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Organ dysfunction assessment score for severe head injury patients during brain hypothermia

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Summary

The purpose of this study was to evaluate the utility of a novel organ dysfunction assessment score developed for patients with severe traumatic brain injury during therapeutic brain hypothermia.

The Brain Hypothermia Organ Dysfunction Assessment (BHODA) score is calculated through the combined assessment of 6 indices: central nervous system (CNS) function, respiratory function, cardiovascular function, hepatosplanchnic circulation, coagulation, and metabolism. The CNS, hepatosplanchnic circulation, and metabolic indices were based on measurements of cerebral perfusion pressure, gastric tonometry, and blood glucose, respectively. Thirty-nine patients with severe closed head injuries (scores of 3 to 8 on the Glasgow Coma Scale) were enrolled. Seven patients (18%) died during hospitalization. Outcome was favorable in 20 patients and unfavorable in 19. The BHODA score proved useful in describing sequences of complications during therapeutic brain hypothermia. A total maximum BHODA score of more than 13 points corresponded to a mortality of 70%. In a multivariate model, the total maximum BHODA score was independently associated with neurological outcome (odds ratio for unfavorable neurological outcome, 2.590; 95% confidence interval, 1.260, 5.327). In conclusion, the BHODA score can help assess multiple organ dysfunction/failure during therapeutic hypothermia and may be useful for predicting outcome.

Keywords: Traumatic brain injury; hypothermia; organ dysfunction syndrome; subdural hematoma.

Introduction

Growing evidence suggests that therapeutic brain hypothermia (THT) confers neuroprotective effects in subgroups of patients with neurological damage. Yet THT remains controversial as a strategy for severe traumatic brain injury (TBI), in part because of its many side effects during the cooling phase. The systemic organ function of TBI patients and the pathophysiological response to hypothermia are important to recognize and evaluate. The Sequential Organ Failure Assessment (SOFA) score is useful for assessing organ dysfunction and failure over time, as well as predicting outcome in critically ill patients. When TBI patients undergo THT, however, the SOFA score has only limited usefulness in evaluating cardiovascular response and central nervous system (CNS) due to sedation. As an alternative, we developed a novel organ dysfunction assessment score suitable for TBI patients undergoing THT. The purpose of this study was to evaluate the utility of this score.

Material and methods

Severe TBI patients with a Glasgow Coma Score (GCS) ≤ 8 on admission and suffering from acute subdural hematoma with cerebral contusion were enrolled in our study between January 1996 and December 2000. All patients underwent THT immediately after surgery, as previous described [6, 7]. The target brain temperature was 33 to 34 °C maintained for 48 to 72 hours. Basic treatment included sedation with midazolam (1–3 μg/kg/min), analgesic with buprenorphine (1–2 μg/kg/min), and muscle relaxant. PaCO2 concentrations were maintained at 35 to 40 mmHg and PaO2 levels were maintained above 100 mmHg. A ventricular pressure monitoring probe (Camino, Integra Neurosciences, Plainsboro, NJ) was inserted to measure ICP and ventricular temperature in each patient. Mean arterial pressure was kept above 90 mmHg and the ICP was kept below 20 mmHg. No patient underwent combined barbiturate coma therapy or active hyperventilation. Insulin generally was not administered in patients with glucose levels of less than 200 mg/dl. After THT, the patients were gradually rewarmed at a rate of 1 °C per day.

The BHODA score (Table 1) was calculated on admission and once for every 24-hour period until discharge. The worst value for each parameter was used to calculate the score for each 24-hour period. The total maximum BHODA score was calculated by summing the worst scores for each of the components. Neurological outcome was assessed at hospital discharge by the Glasgow Outcome Scale, and was dichotomized into favorable outcome (good recovery or mild disability) or unfavorable outcome (severe disability, vegetative state, or death).

Table 1. *Brain Hypothermia Organ Dysfunction Assessment (BHODA) score*

Variables	BHODA score				
	0	1	2	3	4
CNS					
– CPP (mmHg)	>70	≤70	≤65	≤60	≤55
Respiratory					
– PaO2/FiO2 (mmHg)	>400	≤400	≤300	≤200	≤100
Cardiovascular					
– PAR	7–10	10.1–15.0 or <7	≤20	≤30	30<
Hepatosplanchnic					
– CO2 gap (mmHg)	<10	≤15	≤20	≤25	25<
Coagulation					
– Platelet ($\times 10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Metabolism					
– Blood glucose (g/dl)	<170	170≤	200≤	230≤	260≤

CNS Central nervous system; *CPP* cerebral perfusion pressure; *PAR* pressure-adjusted heart rate defined as the product of the heart rate multiplied by the ratio of the right atrial (central venous) pressure to the mean arterial pressure. CO2 gap was defined as the difference between gastric mucosal PCO2 and arterial PCO2.

