ORIGINAL ARTICLE

The Role of Thyroid Hormone Administration in Potential Organ Donors

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Hypothesis: Levothyroxine sodium therapy should be used in brain-dead potential organ donors to reverse hemodynamic instability and to prevent cardiovascular collapse, leading to more available organs for transplantation.

Design: Prospective, before and after clinical study.

Setting: A surgical intensive care unit of an academic county hospital.

Patients: During a 12-month period (September 1, 1999, through August 31, 2000), we evaluated 19 hemodynamically unstable patients with traumatic and nontraumatic intracranial lesions, who were candidates for organ donation following brain death declaration.

Interventions: All patients were resuscitated aggressively for organ preservation by fluids, inotropic agents, and vasopressors. If, despite all measures, the patients remained hemodynamically unstable, a bolus of 1 ampule of 50% dextrose, 2 g of methylprednisolone sodium succinate, 20 U of insulin, and 20 µg of levothyroxine sodium was administered, followed by a continuous levothyroxine sodium infusion at 10 µg/h.

Results: There was a significant reduction in the total vasopressor requirement after levothyroxine therapy (mean ± SD, 11.1 ± 0.9 µg/kg per minute vs 6.4 ± 1.4 µg/kg per minute, $P = .02$). Ten patients (53%) had complete discontinuation of vasopressors. There were no failures to reach organ donation due to cardiopulmonary arrest.

Conclusions: Levothyroxine therapy plays an important role in the management of hemodynamically unstable potential organ donors by decreasing vasopressor requirements and preventing cardiovascular collapse. This may result in an increase in the quantity and quality of organs available for transplantation.

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ORGAN transplantation has become the preferred treatment for end-stage cardiac, pulmonary, renal, hepatic, and endocrine failure. With improving anesthetic, surgical, and immunologic techniques, the indications for transplantation are increasing, with a parallel increase in the number of potential recipients. However, the number of available donor organs has not increased sufficiently to match this high demand and, as a result, many patients do not receive the transplants they need. Because of the discrepancy between supply and demand, as many as 3000 patients die each year in the United States while waiting for an organ transplant and as many as 100 000 potential candidates die before they are even placed on the waiting list.[1]

Cadaveric (brain-dead) donors with intact circulation contribute most of the organs for transplantation.[2] Brain death is associated with complex hemodynamic, endocrine, and metabolic disturbances leading to multiorgan system failure and subsequent cardiopulmonary arrest.[3] Even with aggressive management, as many as 25% of the potential organ donors are lost due to hemodynamic instability.[4,5] Even more organs are lost as a consequence of the high dose of vasopressor required to maintain adequate perfusion to the brain-dead organ donor. It has been suggested that this hemodynamic instability is a result of diminished levels of circulating thyroxine (T_4) levels.[3,6-9] This in turn leads to a reduction of myocardial energy stores (ie, adenosine triphosphate, creatine phosphate, and glycogen) and a shift from aerobic to anaerobic metabolism, resulting in hemodynamic instability and the need for inotropic support. Some studies suggest that replacement of T_4 may reverse these derangements and stabilize the hemodynamic profile, resulting in a significant increase in potential organ donors that would otherwise be lost due to cardiovascular collapse.[4,8,9] However, the findings of several studies have failed to show this benefit.[10-13] As a result of the inconsistent findings reported in the literature, hormonal therapy has not been fully embraced by the transplantation community. Its use remains sporadic and controversial.

In this study, we examine the effects of levothyroxine sodium administration in hemodynamically unstable brain-dead po-

PATIENTS AND METHODS

After approval by the institutional review board of the Los Angeles County–University of Southern California Medical Center, all patients with traumatic or nontraumatic intracranial lesions were followed up prospectively during a 12-month period (September 1, 1999, through August 31, 2000). Only patients admitted to the surgical intensive care unit with unsurvivable head injuries, resulting in the declaration of brain death, were considered for this study. Brain death is a clinical determination at our center, based on the results of an apnea test and the absence of brainstem reflexes (ie, corneal reflex, pupillary light reflex, oculocephalic reflex, oculovestibular reflex, and cough and gag reflex).[14] Each patient had 2 brain death declaration examinations performed at least 6 hours apart. Whenever the clinical evaluation was believed to be inadequate, a radioisotopic brain-flow scan was performed for brain death declaration.

