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Original Research Article

The therapeutic concept and analysis of the effect of hormone package therapy in brain dead organ donors

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ABSTRACT

Background: The present study aimed to assess the effect of hormone package therapy on hemodynamic stability in brain dead organ donors.
Methods: In this study, patients were divided into two groups: one administered hormone package therapy, defined as simultaneous treatment with vasopressin, thyroxine and corticosteroids; and the other administered conventional therapy. Clinical findings and hemodynamic parameters were compared to analyze the effect of hormone package therapy on hemodynamic stability. Associations between hormone package therapy and hemodynamic variables were assessed by univariate and multivariate logistic regression analyses.
Results: A total of 109 patients were included in the study. Based on time of enrollment, 54 and 55 patients received conventional and hormone package therapy, respectively, with 32 (59.3%) and 45 (81.8%), respectively, achieving hemodynamic stability. High-doses of a single vasoactive agent in the hormone package group better maintained hemodynamic stability and norepinephrine use compared to conventional treatment. Univariate and multivariate analyses showed that an abnormal suprasellar cistern, midline shift, low free T3, axillary temperature >36.5°C and central diabetes insipidus were associated with the effects of hormone package therapy.
Conclusions: Hormone package therapy can help maintain hemodynamic stability in brain dead donors and reduce the use of vasoactive agents, thereby improving the quality of donated organs and the success rates of organ donations.

Keywords: Brain death, Drug combination, Organ donation, Vasopressin, Thyroxine, Corticosteroids

INTRODUCTION

Brain dead patients have become an important source of organs for transplantation in China.[1,2] After brain death, patients experience hemodynamic instability, manifesting primarily as a reduction in blood pressure. If not treated effectively, hemodynamic instability can eventually lead to cardiac death.[3] Because pituitary-related hormones are thought to decrease after brain injury and treatment with these hormones is thought to maintain hemodynamic stability, brain dead patients who are potential organ donors are administered Hormone replacement therapy (HRT).[4] Several studies in small numbers of patients have reported that HRT can maintain hemodynamic stability in brain dead patients, but there have been no such reports from China.[3] Our management of brain dead organ donors showed that HRT differed for donors with and without brain death, with HRT in brain dead donors involving the simultaneous administration of combinations of three types of hormones.

METHODS

General information

The clinical data of brain dead organ donors, admitted to the First Affiliated Hospital of Sun Yat-sen University from October 2017 to December 2018, were prospectively collected; these data included patient age, sex, diagnosis, history of diabetes mellitus, hypertension, types and doses of hormones, and types and doses of initial and final vasoactive drugs. Patients were included if they were aged >1 year and ≤60 years and met the criteria for brain death and hemodynamic instability. Brain death was defined according to Chinese criteria and practical guidelines as deep coma (Glasgow coma score=3) of known cause, lack of spontaneous respiration, disappearance of brainstem reflex, and electrical silence and cerebral circulation arrest on an Electroencephalogram (EEG).[1, 2] Hemodynamic instability was defined as maintenance of systolic blood pressure >90 mmHg (1 mmHg=0.133 kPa) with a single large dose of a vasoactive drug (such as norepinephrine) or a combination of several vasoactive drugs. A high dose of norepinephrine was defined as >1 μg/kg/min, whereas high doses of epinephrine and dopamine were each defined as >10 μg/kg/min [3].

Patients in the conventional therapy group received intravenous infusions of vasoactive drugs and $NaHCO_2$. Patients in the hormone package group were treated with vasopressin, thyroid hormone, and glucocorticoid. Vasopressins included pituitrin, desmopressin and terlipressin, with the agent selected based on urine volume and serum Na^+ level. Patients with polyuria and low serum Na^+ were administered pituitrin or desmopressin, whereas patients with oliguria and high serum Na^+ were administered terlipressin. Patients were also administered L-thyroxine sodium tablets (thyroid hormones) through a gastric tube and methylprednisolone (glucocorticoid) pumped continuously after a loading dose (Table 1). Hemodynamic stability was defined as a reduction in the dose or type of vasoactive drugs and systolic blood pressure >90 mmHg.

