Endocrine Considerations of the Pediatric Organ Donor

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J Pediatr Intensive Care 2016;5:205–212.

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Abstract

Keywords

- brain death
- organ procurement
- endocrine system diseases
- hormone
- donation
- organ donor management

Patients determined to be neurologically deceased exhibit potentially harmful changes in various endocrine pathways due to disruptions of the body's neurohormonal control mechanisms. These deviations from endocrine homeostasis lead to hemodynamic, metabolic, and immunologic aberrations that are associated with reduced graft procurement and function for the purposes of organ donation. Existing literature has attempted to describe the pathophysiology that associates disruptions in endocrine pathways with organ dysfunction, both to increase understanding and to identify strategies to support the donor. For example, diabetes insipidus due to arginine vasopressin deficiency is commonly encountered, and should be anticipated. The significance of abnormalities in other pathways such as those involving cortisol and thyroid hormone is less established; however, there is increasing support for treating potential organ donors with combined hormonal therapies. While there are published documents aimed at guiding management of organ donors in general, many controversies exist and pediatric-specific literature is scarce. This article aims to review several of the important endocrine-specific aspects of managing the neurologically deceased organ donor, with an emphasis on pediatrics where information is available.

Introduction

Based on data from the Organ Procurement and Transplant Network, there are almost 2,000 children in the United States currently on the waitlist for an organ transplant.¹ While efforts to raise awareness and increase the organ donor pool are ongoing, up to one-third of pediatric patients listed for a transplant will not receive it. Given the scarcity of available organs, it is important that all opportunities for organ donation and transplantation are managed with the utmost care and attention to improve the quality and quantity of transplants.

The process of organ transplantation is often lengthy, as it includes identification of the appropriate donor candidate, obtaining consent, donor/recipient matching, and organ procurement logistics. A review of 1,554 organ donors revealed that the average time from neurologic declaration of death to organ procurement was 34 hours, and that in 15% of cases,

procurement took place greater than 48 hours after declaration.² During this time period, the potential donor must be aggressively managed to minimize end-organ dysfunction, increase the number of organs available for surgical recovery, and optimize the posttransplant graft function. This is important as it has been shown that almost one-quarter of potential pediatric donors were unable to donate due to preprocurement instability.³ In addition, meeting organ donor management goals (normal cardiac, pulmonary, renal, and endocrine parameters) increases the likelihood of high-yield organ procurement (four or more organs).⁴

Efforts at optimizing organ availability and function have included a focus on the endocrine systems that become dysregulated with neurologic death. Several pathways involving neurohormonal signaling are known to participate in maintaining hemodynamic, metabolic, and immunologic homeostasis. As a result, dysregulation of these endocrine systems may

received
September 27, 2015
accepted after revision
November 25, 2015
published online
May 17, 2016

Issue Theme Endocrinology in Pediatric Critical Care; Guest Editors: Kusum Menon, MSc, MD, and Dayre McNally, MSc, PhD

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DOI <http://dx.doi.org/10.1055/s-0036-1583286>.
ISSN 2146-4618.

contribute to end-organ damage. Investigation of these pathways during the state of neurologic death has attempted to identify targets for therapeutic intervention, such as exogenous hormone replacement, with the goal of improving graft function and transplant outcomes.

In general, although the endocrinology of neurologic death has been studied broadly, there is a lesser amount of prospective evidence involving pediatric organ donors. Thus, much of pediatric clinical practice is guided by information from adult and animal literature. While general management guidelines for the potential organ donor are available,^{5,6} this article aims to review important endocrine-specific aspects of managing the pediatric organ donor after neurologic declaration of death.

Physiology

The majority of pediatric organs are procured from donors who have been declared neurologically deceased (i.e., brain death).⁷ Neurologic death may occur as the end result of numerous triggers, such as trauma, hypoxia, or infection. Regardless of etiology, the common final cascade of events involves a rapid increase in intracranial pressure followed by cerebral herniation and brainstem ischemia. This process causes significant disruption to the neurological and hormonal mechanisms responsible for maintaining the body's autonomic, immunologic, and hormonal homeostasis.

