBI decreased from 54 to 43% in Japan from 1998 to 2004 according to the Japan Neurotrauma Data Bank, TBI is still associated with high mortality and morbidity.

The outcome of severe TBI is related to the initial Glasgow coma scale (GCS) score (especially the GCS motor score), computed tomographic (CT) abnormalities, pupillary function, age, associated injuries and complications, hypotension, and hypoxemia.[1-4] The outcome is also influenced by secondary brain injury, which is usually considered as a cascade of molecular injury mechanisms. These mechanisms include neurotransmitter-mediated excitotoxicity induced by glutamate, free-radical injury to cell membranes, electrolyte imbalances, mitochondrial dysfunction, inflammatory responses, apoptosis, and secondary ischemia.[5-10] These lead to cerebral edema and increased intracranial pressure (ICP), which exacerbate the brain injury. ICP, cerebral perfusion

pressure, brain tissue oxygen, cerebral autoregulation, and extracellular chemistry are thought to be indices for detecting secondary brain injury. ICP is usually used in neurointensive care, but its increase is associated with secondary brain injury.

Persson and Hillered performed the first microdialysis study on the human brain after TBI.[11] It is recognized that extracellular metabolic markers can be used to detect secondary brain injury earlier and predict outcomes more accurately than ICP. Using extracellular markers, many studies have reported that extracellular chemistry is related to the outcome of patients with TBI. In these studies, samples were usually collected and analyzed for 7 days, or at least for 3 days. No study has reported that extracellular chemistry predicts outcome in < 3 days. Moreover, in other studies, both focal brain and diffuse brain injuries have been often discussed, although they are thought to involve different pathophysiology. There is still little information about the relationship between extracellular chemistry in a shorter period and the outcome of patients with focal brain injury.

Materials and Methods

Patient Enrollment

Ethical approval for the study was granted by the Ethical Committee of Nippon Medical School Hospital. This study involved 30 patients with severe TBI associated with focal brain injury who were admitted to the department from 2009 to 2011. Focal brain injury was defined as acute subdural hematoma, acute epidural hematoma, and cerebral contusion without diffuse brain injury. All patients underwent surgery, including hematoma removal and/or decompressive craniectomy. Informed consent was obtained from all patients or their family as alternated to enroll this study.

Surgical Management and Neurointensive Care

The initial management and operative procedures of these patients were performed in line with the protocols described in the Japanese guidelines for the treatment and management of severe TBI, second edition,[12] and the guidelines for the management of severe TBI, third edition.[13] The patients remained in the intensive care unit (ICU) for 7 days after surgery, in accordance with the above protocols.

Microdialysis

Microdialysis procedures were performed with reference to Bellander's consensus as follows[14]: After surgical hematoma removal, a microdialysis probe (CMA70; CMA Microdialysis, Stockholm, Sweden), with a 10-mm membrane and 20,000-Da-molecular weight cutoff, was inserted into the white matter to a depth of 1 to 2 cm from the brain surface from which the hematoma had been removed. A CMA103 perfusion pump (CMA Microdialysis) was connected in the operating theater, and normal saline was perfused through the catheter at a rate of 0.3 µL/min; the microdialysate was collected and frozen in 60-minute samples for the initial 168 hours (7 days) after admission to the ICU. The initial 60-minute sample was not used for analysis because this was

the time allowed for stabilization of the probe. 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, lactate, pyruvate, glycerol, and glutamate were measured, and lactate/pyruvate (L/P) and lactate/glucose (L/G) were also calculated in all samples.

Outcome

The outcome was evaluated using the Glasgow outcome scale when the patients were discharged or transferred to other hospitals. A favorable outcome was defined as good recovery (GR) or moderate disability (MD) and an unfavorable outcome was defined as severe disability (SD), persistent vegetative state (PVS), or death (D). The outcome was also evaluated as survival or mortality.

