ORIGINAL ARTICLE

First Prospective Study on Brain Stem Death and Attitudes Toward Organ Donation in India

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Organ donation following brain stem death is infrequent in India. There is no prospective study on prevalence of brain stem death and causes of non-donation. Consecutive patients admitted to intensive care unit from Sep 2006 to Sep 2008 were studied prospectively. Families of those with brain stem death were approached for organ donation by transplant coordinator. Extensive awareness drive was launched. Reasons for non-donation, if any, were documented. Of 2820 patients admitted, 994 (35%) were on mechanical ventilator and 657 (23%) died. Brain stem death could be diagnosed in 55, 37 males, median age 46 years (range 7 to 87 years) i.e., 1.9% of all admissions and 8.3% of all deaths. Among neurology and neurosurgery patients brain stem death was seen in 45 of 1037 (4.3%) admissions and 45 of 161 (27.9%) deaths. Complications of brain stem death were hypotension in 49, diabetes insipidus in 17 and hypertension in 5 patients. Of 33 families counselled, 16(48%) consented to organ donation. In 14(42%), organs and tissues retrieved and transplanted included 13 livers, 23 kidneys, 25 corneas and 5 cardiac valves. Consent was more likely in females (10 of 14 as compared to 6 of 19 males, $p = 0.037$). Consent did not correlate with age of donor or medico-legal issues ($p = 0.227$ & 0.579 respectively). Trained staff with requisite systems in place produced significant organ donation rates. Religious issues and medico legal concerns were not a major hurdle towards organ donation. Female patients with brain stem were more likely to become organ donors. ***Liver Transpl 15:1443-1447, 2009.*** © **2009 AASLD.**

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Brain stem death (BSD) is diagnosed when there is a triad of irreversible loss of consciousness, apnea, and absence of brainstem reflexes.[1,2] Donation after brain death (DBD) can save several lives through the transplantation of organs such as the heart, lungs, liver, kidneys, pancreas, and small bowel. In Western countries, DBD is the single largest source of organs for transplantation. However, a large number of potential donors with BSD fail to convert to organ donors. In the United Kingdom, a large audit involving 2740 potential heart-beating donors reported that 41% of the families of potential donors denied consent.[3] In the Unites States, it has been proposed to strive for a conversion rate of 75% and 3.75 organ transplants per donor.[4]

DBD is rare in India. Only 5% of all patients with end-stage kidney disease are successful in undergoing kidney transplantation.[5] To date, only 450 liver transplants have been performed in a country in which over 200,000 succumb to terminal liver disease and its complications annually.[6] The majority of the kidney and liver transplant programs in India are based on living related organ donation. Awareness of DBD is poor, and it is estimated that the deceased organ donation rate is a dismal 0.05 per million people, in contrast to 20 to 33 per million in Western countries, the highest rate being in Spain.[7] The Transplantation of Human Organs Act of 1994 provided for the regulation of the removal, storage, and transplantation of human organs for therapeutic purposes in India.[8] The act recognized the concept of BSD and gave legal sanction for DBD, but it failed to provide a much needed boost to altruistic organ donation. Until recently, India remained the favored destination for organ tourism: because of poverty, organs were sold to anyone willing to pay the price. The

Abbreviations: AORTA, Armed Forces Organ Retrieval and Transplantation Authority; BSD, brain stem death; DBD, donation after brain death; ICU, intensive care unit; NOK, next of kin; $PaCO_2$, partial pressure of arterial carbon dioxide.

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TABLE 1. Donor Management Protocol: Targets and Monitoring

Parameter	Target
Systolic blood pressure	100-180 mm Hg
Mean arterial pressure	60-80 mm Hg
Central venous pressure	5-10 mm Hg
Temperature	35-37.2°C
Urine output	0.5-1 mL/kg/hour
Hemoglobin	>9 gm/dL
Blood glucose	70-110 mg/dL
Serum sodium	135-150 mEq/L
Serum potassium	3.5-5 mEq/L

reasons for the lack of deceased organ donation in India are poorly understood. Even though illiteracy and strong social and religious beliefs are thought to be responsible, it has been speculated by many that a lack of awareness among doctors and general public is the main reason. With no systems in place, perhaps we never asked nicely!

The Armed Forces Organ Retrieval and Transplantation Authority (AORTA) was established at our hospital with the aim of promoting DBD. The functions of AORTA included a 24-hour referral service for organ donation, maintenance of a donor registry, family counseling, and support for and coordination of organ retrieval and transplantation activity between various hospitals. We report the first prospective study from India on the prevalence and profile of patients with BSD and the possible reasons for nondonation.