All patients were managed aggressively by a dedicated surgical intensive care unit team using a standard protocol for resuscitation. Vasopressors such as epinephrine hydrochloride (at levels >5 µg/kg per minute) were used if the mean arterial pressure remained less than 70 mm Hg despite adequate fluid resuscitation. Donors who required a combined vasopressor need of greater than 10 µg/kg per minute (either epinephrine hydrochloride or dopamine hydrochloride alone, or in combination) were then entered into the T_4 protocol. This group of hemodynamically unstable brain-dead patients served as our study population. Rapid intravenous boluses of 1 ampule of 50% dextrose, 2 g of methylprednisolone sodium succinate, 20 U of insulin, and 20 µg of levothyroxine sodium were given, followed by a continuous intravenous levothyroxine sodium infusion of 10 µg/h. Vasopressors were then titrated as needed.

Complications of brain death were treated accordingly. Disseminated intravascular coagulopathy was treated with blood and blood products. Diabetes insipidus was treated with fluid replacement and intravenous desmopressin acetate. Electrolyte levels were aggressively corrected; hypothermia was avoided.

Each patient served as his or her own control whereby hemodynamic and metabolic data were obtained hourly prior to and after levothyroxine administration either until organ donation or until life support was discontinued. Cardiac function was evaluated using invasive arterial pressure and pulmonary artery catheter monitoring. Measurements included the following: mean arterial pressure, heart rate, cardiac index, oxygen delivery index, oxygen consumption index, and oxygen extraction ratio. Blood samples were obtained for measurements of the levels of hemoglobin, base deficit, electrolytes, and lactate.

Data were collected prospectively and expressed as mean ± SD. Statistical analysis was performed using the *t* test. A difference before and after levothyroxine treatment was considered statistically significant at $P<.05$.

Comparison of Hemodynamic Data Before and After the Administration of Levothyroxine*

Variable	Levothyroxine Sodium Administration		*P* Value
	Before	After	
Vasopressor, µg/kg per minute	11.1 ± 0.9	6.4 ± 1.4	.02
Heart rate, beats/min	120 ± 3	113 ± 2	.01
Cardiac index, L/min per square meter	4.59 ± 0.1	4.57 ± 0.1	.46
Oxygen delivery index, mL/min per square meter	656 ± 32	695 ± 53	.18
Oxygen consumption index, mL/min per square meter	107 ± 7	123 ± 6	.02
Oxygen extraction ratio, %	16 ± 1	18 ± 1	.03
Base deficit	–2.1 ± 0.4	–2.8 ± 0.6	.14
Hemoglobin, g/dL	11.77 ± 0.23	11.81 ± 0.23	.40

*Data are given as mean ± SD.

tential organ donor patients, to determine its use in organ transplantation. Our hypothesis is that levothyroxine therapy can reverse the hemodynamic instability and prevent cardiovascular collapse in this group of patients, leading to an increase in available organs for transplantation.

RESULTS

During the 12-month period, a total of 28 patients were candidates for organ donation. Nine patients were excluded secondary to hemodynamic stability. The remaining 19 patients (15 males and 4 females) who had an average age of 39 ± 14 years (age range, 14-63 years) composed the study population. In 16 patients the cause of brain death was trauma. Six of the 16 trauma patients had head gunshot wounds, while the remaining 10 had blunt trauma. The 3 nontrauma patients included 1 patient with a spontaneous subdural hematoma, 1 patient with an ischemic stroke, and 1 patient with a massive subarachnoid hemorrhage.

The **Table** compares the hemodynamic profile before and after the administration of levothyroxine. There was a statistically significant decrease in vasopressor support after the administration of levothyroxine (11.1 ± 0.9 µg/kg per minute before vs 6.4 ± 1.4 µg/kg per minute after levothyroxine administration, $P=.02$). All patients had a reduction in vasopressor requirement. Ten (53%) of the 19 patients were completely weaned off vasopressors. The **Figure** shows the influence of levothyroxine on the vasopressor requirements with respect to time. Eleven of the 19 patients responded with a decrease in the vasopressor requirements within the first 2 hours of levothyroxine administration. By the end of 4 hours, all patients had a response. Three patients developed severe hypertension (systolic blood pressure, >180 mm Hg), which quickly resolved once therapy with levothyroxine was discontinued. This was thought to be from clinical hyperthyroidism.

