Review article

Care of the brain dead organ donor

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Abstract

Organ donation is becoming more common but there is still a large gap between the number of people requiring transplants and the organs donated. There are set criteria for organ donation. When organ donation is considered after brain death, the physician must ensure that the prerequisites for testing are met and proceed to establish brain death using standard guidelines. The pathophysiological changes that occur after brain death must be borne in mind and utmost care should be given to counter those changes that would result in dysfunction of the donated organs. The brain dead patient must be maintained as stable as possible in the ICU. General nursing and medical care must continue. Core temperature must be maintained and infections must be treated. Blood pressure is best maintained with fluids and minimal vasopressors. Low tidal volume ventilation, optimal levels of positive end-expiratory pressures to maintain minimal FIO_2, will maintain airways open and reduce extravascular lung water. Maintain euvolaemia. Maintain urine output at 0.5–3 ml/kg/h. Electrolyte abnormalities must be corrected. Maintain blood glucose concentrations between 120-180 mg %. Triple hormonal therapy improves organ function. Organ retrieval is performed in an operation theatre and a well conducted anaesthetic care is essential for the viability of these organs. One brain-dead organ donor can potentially donate 'lives' to eight individuals. To enhance or preserve the maximum potential of the donated organs, the anaesthesiologist and intensivist play a vital role in preserving the organs as best as possible.

Keywords: Brain death, organ preservation, organ donation

Introduction

Organ donation is one of the areas receiving a major thrust in the present day. At this juncture, fully functioning complete human vital organs such as the heart, lungs, kidneys and liver cannot be synthesised and have to be donated by someone to replace nonfunctioning organs in another human being. While one of the kidneys and part of the liver can be donated by a live donor, the lungs and the heart have to obtained either from a 'live', brain-dead donor or a fresh cadaver. A brain dead organ donor can donate organs to save lives of up to eight people.

Even though there has been an increase in the awareness among the people about organ donation and centres performing organ transplants, there has been only a marginal increase in actual transplants. There is still a large gap between the number of people requiring transplants and the organs donated. While the rate of organ donation is 25.6 per million in the USA, 18.3 per million in the UK, it is 0.26 per million in India.[1-4] The low rates in our country can be attributed to reluctance of the family, superstitions, low awareness among both the physicians and lay people as well as costs incurred with transplants.

National Organ and Tissue Transplant Organisation (NOTTO) is a national organisation set up under Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.[5]

National Human Organ and Tissue Removal and Storage Network, a division of NOTTO has been mandated as per the Transplantation of Human

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Organs (Amendment) Act 2011. This network coordinates the procurement and distribution of Organs and Tissues and maintains registry of Organs and Tissues Donation and Transplantation in the country. This organisation has laid down guidelines related to organ procurement and distribution across the country.[5]

Who can donate

Organ donation can be of three types: live donor, donation after brain death (DBD) or donation after cardiac death (DCD). Organs retrieved from a 'haemodynamically stable', otherwise healthy brain-dead donor may be expected to last much longer in the recipient than those retrieved some hours ago from a cadaver, simply because the preservation of the organs is much better.

Donation after brain death

Diagnosis of brain death

The guidelines for diagnosing brain death were formulated initially in 1995 and reviewed in 2010 by the American Academy of Neurology.[6] The physician must establish the following three criteria:

1. **Prerequisites for testing:** The patient must be comatose and the coma must not be reversible. All reversible causes of coma such as hypothermia, hypotension, medications or metabolic reasons must be ruled out. The core body temperature must be greater than 35°C. If therapeutic hypothermia was instituted in the patient, at least 24 hours should have elapsed after it has been discontinued. The systolic blood pressure must be greater than 90 mm Hg and the mean blood pressure must be greater than 60 mm Hg, even if vasopressors are being used. The effect of any sedative drugs if used must have worn off. Thiopentone, if used as an infusion in high doses may need 2-3 days to wear off. Similarly renal and hepatic impairment also delays elimination of drugs. In the absence of any renal or hepatic impairment, 24 hours of stopping the sedative drug should be sufficient to ensure their elimination from the body. Any effect of neuromuscular blockers must be ruled out, if necessary using a nerve stimulator.

