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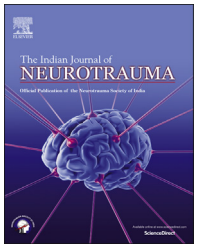

Review Article

Diagnosis of brain death and management of brain dead organ donor

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ABSTRACT

Care of a severe brain injury is one of the most daunting tasks in critical care and the importance of golden hour and quick treatment cannot be overemphasized while dealing with such patients.

On many occasions the severity of injury or the unfortunate incident of not getting timely help may see many a patient evolve to the condition of brain death. It is important to understand that brain death for all practical reasons is death and there is futility of medical science in the treatment of this condition which is a prerequisite for organ donation and transplantation.

Certification of brain death and thus facilitation of organ donation results in many patients getting a new lease of life. This article provides a concise but complete review of the diagnosis of brain death and the management of a brain death organ donor.

1. The evolution of brain death

Mollaret and Goulon coined the term "Coma depasse" which means irreversible coma after studying 23 patients who were unconscious, had no brain stem reflexes, no respiratory efforts and no electric activity seen on an Electroencephalogram. An Adhoc Committee at Harvard Medical School in 1968 conceptualized and defined brain death or irreversible coma.[1] It was in 1976 that UK Royal Medical Colleges defined brain death as complete irreversible loss of brain stem function and specified clinical criteria to certify brain death. In 1981 USA Presidents Commission recommended confirmatory tests to reduce the required period of observation. However, the commission recommended a period of 24 h observation for patients with anoxic brain damage. The Transplantation of Human Organ Bill was introduced in the Lok Sabha on 20th August 1992 and became the Transplantation of Human Organ Act in 1994 which essentially follows the UK definition of brain stem death. Hence in India it is brain stem death and not brain death as it were in the United States. Hence there is no need for confirmatory tests like EEG, radionuclide scans, transcranial dopplers or angiography. Essentially in India, this makes the diagnosis of brain death clinical and confirmatory tests are used only in the event of disagreement between the Doctors certifying brain death.

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2. Diagnosis of brain death in India

The Transplantation of Human Organs Act, 1994 (Central Act 42 of 1994), lays down the definition of death as follows: 'Deceased person' means a person in whom permanent disappearance of all evidence of life occurs, by reason of brain-stem death or in a cardiopulmonary sense at any time after live birth has taken place. It goes on to state that 'brain-stem death' means the stage at which all functions of the brain stem have permanently and irreversibly ceased.

Clinical examination forms the cornerstone in the diagnosis of brain death. However, before embarking on the clinical examination certain prerequisistes have to be satisfied

a) the cause of coma should be clear
b) cause of coma is irreversible
c) absence of following confounding factors should be ascertained
   1. alcohol or drug intoxication
   2. hypothermia
   3. muscle relaxant
   4. primary hypothermia
   5. depressant medications like benzodiazepines and opiods
   6. metabolic causes
   7. hypovolemic shock
   8. endocrinal disturbances

As per the Transplantation of Human Organ Act of 1994, brain death certification would require 4 Doctors i.e.

1) the treating Doctor
2) Doctor in charge of the hospital
3) independent specialist of unspecified specialty
4) neurologist or neurosurgeon

All the above mentioned Doctors would carry out tests documenting the cessation of brain stem activity. However, the onus for certification would lie on the neurologist and neurosurgeon with others confirming the findings.