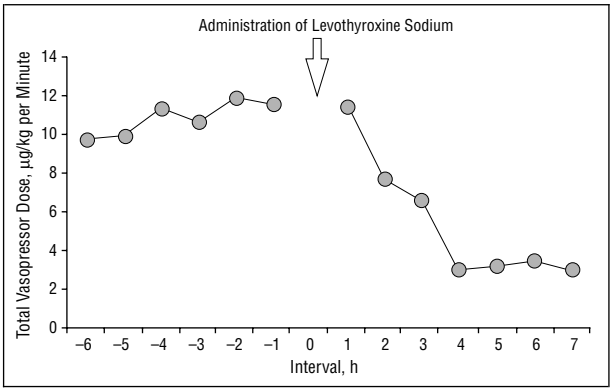
Ten of the 19 patients underwent successful organ donation for a total of 33 organs. Organs were not harvested from the remaining 9 patients because of family refusal. No patient suffered cardiovascular collapse.

COMMENT

As of January 6, 2001, there were 74 000 people awaiting organ transplantation in the United States.[15] In 1999, there were a total of 21 700 transplantations performed.[15] With such a large gap between the number of people who need tranplants and the number of people who actually receive them, it is inevitable that waiting times are prolonged. Subsequently, as many as 10% of the adults on the waiting list die prior to organ transplantation.[16] The significant organ shortage has led to a variety of novel methods to expand the donor pool. Both younger and older donors are routinely used.[17] The use of organs from living-related donors, living-unrelated donors, and asystolic donors has increased.[2] Split-liver transplantations have had excellent results and are used more frequently.[1,17] The use of organs from bacteremic donors, those who died of carbon monoxide, cyanide, and methanol poisoning, or higher-risk donors have been used to increase the donor pool.[2,17,18] Public education has been pursued aggressively to help solve the problem of organ shortage.[19] Despite these attempts, the difference between supply and demand continues to widen. With no substantial increase in the number of donors in the foreseeable future, it then becomes increasingly necessary to maximize the use of organs from the existing donor pool.

To fully maximize organ retrieval from the existing donor pool, the cardiopulmonary collapse that is frequently seen in brain-dead patients must be prevented. Presently, as many as 25%, or 27 000 existing brain-dead potential organ donors, are lost due to cardiovascular collapse each year.[4,5] An additional percentage of organs are deemed unsuitable because of the high dose of vasopressors often required to maintain organ perfusion in a large number of patients. This combination of events leads to an unacceptably high number of potential organs that are lost. In our study, we have shown that using intravenous levothyroxine not only prevented cardiopulmonary arrest, but also allowed complete vasopressor withdrawal in 10 patients (53%).

Brain death is associated with profound physiological disturbances resulting in a diffuse vascular regulatory injury and a diffuse metabolic cellular injury.[3] The net result is a progressive deterioration of all organs of the body, resulting in cardiopulmonary collapse and asystole. Administration of catecholamines seems to be the only aid for inotropic support and organ perfusion.[20] However, the use of exogenous catecholamines is associated with poor graft function and reduced graft survival.[21,22] Many transplant centers consider the donor heart to be unsuitable if dopamine requirements exceed 10 to 15 µg/kg per minute.[9] Even with maximal vasopressor support, cardiovascular collapse is inevitable. Many animal studies demonstrated that the cardiovascular deterioration was associated with a shift of cellular metabolism from aerobic to anaerobic, with depletion of glycogen and myocardial high-energy stores, and with the accumulation of lactate.[23,24] This was associated with low levels of circulating triiodothyronine, cortisol, and insulin, and reversal of cardiac deterioration was seen with hormonal replacement therapy.[7,25] Applying this concept to human brain-dead organ donors, Novitzky et al[25] showed a significant improvement in the cardiovascular status, a reduction in inotropic support, and a reduction in the number of brain-dead potential organ donors who were considered too unstable for heart donation.



