Organ Donation : Intensive Care Issues in Managing Brain Dead

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Abstract

Organ donation and transplantation is one of the most powerful and dramatic practices in modern medicine. It is the pinnacle of centuries of dreams, massive amounts of accrued knowledge and impressive technical developments. One organ donor has the potential of saving more than five lives and impacting the quality of life of many others via tissue donation. The clinical team has a responsibility to the donor families and the recipient patient to do everything possible to provide best practices supported by the best evidence. These standardized best practices should come from the published evidence which is adapted for use in the specific environment, culture, and infrastructure of the institution.

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Introduction

In response to a traumatic brain injury or physiological “insult” to the brain (e.g., hemorrhagic or ischemic stroke), some patients suffer global and irreversible loss of brain stem function, leading to a diagnosis of brain death. Some of these patients may be candidates for organ and tissue donation, a decision mediated by the patient’s previously expressed wishes, sometimes in the form of an advance directive or organ donor card, and the preferences of the patient’s family. Organ donation is truly a family-driven process and can be affected by various social, educational and spiritual considerations. An organ procurement organization (OPO) representative or specially trained hospital staff member is typically responsible for communicating with family members about the process of organ donor management. Because significant emotional issues may be involved with the loss of a loved one, educating the family and sincere sensitivity regarding their needs and wishes are crucial to the organ donation process. Organ donation also includes a complex set of medical practices [1,2]. Key steps in beginning the process involve diagnosing and managing the brain dead patient.

The Issues

A major issue in a hospital’s neurocritical care unit (NCU) is management of the brain dead cadaver with a focus on optimizing the preservation and transfer of the donor organs. Managing the organ donor following determination of brain death involves a comprehensive

system for medical care of the donor, which may include administering appropriate medications to maintain basic body and organ functions within physiological limits [3].

Organ preservation prior to withdrawal of extraordinary means of support (e.g pharmacologic support of hemodynamics, ventilator support of respiration) involves both monitoring and maintaining physiologic values within set parameters to avoid damage and maintain organ function. These parameters include blood pressure, respiratory rate, and fluid and electrolyte status. Function and levels can be maintained through administration of medications such as corticosteroids and thyroid hormones, as well as through adjustments to ventilator settings and fluid administration to maintain respiratory rate and electrolyte balance.

Synchronous management of the brain dead cadaver, the patient’s family and the members of the clinical team is crucial to ensure functioning of the implanted organ once it is transplanted. Transferring the organ from donor to recipient should be executed as quickly as possible. The wishes of family members and the actions of the care team and of the OPO representatives are important elements in managing the process outcomes.

Methodology in Maintenance

Obtaining a complete and detailed medical history is critical, even if the available time is limited. Discussion with the family should start with a thorough explanation of the patient’s grave condition and the process of organ donation. A definition of relevant medical terminology

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such as circulatory arrest and brain death may be useful in avoiding miscommunication later [4].

Next, the patient's donor candidacy must be assessed. In most cases, an overwhelming infectious process or an active malignancy would preclude donation [5], therefore these diagnoses should be ruled out along with other preexisting conditions that may impact the functional capacity of various organs and preclude their use [6]. Significant and devastating physiologic changes may begin to evolve over several hours before brain death. The longer the duration of this process, the more likely complications will occur, with the potential to abort possible functional organ recovery. In this phase, supportive care is first and foremost directed toward the dying patient. Nonetheless, it is appropriate to prepare for a therapeutic shift from cerebral protective measures to optimizing donor organs immediately after brain death.

Once the diagnosis is made, it is essential that the family understands that brain death is irreversible and that their loved one is "dead." Affording the family time in a private setting after the pronouncement of brain death increases the rate of consent to donate organs. It is best if the request is made by experienced personnel to properly address any and all concerns the members of the family may have [7]. The successful identification and conversion of the potential donor to an actual donation requires an integrated team approach.

Brain death has been defined previously in various ways [8]. Current guidelines and diagnostic criteria are established with one common goal - unquestionable clinical diagnosis of irreversible loss of all brain functions (Table 1) [9]. Confirmatory studies, (Table 2) such as a cerebral angiogram, are not mandatory. Secondary to a multitude of physiologic abnormalities, graft survival from brain-dead donors is inferior to living-unrelated donors, despite better HLA matching [10].

Physiological Changes in Brain Dead

Herniation is followed by a resolution of the sympathetic surge and a subsequent variable loss of sympathetic tone. Vasodilatation and reperfusion injury occurs. Hypotension, arrhythmias, endocrine deficiencies, electrolyte changes and hypothermia develops in majority of the donors. High-energy stores are depleted, Ca^{2+} influx overwhelms the ionic pumps, endothelial swelling develops and reactive oxygen species accumulate secondary to insufficient perfusion.