During the process of brainstem ischemia and herniation, the regulation of sympathetic and parasympathetic activity becomes unbalanced. Periods of unopposed sympathetic activity result in tachycardia and hypertension, known as "sympathetic storming." This state of increased cardiac output with elevated systemic vascular resistance may lead to dysfunction of the heart and other organ systems.^{8,9} Animal models have shown that sympathetic storming occurs within minutes of rapid increases in intracranial pressure, and coincides with elevated levels of circulating catecholamines.¹⁰ Within hours of this initial phase, there is invariably a shift into a state of decreased systemic vascular resistance accompanied by significantly reduced levels of circulating catecholamines.¹¹

Cerebral ischemia and neurologic death are also associated with an upregulation of several proinflammatory molecules.^{12–15} Immune system-mediated damage is suspected to alter the immunogenicity of donor organs in a manner that increases their susceptibility to recipient host responses.^{16,17} For example, when compared with controls, neurologically deceased rats expressed elevated levels of tumor necrosis factor- α and interleukin-1 β , a finding that persisted for days in recipients following experimental transplantation.¹⁸ Rats receiving renal transplants from neurologically deceased donors have also demonstrated increased graft infiltration by macrophages and neutrophils compared with living donors.¹⁹ Other non-antigen-related immune pathways may also lead to organ dysfunction in neurologic death, such as reactive oxygen species formation with postischemic reperfusion injury.^{20,21}

From a hormonal perspective, the combination of increased intracranial pressure, ischemia, and inflammatory-mediated damage in neurologic death interferes with hypothalamus and

pituitary functioning. As a result, several hormonal axes begin to fail.^{22–24} The posterior pituitary seems to be more susceptible to injury and functional impairment than the anterior pituitary.^{25,26} It is suspected that this is likely a result of ischemic damage to neurons deep within the hypothalamus that supply and regulate hormone secretion of the posterior pituitary. In contrast, the anterior pituitary may retain more functionality owing to the preservation of a degree of extracranial blood supply via the hypophyseal arteries.²⁵

This particular pattern of hypothalamic and pituitary dysfunction forms the basis of the remainder of this review. Arginine vasopressin (AVP) deficiency due to posterior pituitary insufficiency is the most common finding and will be discussed first. This will be followed by a review of thyroid hormone and cortisol, the activities of which are more variably affected in neurologic death. We will then conclude by reviewing the evidence for combined hormonal therapy as well as other future directions in endocrine aspects of organ donor management.

Specific Hormone Dysfunction

Arginine Vasopressin

AVP is a peptide that is formed in the hypothalamus and then stored in as well as secreted from the posterior pituitary. Its activity upon the V1 receptors of vascular smooth muscle leads to vasoconstriction (i.e., its "vasopressor" effect), and its activity upon the V2 receptors within the renal collecting system promote the reabsorption of free water (i.e., its "antidiuretic" effect).²⁷ Secretion of AVP from the posterior pituitary is impaired in over three-quarters of potential pediatric organ donors.²⁸ Given its high frequency in children, AVP deficiency and its consequences should be anticipated.

Diabetes Insipidus

Based on feedback from osmoreceptors and baroreceptors, AVP regulates extracellular fluid volume by modulating the reabsorption of water from the kidneys. Accordingly, a lack of AVP leads to unregulated renal losses of free water resulting in a state of diabetes insipidus. Although there are no validated diagnostic criteria, diabetes insipidus should be presumed if, in response to fluid deprivation, urine output remains excessive (>4 mL/kg/hour) as well as dilute (<200 mOsm/kg H₂O) and is associated with hypernatremia (>145 mmol/L) and an increased serum osmolality (>300 mOsm/kg H₂O).⁶