PATIENTS AND METHODS

This prospective study was conducted at a tertiary care facility with 17 beds in the intensive care unit (ICU); it catered to 8 medical patients and 9 surgical patients from September 1, 2006 to September 30, 2008. All patients admitted to the ICU during the study period were included. Those with an established cause of coma with computed tomography scan evidence of brain damage, on a mechanical ventilator for more than 6 hours, under no sedation or effect of muscle relaxant, and with no evidence of confounding factors such as hypothermia (<35°C) or drug intoxication were clinically tested for BSD. No response to painful stimuli and absent brain stem reflexes (an absence of the pupillary light reflex, corneal reflex, doll's eye movement, and gag reflex, no deviation of eyes on the cold calorie test, and the apnea test) were used to diagnose BSD. These tests were performed by 4 doctors of the hospital from the BSD committee duly approved by the appropriate state medical authority and headed by the chief administrative officer in accordance with the guidelines of the Transplantation of Human Organs Act of 1994. All the tests for BSD were repeated after 6 hours. The protocol for the maintenance of patients with BSD by the intensivist is shown in Table 1.

The parameters studied included age, sex, diagnosis, date of admission to the ICU, date and time of the two sets of tests for BSD, clinical and biochemical parameters, blood and urine cultures. Human immunodeficiency virus antibody, hepatitis B surface antigen, antibody to hepatitis C virus, venereal diseases research laboratory test for syphilis, and immunoglobulin G antibody to cytomegalovirus were also noted. Complications, if any, such as hypotension, hypertension, cardiac arrhythmias, and diabetes insipidus (defined as a urine output > 200 mL/hour when diuretics were not being used and there were no other causes of polyuria) were recorded. The requirement for inotropes and the duration of stay on a mechanical ventilator after the second set of tests for BSD were noted.

Once BSD was diagnosed, exclusion criteria for the counseling of family members included age above 80 years, malignancy (except for low-grade primary brain tumors), severe multisystem dysfunction, systemic infection, intravenous drug abuse, and positivity for hepatitis B surface antigen, antibody to hepatitis C virus, or human immunodeficiency virus.

Counseling Protocol

After the second set of tests for BSD, the family members of potential donors were approached for possible organ donation by a transplant coordinator. Informed written consent from the next of kin (NOK) was taken by the coordinator for the removal of organs and tissues from the deceased donor. If the family of the patient with BSD refused organ donation, the reasons for refusal, if any, were documented.

AORTA Protocol for Medicolegal Patients

Medicolegal patients, that is, those hospitalized with head injury due to road traffic accidents or criminal acts requiring a police investigation, are usually considered a deterrent to organ donation in India because of the involvement of multiple agencies and complex documentation. Moreover, all such patients who expire have to be subjected to a postmortem examination only at a hospital earmarked for a zone of the city by the government. We evolved a protocol for medicolegal patients with BSD to facilitate organ donation and save precious time in a deceased donor setting. As soon as the family consented to donation, 2 teams were dispatched simultaneously, regardless of the time of day or night. One team reached the police station along with the NOK of the deceased to complete the documentation. The policemen ascertained whether any foul play was suspected and recorded the statement of the NOK and other witnesses. After explaining the nature of injury and the organs to be retrieved, the second team obtained a no-objection certificate from the doctor on duty in the hospital earmarked for the postmortem examination. Once clearance was obtained from the police and the postmortem authorities, usually in a matter of few hours, the retrieval teams swung into action. The head surgeon of the retrieval team issued a certificate to the postmortem team, stating the organs retrieved and any unusual findings noted during the re-

trieval. The transplant coordinator then shifted the donor to a prearranged vehicle with full dignity for the postmortem examination, after which the mortal remains were expeditiously handed over to the family for last rites.

Awareness Drive

An extensive drive was launched by AORTA to promote deceased organ donation in the country. Information on BSD and organ donation was disseminated by lectures, posters, billboards, and extensive coverage of all organ donations in the national newspapers and periodicals. An organ donor registry was established at the hospital, and donor cards were issued by which individuals could pledge to donate their organs in case of BSD. Organ pledging ceremonies involving prominent personalities, including movie stars and athletes, were conducted and given widespread media coverage. The families of organ donors were honored in public ceremonies and given plaques, and thus the message of organ donation was spread.

Statistical Analysis

Statistical analysis was done with STATA 9 software. The paired *t* test was used to compare variables, and a *P* value of <0.05 was taken as significant.