   The serum electrolyte levels must be normal. Renal and hepatic dysfunction as a cause of coma must be ruled out. Similarly endocrine disorders such as hypothyroidism must be ruled out, if there is any clinical evidence of it.

2. **Clinical testing:** At first, the presence of coma must be established. There should be no eye opening, no verbal or motor response. There should be no response to noxious stimulus applied to any part of the head and neck. Presence of spinal reflexes do not preclude brain death but the brain stem reflexes must be absent.

   Each of the cranial nerves is examined for their function through various reflexes. The olfactory nerve (first cranial nerve) alone cannot be tested as it is a purely sensory nerve. Pupillary reflex, both direct and consensual checks the afferent optic nerve (second cranial nerve) and the efferent oculomotor nerve (third cranial nerve). The corneal reflex requires the afferent trigeminal nerve (fifth cranial nerve) and the efferent facial nerve (seventh cranial nerve) to be intact. The gag reflex (pharyngeal reflex) tests the glossopharyngeal nerve (ninth cranial nerve) while the cough reflex tests the vagus (tenth cranial nerve).

   The ears must be examined for the presence of any wax to ensure there is a clear ear canal to conduct the caloric test. The cold caloric test is conducted by injecting ice cold saline (50 ml each side) using a syringe and a catheter and the eyes are observed for nystagmus for 60 seconds thereafter. The afferent for this reflex is the vestibulocochlear nerve and the efferent, third, fourth and the sixth cranial nerves. Any movement in the eyes preclude brain death.

3. **Absent respiratory drive after a carbon dioxide challenge:** The patient's respiratory function must be adequate to conduct an apnoea test. Acute lung injury or similar respiratory conditions may produce hypoxia during apnoea testing and thus may preclude it. Similarly, high cervical spine injury may be a contraindication to the conduct of apnoea testing.

If such conditions do not exist, one may proceed to do apneoa testing. The head end of the bed is elevated to 30°. The patient is preoxygenated for about ten minutes with 100% oxygen. An arterial blood gas is obtained to ensure that the PaO_2 is > 200 mm Hg and $PaCO_2$ is 35-40 mm Hg. A suction catheter of about 10 F size is inserted through the endotracheal tube, down to the carina and a flow of 2-4 L/min of oxygen is set. A nonrebreathing circuit with 5 cm H_2O PEEP valve may also be used. The patient is continuously observed for any chest movement. A capnograph may be kept connected to check for any respiratory efforts. At the end of eight to ten minutes, an arterial blood gas sample is taken for analysis. The pH must not be greater than 7.3 and the PCO_2 must be greater than 60 mm Hg or 20 mm Hg above baseline if the patient has a baseline $PaCO_2 \geq 40$ mm Hg. There should be no spontaneous respiratory efforts at all. If apnoea continues, it is said to be a positive apnoea test.

If the patient desaturates during apnoea testing (≤ 85% for > 30 s), the test is terminated, the patient oxygenated and the test retried with T piece and CPAP of 10 cm H_2O.

All the tests must be repeated by another intensivist and recorded. Once brain death has been certified on two occasions by two physicians, neither of whom is from the transplant team, the patient can be declared brain dead. The second examination for brain death can be done any time in the UK but must be conducted 6 hours after the first evaluation in India. Brain death can be declared only after the second evaluation after which the family can be consented for donation of organs.

If there are any contraindications to such testing but there is a high clinical suspicion of brain death, other tests such as cerebral angiography, magnetic resonance angiography, CT angiography or a transcranial Doppler may be required to demonstrate absence of cerebral blood flow.

Pathophysiological changes after brain death

The body undergoes a multitude of physiological changes after brain death.[7] These responses vary from patient to patient and depends on the primary disease condition and therapy instituted.