Although the mechanism has not been established, diabetes insipidus has the potential to impair organ function beyond that simply resulting from diuresis, hypovolemia, and hemodynamic instability. It has been postulated that rising serum sodium and osmolality levels result in the accumulation of compensatory idiogenic osmoles in donor organs.²⁹ Once transplanted into the recipient with an osmolar environment within the normal range, these organs may be subjected to damage as a result of significant intracellular fluid shifts. An early review of 181 consecutive liver donors suggested that a final serum sodium level > 155 mmol/L was associated with higher rates of early graft loss compared with those whose final serum sodium level was ≤ 155 mmol/L (33.3 vs. 11.6%;

$p < 0.05$).²⁹ However, a subsequent retrospective analysis of 250 liver transplants which controlled for degree of liver disease and type of preservative solution did not find such an association.³⁰ A more recent multicenter prospective study of 961 liver donors did find that lower serum sodium levels (specifically at 12–18 hours post-organ donation authorization) were independently associated with short-term graft survival, although only marginally (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.90–0.99).³¹ When balanced with the risks of maintaining control of serum sodium, and the availability of inexpensive management strategies, current practice should include the avoidance of hypernatremia.

Potential organ donors with diabetes insipidus may be managed with an intravenous AVP infusion or desmopressin. As will be discussed in further detail, an AVP infusion is the preferred agent for patients with concomitant hypotension. It provides the dual benefits of antidiuresis and hemodynamic support. AVP infusions may also be used effectively in pediatric patients with diabetes insipidus alone³²; however, concerns around possible interference with end-organ circulation exist based on animal models of splanchnic blood flow.³³ For this reason, in normotensive patients, high doses of AVP should be avoided.

Diabetes insipidus without hypotension may also be managed with desmopressin (1-desamino-8-D-arginine vasopressin, or DDAVP). Desmopressin is an AVP analogue whose mechanism of action is highly specific for the V2 vasopressin receptors in the renal collecting system.³⁴ This property allows desmopressin to inhibit diuresis with virtually no

vasopressor side effect. Multiple routes of administration are available, but the intravenous route is preferred in the organ donor. Although concerns for potential thrombogenic complications have been raised with desmopressin use, it does not seem to impair graft survival. One trial of 97 adult organ donors randomized to receive desmopressin or nothing for diabetes insipidus demonstrated no impairments in preprocurement renal function or posttransplant need for dialysis in those who received desmopressin.³⁵ A more recent retrospective analysis of 458 neurologically deceased adult kidney donors suggested that those treated with desmopressin actually had improved prerecovery renal function (creatinine, 97 ± 44 vs. 124 ± 106 $\mu\text{mol/L}$; $p < 0.001$).³⁶

Although there is no literature examining the management of pediatric organ donors specifically with diabetes insipidus in the absence of hypotension, both AVP and desmopressin are considered acceptable treatment options, with desmopressin being preferred in normotensive patients. There are no established dosing guidelines for pediatric organ donors; however, suggestions based on the limited pediatric experience are shown in ► **Table 1**. If AVP is being used, careful attention should be directed toward the differences in infusion dosing for the treatment of diabetes insipidus compared with hypotension. In either case, AVP infusions or desmopressin boluses should be titrated to target serum sodium levels of 130 to 155 mmol/L and urine output of 0.5 to 3 mL/kg/hour. If needed, AVP and desmopressin may also be used simultaneously for patients with both significant hypernatremia and hypotension.⁵