Analyses of continuous, normally-distributed variables within and between groups were undertaken using the appropriate Student *t*-test. Non-normally distributed continuous variables were analyzed using the Mann-Whitney *U*-test. Categorical variables were analyzed using Fisher exact test. A p value of <0.05 was considered significant. The results are presented as mean $\pm$ SD, except where otherwise indicated.

Results

Overall outcome

This study investigated a population of 39 patients with a mean age of 50.4 $\pm$ 15.4 years (range: 18 to 72 years). The post-resuscitation GCS of non-survivors (GCS 4) was significantly lower than that of survivors (GCS 6) ($p = 0.0009$). Seven patients (18%) died during hospitalization.

Organ dysfunction/failure during THT

The BHODA scores were analyzed at 4 time points for each index to identify significant differences: at the beginning of cooling, during the cooling phase, during the rewarming phase, and at the end point of THT. Scores for the respiratory system, hepatosplanchnic circulation, coagulation system, and metabolic system were significantly higher in non-survivors at all points. The score for the CNS was also significantly higher in non-survivors, but only at 3 time points (cooling phase, rewarming phase, and end point of THT).

Table 2. *Hospital mortality and neurological outcome by quartile of the total maximum BHODA score*

Total maximum BHODA score	0–6	7–8	9–12	13–24
Survivors, n (%)	6 (100)	14 (100)	9 (100)	3 (30)
Nonsurvivors, n (%)	0 (0)	0 (0)	0 (0)	7 (70)
Favorable, n (%)	3 (50)	14 (100)	3 (33)	0 (0)
Unfavorable, n (%)	3 (50)	0 (0)	6 (67)	10 (100)

$p < 0.0001$ for the difference between survivors and non-survivors; $p = 0.0002$ for the difference between patients with favorable and unfavorable outcome.

Hospital mortality and neurological outcome

Hospital mortality and neurological outcome by quartile of the total maximum BHODA score are shown in Table 2. The quartile of patients with the highest score had a hospital mortality of 70%, while the quartile of patients with the lowest scores had a hospital mortality of 0%. All of the patients in the quartile with the highest total maximum BHODA score had an unfavorable outcome. A multivariate model was created to assess the independent association of multiple organ dysfunction/failure and neurological outcome. After controlling for age, post-resuscitation GCS, and the BHODA score at the cooling phase, the neurological outcome was independently associated with the degree of multiple organ dysfunction/failure (odds ratio for unfavorable neurological outcome, 2.590; 95% C.I., 1.260, 5.327 for maximum BHODA score).

Discussion

Non-neurological organ dysfunction is common in patients with severe TBI and is independently associated with worse outcome. Respiratory and/or cardiovascular failure are more frequent in severe TBI than failures in other organs. Zygun [17] suggested that the potential mechanisms of organ dysfunction in severe TBI may be divided into neurogenic causes and complications from therapies. The primary etiological theory singles out catecholamine release as the neurogenic cause of myocardial dysfunction and pulmonary edema. According to a report by Dujardin *et al.* [2], 41% of TBI patients showed echocardiographic evidence of myocardial dysfunction after brain death.

Pulmonary edema fluid analysis indicated that both hydrostatic edema and permeability edema might be present in patients with neurogenic pulmonary edema [11]. Pulmonary constriction due to catecholamine surge increases capillary pressure and hydrostatic edema, thereby disrupting the basement membrane and ultimately producing permeability edema.

Barbiturate coma therapy is one of the main ICP-oriented therapies. The use of barbiturates has been associated with an increased incidence of pneumonia. Thiopental inhibits tumor necrosis factor and alpha-induced activation of nuclear factor kappaB by suppressing kappaB kinase activity [8]. It should be noted that cerebral perfusion pressure (CPP)-oriented therapies administered to optimize cerebral blood flow may be linked with an increased occurrence of respiratory failure. Robertson *et al*. [10] reported a five-fold increase in the occurrence of acute respiratory distress syndrome in a group managed with a higher CPP protocol (70 mmHg vs. 50 mmHg). The updated CPP guidelines from the Brain Trauma Foundation and the American Association of Neurological Surgeons recommend the following: ''CPP should be maintained at a minimum of 60 mmHg. In the absence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors should be avoided because of the risk of acute respiratory distress syndrome.''