Cardiovascular changes: Brain death is initially associated with an intense sympathetic discharge (catecholamine storm) leading to hypertension and tachycardia. It is akin to one last effort by the body to survive. The intense vasoconstriction can lead to hypertensive crisis, shift of fluid from the peripheral compartments to central compartments, visceral ischaemia and, even myocardial ischaemia and dysfunction. This phase is usually brief and occurs because of rise in intracranial pressure. This is followed by a sustained second phase characterised by hypotension due to profound vasodilatation (vasoplegia) and bradycardia (parasympathetic stimulation) as a response to medullary death (coning and unresponsive vasomotor centres).This leads to hypoperfusion of various organs leading to their damage.

Respiratory changes: Brain death is not only associated with cessation of breathing but also parenchymal changes in the lung. Pulmonary oedema is common and may be due to increased hydrostatic pressure associated with the first phase of cardiovascular response. Brain death also results in the release of inflammatory mediators, capillary leak, increased extravascular lung water and acute lung injury.

Endocrine and metabolic responses to brain death: Anterior pituitary failure leads to disturbances in cortisol, thyroid and insulin leading to extensive metabolic changes. Hyperglycaemia due to insulin deficiency and sick thyroid syndrome due to reduced thyroid hormones are frequently seen. Posterior pituitary dysfunction produces diabetes insipidus leads to diuresis, hypovolaemia and hypernatraemia. Hypothalamic dysfunction causes disturbances in body temperature and can result in an initial hyperthermia but is followed by hypothermia as heat production is also reduced due to reduction in metabolic activity.

Disseminated intravascular coagulation: This can occur due to massive tissue thromboplastin release. Thus, brain death due to isolated head injury will not remain nonfunctioning brain alone but will soon be followed by pathophysiological changes in the rest of the body leading to progressive decline in their function and viability. Hence, organ donation must be done as soon as possible once brain death is confirmed to maximise viability of the transplanted organs.

Donation after cardiac death

Organ donation can be performed after cardiac death also but the viability of the transplanted organs can be compromised because of tissue reperfusion injury. Two types of organ donation after cardiac death (DCD) are described: *Controlled DCD* where cardiac arrest is imminent and the transplant team is ready to procure organs in anticipation of such arrest. *Uncontrolled DCD* is the term given to organ donation from patients who were brought dead, or had an unsuccessful resuscitation. Organs from controlled DCD would be expected to be more viable. In controlled cardiac arrest situations, a period of two to five minutes is allowed after cardiac arrest to ensure irreversibility after which the donation can take place. One advantage of DCD is that the intense pathophysiological changes after brain death are not seen and the organs may be more viable. However, tissue reperfusion injury can be a problem, especially if there has been a prolonged period of hypoperfusion prior to cardiac arrest. The best organs for donation are harvested from patients who have impending cardiac arrest, who are normally perfused and who have not sustained brain death. Patients with cerebral death and those who have minimal chance of recovery belong to this category.

Criteria for donation[6]

Standard criteria donor

The standard criteria donor (SCD) is a donor < 50 years old and is diagnosed to have brain death from any cause.

Extended criteria donor

The terms extended criteria donor, nonstandard donor, suboptimal donor, marginal donor, inferior donor and high risk donor are synonyms. Use of extended criteria donors increases the donor pool and even though the function of these may not be as good as those from standard criteria donor, they are still better than the native organs.

The extended criteria donor (ECD) for kidney donation is any donor > 60 years old, or a donor >50 years with two of the following: a h/o high blood pressure, serum creatinine ≥ 1.5 mg %, or death resulting from a stroke.

In liver transplantation, important ECD variables include advanced age (> 55 years), prolonged hospital stay (> 5 days), prolonged ischaemia time (cold ischaemia time > 10 h, warm ischaemia time > 40 min), and macrosteatosis.

Poor oxygenation at the time of harvest, purulent secretions and more than 20 pack-year smoking history are high risk factors for lung transplant.

The recipient must be informed that the transplant is from an extended criteria donor. If there is any dysfunction in the donor, it is possible to transplant both the kidneys into the same recipient (dual kidney transplant), expecting that the combined function of both kidneys will take care of the patient's needs.