The tests required in the certification of brain death involve:

1) demonstration of a state of extreme coma or unarousable unconsciousness
2) absence of brain stem reflexes
3) apnea even after respiratory challenge

1) *Demonstration of a state of extreme coma or unarousable unconsciousness.*
   Absence of response to a deep painful stimulus like
   a) nail bed pressure
   b) supraorbital ridge pressure
   c) sternal rub
2) *Absence of brain stem reflexes.*
   a) pupillary reflex (midbrain function; Reflex: afferent nerve II and efferent nerve III.) – no response to bright light shone into the eye
   b) facial sensation and motor response
      corneal reflex (Reflex: afferent nerve V and efferent nerve VII) – no response to wisp of cotton wool/ swabstick being touched to the edge of cornea jaw reflex – absent facial
      grimace – absence of grimace to deep painful stimulus like nail bed pressure
   c) pharyngeal reflex and tracheal reflex afferent nerve IX and efferent nerve X. Absence of gagging on stimulating the post pharyngeal wall/coughing or "bucking" on suction through the endotracheal tube (bronchial stimulation).
   d) absence of oculo-vestibular reflex(cold caloric test) – No deviation of the eyes with irrigation of the tympanic membrane (clear of cerumen or clotted blood) with head placed at 30° each ear with 50 ml of cold water (allow 1 min after injection and at least 5 min between testing on each side)
   e) absence of oculocephalic reflex (commonly known as dolls eye movement) – The examiner holds the patient's eyes open and the head is turned suddenly from the neutral position to 90° on both sides. When the reflex is intact the eyes turn opposite to the side of head movement as if lagging behind. The reflex is absent when the eyes move with the head and do not move within the orbit (performed only when no fracture or instability of the cervical spine is absent).
3) *Apnea test.*
   Considered as the most essential and integral part of the component of brain death determination which needs to be performed in the right way. The test could be termed as a brain challenge which includes:
   (a) Disconnection from ventilator for till arterial CO_2 rises to critical level
   (b) Preventing hypoxia during this time
   (c) Looking for spontaneous respiratory efforts

Prerequisites for the test

1) Core temperature 36.5 °C or 97 °F
2) Systolic blood pressure >90 mm Hg
3) Euvolemia or positive fluid balance in the previous 6 h
4) Normal pCO_2
5) Normal pO_2

Following normalization to $PaCO_2$ to 40 mm of Hg and preoxygenation for a period of 10 min the patient is disconnected from the ventilator with all monitoring devices attached after placing a catheter placed at the carina with oxygen being provided at rate of 6–8 L/min.

A positive apnea test is said to have occurred in the absence of spontaneous respiratory efforts at the end of 6 min and arterial pCO_2 more than or equal to 60 mm Hg or the rise is by 10–15 mm above the baseline (i.e. 2 mm rise per minute). The test is indeterminate if respiratory movements are absent, and arterial pCO_2 is less than 60 mm Hg. In such a scenario if the hemodynamics allows the test could be prolonged till a $PaCO_2$ of greater than 60 mm of Hg were achieved.

The above mentioned examination should be repeated by the team of Doctors separately two times at least 6 h apart in order to certify brain death in the purview of organ donation

and none of the Doctors involved in the certification should be involved with any aspect of organ harvesting and transplantation.

In most case scenarios, the brain death determination is completely clinical and does not require the help of confirmatory tests, however, in the event of discrepancy of diagnosis among the certifying Doctors or in the event that some test cannot be completely successful then the following confirmatory tests may be used. In order of sensitivity conventional angiography, EEG, transcranial Doppler ultrasonography, technetium-99m cerebral blood flow scan and somatosensory evoked potentials.

3. Management of brain dead organ donor

Brain death can provide a new lease of life to a recipient and optimum management of a brain death organ donor will help the cause effectively.

A brain dead organ donor is known to go through many complications like arrhythmia, diabetes insipidus, metabolic acidosis, DIC, infections, pulmonary edema, hypothermia, endocrine disturbances etc.

The following monitoring are considered essential during the management of brain dead organ donor

1) continuous ECG
2) pulse oxymetry
3) end tidal carbondioxide monitoring
4) arterial blood pressure monitoring
5) central venous pressure monitoring
6) hourly urine output monitoring
7) core body temperature monitoring
8) input/output monitoring

The "100 rule" is a very easy method of remembering the goals to be achieved during maintenance of an organ donor systolic arterial pressure >100 mm Hg, urine output >100 ml h^{-1}, PaO_2 >100 mm Hg, hemoglobin concentration >100 g L^{-1} and blood sugar 100% normal (added later).[2]

The most common problems that warrant immediate attention are hypotension, hypothermia and diabetes insipidus.