The following concepts prompted the development of the SOFA score and formed its basis: 1) Organ dysfunction/failure is a process rather than an event. As such, it should be seen as a continuum rather than a condition which is simply ''present'' or ''absent''; 2) The evaluation of organ dysfunction/failure should be based on a limited number of simple yet objective variables which can be easily and routinely measured in every institution [16]. The SOFA score can help quantify the degree of organ dysfunction/failure and is useful to predict outcome in critically ill patients [3]. The score has only limited usefulness in evaluating systemic organ dysfunction during THT, however. When severe TBI patients undergo THT, the concomitant treatment with sedatives, analgesics, muscle relaxants, and other medications generally makes it impossible to evaluate CNS function by the SOFA score. As an alternative, we created a novel organ dysfunction assessment score specialized in THT.

The BHODA score is a set of indices covering 6 physiological functions: CNS function, respiratory function, cardiovascular function, hepatosplanchnic circulation, coagulation, and metabolism. The CNS function, hepatosplanchnic circulation, and metabolic indices are based on measurements of CPP, gastric tonometry, and blood glucose, respectively. The inability of patients to respond to stimulation under THT makes the GCS inappropriate as an index of CNS function. Accordingly, the BHODA score uses CPP as the CNS index. Hypothermia is initially associated with sinus tachycardia and the subsequent development of bradycardia. The index of cardiovascular function in the BHODA score is based on the pressure-adjusted heart rate (PAR), defined as the product of the heart rate multiplied by the ratio of the right atrial (central venous) pressure to the mean arterial pressure. Hypothermia may decrease peripheral blood flow because of vasoconstriction, thereby decreasing the transfer of heat from the core to the periphery. In this case, it is difficult to maintain the target temperature by a water blanket. Dobutamine, an agent proven effective in controlling body temperature without inducing hypotension, can be used to increase the peripheral blood flow and improve heat conduction when administered concomitantly with fluid replacement therapy. For these reasons, PAR was selected as the index of cardiovascular function. PAR is also used as an index of cardiovascular function in the Multiple Organ Dysfunction (MOD) score [9]. Application of PAR in the BHODA score differs slightly, however, as 1 point is added when the PAR is calculated at less than 7 points.

Kinoshita *et al*. [6] showed that patients run the risk of impairing hemodynamics during THT. Systemic vasoconstriction under hypothermia may obscure the hypovolemic condition and hypoperfusion. At the point of oxygen metabolism, ''masked hypoperfusion'' can increase oxygen debt. Lactate concentration usually increases under hypothermia due to the fat and glucose metabolic alteration. This makes it difficult to estimate the oxygen debt by monitoring the lactate concentration alone. The pulmonary artery catheter is invasive and carries a risk of complications and higher cost. Gastric tonometry is a novel method used for indirect evaluation of regional blood flow within the splanchnic vascular bed. The measurement of the PCO2 gap (the difference between gastric mucosal PCO2 and arterial PCO2) may make it possible to accurately evaluate oxygen demand/supply status at the level of microcirculation [4]. Tonometric measurement by the air-gas method is likely to be reliable at around 34 °C [1]. The BHODA score also incorporates the

hepatosplanchnic circulation calculated by PCO2 gap, as the tissue oxygen debt has been established as a common pathophysiological process leading to multiple organ failure. Venkatesh *et al.* [15] suggested that TBI patients developed splanchnic ischemia. A prospective randomized study by Van den Berghe *et al.* [13] recently identified a reduced mortality in critically ill patients under aggressive control of blood glucose levels (target < 110 mg/dl). Van den Berghe's group also reported that intensive insulin therapy reduces mean and maximal ICP in patients with isolated brain injury [14]. Kinoshita *et al.* [5] found that posttraumatic hyperglycemia in acute phase aggravates histopathological outcome and increases the accumulation of polymorphonuclear leukocytes. Patients with unfavorable outcome in our study had higher blood glucose concentrations than the patients with favorable outcome. Hypothermia decreases insulin sensitivity and insulin secretion, thereby facilitating the development of hyperglycemia. Hypothermia may modulate the physiological role of insulin in the regulation of target cell metabolism [12]. It remains unknown whether THT combined with intensive insulin therapy actually improves neurological outcome.

We developed the BHODA score by closely monitoring clinical experience in the management of complications during THT, and evaluated its utility in a small population of patients. The total maximum BHODA score in this multivariable logistic regression model may contribute to the prediction of hospital mortality, assuming that all other factors are held constant. Further clinical prospective studies will be required to clarify the utility of the BHODA score.

Conclusion

Our study shows that the BHODA score may be useful for assessing the evolution of organ failure over time in patients with TBI. The progress of multiple organ dysfunction/failure in this patient population was associated with worse outcome independent of age and post-resuscitation GCS.

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