Note the influence of the administration of levothyroxine on vasopressor requirements. Time 0 indicates the start of levothyroxine administration.

This sparked considerable debate over the role of hormone therapy in potential organ donors. Several studies have shown that thyroid replacement therapy is beneficial, especially in the hemodynamically unstable organ donor.[3,26,27] This benefit is even more pronounced in cardiac transplantation and heart graft function.[9,28,29] However, this benefit may be lost in liver and other organ transplantation.[30,31]

Low levels of thyroid hormone, as well as other pituitary hormones, are seen with brain death, but the significance is not clearly understood. Robertson et al[10] found that although brain death was associated with decreased levels of thyroid hormone (free triiodothyronine), it was not associated with hemodynamic deterioration. Similarly, Goarin et al[11] found no correlation between thyroid hormone levels and hemodynamic status. Furthermore, the administration of thyroid hormone was not associated with an improvement in hemodynamic status and cardiac function. Other studies have confirmed that thyroid hormone replacement is unnecessary and may even be detrimental.[12,13] Randell and Hockerstedt[32] showed no beneficial effects with thyroid hormone therapy, and a trend toward worsening metabolic acidosis with its administration.

As a result of the inconsistent findings reported in the literature, thyroid hormone replacement therapy remains controversial. Because of our previous anecdotal experience, according to which levothyroxine therapy is beneficial, we undertook this study to evaluate the existing controversy. In contrast to other studies, we included a highly selected part of the population, hemodynamically unstable brain-dead potential organ donors who were already at risk for cardiovascular collapse. Our data demonstrate a significant reduction in vasopressor requirements immediately following levothyroxine administration. More than 50% of the patients had their vasopressor requirement discontinued. Novitzky et al[7] postulated that the thyroid hormone exerts its effect at the mitochondrial level, reversing anaerobic metabolism to aerobic, thereby improving cardiovascular function. This may be true, but not fully explained by our results, as the base deficit was the same before and after the administration of levothyroxine. Another explanation is that levothyroxine therapy may potentiate the effects of endogenous catecholamines or act

as a vasopressor itself.[33,34] We also found a significant increase in oxygen consumption with a trend toward increased oxygen delivery. This has been cited as an undesirable effect of levothyroxine therapy.[3] We believe that improving oxygen use may cause improvement of the cardiovascular status of these patients. Further research needs to be done to understand the mechanism of action of levothyroxine therapy.

The implications of this study are important. By decreasing vasopressor support in brain-dead patients, more organs should become suitable for transplantation. In addition, the number of donors lost due to cardiovascular collapse would be significantly reduced. In a time where the gap between organ supply and organ demand is widening, maximizing the amount of organs per donor could be the start of reversing this trend.

A major limitation of our study is the absence of a control group. Although each patient served as his or her own control, a stronger conclusion could have been made by the addition of a proper control group. We are in the process of conducting a randomized controlled trial on the effects of levothyroxine therapy in this group of patients. A second limitation is that we did not measure thyroid hormone levels in any of the study patients. Although levothyroxine administration was effective in reducing vasopressor requirements, our conclusions would have been stronger by documenting T_4 levels before and after treatment. A third limitation is the relatively high dose of levothyroxine we used. We used 10 µg/h, whereas others have used less[32] or more[11] than this dose. The optimal dose is not known and will require additional research. Only 3 patients suffered hypertension from the high levothyroxine dose, which quickly disappeared once the levothyroxine therapy was discontinued. No other adverse events were noted. Another important limitation is the lack of posttransplantation follow-up of the organs that were actually donated. Ensuring posttransplantation organ viability is just as important as preventing cardiovascular collapse prior to organ donation. Additional research is necessary to document the exact effect on posttransplantation organ function. Finally, steroids were also given to all patients as an initial bolus and could account, in part, for the decrease in vasopressor dose.

CONCLUSIONS

Levothyroxine therapy plays an important role in the management of hemodynamically unstable potential organ donors by decreasing vasopressor requirements and preventing cardiovascular collapse. This may result in an increase in the quantity and possibly quality of organs available for transplantation.

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