Statistical Analysis

Values are presented as median, the first quartile, and the third quartile because the data did not show a normal distribution and had some extreme outliers. Data were analyzed by Mann-Whitney's U test. Statistical analyses were performed with StatFlex version 6.0 (Artech Co., Ltd.). $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Of the 30 patients included in this study, 22 (73.3%) were male and 8 (26.7%) were female. The median (interquartile range) age of the patients was 68 (46–77) years. From the initial postresuscitation use of the GCS, the median score was 7 (3.8–7); E 1 (1–2), V 1 (1–1.3), and M 4 (1–5). Based on the initial CT scan appearance, 21 (70.0%) patients had acute subdural hematoma, 4 (13.3%) had acute epidural hematoma, and 5 (16.7%) had cerebral contusion. Total 12 (40.0%) patients were treated with hypothermia. At discharge, 10 (33.3%) patients had a favorable outcome (GR, 5 patients; MD, 5 patients) and 20 (66.7%) had an unfavorable one (SD, 4 patients; PVS, 8 patients; D, 8 patients).

A comparison of patient characteristics is presented in ►Table 1. Age, sex, initial GCS score, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature were similar between the favorable and unfavorable groups and the survival and mortality groups. The rate of patients with acute epidural hematoma was higher in the favorable outcome group than in the unfavorable outcome group. The rate of patients with acute subdural hematoma was higher in the survival group than in the mortality group. The rate of patients with therapeutic hypothermia did not differ significantly between the groups.

The extracellular chemistries were also compared between the favorable and unfavorable groups (►Table 2). The medians of glycerol and L/P in the favorable group were significantly lower than those in the unfavorable group (124 µmol/L vs. 808 µmol/L, $p = 0.002$; 31 vs. 48, $p = 0.021$, respectively). The median of glucose in the favorable group

Table 1 Comparison of patient characteristics between favorable and unfavorable groups and between survival and mortality groups

	Favorable (n = 10)	Unfavorable (n = 20)	p Value	Survival (n = 22)	Mortality (n = 8)	p Value
Age	57 (29–77)	73 (55–77)	0.159	64 (44–76)	75 (56–79)	0.372
Sex (M/F)	9/1	13/7	0.210	5/3	17/5	0.643
GCS	7 (3–7)	6 (3.3–7.8)	0.759	7 (4–8)	4 (3–5.8)	0.053
E	1 (1–1)	1 (1–2.8)	0.180	1 (1–3)	1 (1–1)	0.285
V	1 (1–2)	1 (1–1)	0.560	1 (1–2)	1 (1–1)	0.095
M	4.5 (1–5)	3 (1–4)	0.266	4 (1–5)	2 (1–3.5)	0.156
Systolic BP (mm Hg)	147 (139–167)	171 (130–188)	0.991	164 (140–181)	145 (119–180)	0.709
Diastolic BP (mm Hg)	83 (82–93)	88 (65–99)	0.799	88 (81–99)	65 (54–81)	0.103
HR (beats/min)	78 (68–96)	100 (84–108)	0.066	87 (75–104)	97 (88–109)	0.277
RR (breaths/min)	20 (10–24)	19 (17–24)	0.755	19 (13–24)	19 (18–24)	0.454
BT (°C)	35.2 (34.8–36.0)	35.7 (35.1–36.1)	0.364	35.5 (35.1–36.3)	35.3 (34.7–36.0)	0.540
Diagnosis						
ASDH	13	8	0.675	13	8	**0.031**[a]
AEDH	4	0	**0.008**[a]	4	0	0.195
CC	3	2	0.300	5	0	0.140
Therapeutic hypothermia	4	8	1.000	8	4	0.678

Abbreviations: AEDH, acute epidural hematoma; ASDH, acute subdural hematoma; BP, blood pressure; BT, blood temperature; CC, cerebral contusion; F, female; GCS, Glasgow coma scale; HR, heart rate; M, male; RR, respiratory rate.
[a]Significant differences ($p < 0.05$) in bold type.