Who is not a donor

The following patients are not to be considered as organ donors: Age > 85 years, metastatic carcinoma, other malignancies, active or untreated tuberculosis, HIV, neurodegenerative disorders, probable or definitive case of human spongiform encephalopathy. Overwhelming bacteraemia or fungaemia also may preclude organ donation.

Grey areas

Donors may be positive for hepatitis B or C. Such organs can still be transplanted to recipients who are also correspondingly positive. Active infection in the donor must be ruled out but testing positive for the antibody alone does not preclude them from being donors to recipients who have the antibody. Donors with Hepatitis B rarely test positive for the virus but Hepatitis C donors may carry the virus also. In such cases, the recipients will require antiviral medications for an extended period of time. Informed consent must be taken in advance from

recipients for accepting organ donation from patients with Hepatitis B or C antibody. The advantages are that the waiting period is reduced and potentially useful organs are utilised.

Care of the brain dead organ donor in the ICU

Once brain death is declared, there is a tendency to ignore care towards such patients considering the futility of care in them. However, it is important to remember that brain death is associated with a number of pathophysiological changes which can be detrimental to the viability of the transplanted tissues and organs. Hence, in the best interests of the potential recipients, every effort should be made to minimise such damage and extend the life of the transplanted organ.

General care: The patient is managed in ICU as it facilitates nursing and medical care, and support for relatives. General nursing and medical care must continue. Stop unnecessary drugs and infusions. Reduce heat loss. Actively warm if necessary to maintain core temperature >35°C. Actively identify and treat any current infections.

Cardiovascular management: Minimum invasive cardiovascular monitoring includes arterial and central venous pressure. Cardiac output monitoring is preferred but is not mandatory. A patient who is brain dead most often has hypotension due to vasoplegia. Hypotension is initially treated by maintaining euvolaemia using crystalloids. The use of hydroxyethyl starch is not advocated in critically ill patients and so, it is best avoided.[8] If volume expansion alone is not enough, dopamine is used as the initial vasopressor. If it is still refractory, vasopressin (0 – 2.4 units/h) may be used. When dopamine 10 μg/kg/min is inadequate, small doses of norepinephrine may be used. However, high doses of norepinephrine (> 0.05 μg/kg/min) should not be used as it can cause myocardial dysfunction.[9] Blood pressure is best maintained with optimal fluid management and minimal vasopressors. Large doses of vasopressors can cause myocardial dysfunction and reduce survival of a cardiac transplant. *Cardiovascular goals:* Heart rate 60–120 beats/min, systolic blood pressure 100 mm Hg, mean blood pressure ≥70 mm Hg, central venous pressure 6–10 mm Hg and urine output 0.5–2.5 ml/kg/h. Obtain an ECG and echocardiogram to evaluate the cardiac function. A coronary angiogram may be required in an older donor with a possibility of coronary artery disease.

Respiratory management: Low tidal volume ventilation (tidal volume of 6-8 ml/kg), optimal levels of positive end-expiratory pressures to maintain minimal FIO_2, will maintain airways open and reduce extravascular lung water. Recruitment manoeuvres may be used, especially after apnoea testing to open up collapsed alveoli. The cuff pressure must be below 25 cm H_2O and the patient must be nursed in 25° head up position**. Blood gases:** pH: 7.35–7.45, $PaCO_2$: 35-45 mm Hg, PaO_2: ≥ 80 mm Hg, SpO_2 ≥95%. A chest X-ray may be obtained after recruitment manoeuvres. Bronchoscopy is done if indicated and cultures taken as necessary.

Fluids and nutrition: Review fluid balance. Avoid hypovolaemia. Hypervolaemia must also be avoided as it can increase extravascular lung water and reduce the longevity of a lung transplant. The central venous pressure must be maintained < 10 mm Hg to maximise viability of heart and lungs without compromising other organ function. If necessary, use diuretics. Administer maintenance fluids (can use enteral route). Monitor urine output and maintain at 0.5–3 ml/kg/h. If urine output is > 4 ml/kg/h, consider diagnosis of diabetes insipidus and treat with vasopressin infusion or DDAVP. Hypernatraemia and other electrolyte abnormalities must be corrected. Continue nutrition and maintain blood glucose concentrations between 120-180 mg%.