Table 1 Suggested hormone dosing for pediatric organ donors

Hormone and Indication	Dosing range			Comments
Arginine vasopressin (AVP) for diabetes insipidus	0.0002–0.01 units/kg/h infusion			Titrate to urine output 0.5–3 mL/kg/h, and serum sodium 130–155 mmol/L
Desmopressin (DDAVP) for diabetes insipidus	0.25–1 µg IV every 6 hours			
Arginine vasopressin (AVP) for vasodilatory shock	0.0003–0.0025 units/kg/min infusion			Titrate to normal blood pressure for age and markers of cardiac output
Methylprednisolone for immunosuppression	15–30 mg/kg IV once daily (suggested maximum dose: 1,000 mg)			Collect immunotyping samples prior to administration
Insulin for hyperglycemia	0.02–0.1 units/kg/h infusion			Monitor for hypoglycemia, consider avoiding use in pancreas procurement
Thyroxine (T4) for hypothyroidism ⁵¹	Age	Load (µg/kg)	Infusion (µg/kg/h)	Consider use with refractory hypotension and/or cardiac dysfunction
	0–6 mo	5	1.4	
	6–12 mo	4	1.3	
	1–5 y	3	1.2	
	6–12 y	2.5	1	
	12–16 y	1.5	0.8	
	>16 y	0.8	0.8	
Combined hormonal therapy <ul style="list-style-type: none">• AVP/desmopressin• Thyroxine (T4)• Methylprednisolone• (± Insulin)	As above			Routine use in pediatric organ donors eligible for heart, lung, and/or kidney procurement, as well as those demonstrating cardiac dysfunction

Hypotension

A state of hypotension often occurs as a result of a multiple issues in the potential organ donor, including insufficient preload, myocardial dysfunction, autonomic dysregulation, and catecholamine depletion. As with any intensive care unit patient, it is important to begin by replenishing preload,^{28,37} while recognizing that many patients will still require vasoactive support. Given that the sequence of brainstem ischemia and herniation typically results in diminished sympathetic activity as well as AVP deficiency, optimizing vascular tone becomes a priority.

Owing to its effects on contractility and vasoconstriction, dopamine has long been considered the first-line agent for treating hypotension in the organ donor.⁵ However, the early and even primary use of AVP has begun to gain acceptance. The only pediatric data available comes from a retrospective analysis of 63 organ donors who received various combinations of vasoactive therapies at the treating physician's discretion.²² Compared with 29 age-matched controls, the 34 donors administered AVP demonstrated significantly higher mean arterial pressure at organ procurement (80 ± 14 vs. 68 ± 22 mm Hg; $p < 0.01$) and an increased ability to wean other vasopressors. However, organ recovery and function was not different between groups in this study. Other studies involving adult organ donors have also shown improved hemodynamic stability and reduced catecholamine administration associated with the use of AVP.^{38–40} This finding is considered advantageous as it may limit excessive catecholamine-driven demands on an already compromised heart. Supporting this idea, a retrospective analysis of 12,322 donors demonstrated that AVP use was associated with higher numbers of organs retrieved per donor (3.75 vs. 3.33 ; $p < 0.001$) and independently associated with lung recovery on multivariate analysis (adjusted OR, 1.22 ; 95% CI, $1.11–1.34$).⁴¹ Another large review of 10,431 donors suggested that AVP administration was associated with fewer instances of organ refusal due to poor function (OR, 0.93 ; 95% CI, $0.91–0.96$) and independently associated with high-yield (four or more) organ recovery on multivariate analysis (adjusted OR, 1.82 ; 95% CI, $1.65–2.00$).⁴²

As such, there is growing support for the use of AVP in the treatment of hypotension in organ donors, and as discussed previously, AVP is a good option for hypotensive patients with concurrent diabetes insipidus. Preliminary pediatric evidence suggests it may also spare catecholamine usage in the presence of circulatory compromise.²² However, caution should still be maintained when administering AVP, as reductions in splanchnic blood flow have been demonstrated when compared with dopamine.³³ Additional benefit may be conferred to hemodynamically unstable patients when AVP is used in combination with other hormone therapies.^{41,42} Suggestions for dosing AVP in hypotension are shown in ►Table 1.

Thyroid Hormone

The anterior pituitary secretes thyroid-stimulating hormone (TSH), which regulates thyroid release of triiodothyronine (T3) and free thyroxine (T4). In healthy individuals, thyroid

hormones are known to play a role in modulating cardiac function as well as vascular resistance.⁴³ Given this knowledge, and the results of an early animal model of neurologic death which suggested a reversal of anaerobic metabolism with T3 administration,⁴⁴ there has been increased interest in organ donor thyroid function.

