대한중환자의학회지 : 제 23 권 제 1 호
Vol. 23, No. 1, June, 2008

■원 저■

Hormonal Changes of the Brain-Dead Organ Donors: A 3-Year Experience

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Background: Success of transplantation is critically dependent upon the quality of the donor organ and optimal management. Recently, hormonal replacement therapy has been reported to result in rapid recovery of cardiac function and enable significantly more organs to be transplanted, while some other studies show conflicting results. The aim of this study is to comprehensively evaluate changes in basal circulating hormonal levels of the brain-dead organ donors.

Methods: We reviewed the records of all brain-dead patients between January, 2004, and June, 2007. Hemodynamic variables, plasma hormone levels were recorded at following time points: admission to the ICU (T1, baseline), 30 minutes (min) after first apnea test (T2), 30 min after second apnea test (T3), before operation for harvesting (T4). Hormonal measurements included cortisol, adrenocorticotrophic hormone, triiodothyronine (T_3), thyroxine, free thyroxine, thyroid-stimulating hormone, growth hormone, and testosterone.

Results: Nineteen patients were included in this study. Comparisons of hemodynamic parameters and hormonal levels to baseline values revealed no significant changes throughout the study period. When the patients were divided into 2 groups according to the requirement of norepinephrine (either >0.05 or $\leq 0.05\ \mu g/kg/min$), patients requiring $>0.05\ \mu g/kg/min$ of norepinephrine had T_3 level below the normal range at significantly more time points of measurement (7 vs. 0).

Conclusions: In this comprehensive assessment of hormonal levels in brain-dead organ donors, we could not observe any significant changes during the ICU stay. Replacement therapy of T_3 may be considered in patients requiring $>0.05\ \mu g/kg/min$ of norepinephrine.

Key Words: Brain-dead organ donors, Hormonal replacement therapy, Thyroid hormone levels, Vasopressor

INTRODUCTION

Despite advances in medical management strategies, transplantation is still being considered as the only definitive treatment for patients with end-stage cardiac, pulmonary and hepatic disease.[1] Organ transplantations from brain-dead donors have increased since the first successful kidney transplantation in 1979 and 597 transplants were performed from 141 brain-dead donors in 2006 in Korea. However, the demand for transplantable organs continues to exceed the supply. The success of transplantation is critically dependent upon the quality of the donor organ and optimal management. Optimal management of brain-dead donors is important for the maximal utilization and also right timed operation, because hemodynamic stability is a key part of successful organ recovery.

A characteristic feature of brain death is the sympathetic storming, causing extreme hypertension and tachycardia, followed by loss of sympathetic tone and massive vasodilatation leading to hemodynamic instability.[2] Also, various functional components of the pituitary and hypothalamic regulatory systems may also become affected as ischemia spreads, resulting in decreased circulating levels of triiodothyronine (T_3), cortisol/adrenocorticotrophic hormone (ACTH), insulin and arginine vasopressin.[2-5] Recently, hormonal replacement therapy has been reported to result in rapid recovery of cardiac function in both experimental animals and humans, and to enable significantly more organs to be transplanted,[6-8] while some other studies show conflicting results.[9,10] In this study, we investigated the hormonal changes during organ donor management in intensive care unit (ICU) and evaluated correlation of the hormonal levels with hemodynamic parameters and the amount of vasopressor needed to maintain blood pressure in the

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brain-dead donors. The aim of this study is to comprehensively evaluate changes in basal circulating hormonal levels of the brain-dead organ donors.

MATERIALS AND METHODS

We reviewed the records of all brain-dead patients that successfully donated organs between January, 2004, and June, 2007. We examined donors with regard to age, sex, diagnosis, number of organs donated, type of organ donated, the presence or absence of brain-death associated complications. We adopted a new policy of aggressive donor management for potential organ donors since January, 2004. This policy involves early identification of potential organ donors, admission to the surgical ICU, and management by a dedicated team using a predefined protocol. The protocol for aggressive donor management includes the following elements: (i) pulmonary artery catheterization to monitor hemodynamic status and tissue perfusion, (ii) aggressive intravenous fluid resuscitation, (iii) vasopressor infusion in case of mean arterial pressures under 70 mmHg despite fluid resuscitation, (iv) identification of brain death related complications and prompt interventions. However, this protocol did not include hormone replacement therapy at that time. Neurogenic pulmonary edema was treated supportively utilizing high positive end expiratory pressure ventilation; diabetes insipidus was treated with fluid replacement and vasopressin infusion; disseminated intravascular coagulopathy and thrombocytopenia were treated with blood and blood products; electrolyte abnormalities and acidosis were treated accordingly; and hypothermia was either avoided or if present treated with external warming methods. Dopamine was used as the primary vasopressor to potential donors with hemodynamic instability; norepinephrine was used when requirements for dopamine exceeded dosage of 10 μg/kg/min. In addition, to evaluate the need for additional hormone-replacement therapy, high-dose vasopressor was defined when the dose of norepinephrine exceeded 0.05 μg/kg/min.