Activation of inflammatory mediators such as the complement system, thromboxanes, platelet and leukocyte factors are central to the pathophysiologic events after onset of brain death. As time progresses, there is a progressive leukocyte influx into solid organs with a continuous inflammatory deterioration that

Table 1

Clinical criteria for brain death

Exclude

- Hypothermia (less than 32°C), neuromuscular blocking agents
- Central nervous system depressants (intoxicant, poison, sedative, hypnotic, narcotic, etc.)
- Central nervous system pathology (Locked-in syndrome, Guillain-Barre syndrome, encephalitis, etc.)
- Acute metabolic derangements (Hepatic coma, uremic coma, hypoglycemia, abnormal pH or electrolyte, etc.)

Examination

- Unresponsiveness, absence of cerebral and brainstem functions
- Absence of corneal reflexes and pupillary response to light
- Absence of pharyngeal and tracheal reflexes
- Absence of caloric response
- Absence of respiratory drive at a partial pressure of arterial carbon dioxide that is 60mm Hg, or 20mm Hg above normal base-line values

Interval between two evaluations (by patient's age) for confirmation of brain death

- Term to 2 month old : 48 hours, 2 month to 1 year old : 24 hours, 1 to 18 year old : 12 hours
- Above 18 year old : Interval is optional (As per THOA guidelines it is 6 hours)

Confirmatory tests

- Term to 2 month old : 2 confirmatory tests
- 2 month to 1 year old : 1 confirmatory test
- Above 1 year old confirmatory test is optional (in Indian context it is 6 hours)

Table 2

Confirmatory tests to establish brain death

- Electroencephalogram
- Transcranial doppler ultrasonogram
- Spiral computer tomogram
- Magnetic resonance imaging
- Cerebral angiogram
- Technetium (Tc 99m) cerebral scintigram

enhances the immunogenicity of the graft. There is a measurable increase of inflammatory compounds: intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1, E-selectin, interleukin-6, interferon- γ , macrophage inflammatory protein-1 α , tumour necrosis factor- α and countless others [3].

Donor Management

Brain-dead donor management has come a long way from the old fashioned passive waiting for the organ retrieval team to arrive. Standardized and systematic critical care therapy was repeatedly found to increase the quantity and the quality of transplanted organs [11]. Hypotension, which is frequently multifactorial, affects almost all patients after brain death [12]. Hypovolemia can be secondary to numerous factors, such as traumatic blood loss, central diabetes insipidus, prior fluid restriction and diuretic therapy.

Loss of sympathetic tone compounds the problem by

giving rise to vasodilation, blunted vasomotor reflexes and impaired cardiac contractility. Multiple variations of cardiovascular support algorithms have been published with the same underlying intent—achieving better postoperative graft function, through optimizing organ preservation before organ recovery from the donor. The first step is restoration of euvoemia, before aggressive pharmacological therapy is initiated. There is no convincing evidence as to whether crystalloid or colloid fluids carry more benefit. However, maintaining the intravascular volume and colloid oncotic pressure within the physiologic range and a hemoglobin concentration above 10 g/dL are reasonable therapeutic goals. Frequently, a combination of blood components, crystalloid and albumin is infused to achieve a central venous pressure of 6–10 mm Hg. 31-hydroxyethyl starch is avoided in an attempt to prevent renal tubular injury and impaired postoperative renal graft function [13].

Optimizing oxygen delivery is aggressively pursued to prevent metabolic deterioration of donor organ function. Echocardiography and/or pulmonary artery catheter monitoring are used to assess preload, cardiac output and guide vasoactive therapy. Once cardiac filling is restored, intravenous catecholamines are infused to improve contractility and vascular resistance, maintain a cardiac index over 2.4 litres/min/m² and a mean arterial blood pressure above 60 mm Hg.

Conventional wisdom suggests minimal use of catecholamines for fear of excessive vasoconstriction, depletion of myocardial high-energy substrates and adrenergic receptor down regulation. There is some evidence supporting dopamine as a first choice inotrope, in doses of less than 10 mcg/kg/min. The same analysis found that norepinephrine administration was associated with an increased incidence of cardiac graft failure, but similar negative effect was not observed with dopamine, dobutamine, and epinephrine [14]. In addition to the improved oxygen delivery, there are further possible explanations for the salutary effects of adrenergic drugs. These include oxygen-radical scavenging, inhibition of inflammatory mediators and modification of leukocyte adhesion [15].

Diabetes insipidus secondary to pituitary infarction reportedly occurs and massive polyuria, hypovolemia, hyperosmolality, hyponatremia, hypokalemia and other electrolyte abnormalities need to be corrected pharmacologically along with volume replacement. The therapeutic end point of desmopressin or vasopressin therapy is an hourly urine output of 0.5 to 2 mL/kg [16].