Potential organ donors have been shown to be deficient in T3, but maintain preserved T4 and TSH levels.^{25,26} Despite the initial study demonstrating reversal of anaerobic metabolism in a neurologically deceased baboon model,⁴⁴ results supporting the efficacy of T3 administration in human organ donors have been inconclusive.^{45–48} Further to these early studies, two more recent large-scale retrospective adult transplant database analyses have added newer but still somewhat conflicting information.^{49,50} The first compared 30,962 organ donors who received either T3/T4 supplementation to 32,631 who did not, and found that more organs were procured from the group who received supplementation (3.35 ± 1.76 vs. 2.97 ± 1.72 ; $p < 0.0001$). The second study reviewed thyroid hormone therapy in 74,180 organ donors from the years 2001 to 2012, and found that while thyroid hormone treatment rates rose from 25 to 75% during the study period, the mean number of procured organs was unchanged (3.51 vs. 3.50 ; $p = 0.08$). This study, however, did not compare those receiving thyroid hormone to those who did not, and did not control for possible changes in the organ donor pool and organ recovery methods over time.

Only one study of thyroid hormone treatment in pediatrics is available, and examined the administration of supplemental T4.⁵¹ In this retrospective analysis of 171 pediatric organ donors, the 91 children who were treated with a bolus and infusion of T4 at the discretion of the treating physician demonstrated significant reductions in a composite vasopressor usage score, a finding which persisted following multivariate adjustment. Graft function and transplant outcomes were not investigated as part of this study. It should be recognized that intravenous forms of the more biologically active T3 are costly and unavailable in many countries, which prohibit its use and also limit its study.

Although pediatric-specific literature is scarce, the overall data to date suggest that treatment with thyroid hormone may improve hemodynamic stability and increase organ procurement. The time associated with current conventional thyroid hormone diagnostic techniques makes them impractical for use in the acute setting. Thus, circumstances in which empiric thyroid hormone therapy should be considered include refractory hemodynamic instability and/or demonstrated cardiac dysfunction by echocardiography. In these instances, both intravenous T3 and T4 are acceptable forms of treatment, although only T4 has been studied in pediatric organ donors. There are no established dosing regimens in pediatric neurologic death; however, ►Table 1 outlines suggestions for T4 administration.

Corticosteroids

The anterior pituitary secretes adrenocorticotrophic hormone (ACTH), which stimulates cortisol release from the adrenal

glands.⁵² Cortisol has numerous functions in healthy individuals, but its most relevant roles in the organ donor are maintaining hemodynamic stability and modulation of the body's immune system.⁵³

Adrenal Insufficiency

Whether potential organ donors develop a state of adrenal insufficiency and/or suppression is unclear. A study of 37 adults with severe traumatic brain injury revealed that compared with matched nonneurologically deceased patients, the 17 neurologically deceased individuals had significantly lower circulating cortisol levels (234 ± 171 vs. 469 ± 182 nmol/L; $p < 0.001$) and significantly reduced peak cortisol response to ACTH administration (466 ± 174 vs. 659 ± 157 nmol/L; $p = 0.001$).²³ In this small, poorly powered cohort study, adrenal insufficiency (defined as serum cortisol level < 497 nmol/L, 30 minutes after the administration of low-dose tetracosactrin [250 µg]) was not associated with differences in heart rate, blood pressure, or need for inotropic support.

A more recent prospective multicenter cluster study of 208 neurologically deceased adults has replicated these results and further trialed steroid replacement therapy (50 mg bolus of hydrocortisone, followed by 10 mg per hour continuous infusion).⁵⁴ Of the 121 patients for whom ACTH stimulation data were available, 94 (77%) were considered not to be adrenally sufficient (either baseline random serum cortisol < 497 nmol/L, or < 248 nmol/L increase in serum cortisol 60 minutes after the administration of 250 µg of tetracosactrin). In this study, compared with controls, the group receiving steroid replacement had reduced need for norepinephrine (mean, 1.18 ± 0.92 vs. 1.49 ± 1.29 mg per hour; $p = 0.03$), shorter time on norepinephrine (median, 874 vs. 1,160 minutes; $p < 0.0001$), and a higher proportion who were able to wean norepinephrine support (33.8 vs. 9.5%; $p < 0.0001$). Steroid use, however, was not associated with higher organ procurement or improved graft function.