Brain-death diagnosis was confirmed when an irreversible catastrophic structural brain lesion resulted in unresponsiveness to noxious pain stimuli and abolition of brainstem reflexes (papillary light responses, corneal reflexes, vestibuloocular tests, tracheobronchial stimulation) in the absence of hypothermia, metabolic or electrolyte disturbances, and depressant drugs. Testing for apnea was performed using guidelines after all other brain-death criteria had been fulfilled.[11,12] The interval between two evaluations for diagnosis of brain death was 6 hours when age of brain-dead donor was more than 6 years.

Hemodynamic variables, arterial blood gas analyses and ventilator mode were recorded at the following points: admission to the ICU (T1), 30 minutes (min) after first apnea test (T2), 30 min after second apnea test (T3), before operation for harvesting (T4). Hemodynamic measurements included mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI). Blood sampling for the hormone levels was performed at the same points. Hormonal measurements included cortisol, ACTH, growth hormone (GH), testosterone and the thyroid hormone levels as measured by T_3, thyroxine (T_4), free thyroxine (fT_4) and thyroid-stimulating hormone (TSH). However, blood sampling for cortisol and ACTH was performed twice at the morning of ICU day 1 and at the evening of ICU day 2; testosterone was sampled only in male patients. Determination of T_3, T_4, fT_4, TSH, cortisol (sensitivity: 0.02 μg/dl) and testosterone was performed using a chemiluminescent immunoassay (ADVIA Centaur, Simens, New York, USA), and Determination of ACTH (sensitivity: 1.2 pg/ml) and GH was performed using an immunoradiometric assay (Gamma counter COBRA II, Packard, Meriden, USA). Operative harvesting of the allografts generally occurred within 12 hours of the declaration of clinical brain death.

Statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean±standard deviation (SD) or number of patients. Changes between time points within the group were compared using univariate analysis of variance with post hoc comparisons using the Dunnette's test. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 23 patients were admitted to the ICU after clinical brain death during the three-year period. Four patients were excluded due to incomplete data collection of hormonal levels. The other 19 patients (14 men, 5 women), having a mean age of 32±13 yrs (range, 12 to 63 yrs), were included in this study. The cause of brain death was cerebrovascular disease in 11 cases (58%), cerebral anoxia related to cardiac arrest in 5 cases (26%), and head trauma in 3 cases (16%).

Comparisons of hemodynamic parameters to baseline values revealed no significant changes throughout the study period, except CVP which was significantly increased at T4 (p=0.031, Table 1). No significant changes in hormonal levels were ob-

served throughout the study period compared to baseline values (Table 2). Concentrations of cortisol were 11.3±10.6 μg/dl at the evening of ICU day 1 and 12.0±11.4 μg/dl at the morning of ICU day 2. Concentrations of ACTH were 10.6±4.9 pg/ml at the evening of ICU day 1 and 17.3±42.0 pg/ml at the morning of ICU day 2. Concentration of cortisol and ACTH were below normal in 13 and 17 patients at the evening of ICU day 1, in 12 and 15 patients at the morning of ICU day 2.

Distributions of brain-dead donors according to their thyroid hormone levels at each time point are shown in Table 3. The number of low T_3 donors was 1, 1, 2 and 3 at T1, T2, T3, and T4, respectively in all four patients. One of them showed sustained T_3 level below the normal range during the study. Three of them showed T_3 level below the normal range at T3, T4, and T4, respectively. To determine if there were differences in thyroid hormone levels and requirement of vasopressor, all thyroid hormone values were separated according to the high or low dose of vasopressor regardless of time of blood sampling. When the patients were divided into 2 groups according to the requirement of norepinephrine (either >0.05

Table 1. Changes in Hemodynamic Variables and Requirement of Vasopressors

Parameters	T1	T2	T3	T4
HR (beats/min)	99±24	100±18	102±20	99±19
MAP (mmHg)	89±20	93±16	86±15	88±11
PCWP (mmHg)	11±5	13±6	15±11	14±4
CVP (mmHg)	6±2	6±2	7±3	8±3*
CI ($L/min/m^2$)	3.8±1.4	4.0±1.1	4.0±0.9	3.8±1.1
SVRI (dynes · sec · cm^{-5}· m^2)	1756±773	2066±793	1969±460	1429±276
PVRI (dynes · sec · cm^{-5}· m^2)	178±63	189±175	158±66	156±95
Dopamine (μg/kg/min)	5.9±7.8	4.6±4.2	4.8±4.1	4.1±4.4
Norepinephrine (μg/kg/min)	0.10±0.17	0.12±0.18	0.13±0.14	0.12±0.12