Arrhythmias are reported in brain-dead donors with a highly variable prevalence [17], which could be due to the myocardial injury from massive sympathetic surge

during brain herniation and various electrolyte abnormalities. Tachycardia is usually due to exogenous catecholamines and responds well to changing to a different vasopressor or administering an intravenous β blocker. Bradyarrhythmias present more of a therapeutic challenge because, by definition, brain dead patients have no vagal tone and anticholinergic drugs are ineffective in increasing their heart rates. If strong chronotropic agents like isoproterenol are unsuccessful, electrical pacing is indicated to prevent circulatory compromise. Agonal arrhythmias (ventricular fibrillation, asystole) tend to be very resistant to all therapeutic interventions. This is just one more reason for expeditious organ retrieval.

Pulmonary complications manifest often in the brain-dead donor secondary to neurogenic pulmonary edema [18]. Optimal respiratory care includes avoidance of lung injury from suboptimal mechanical ventilation strategies and prevention of aspiration pneumonitis. Excessive fluid resuscitation is an easily correctable cause for relative hypoxemia (low PaO₂/FiO₂ ratio). Judicious intravenous fluid administration, corticosteroids [19], diuretic therapy and aggressive pulmonary toilet have all been documented to improve lung procurement and successful transplantation [20]. Therefore, final decision on the suitability of the donor's lungs should not be determined before treatment options have been appropriately used to optimize gas exchange and pulmonary function. Chest radiographs and fiberoptic bronchoscopy are undertaken to assist in the decision-making.

Hypothermia develops in approximately half of all donors. Lack of hypothalamic temperature regulation and generalized vasodilatation are the two main causes of donor poikilothermia. Prevention of heat loss by application of forced air blankets, heated mattresses and administration of warmed intravenous fluids is more effective than restoration of normothermia in a hypothermic donor.

Hyperglycemia rarely represents a pancreatic insufficiency in brain dead donors. It is most often a sign of peripheral insulin resistance [21]. Prompt correction of hyperglycemia is desirable to avoid hyperosmolality, osmotic diuresis, electrolyte abnormalities and the resulting cardiac instability.

Coagulopathy, secondary to thrombocytopenia, hypothermia, massive release of plasminogen activator, and other tissue compounds, frequently requires transfusion of different blood components [22]. Accepted therapeutic end points are an international normalized ratio below 2.0 and a platelet count over 50,000/mm³.

Endocrine deficiency of variable degree was found

in several human studies of the brain dead. Posterior pituitary infarction and partial destruction of the anterior pituitary are commonly identified on autopsy. Hormone replacement therapy should be strongly considered to stabilize the hemodynamically marginal donor [23].

Alone or in combination, administration of thyroid hormone, corticosteroids, vasopressin and insulin, were found to improve cardiac function in animals and humans. This improvement resulted in significantly increased number of adequate organs for transplantation and improved graft-survival [24].

Cytoprotective therapy has been the focus of numerous investigations with the intent to reduce the initial inflammatory process in the donor. Ischemic preconditioning, anti-intercellular adhesion molecule antibody, anti-C5a, selectin inhibitors, n-acetyl cysteine, mannitol and corticosteroids are used in various treatment protocols with varying degrees of success.

Organ Retrieval: Issues in the Operation Theatre

Donor care during the organ retrieval surgery presents a unique combination of various challenges beyond the scope of the anesthesiologist's daily practice [25]. The clinical focus must shift from patient preservation, to that of organ preservation.

Typically, multiple surgical teams work during the procedure both sequentially and concurrently. The importance of interdisciplinary communication cannot be overemphasized and the anesthesiologist has a special opportunity to facilitate information sharing and constructive interaction. There may be some variations in individual donors, however standard organ removal is as follows: heart and lungs first, followed by subsequent hepatectomy, pancreatectomy and bilateral nephrectomies [26].

Cardiovascular function, oxygenation, acid-base balance, electrolyte levels, glucose and temperature are maintained within the physiologic range. Urine output in excess of 100 mL/hour is recommended. Heparin, phentolamine (vasodilator), antibiotics and corticosteroids are administered according to the consensus of the multispecialty team. Neuromuscular blocking agents are given to provide an optimal surgical exposure and suppress the possibility of spinal-reflex-induced patient movement.

Generally, there is no need for mechanical ventilation and the presence of the anesthesiologist after the cross-clamping of the aorta. The time of this maneuver is reflected on the written record. Obviously, this is not considered the "time of death". That was established at the time of brain death declaration [25].

Organ Care

Quick and uniform cooling considerably minimizes warm ischemic damage to the various organs. However, because cooling to about 4°C does not completely arrest metabolic processes in the cells, utilization of a correct washout technique and an appropriate preservation solution is crucial for organ viability. Complete washout of all blood cells from the vascular space ensures uniform distribution of the preservative throughout micro vessels resulting in decreased immune reaction and formation of oxygen-free radicals upon reperfusion [27].