There are a number of societies who have specific guidelines in the management of a brain dead organ donor. Below mentioned is the summary of the various techniques in the maintenance of a brain dead organ donor which helps in facilitating optimal organ retrieval and transplant success.

4. General care

Standard monitoring as mentioned above
Maintain heart rate between 60 and 120/min, CVP – 6–10 mm of Hg
Regular monitoring of electrolytes and appropriate correction
Treatment of infection with appropriate antibiotics
Aggressive warming in order to keep core temperature >35°
Stop unnecessary drugs like opiods, sedatives and analgesics
Head up position
Continuation of enteral nutrition as tolerated
Target HB of 9–10 g/dl to optimize cardiopulmonary function in unstable hemodynamics
Hb – 7 g/dl is acceptable in stable brain dead patients

5. Specific management

5.1. *Hypotension management*

Hypotension could result due to absolute hypovolemia, neurogenic shock or myocardial dysfunction. Cause based management would be the need of the hour and optimal fluid therapy is the cornerstone of management. Central venous pressure, echocardiography or other minimally invasive monitoring should be used judiciously in the management of fluids. Basing the fluid management purely on the basis of urine output would be erroneous due to the presence of diabetes insipidus in most cases. Vasopressor and inotrope use should be minimized as much as possible and at times a pulmonary artery catheter may be utilized for optimal management. Some transplant services have catecholamines in their donor preservation algorithm to exploit their reported anti-inflammatory and preservation effects.[3–5] Increased cardiac graft dysfunction, however, has been noticed with the use of high dose nor-adrenaline infusion.[6] Vasopressin could be effectively used in these cases as vasopressin is known to help to reduce the doses of nor-adrenaline. In fact some societies like the Canadian societies have recommended vasopressin as the first choice in donor resuscitation.[7] There may be a dilemma in fluid management between generous fluid administration (which tends to benefit kidneys and liver) and fluid restriction (which tends to benefit lungs and heart). However, an adequate trade off is not difficult with experience and avoidance of a positive fluid balance is important.

5.2. *Respiratory system support*

Maintain tidal volume of 6–8 ml/kg to achieve $ETCO_2$ in normal range with avoidance of >30 plateau pressures and assuring SpO_2 > 93%. Application of peep to 4–6 cm H_2O is advisable in order to prevent microatalectasis. However, some guidelines for management of lung donors suggest larger Vt of 10–12 ml/kg.[8] A reasonable compromise seems to be the Canadian recommendation of 8–10 ml/kg.[7] If the patient is not going to be a lung donor, possibly Vt should be reduced to 6–8 ml/kg so that worsening ALI/ARDS does not affect the function of other organs.[9]

5.3. *Diabetes insipidus and hyperglycemia management*

Immediate diagnosis and appropriate treatment are very important when this condition arises. This condition should be suspected in the presence of large urine volume (>4 ml/kg/h) with rising serum sodium. Time should not be wasted in

waiting for investigations like urine specific gravity, serum osmolarity. Prompt replacement of intravenous fluids should be commenced with 0.45% normal saline. If it is still difficult to get the sodium down then it would be reasonable to start 5% dextrose Utilization of desmopressin is very essential in this scenario (vasopressin can also be used, however, it does have undesirable splancnic and renal vasoconstrictive effects). DDAVP is an analog of arginine vasopressin with enhanced anti-diuretic potency, negligible vasopressor activity and a prolonged half-life compared with vasopressin. Dose of DDAVP in adults is 1–2 μg s.c. or i.v., then 1–2 μg s.c. or i.v. PRN to achieve urine output < 3 ml/kg/h. Aim to normalize the sodium as hypernatremia is associated with hepatic dysfunction and graft loss.[10] Use of catecholamines and dextrose caused hyperglycemia which needs to be controlled with i.v. insulin infusion.