Because hormone package therapy was introduced at our center in April 2016, the patients in this study were divided into two groups based on time of admission. Patients in the conventional therapy group were admitted from October 2017 to April 2018 and patients in the hormone package therapy group from May 2018 to December 2018. Hemodynamic stability, dosage of vasoactive drugs and other factors in the two groups were compared by $\chi 2$ and Fisher exact probability tests, as appropriate. Factors associated with the effectiveness of hormone package therapy were assessed by univariate and multivariate analyses. All statistical analyses were performed using SPSS (version 23.0) software, with $p<0.05$ defined as statistically significant.

RESULTS

Of the 183 brain dead patients admitted from October 2017 to December 2018, 109 were included in this study (Table 2), including 54 admitted between October 2017 and April 2018 and treated with conventional therapy, and 55 admitted between May 2018 and December 2018 and treated with hormone package therapy. Of these groups, 32 (59.3%) in the conventional therapy group and 45 (81.8%) in the hormone package therapy group achieved hemodynamic stability (χ^2=6.69, p=0.009, Table 3). The hemodynamic stability rate of patients in the hormone package therapy group treated with a single vasoactive drug (69.1%) was significantly higher than that of similar patients in the conventional therapy group (18.5%) (χ^2=28.28, p<0.001, Table 4).

Table 1: The hormone package therapy.[13]

Type	Dosages
Levothyroxine sodium (tablets)	Adult: 50-100 μg, through a gastric tube, once a day to once every 12 hours
	Child: 12.5-25 μg, through a gastric tube, once a day to once every 12 hours
Methylprednisolone	Adult: 40 mg intravenous injection firstly, then 10 mg/h intravenous pump starting
	Child: 10-20 mg intravenous injection firstly, then 2-5 mg/h intravenous pump starting
Vasopressins	
Pituitrin	Adult: 1-2 U/h intravenous pump starting
	Child: 0.25-0.5U/h intravenous pump starting
Desmopressin	Adult: 1-2 U/h intravenous pump starting
	Child: 0.25-0.5U/h intravenous pump starting
Terlipressin	Adult: 100-200 U/h intravenous pump starting
	Child: 25-50U/h intravenous pump starting

The rate of treatment with high-dose vasoactive drugs was significantly lower in the hormone package group (38.2%) than in the conventional group (77.8%) (χ^2=17.51, p=0.000, Table 5), and the rate of treatment with norepinephrine was also significantly lower in the hormone package group (36.4%) than in the conventional group (83.3%) (χ^2=24.97, p=0.000, Table 6).

Table 2: General information of brain death donors in hormone package and conventional therapy group.

Group	Age (year)	Gender		Diagnosis		DM	Hypertension	Time to confirm brain death (days)
		M	F	TBI	ICH			
Hormone package	29.45±14.56	46	9	36	19	11	16	5.46±13.06
Conventional therapy	32.69±18.47	44	10	34	20	9	13	5.86±11.32
	1.98		0.038		0.073	0.263	0.351	1.982
P	0.218		0.767		0.786	0.607	0.553	0.865

TBI: traumatic brain injury; ICH: intracerebral hemorrhage; DM: diabetes mellitus.

Table 3: Comparison of hemodynamic stability rate between two groups.

Group	Hemodynamic stability	Hemodynamic instability	Hemodynamic stability rate (%)	χ^2	P
Hormone package	45	10	81.8		
Conventional therapy	32	22	59.3	6.69	0.009

Table 4: Comparison of hemodynamic stability rate of single vasoactive drug between two groups.

Group	Single vasoactive drug	Several vasoactive drugs	Hemodynamic stability rate (%)	χ^2	P
Hormone package	38	17	69.1		
Conventional therapy	10	44	18.5	28.28	0.000

Table 5: Comparison of the rate of treatment with high-dose vasoactive drugs between two groups.

Group	Yes	No	Rate of treatment (%)	χ^2	P
Hormone package	21	34	38.2		
Conventional therapy	42	12	77.8	17.51	0.000

Table 6: Comparison of the rate of treatment norepinephrine between two groups.