RESULTS

Of 2820 patients admitted to the ICU during the study period, 994 (35%) were on a mechanical ventilator, and 657 (23%) died. Of these, 1037 (37%) admissions were related to neurology and neurosurgery, and 1783 (63%) were related to other specialties. BSD could be diagnosed in 55 patients, that is, in 1.9% of all admissions and 8.3% of all deaths. In neurology/neurosurgery patients, BSD was seen in 45 of 1037 admissions (4.3%) and 45 of 161 deaths (27.9%).

Of the 55 patients with BSD, 37 were male. The median age of the BSD patients was 46 years (range: 7-87 years), and the median duration on a mechanical ventilator after the second set of tests was positive for BSD was 13 hours (range: 1-72 hours). An apnea test was performed 117 times and was negative on 7 occasions, twice because of spontaneous ventilatory movements and 5 times because of a failure of the partial pressure of arterial carbon dioxide ($PaCO_2$) to rise. The apnea test was never abandoned because of the occurrence of complications.

The causes of BSD are shown in Table 2. All 14 patients with head injuries were registered as medicolegal cases. The observed complications of brain stem dysfunction were hypotension in 49 patients, diabetes insipidus in 17 patients, and hypertension in 5 patients. The reasons for unsuitability for organ donation in 21 patients were age above 80 years in 2, malignancy (including high-grade brain tumors) in 9, multiorgan system failure in 11, and documented sepsis in 14. In 1 patient, the treating neurosurgical team could not be convinced to counsel the NOK about BSD following surgery for a brain tumor.

TABLE 2. Causes of Brain Injury in 55 Patients with Brain Stem Death

Head injury	14
Intracerebral hemorrhage	6
Hypoxic brain damage	8
Subarachanoid hemorrhage	8
Brain tumor	6
Brain tumor (operated)	5
Cerebral infarction	3
Subdural hematoma	2
Subarachanoid hemorrhage (operated)	2
Tubercular meningitis	1

TABLE 3. Causes of Refusal to Donate by Families of 21 Potential Donors Who Did Not Give Consent

Difference in opinion of family members toward consent	8
Fear of criticism by society	4
Concern with quality of patient care	4
Brain death concept not understood	4
Fear of mutilation	4
Negative publicity of organ trade	3
Hope for a miracle	3
Reincarnation beliefs	2
Religious concerns	1
Medicolegal concerns	1
Not wanting to do something for unknown people	1

NOTE: Several families gave more than one reason.

Of the 33 potential donors with BSD whose families were counseled, 16 (48%) consented to organ donation. Having an Armed Forces background, the consenting and nonconsenting families were matched for educational level and employment status. One patient with BSD had a cardiac arrest before organ retrieval, whereas another was found to have gangrene of the large bowel, and organ retrieval was aborted. In 14 donors (42%), the retrieved and transplanted organs and tissues included 13 livers, 23 kidneys, 25 corneas, and 5 cardiac valves. Two families had reservations about the donation of eyes because of reincarnation beliefs. The reasons for refusal of organ donation by 17 families are shown in Table 3. Consent to organ donation was more likely in females (10 of 14 females versus 6 of 19 males, $P = 0.037$). There was a trend toward higher consent for organ donation in patients older than 50 years [9 of 15 (60%) versus 7 of 18 (38%) less than 50 years old, $P = 0.227$]. Medicolegal issues did not affect the organ donation rate [consent in 6 of 14 medicolegal cases (43%) versus 10 of 19 other cases (53%), $P = 0.579$].

DISCUSSION

The data on the prevalence of BSD in this prospective study, the first of its kind from India, are similar to those reported from the West.[9,10] In India, the diagnosis of BSD is based on bedside tests, and no special tests such as electroencephalogram or cerebral angiography are mandatory. Four doctors, one of whom has to be a neurophysician/neurosurgeon, carry out the tests for BSD, which have to be repeated after 6 hours. The apnea test remains the cornerstone of diagnosis of BSD. Complications such as hypotension and cardiac arrhythmias have been reported during apnea testing. In a study from the Mayo Clinic, complications occurred in 38 of 145 apnea tests (26%), and they were more likely in patients with unfavorable factors such as inadequate pre-oxygenation and electrolyte abnormalities.[11] Hypotension, defined as a fall in systolic blood pressure of 15%, developed in 35 of 145 cases (24%), whereas cardiac arrhythmias were seen in $<1\%$ of patients. Pre-oxygenation replaces alveolar nitrogen and facilitates oxygen transport. We did not encounter any complications during the 117 apnea tests performed, possibly because prerequisites such as pre-oxygenation with 100% oxygen for 10 minutes and correction of acid-base and electrolyte abnormalities were conducted meticulously; these findings are similar to those reported by Belsh et al.[12] High levels of $PaCO_2$ (average $>$ 89 mm Hg) have been shown to correlate with the incidence of hypotension.[13] In our study, the peak $PaCO_2$ value was only 70 mm Hg.