5.4. *Arrhythmia*

Atropine is ineffective for bradycardia after brain death has occurred and optimization of magnesium, potassium, calcium and sodium forms the basis of avoidance of arrhythmias.

5.5. *Endocrine support*

As per a retrospective cohort study triple hormone therapy increased kidney liver and heart utilization in donors and improved 1 year survival in transplanted kidneys and heart as per a retrospective cohort study.[11] The decision to administer these drugs should be on a case by case basis. In patients with hemodynamic instability inspite of volume loading and vasoactive medication the use of combined hormonal therapy as mentioned below may be reasonable.

- T3 (tri-iodothyronine); 4 μg bolus followed by infusion at 3 μg/h.
- Vasopressin, 1 IU bolus followed by 2.4 units/h infusion
- Methylprednisolone, 1 g i.v. every 24 h

The use of methylprednisolone is associated with improved oxygenation, reduced increases in extravascular lung water,[12] and increased lung yield. Inflammation in the liver,[13] heart,[14] and kidney[15] is also reduced.

- Insulin as indicated by blood sugars, minimum 1 unit/h

Final decisions about transplant ability rest with the relevant transplant teams.

The benefits of delay in organ retrieval to improve the condition of organs must be balanced against the risk of increasing distress in the patients' family. Brain dead organ donor management, goals, etc are subject to considerable variability and it is just time before "care bundles" for brain dead donors will come into place similar to sepsis care bundles. Reputable societies like the I.S.N.A.C.C will probably provide the platform for research in this field as currently evidence based care is currently not optimally delivered to all such donors.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *JAMA*. 1968 Aug 5;205(6):337–340.
2. Gelb AW, Robertson KM. Anaesthetic management of the brain dead for organ donation. *Can J Anaesth*. 1990 Oct;37(7):806–812.
3. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA*. 2009 Sep 9;302(10):1067–1075.
4. Schnuelle P, Yard BA, Braun C, et al. Impact of donor dopamine on immediate graft function after kidney transplantation. *Am J Transplant*. 2004 Mar;4(3):419–426.
5. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. *Transplantation*. 2001 Aug 15;72(3):455–463.
6. Stoica SC, Satchithananda DK, White PA, et al. Noradrenaline use in the human donor and relationship with load-independent right ventricular contractility. *Transplantation*. 2004 Oct 27;78(8):1193–1197.
7. Shemie SD, Ross H, Pagliarello J, et al. Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. *CMAJ*. 2006 Mar 14;174(6):S13–S32.
8. Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. *Am J Transplant*. 2002 Sep;2(8):701–711.
9. Mascia L, Mastromauro I, Viberti S, Vincenzi M, Zanello M. Management to optimize organ procurement in brain dead donors. *Minerva Anestesiol*. 2009 Mar;75(3):125–133.
10. Totsuka E, Dodson F, Urakami A, Moras N, Ishii T, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. *Liver Transpl Surg*. 1999 Sep;5(5):421–428.
11. Novitzky D, Cooper DK, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation*. 2006 Dec 15;82(11):1396–1401.
12. Venkateswaran RV, Patchell VB, Wilson IC, Mascaro JG, Thompson RD. Early donor management increases the retrieval rate of lungs for transplantation. *Ann Thorac Surg*. 2008 Jan;85(1):278–286. discussion 286.
13. Kotsch K, Ulrich F, Reutzel-Selke A, Pascher A, Faber W, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg*. 2008 Dec;248(6):1042–1050.
14. McLean KM, Duffy JY, Pandalai PK, et al. Glucocorticoids alter the balance between pro- and anti-inflammatory mediators in the myocardium in a porcine model of brain death. *J Heart Lung Transplant*. 2007 Jan;26(1):78–84.
15. Kainz A, Wilflingseder J, Mitterbauer C, et al. Steroid pretreatment of organ donors to prevent postischemic renal allograft failure: a randomized, controlled trial. *Ann Intern Med*. 2010 Aug 17;153(4):222–230.