Blood and coagulation: Consider need for transfusion if anaemic (Hb < 8 g%). Coagulation abnormalities must be treated. Thromboprophylaxis must be continued to avoid pulmonary thromboembolism.

Metabolic state: Various hormones including thyroid, antidiuretic hormone, cortisol that arise from pituitary are better replaced to maintain homeostasis. Methyl prednisolone is administered instead of cortisol. Triple hormonal therapy (THT) is provided to all donors (although cortisol levels may be normal) Methylprednisolone (15 mg/kg

q24 h) (≤ 1 g), L-thyroxine 100 μg followed by 50 μg q12h and Vasopressin ≤ 2.4 units/h (0.04 units/min) IV infusion. THT improves organ function.[10,11]

Anaesthesia for the brain dead organ donor

Organ retrieval is performed in an operation theatre under sterile conditions and a well conducted anaesthetic care is essential for the viability of these organs.

Preliminaries: Confirm that consent for organ retrieval has been obtained from the relatives. If it is a medicolegal case, confirm that permission has been obtained from appropriate authorities.

Operation theatre preparation: The operation theatre must be prepared to provide full anaesthesia. Inotropes, vasopressor and vasodilator infusions must be loaded and ready to be used. Opiates, inhaled anaesthetics, neuromuscular blockers, pressure bags and intravenous fluids are kept ready. Invasive monitoring must be available.

Preoperative assessment: These patients, designated ASA PS VI, are intubated endotracheally and possibly receiving some kind of haemodynamic support. Review previous history, management in ICU especially degree of ventilator and inotropic support and all investigations including biochemistry reports, electrocardiogram, chest x-ray, arterial blood gases and echocardiography. Check the patency of arterial line and CVP lines, and also the ongoing drug infusion therapy.

Transfer to operating room: Transport of this patient must be done with care to maintenance of airway, continued monitoring and various infusions.

Monitoring in OR: Intraoperative monitoring must include 5-lead electrocardiogram, pulse oximetry, capnography, invasive arterial blood pressure, central venous pressure and nasopharyngeal temperature.

Surgical steps: The surgical technique involves laparotomy with extended sternotomy. A long midline incision is made from the suprasternal notch to the pubis. Depending upon the stability of the donor, either the thoracic or the splanchnic dissection may follow. In a haemodynamically stable donor, dissection can be slower. Cold and heparinised preservative solution is flushed through the circulation. In an unstable patient, the abdominal organs are rapidly flushed and cooled, removed en bloc. In such cases, thoracic organs may not be retrieved. Further separation of abdominal organs is done outside the body. If the pancreas is to be harvested, the duodenum is flushed with an antibiotic or betadine solution through a nasogastric tube. The portal circulation is cannulated.

The abdominal aorta is ligated and cannulated just above the bifurcation. The heart is arrested, the aorta is clamped at the diaphragm, and the organs are flushed with preservative solution. Quick uniform cooling is essential to minimise warm ischaemic damage to the various organs. The UW (University of Wisconsin) solution is commonly used as the preservative solution. It maintains the colloid-oncotic, osmotic, and electrolyte balance across cellular membranes in the preserved organ. In general the order of organ removal is as follows: heart and lungs first, followed by removal of liver, pancreas and both kidneys. Corneas are the last to be retrieved.

Intraoperative management: The main aim of intraoperative management is to maintain homeostasis for organ preservation. The surgical incision and subsequent stimulation can cause mass reflex, which is a summation of spinal reflexes and catecholamine release leading to hypertension, tachycardia, perspiration and involuntary movements. Lazarus sign refers to the movements of the arm and hand towards the body in response to skin incision. To prevent these responses, the patient must be anaesthetised and paralysed before skin incision. Vecuronium 0.1 mg/kg and fentanyl 1 – 1.5 μg/kg is given followed by ventilation using oxygen and air mixture and isoflurane or sevoflurane. The inhaled anaesthetics may improve survival of the organs through ischaemic preconditioning and reducing ischaemia reperfusion injury. Fluids, vasopressors and vasodilators are used as required to maintain haemodynamic stability. Only short acting beta blocker should be used if necessary. The CVP must be maintained between 6-10 mm Hg till

heart and lungs are harvested. Thereafter, the CVP may be increased to 10-12 mm Hg before kidneys are harvested. Haemoglobin is maintained at 10 g%. If colloids are required, albumin must be used. Starch solutions must be avoided. Hypothermia must be treated and temperature maintained above 35°C. Excessive urine output is replaced with 0.45% saline. Insulin infusion is used as necessary to maintain blood glucose.