Values are mean±SD. T1: after admission to ICU; T2: 30 min after first certification; T3: 30 min after second certification; T4: before operation; HR: heart rate; MAP: mean arterial pressure; PCWP: pulmonary capillary wedge pressure; CVP: central venous pressure; CI: cardiac index; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index. *$p<0.05$ compared with T1.

Table 2. Change of Plasma Hormone Levels

	T1	T2	T3	T4	Range	Normal range	Sensitivity
T_3 (ng/ml)	0.74±0.15	0.87±0.30	0.90±0.33	0.90±0.30	0.48～1.62	0.6～1.8	0.1
T_4 (μg/ml)	5.18±1.56	5.16±1.99	5.17±2.01	5.48±2.14	1.28～11	4.5～10.9	0.3
fT_4 (μg/ml)	0.86±0.26	0.89±0.26	0.93±0.35	0.97±0.43	0.3～2.18	0.89～1.76	0.1
TSH (μIU/ml)	1.28±1.77	1.94±2.33	2.02±1.05	1.74±1.48	0.01～8.12	0.35～5.5	0.01
GH (ng/ml)	6.1±8.4	11.2±13.9	11.1±12.5	16.1±20.7	0.12～77	0.1～0.33	0.05
Testosterone (ng/dl)	62.1±35.4	79.6±64.1	75.9±67.8	65.4±55.5	10～262	241～827	10

Values are mean±SD. T1: after admission to ICU; T2: 30 min after first certification; T3: 30 min after second certification; T4: before operation; T_3: triiodothyronine; T_4: thyroxine; fT_4: free thyroxine; TSH: thyroid-stimulating hormone; GH: growth hormone.

Table 3. Brain-Dead Donors' Distribution according to Their Thyroid Hormone Levels

	T_3			T_4			fT_4			TSH		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal	Below normal	Normal	Above normal	Below normal	Normal	Above normal
T1	1	15		5	11		8	8		8	7	1
T2	1	18		8	11		10	9		7	10	2
T3	2	17		7	12		9	10		7	10	2
T4	3	16		7	12		8	9	1	5	12	

Values are number of patients. T1: after admission to ICU; T2: 30 min after first certification; T3: 30 min after second certification; T4: before operation; T_3: triiodothyronine; T_4: thyroxine; fT_4: free thyroxine; TSH: thyroid-stimulating hormone.

Table 4. Requirement of Vasopressors during ICU Management Compared with Thyroid Hormone Levels

	High-dose vasopressors	Low-dose vasopressors or none
T_3		
Below normal	7	0
Normal to high	37	29
T_4		
Below normal	17	10
Normal to high	27	19
fT_4		
Below normal	22	13
Normal to high	21	16
TSH		
Below normal	17	10
Normal to high	27	19

Values are number of data sets. T_3: triiodothyronine; T_4: thyroxine; fT_4: free thyroxine; TSH: thyroid-stimulating hormone.

or $\leq 0.05\ \mu g/kg/min$), patients requiring $>0.05\ \mu g/kg/min$ of norepinephrine had T_3 level below the normal range at significantly more time points of measurement. In addition, at all time points when the T_3 levels were below the normal range, all of the donors required high dose vasopressors infusion (Table 4). The number of patients requiring high-dose vasopressor was 11 (58%), 10 (53%), 12 (63%) and 12 at T1, T2, T3, and T4, respectively. There were no differences in the requirements of dopamine between low T_3 donors and normal T_3 donors.

There were 16 kidney and liver donors, and 3 kidney only donors. Also, 5 of kidney and liver donors underwent heart harvest; 1 underwent heart and lung harvest; 3 underwent pancreas harvest. The lengths of stay in the ICU and hospital were 2.1±0.5 days and 10.8±12.2 days, respectively. The brain death associated complications were coagulopathy (2 patients), thrombocytopenia (2 patients), cardiac ischemia (6 patients), acidosis (1 patient), neurogenic pulmonary edema (3 patients), renal failure (3 patients) and diabetes insipidus (8 patients). The patients used vasopressin due to diabetes insipidus were 2, 2, 2 and 2 at T1, T2, T3, and T4, respectively.