There is no evidence to date that reduced cortisol levels at baseline or in response to ACTH administration in potential pediatric organ donors are associated with poorer transplant outcomes. As such, routinely administering glucocorticoids to all organ donors in isolation for the purposes of steroid replacement is not recommended. However, steroid stress dosing should be considered in those with preexisting known or clinically suspected adrenal insufficiency.

Inflammatory Cascade

The proinflammatory state triggered by neurologic death and the organ procurement process is associated with reduced graft functionality.^{55–57} Molecular studies have shown that some inflammatory molecules, but not all, may be modulated by steroid treatment.¹⁵ For this reason, glucocorticoid therapy aimed at immunosuppression in organ donors has been proposed to regulate the immune response and improve graft survival.

Early observational trials involving heart and lung donors treated with corticosteroids suggested improved lung function and procurement rates of both organs.^{58,59} However, a

recent systematic review of 11 randomized controlled studies and 14 observational studies did not show similar effects.⁶⁰ Most studies involved adult organ donors treated once daily with methylprednisolone doses ranging from 1 to 5 g. The most common primary outcome in the randomized controlled trials was graft survival in kidney as well as liver transplant patients, and was largely equal in groups exposed to steroid treatment. Outcomes involving hemodynamic stability, organ procurement, and patient survival were not well characterized by these studies. A meta-analysis was not possible due to excessive heterogeneity of the randomized controlled trials, which were also reported to generally be of poor quality and at high risk of bias.

Despite the absence of robust literature, and any evidence in pediatrics, many institutions currently routinely treat potential lung donors, including children, with corticosteroids at variable and often immunosuppressant doses. A recent review of data collected prospectively from 132 consecutive adult organ donors suggested that low-dose steroid therapy (300 mg hydrocortisone load followed by 100 mg every 8 hours) resulted in similar oxygenation, hemodynamics, and organ procurement compared with high-dose steroid therapy (15 mg per kilogram of methylprednisolone once daily).⁶¹ While optimal pediatric regimens are unknown, high-dose therapy continues to be suggested (see ► **Table 1**).^{5,6} It is also recommended that donor/recipient matching bloodwork is sent prior to the initiation of corticosteroids to avoid any potential interference with immunotyping.

Combined Hormonal Therapy

The combination of AVP, thyroid hormone, and glucocorticoid is considered combined hormonal therapy (CHT). Although individually their effectiveness remains somewhat unclear, especially for corticosteroids and thyroid hormone replacement, there is emerging evidence to support the use of CHT.

A retrospective review was undertaken involving over 40,000 neurologically deceased organ donors from the years 2000 to 2009 for whom detailed hormonal treatment information was available (i.e., AVP, thyroid hormone, corticosteroid, and insulin). The study employed advanced epidemiological methods to compare individual and multiple organ procurement rates with all possible combinations of the four hormones (16 total possibilities, including no hormones). The findings suggest that the combination of AVP, thyroid hormone, and corticosteroids was important in maximizing organ procurement. The addition of insulin to the regimen also provided mild benefit, but may be detrimental to procurement of the pancreas.⁶²

A retrospective observational analysis of over 4,000 heart transplant recipients for whom complete hormonal information was available has suggested similar findings.⁵⁹ All possible combinations of therapy with AVP, thyroid hormone, and corticosteroids were investigated and it was determined that CHT had the least early graft dysfunction (OR, 0.45; 95% CI, 0.28–0.72) and lower mortality at 1 month posttransplant (OR, 0.47; 95% CI, 0.27–0.83). Donors treated with steroids alone or steroids plus thyroid hormone also had reduced early graft dysfunction, but to a lesser extent than those who received CHT.