Table 2 Median (interquartile range) values of monitored parameters with respective statistical significances for each group

	Favorable (n = 10)	Unfavorable (n = 20)	p Value	Survival (n = 22)	Mortality (n = 8)	p Value
Glucose (mmol/L)	30 (20–39)	20 (16–27)	0.090	25 (19–36)	77 (63–106)	**0.035**[a]
Lactate (mmol/L)	38 (19.5–62)	63 (31.8–93.5)	0.129	38 (20–64)	73 (63–106)	**0.018**[a]
Pyruvate (µmol/L)	1.5 (1.0–2.0)	1.0 (1–1.2)	0.178	1.0 (1.0–2.0)	1.0 (0.2–1.2)	0.077
Glycerol (µmol/:)	124 (90–171)	808 (426.3–1549)	**0.002**[a]	168 (117–741)	1,462 (808–1930)	**0.002**[a]
Glutamate (µmol/L)	11 (9.5–31.5)	22.5 (7.3–94.3)	0.355	14 (7–32)	95 (32–296)	**0.019**[a]
L/P	31 (25–35)	48 (33–77)	**0.021**[a]	32 (26–39)	124 (51–225)	**< 0.001**[a]
L/G	1.20 (0.60–2.40)	2.80 (1.40–6.80)	0.071	1.46 (0.66–3.00)	4.52 (2.76–11.99)	**0.004**[a]

Abbreviations: L/G, lactate/glucose; L/P, lactate/pyruvate.
[a]Significant differences ($p < 0.05$) in bold type.

was not significantly higher than that in the unfavorable group; however, it showed a tendency to be higher. Moreover, the median of L/G in the favorable group tended to be lower than that in the unfavorable group, although the difference was not significant (►**Fig. 1**). The extracellular chemistries were also compared between the survival and dead groups. All parameters apart from pyruvate differed significantly between the survival and mortality groups (glucose, 25 mmol/L vs. 77 mmol/L, $p = 0.035$; lactate, 38 mmol/L vs. 73 mmol/L, $p = 0.018$; glycerol, 168 µmol/L vs. 1,462 µmol/L, $p = 0.002$; glutamate, 14 µmol/L vs. 95 µmol/L, $p = 0.019$; L/P, 32 vs. 124, $p < 0.001$; L/G, 1.46 vs. 4.52, $p = 0.004$).

Discussion

This study revealed that extracellular glycerol and L/P in the first 24 hours were independently associated with a favorable outcome following TBI. It also revealed that extracellular glucose, lactate, glycerol, glutamate, L/P, and L/G for the first 24 hours were independently associated with survival.