DISCUSSION

In the present study, we have shown that plasma T_3 level correlated with requirements of vasopressor during brain-dead donor management in ICU. Although the basal concentration of the anterior pituitary hormones varied considerably relative to the normal range, all were above the sensitivity of the assay in almost all cases. The concentrations of cortisol, ACTH and testosterone were below normal in most of our patients; the concentration of GH was markedly elevated and was more than 5 ng/ml in 59% of the cases at T2, T3 and T4.

Sequential systemic physiologic changes occur as different areas of the brain stem become ischemic. Pontine ischemia results in mixed vagal and sympathetic stimulation, characterized by bradycardia and hypertension; medulla ischemia results in unopposed sympathetic stimulation as ischemia spreads.[2] The function of the pituitary and hypothalamic regulatory system may also become affected as ischemia spreads; a number of hormonal changes occur after brain stem death and reflect anterior and posterior pituitary failure. Not all these hormonal dysfunction are seen in every potential organ donor. The incidence and severity of the derangement depends upon the etiology and time course of brain stem death, and also increases with time after the onset of brain stem death.[2] The basal hormone concentrations changed insignificantly during ICU management after the clinical brain death in this study. Since the half-life of the anterior pituitary hormones is less than 1 hour,[13] these hormones, therefore, was undoubtedly being released until operation for harvest. The excess increase of GH may be related to a stress reaction or triggered by the insulin-induced drop in serum glucose.[14] Although anti-diuretic hormone (ADH) was not included in this study, brain death is typically accompanied by diabetes insipidus (DI) reflecting posterior pituitary insufficiency. There was early depletion of ADH and development of DI in almost 80% of brain stem dead organ donors.[15] In this study, there were 8 patients (42%) with DI and treated with continuous IV vasopressin infusion.

Several studies have highlighted hemodynamic instability, myocardial injury, and impairment in cardiac function after brain death.[16-19] This cardiovascular deterioration is associated with impaired cellular oxygen utilization, a shift from aerobic to anaerobic metabolism, depletion of glycogen and myocardial high-energy stores, and the accumulation of lactate.[20,21] This irregular metabolism has been associated with low levels of T_3, T_4, and to a lesser extent cortisol and insulin.[22] The etiology of this hypothyroid state may be a result of lower than normal TSH levels caused by irreversible damage to the hypothalamus and pituitary, as well as decreased peripheral conversion of T_4 to more potent T_3. In this study, low incidence of low serum T_3 concentration was documented in our brain-dead patients. Some of our patients had a decrease in circulating T_4 and TSH concentration, whereas the serum T_3 concentrations were

in the normal ranges in most of them. There were no differences in hemodynamics between low T_3 donors and normal T_3 donors; however, we found significant correlation between low T_3 levels and requirements of high-dose vasopressor. These results suggest that serum T_3 concentration was a major determinant of cardiac function in our brain-dead patients.

The effects of T_3 administration in brain-dead patients sparked debate considerable and led to several studies. Several studies documented that no correlation with their hemodynamic status and lower levels of T_3 in brain-dead patient.[23,24] Other studies showed a benefit only in hemodynamically unstable donors.[25,26] Other studies showed that T_3 or T_4 administration improved cardiovascular status, and reduced inotropic support and the number of donors lost cardiac instability in human brain-dead patients.[7,27] Since most of the beneficial effects of T_3 is cardiac function,[28,29] hormonal replacement therapy including T_3 was recently recommended for donors with a left ventricular ejection fraction less than 45% and/or with unstable hemodynamics.[30] Recently, Rosendale et al[8] showed a substantial increase in the number of organs transplanted from donors receiving three-drug (T_3/T_4, methylprednisolone, arginine vasopressin) hormone-replacement therapy in the large retrospective analysis of 10,292 donors. In this study, we observed substantial decrease in plasma hormone including cortisol, ACTH, T_4, fT_4 and TSH, and DI, reflecting depletion of ADH. We think that these observations will provide the foundations for the efficacy and optimal timing of hormonal replacement therapy in our hospital. The limitation of this study is that the number of donors was not enough to analyze statistically the correlation between low T_3 donors and requirement of high-dose vasopressor.

In conclusion, we showed substantial decrease in cortisol, ACTH, T_4, fT_4 and TSH, and significant correlation between T_3 concentrations and vasopressor support in brain-dead patients. The addition of hormone therapy in association with an aggressive donor management protocol may help reduce vasopressor support, moreover, maximize the number of organs retrieved from hemodynamically unstable donors. In a time when the transplant waiting list is increasing more than the number of donors, hormonal replacement therapy may be integrated in the management of brain-dead organ donors in ICU.

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