Rule of 100: Invasive monitoring including arterial pressure and central venous pressure is necessary to ensure vitality of the organs. Easily remembered is the 'rule of 100': systolic arterial pressure 100 mm Hg, PaO_2 100 mm Hg, urine output 100 ml/h, haemoglobin concentration 10 g% and blood sugar 100% normal.[4]

Bradycardia will not respond to atropine and a direct acting drug such as isoprenaline may be required. Heparin is administered before cross clamping. If a pulmonary artery catheter is in place, aim for a pulmonary capillary wedge pressure of 6 to 10 mm Hg, cardiac index of 2.4 L/min/m^2 and systemic vascular resistance of 800-1200 dynes.s.cm^{-5}.

Haemodynamic management has been found to be easier if the patient receives hormonal resuscitation which includes administration of methyl prednisolone, vasopressin and l-thyroxine.

Miscellaneous: Prophylactic antibiotics such as broad spectrum cephalosporin must be administered according to local infection control policy. After the dissection of thoracic and/or abdominal organs is complete, the donor is anticoagulated with 300-500 U/kg of heparin prior to cannulation of aorta. The anaesthesiologist may be asked to take blood samples for further investigations such as irregular antibodies. In recent studies, administration of N-acetyl cysteine (NAC) 30 mg/kg one hour before procurement, and 300 mg through portal vein before cross clamping was demonstrated to improve graft survival when compared with control group.[12]

Discontinuation: Any central venous pressure line and pulmonary arterial catheter must be withdrawn before retrieval of heart and lungs. Once the organs are perfused with cold preservative solution, anaesthetic agents can be discontinued. Ventilation may be discontinued at the time of aortic cross-clamping, and this time should be noted on the anaesthetic record. At the end of the operation it is important that the body is closed with proper skin suture in a continuous manner and is cleaned and packed in a respectful way before being handed over to the relatives.

Organ preservation

The retrieved organs are preserved by continuous perfusion of University of Wisconsin solution at 4°C. The adenosine and phosphate in the fluid supplies ATP during cold storage. Alternative solution is histidine-tryptophan-ketoglutarate which has less propensity for hyperkalaemia. The organs are flushed with a colloid before transplantation to prevent hyperkalaemia.

Time frame for reperfusion of organs

The warm ischaemia time is the time from cessation of blood flow into the organ to reperfusion. Shorter the warm ischaemia time, better is the survival of the organ. The accepted cold ischaemia times for the kidney is 24 hours, liver 12 hours, heart 6 hours and lungs 4 hours.[13] Although these are the time limits, better results are seen when these times are shorter. Continuous perfusion of these organs using red blood cells and oxygen has been attempted to prolong their survival but the results remain inconclusive and the technique is very expensive.[14]

Summary

Human organ transplantation is an answer to many patients suffering from organ failures. Although transplantation from living donors is well established, with increasing awareness, donation from brain dead donors or those at the verge of it are on the increase. The anaesthesiologist could be involved in diagnosing and certifying brain death, providing the intensive care required of this donor as well as providing anaesthesia in the operating room during organ retrieval. Therefore, the anaesthesiologist must have a full understanding of the pathophysiology and management of organ donation and transplant.

One brain-dead organ donor can potentially donate 'lives' to eight individuals. Thus organ donation becomes one of the noblest donations of all. To enhance or preserve the maximum potential of the donated organs, the anaesthesiologist and intensivist play a vital role in preserving the organs as best as possible to make such donations worthwhile.

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