Glycerol, an end product of phospholipid degradation, can be used as a marker of membrane disintegration. For example, an eightfold increase in extracellular glycerol concentration 20 minutes after brain injury was identified in an animal experiment.[15] In patients with subarachnoid hemorrhage and
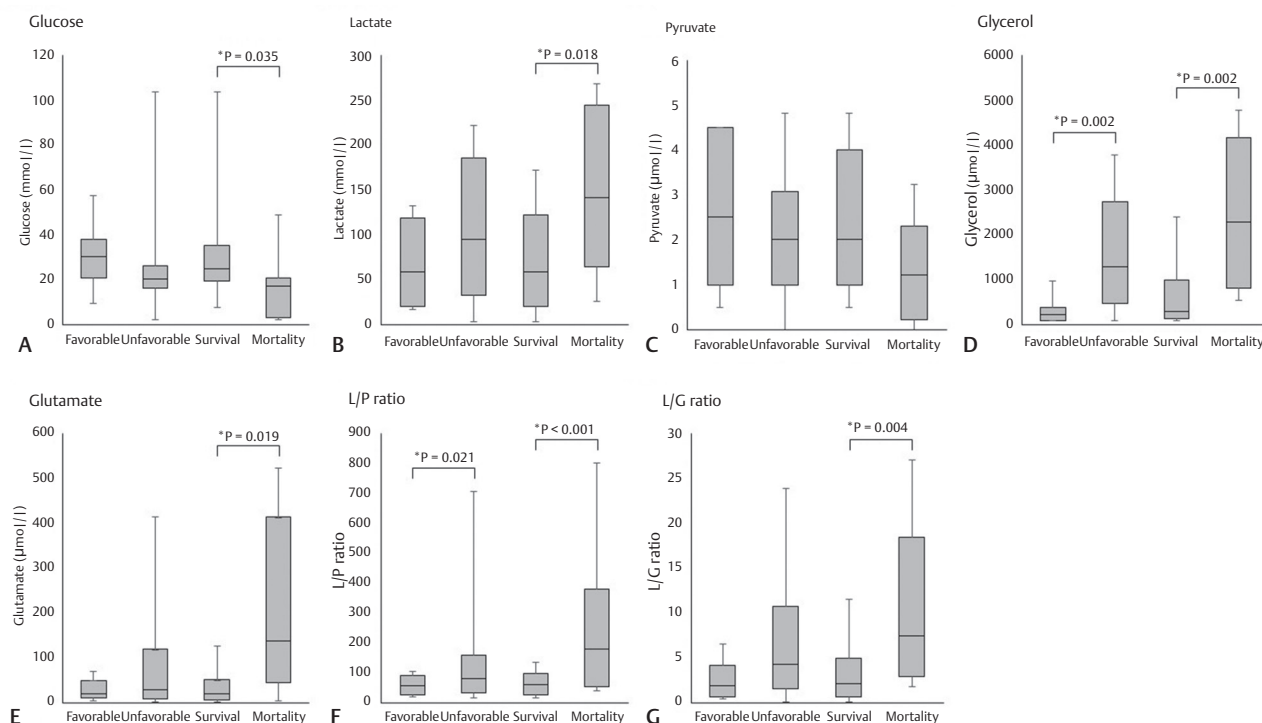
Fig. 1 Comparison of extracellular chemistry between favorable and unfavorable groups and between survival and mortality groups. The median is marked by a horizontal line inside the box. The ends of the box are the upper and lower quartiles. Whiskers indicate maximum and minimum values. Graphs show concentrations of glucose (mmol/L) (**A**), lactate (mmol/L) (**B**), pyruvate (μmol/L) (**C**), glycerol (μmol/L) (**D**), glutamate (μmol/L) (**E**), L/P ratio (**F**), and L/G ratio (**G**).

TBI, a correlation between the occurrence of ischemic events and an increase in cerebral extracellular glycerol concentration has been documented.[16-21] Extracellular glycerol was significantly lower in the favorable group than in the unfavorable group and was also significantly lower in the survival group than in the mortality group. Therefore, extracellular glycerol was the most reliable marker to predict outcome in this study (►**Fig. 1**). When the cutoff value of extracellular glycerol was set to 200, sensitivity and specificity were 0.80 and 0.90, respectively, in predicting a favorable outcome (area under the curve [AUC] 0.85) and 1.00 and 0.59, respectively, in predicting survival (AUC 0.88). In Japan, however, intravenous glycerol is used as an osmotic agent to decrease ICP, and patients with high ICP tend to be administered a lot of glycerol. It is difficult to determine whether glycerol would be a good predictor from the effect of intravenous glycerol.

Glucose plays an important role in brain metabolism. Under normal circumstances, 95% of the energy requirements of the brain are met by the aerobic conversion of glucose. Persistently low extracellular glucose levels correlate with a poor outcome after TBI in humans.[22] In this study, extracellular glucose levels were higher in the patients in the survival group than in those in the mortality group. All patients, except one whose extracellular glucose level was < 20 mg/dL, died. An extracellular glucose level of > 20 mg/dL is thus necessary for survival. Yokobori et al reported that lower extracellular glucose levels prolonged survival in elderly patients with TBI.[23] Hypoglycemia requires attention because extracellular glucose levels are susceptible to the effects of serum glucose levels. Glucose is degraded to pyruvate in the glycolytic pathway. Aerobic reactions use pyruvate to produce ATP, and the anaerobic pathway produces lactate. Thus, pyruvate and lactate, as well as glucose, would be good markers of cerebral metabolism.