Overall, CHT appears to confer some possible benefits in organ procurement as well as transplantation, and has minimal risk associated with its use. Although pediatric-specific data are lacking, CHT (consisting of AVP/desmopressin, thyroid hormone, and corticosteroids) is currently recommended for all pediatric organ donors eligible for heart, lung, and/or kidney procurement, and those demonstrating cardiac dysfunction. Dosing strategies for the various hormones used in CHT are shown in ►Table 1.

Other Hormones

Existing literature exploring hormonal changes following neurologic death has largely been focused on AVP, thyroid hormone, and corticosteroids, as they are directly regulated by the central nervous system and therapeutic strategies for each are readily available. It is likely, however, that the functions of many other hormones are affected following neurologic death and are worthy of study in the context of organ donor management.

Insulin is a peptide synthesized and secreted by the β -cells of the pancreas, and it continues to be secreted to levels that are detectable in the circulation after neurologic death.⁶³ This same study postulated that organ donors develop increased resistance to insulin, as many individuals demonstrated hyperglycemia in the presence of circulating insulin (none had a history of diabetes). Targeting tight glycemic control has gained interest in various critical care populations, but its role in neurologic death has not been well established. Some preliminary evidence suggests a possible association between hyperglycemia and impairment of preprocurement and short-term renal function^{36,64}; however, no therapeutic studies are available. As discussed, insulin has been variably included in some CHT regimens. Recent evidence suggests that insulin likely only provides a small amount of potential benefit compared with the other hormones, and possibly compromises pancreas procurement.⁶²

Glucocorticoids have received substantial attention in organ donor management literature, but mineralocorticoids have been far less studied. One study of circulating hormone levels in pigs found that aldosterone levels steadily fell over the 3-hour period following neurologic death, and in parallel with cortisol.⁶⁵ Although the fall in aldosterone level did not reach statistical significance, measurements were not collected beyond the 3-hour mark. Given that aldosterone is known to regulate fluid and electrolyte homeostasis, its potential role in neurologically deceased organ donor management could warrant further investigation.

There has also been preliminary interest in the potential role of hormones such as progesterone and vitamin D in severe traumatic brain injury. While progesterone is better known for its involvement in signaling within the reproductive system, and vitamin D for its role in calcium and bone metabolism, both have also been found to act as neurosteroid compounds and demonstrate interactions with the central nervous system. A study of progesterone treatment in a rat model of brain injury suggested it reduced proinflammatory molecules such as tumor necrosis factor- α and interleukin-1 β .⁶⁶ Vitamin D deficiency is

common in critically ill children, and has been shown to be associated with hemodynamic instability.⁶⁷ Interactions between vitamin D status and neurohormonal regulation, specifically the adrenal axis, have also been demonstrated.⁶⁸ Recent studies suggest that vitamin D is amenable to rapid normalization in the pediatric population.⁶⁹ While there is currently no information investigating their role following neurologic death, these are both examples of hormones becoming involved in managing critically ill patients and may be translatable to the complex physiology of potential organ donors.

Future Directions

As demands for the quality and quantity of organ transplantations continue to rise, further research aiming to improve graft procurement and survival is essential. The ability to perform large, prospective, randomized studies is limited by the relative infrequency of organ donation at present. In recent years, however, research using large transplantation databases has begun to provide answers. Nonetheless, confirmatory prospective studies utilizing a systematic and collaborative research model will be required to advance our understanding of the hormonal effects on graft suitability, procurement, and function. Pediatric patients in particular are in a position to benefit immensely from organ transplantation, and thus pediatric-specific investigations in all respects should be considered highly valuable.

Contributions

Both Drs. Gupta and Dhanani performed the literature review and drafted the article. Both authors reviewed the manuscript and approved the final version as submitted.

Funding

None.

Conflict of Interest

Dr. Dhanani is the chief medical officer of the Trillium Gift of Life Network.

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