The preservative is responsible for creation of a colloid-oncotic, osmotic and electrolyte balance across cellular membranes in the preserved organ. Such balance is necessary for maintaining a constant cellular volume, membrane integrity, physiologic pH and nutrients. Lack of Na⁺ and K⁺ gradients across the membrane decreases ATP-ase activity and conserves energy. Other components include precursors to quickly restore ATP concentration upon reperfusion, free radical scavengers and antibiotic to control bacterial growth [28,29].

Organ preservation is the supply line for organ transplantation. Currently, the liver, pancreas and kidney can be successfully preserved for up to two days by flushing the organs with the University of Wisconsin (UW) organ preservation solution and storing them at hypothermia (0–5°C). The UW solution is effective because it uses a number of cell impermeant agents (lactobionic acid, raffinose, hydroxyethyl starch) that prevent the cells from swelling during cold ischemic storage [28]. Additionally, the UW solution contains glutathione and adenosine, agents that may stimulate recovery of normal metabolism upon reperfusion by augmenting the antioxidant capacity of the organs (glutathione) or by stimulating high-energy phosphate generation (adenosine) upon reperfusion.

The various techniques discussed above have significantly prolonged the functional viability of procured organs and reduced the time constraints of the entire transplant process like transportation, preparation and surgery.

Legal Issues and Organ Retrieval

The legal issues binding the organ donation specific for India are clearly outlined in the Transplantation of Human Organs Act (THOA) guidelines of 1994, with regular updated amendments. This Act is to provide guidelines for the regulation of removal, storage and transplantation of human organs for therapeutic purposes and for the prevention of commercial dealings in human organs. The issues specific to armed forces in India are based on the similar guidelines formed under the body

Table 3**Post-Brain Death Organ Preservation Protocol**

1. Continue with the non-pharmacological support as per comfort care orders
2. Remove all drugs, except antibiotics and those required to maintain hemodynamics, homeostasis and fluid balance
3. If on cardiac assist devices or cardiac pacers, keep them on until consent discussion
4. 0.9% saline IV at 1 ml/kg/hour to maintain euolemia
5. Ventilation: IPPV, TV 10 ml/kg, PEEP 5 mm Hg, keep plateau pressures - 20 mm Hg
6. Manual lung hyperinflation therapy, immediately after declaration of death
7. Methylprednisolone 15 mg/kg IV bolus
8. T₃ @ 4gm IV bolus, then 3 gm/hour IV infusion
9. Vasopressin 1 unit IV bolus, then 0.5–3.0 units/hour to maintain urinary output of 200 ml/hour
10. Paralytics (vecuronium 0.5 mg/kg IV slow bolus)

Maintain physiology (homeostasis) close to normal:

11. Central venous pressure 6–12 mm Hg
12. Systolic blood pressure of 90–140 (or MAP 60–80) mm Hg
13. Heart rate (60–120 bpm)
14. Core temperature (34–37.5°C)
15. Urine output 0.5–1.0 ml/kg/hour and under 200 ml/hour
16. Oxygen saturation - 92%
17. Normocarbica (pCO₂ 40 mmHg)
18. Arterial pH 7.35–7.45
19. Haematocrit 30%
20. Platelets 50,000/cmm
21. Glycemic control (at 80–200 mg/dL), IV insulin protocol as needed
22. Sodium 130–150 mEq/L
23. Potassium 3.5–5.0 mEq/L
24. Magnesium 1.8–4.5 mEq/L
25. Phosphorus 2.0–4.5 mEq/L

of Armed Forces Organ Retrieval & Transplantation Authority (AORTA). The Director General Armed Forces Medical Services approved the establishment of Armed Forces Organ Retrieval & Transplantation Authority (AORTA) at Army Hospital (Research & Referral), New Delhi on 11 April 2007. The functions of AORTA include a 24-hour referral service for organ donation, maintenance of donor registry, family counseling, support and coordination of organ retrieval and transplantation activity between various service hospitals and civil organizations.

Conclusion

Increasing organ donation is an important and laudable objective. A large disparity exists between the number of patients waiting for transplantation and the number of available organs. Although the daunting task of resolving this incongruence seems practically impossible at present, we must make every effort to identify potential donors, obtain consent, and convert the potential donor into an actual organ donor [30] (Table 3).

We are continuously expanding the volume of live-

donors and investigating new techniques to procure viable organs from the deceased. This includes the increasingly important consideration of donation after cardiac death, at some centers. Still, in many areas of the world, the largest numbers of organs retrieved follow conventional donation after brain death and it is imperative that these donors receive optimal care before and after the diagnosis of brain death.

Conflicts of Interest

None identified

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