Lactate was thought to be a dead-end metabolic product in the anaerobic pathway, but recent studies have demonstrated that it is taken up by astrocytes for oxidative degradation, which is referred to as the astrocyte-neuron lactate shuttle hypothesis.[24] Many studies have also described the elevation in extracellular lactate levels in patients with head injury.[25] In the microdialysis rat fluid percussion model, extracellular glucose levels decreased and dialysate lactate increased 10 minutes after injury induction.[26] Other studies have reported that a high extracellular lactate level is correlated with a poor prognosis in trauma patients.[27] However, lactate alone may not be a consistent marker of ischemia compared with L/P.[28,29] L/P is a marker of changes in the redox state of cells. The largest study on extracellular metabolic markers following TBI suggested that L/P is the most consistent predictor.[29,30] A ratio of < 20 reflects no metabolic complications, whereas that of > 25 is an early warning of metabolic crisis and energy failure.[31,32] In this study, mean L/P in patients with favorable outcome was 31 for the initial 24 hours after admission to the ICU. L/P in was significantly lower in the favorable group than in the unfavorable group and was also significantly lower in the survival group than in the mortality group. When the cutoff value of L/P was set to 40, sensitivity and specificity were 0.60 and 0.90, respectively, in predicting favorable outcomes (AUC 0.76) and 1.00 and 0.77, respectively, in

predicting survival (AUC 0.93). L/P in patients with a favorable outcome did not exceed 40 for 10 hours, and if L/P exceeded 40, additional treatment was administered to obtain a favorable prognosis (►**Fig. 2**). All patients with L/P > 100 at 24 hours died; however, some patients whose L/P decreased < 100 after remaining > 100 for a couple of hours after surgery escaped death (►**Fig. 3**). If L/P exceeds 100, additional treatment should be considered to avoid death.
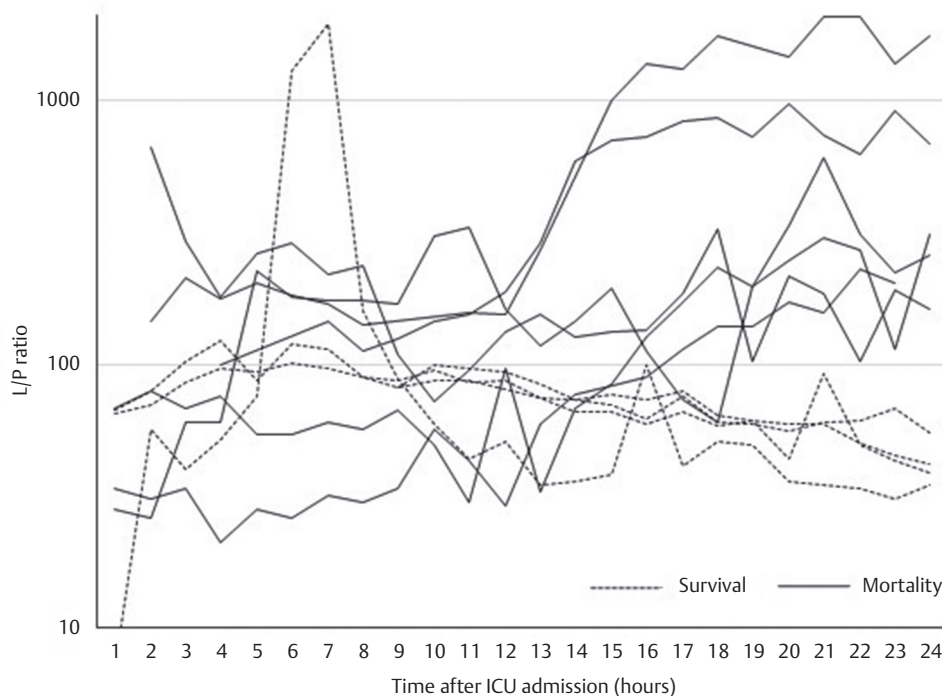