Group	Yes	No	Rate of treatment (%)	χ^2	P
Hormone package	20	35	36.4		
Conventional therapy	45	9	83.3	24.97	0.000

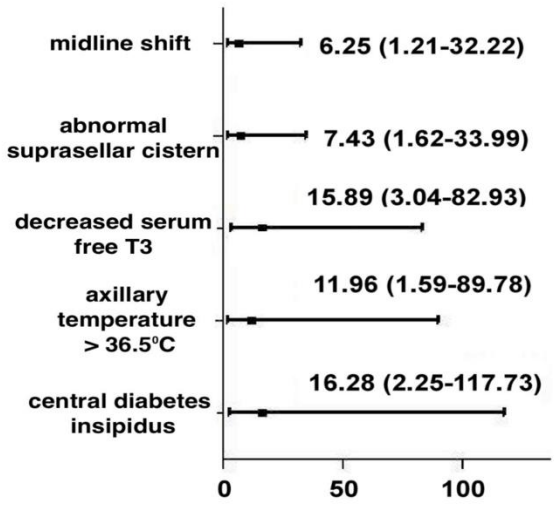

Figure 1: Factors correlated with the effectiveness of hormone package therapy.

The effectiveness of hormone package therapy is based on certain preconditions, such as central venous pressure (CVP) of 8-13 cmH_2O (1 cmH_2O=0.098 kPa), pH 7.4-7.45 and blood glucose <10 mmol/L. Univariate and multivariate analysis showed that abnormal suprasellar cistern (odds ratio [OR]=7.43, 95% confidence interval [CI] 1.62–33.99, p=0.010), midline shift (OR=6.25, 95% CI 1.21–32.22, p=0.028), decreased serum free T_3 concentration (OR=15.89, 95% CI=3.04-82.93, p=0.001), axillary temperature >36.5°C (OR=11.96, 95% CI=1.59-89.78, p=0.016) and central diabetes insipidus (OR=16.28, 95% CI=2.25-117.73, p=0.006) correlated significantly with the effectiveness of hormone package therapy (Figure 1).

DISCUSSION

In China, brain death is defined as irreversible loss of whole brain function including brainstem function.[1,2] This type of irreversible brain injury can lead to pituitary-related hormone failure; therefore, brain dead patients can develop several clinical manifestations, including

diabetes insipidus, electrolyte disturbance, neurogenic pulmonary edema, arrhythmia, hypothermia and lactate acidosis.[4-6] Serum concentrations of thyroid hormones, especially free T_3, are reduced, followed by abnormal metabolism of glucocorticoids and cortisols, resulting in resistance to catecholamines and anaerobic metabolism and leading to hemodynamic instability.[3-6] Insulin, thyroxine and glucocorticoid can improve the utilization of glucose and pyruvic acid, reduce the blood concentrations of lactic acid and free fatty acids, and convert anaerobic to aerobic metabolism. Vasopressin (AVP) can restore vasoconstriction and effective circulating blood volume, as well as contributing to hemodynamic stability.[3,5,6]

HRT has become an important component in the advanced maintenance of brain dead donors. Initially, this therapy included four types of hormones: T_3 or T_4, methylprednisolone, insulin and vasopressin. Subsequently, as insulin control of blood glucose was incorporated into routine maintenance, HRT was optimized to three types of hormones: T_3 or T_4, methylprednisolone and AVP.[7-9] Although HRT has been introduced into clinical practice; its utilization rate in brain dead donors is still low. In the United States, for example, only 8.8-19.9% of brain dead donors are administered HRT.[5] In China, the use of brain dead donors is uncommon, with no relevant study on HRT in these patients. Based on the clinical practice in our center of organ donation by brain dead patients and the pathophysiological characteristics of Chinese people, our initial formulation of HRT consisted of simultaneous and combined administration of vasopressin, thyroid hormone, and glucocorticoid.

Because of the pathophysiological changes that occur after brain death, thyroid hormone was administered to treat hemodynamic instability in these patients. The only oral thyroid hormone available in China is tablets of levothyroxine sodium, which are administered to patients through a gastric tube (Table 1). This is accompanied by intravenous administration of methylprednisolone. Dosages of intravenous methylprednisolone can vary, with studies reporting dosages of 2 g once daily, 1 g every 12 hours, and 15mg/kg once daily.[10-12] Other studies have reported that adult patients are treated with a bolus dose of 250 mg methylprednisolone, followed by maintenance at 100 mg/h. Our study showed that hemodynamics stability could be maintained in adults by intravenous injection of 40 mg/h methylprednisolone.