The median survival on a mechanical ventilator after the diagnosis of BSD was 13 hours (range: 1-72 hours). The time available for counseling and organ retrieval was short, and there is a need to review the law on the mandatory requirement of 6 hours between 2 sets of tests for BSD in India. In the United Kingdom, the time interval between the 2 sets of tests is discretionary, and no time interval is specified.[14]

In previous studies, the majority of BSDs were due to severe head injury resulting from road traffic accidents and trauma due to other causes; this was followed by subarachanoid hemorrhage, intracerebral hemorrhage, cerebral neoplasm, and hypoxic brain injury.[15] The reasons for fewer patients with head injuries in our study could be 2-fold. First, facilities for onsite resuscitation, mechanical ventilation, and evacuation for patients with severe head injuries are not well established in India. Second, patients with head injuries are usually transported to the emergency services of a specialized trauma care facility at a neighboring hospital. In our study, like reports from the West, hypotension and diabetes insipidus were commonly observed complications of BSD, with few patients having hypertension requiring antihypertensive therapy. Of the 55 patients with BSD, 21 (38%) were unsuitable for organ donation because of sepsis, multiorgan failure, or hypotension. The consent rate of 16 of 33 (48%) in our series is comparable to that reported from the West,[16] even though while in Western countries families consent to organ donation because they are certain that this would have been the wish of the deceased relative, in India, it is invariable that the family decides about organ donation in the absence of any antemortem input. The common reasons for refusal were differences in opinion of family members toward consent, fear of criticism by society, concern with the quality of patient care, and failure to understand the concept of BSD. The families of 3 potential BSD donors cited potential organ trade as the major reason for refusal. Some families thought that the patient had "been through enough" and expressed fear of mutilation. A few family members were hoping for a miracle. Previous studies have attempted to determine what factors influence a family's willingness to donate a patient's organs. In a national potential donor audit in United Kingdom, the reasons for denying consent to solid organ donation included an earlier statement to the effect from the patient, relatives not being sure whether the patient would have agreed to donation, relatives not wanting surgery on the deceased or being divided over the decision, and relatives believing that the patient had suffered enough.[4] The refusal rate was much higher in ethnic minorities versus whites (70% versus 35%). A study from the United States indicated that family and patient sociodemographics (ethnicity, patient's age, and cause of death) and prior knowledge of a patient's wishes were significantly associated with a willingness to donate.[17] Family members were more likely to donate if the donors were less than 50 years old. We found no correlation with the age of the donor. Increased donations from females, as seen by us, have not been reported earlier. The reason for this is not apparent, but it may be noted that over 80% of live donors in India are female; perhaps this reflects the bias of a male-dominated society. It has also been shown that the cause of BSD influenced consent for organ donation.[18] When a loved one died as a result of violent death or suicide, the NOK were more likely to consent to donation in an attempt to make sense out of the tragedy. Another study from United States showed no association between consent rates and families' educational attainment or income.[19]

In a retrospective audit of 159 patients with BSD from Chennai, India, it was shown that 30 of the relatives (19%) donated organs from their loved ones.[20] The higher conversion rate reported by us may be attributed to several factors. First, our transplant program was planned in a meticulous manner, and 19 medical and paramedical personnel, including transplant coordinators, were trained for a period of 3 to 12 months at 2 high-volume liver transplant centers in the United Kingdom. Second, a major awareness drive was launched to promote organ donation, including the pledging of organs by celebrities and widespread coverage of every donation in the print and electronic media. One could argue that Asians in Western countries, despite exposure to long-term education and awareness programs on DBD, continue to have donation rates that are lower than those in the native population. Possibly, the "trusting" environment of the armed forces had a positive impact in our study.

During the period of this study, many firsts were

achieved by the team from AORTA. For the first time in the history of the nation, a liver was flown from New Delhi in the north to Hyderabad in the south and transplanted. Over the next few months, kidneys were transported by air from New Delhi to Mumbai, Pune, Lucknow, and Bangalore. This study demonstrates that the previously held concerns about social and religious beliefs as a cause of the lack of organ donation in India are untrue. With proper systems in place, including a highly motivated and trained medical team and an effective awareness program, we were able to achieve organ donation rates similar to those in Western countries.

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