Fig. 2 Time course of lactate/pyruvate (L/P) in the patients with L/P > 100. At 24 hours, all patients with L/P > 100 died. Patients whose L/P decreased < 100 after remaining > 100 for the first couple of hours escaped death. ICU, intensive care unit.
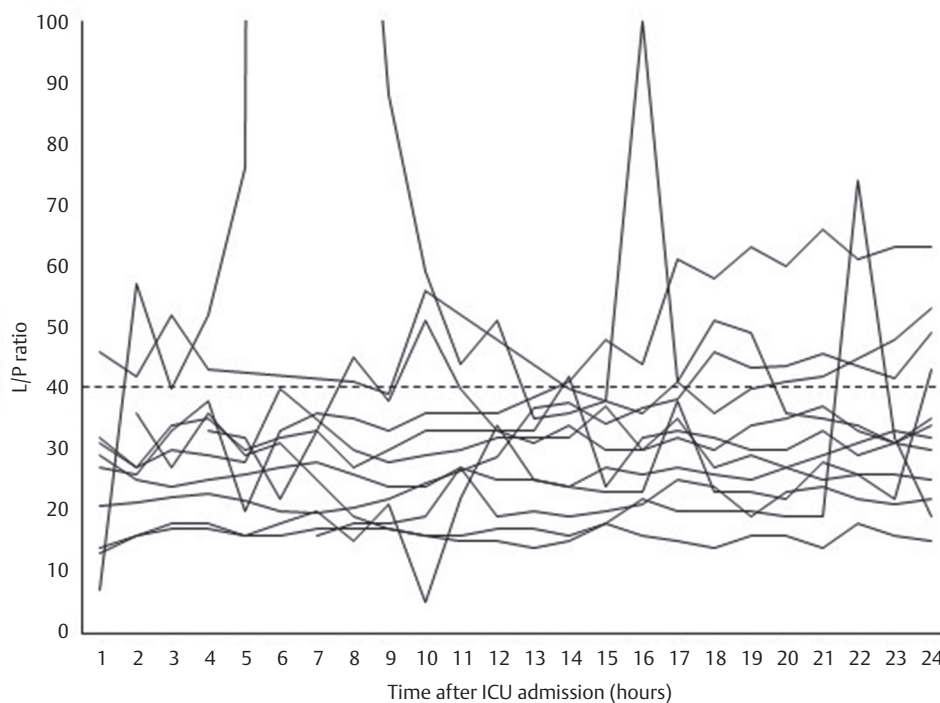

Fig. 3 Time course of lactate/pyruvate (L/P) in the patients with a favorable outcome. Mean L/P in patients with a favorable outcome was 31 for the initial 24 hours after admission to an intensive care unit. L/P in patients with a favorable outcome did not exceed 40 for 10 hours. ICU, intensive care unit.

Glutamate may open neuronal calcium channels, initiating a pathological influx of calcium, and thus provoking cell damage. Bullock et al found that sustained high ICP and poor outcome were significantly correlated with high levels of glutamate.[33] Extracellular glutamate levels differed significantly between the survival and mortality groups in this study.

Because these factors of extracellular chemistry are affected within a few hours of injury, extracellular chemistry can predict patient outcome for severe TBI within the first 24 hours. Extracellular chemistry variables can be measured every hour at the bedside, and these values and trends are expected to become indications of additional treatment.

This study had certain limitations. It was designed as a single-institution observational study; thus, a larger sample size is required to confirm the statistical significance of the results. If patient exacerbation, such as delayed cerebral vasospasm, occurs after 24 hours and there are multiple injuries and complications, it is difficult to predict outcomes. However, if extracellular chemistry variables are monitored every hour, chemical changes can be detected before exacerbation. Because this study did not include patients with diffuse brain injury, it was not revealed whether extracellular chemistry can predict outcomes of such patients within 24 hours and whether the cutoff values as same as those used in patients with focal brain injury can be used.

Conclusion

Cerebral extracellular glycerol and L/P were the most reliable predictors of outcomes in patients with focal brain injury and can discriminate between favorable and unfavorable outcomes in the first 24 hours. In addition, all parameters, except pyruvate, differed significantly between the survival and mortality groups.

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