The synergistic proportions and coordination among the three hormones suggest that they should be administered to brain dead organ donors in a simultaneous and combined fashion, while optimizing body temperature, pH and Central venous pressure (CVP). At dosages higher than those required to achieve its anti-diuretic effects, AVP can act as a non-adrenergic peripheral vasoconstrictor. In China, the most commonly used AVP is pituitrin, which contains oxytocin and an antidiuretic hormone, followed by desmopressin (oral and injected), which mainly acts on the kidneys and has anti-diuretic properties. Terlipressin is a synthetic analogue of vasopressin, mainly acting on viscera and skin, but having no obvious antidiuretic effect.[13,14] Pituitrin and desmopressin have been administered to patients with diabetes insipidus and low serum Na^+ level to maintain effective circulating blood volume and increase serum Na^+ to a level sufficient to maintain hemodynamic stability.[13] Administration of terlipressin to patients with oliguria and high serum Na^+ level was found to adjust blood flow distribution (reducing blood flow to the gastrointestinal tract and skin and increasing effective circulating blood flow); increase renal perfusion and urine volume; improve metabolic acidosis in vivo; increase the efficacy of vasoactive drugs (such as norepinephrine), and achieve hemodynamic stability.[14]

At least one type of vasoactive drug is required to maintain hemodynamic stability in almost all brain dead organ donors. Dosages of these drugs are usually high, with norepinephrine being the most commonly used drug. Our study showed that hormone package therapy can significantly improve the rate of hemodynamic stability of a single vasoactive drug and reduce the use of high doses of vasoactive drugs and reduce the use of norepinephrine. It is important to reduce norepinephrine usage and dosage, as norepinephrine use can depress the quality of donor organs.[3,4,15,16] HRT can also reduce excessive fluid resuscitation and secondary inflammation reactions.[16,17] Hormone exhaustion during the early stages of brain death, however, does not invariably lead to hemodynamic instability. Of the patients in our study, 89.2% presented with hemodynamic instability when treated with HRT, with the remaining 10.8% having transient hypotension. These findings indicate that patients formally determined to be brain dead or presenting with early clinical manifestations of hemodynamic instability should be treated with hormone package therapy.

The application of HRT should be based on the likelihood of hemodynamic failure. Univariate and multivariate analysis showed that midline shift and abnormal suprasellar cistern (compression, disappearance or subarachnoid hemorrhage) on brain CT scans, a decrease in free T3, axillary temperature $>36.5^0$C and central diabetes insipidus correlated significantly with the effectiveness of hormone package therapy. A midline shift and an abnormality in the suprasellar cistern are indirect signs of pituitary injury, whereas central diabetes insipidus is a direct manifestation of pituitary injury. Free T3 directly reflects the in vivo concentration of thyroid hormone. Brain dead patients often experience hypothermia, with a core temperature $\geq 36.8^0$C suggesting that their axillary temperature should be raised to $\geq 36.5^0$C. Maintaining a normal or moderately increased body temperature can enhance the activity of vasoactive drugs.[6,13] The effects of HRT can be maximized by maintaining CVP at 4-8 $cmHO_2$ and pH at 7.35-7.45.[14] In

our study, CVP was maintained at 8-13 $cmHO_2$ and pH at 7.35-7.45. Therefore, the roles of CVP and pH in hormone package therapy were not included in the correlation analysis.

This study had several limitations, such as the small sample size, which prevented subdivision of patient groups by type of vasoactive drugs. In addition, although there was no significant difference between the two groups in confirming the time of brain death, the times from onset to formal confirmation of brain death differed. Because patients in the hormone package therapy were started on treatment only after the formal determination of brain death, this bias in time selection may have influenced the therapeutic effect of hormone package therapy.

CONCLUSION

Hormone package therapy for brain dead organ donors can reduce the utilization of vasoactive drugs and achieve hemodynamic stability. Hormone package therapy therefore may not only increase the success rate of organ donation from brain dead patients, but may also improve the quality of the donated organs.

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