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Clinical and subclinical characteristics of brain-dead donors for liver transplantation in Viet Duc University Hospital

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Abstract:

Since 2010, 49 cases of liver transplants from brain-dead donors were performed at Viet Duc University Hospital. This study is a descriptive cross-section cohort study with a combined analysis of retrospective and prospective occurrences of a series of cases of liver procurement from brain-dead donors in Viet Duc University Hospital from March 2010 to March 2020. The results of this study showed several features: the average age of the brain-dead donors was 29.8±10.9 (18-69), donors were mostly male (7.17/1, 87.8%), and the main cause of brain death was head trauma. Clinically, 40.8 and 63.3% of the subjects were hypothermic and diagnosed with diabetes insipidus, however, the subjects were all well resuscitated before procurement. Therefore, haemodynamic indices and temperatures were maintained at stable levels and there was no statistically significant difference. In subclinical aspects, haemoglobin and platelet levels decreased significantly but remained within the target criteria during resuscitation while blood sodium levels increased significantly during resuscitation when compared with levels at the time of admission ($p<0.001$) thus corresponding to diabetes insipidus. In general, 44.90% of donors were within the ideal standard, and in the extended standard group, the highest rate was electrolyte disorders (32.65%). In conclusion, there are many variations in clinical and paraclinical body signs as well as homeostasis in the brain-dead donors. Of these signs, the most prominent were changes in haemodynamics, temperature, urine output, complete blood count, blood clotting, and blood sodium levels. These are all factors that are included in the criteria to consider the selection of a liver donor.

Keywords: **brain-dead donors, clinical and subclinical characteristics, liver transplantation.**

Classification number: **3.2**

Introduction

Organ transplantation in general, and liver transplantation in particular, is one of the most outstanding medical achievements of the past few decades. However, since its inception, the transplant field has always faced the problem of scarcity of donated organs for all organs and especially the liver. The graft can be the whole liver from a deceased donor (including brain death and cardiac death) or a partial liver from a living donor. Trends in the use of donated organs differ in each region due to cultural issues. For example, in Asia, the main source of liver donation comes from living donors, however, donations from brain dead donors have also been increasing over time [1].

Donor selection is an important first step in obtaining a good quality graft. Ideal criteria of a deceased donor include young age, brain death due to trauma, stable haemodynamics, no hypernatremia, etc., which helps to achieve very good results after transplantation but also limits the number of donor organs [2, 3]. Recently, an expanded criteria of brain-dead donors has been introduced in order to maximize organ donation sources, which includes accepting donors who are elderly, had cardiac arrest, persistent hypotension, severe hypernatremia, or liver steatosis [4, 5]. Rationally considering the clinical and subclinical factors of brain-dead donors helps to balance these two factors while maximizing the quantity of donor organs and ensuring successful results after transplantation. In Vietnam,

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clinical and subclinical changes are mainly considered in terms of anaesthesia and resuscitation [6, 7]. Son, et al. (2016, 2017) [8, 9] was the first authors interested in factors affecting donor selection, but this was a study on donors in France. Therefore, we carried out this study to evaluate clinical and subclinical characteristics of brain-dead subjects at Viet Duc University Hospital.

Subjects and methods

Subjects

There were 49 subjects all over 18 years old, diagnosed with brain-death, and underwent multiple organ procurement with recipients of orthotopic liver transplantation at the Viet Duc University Hospital from May 2010 to May 2020.

Selection criteria: donors who were over 18 years old with severe cerebral injuries (e.g., head trauma, cerebral vascular accident, ruptured cerebral vascular aneurysm…) and diagnosed brain-dead according to Ministry of Health's criteria. The livers were procured and transplanted to the corresponding recipient in Viet Duc University Hospital with complete medical records.

Methods

Descriptive, cross-sectional study of a series of cases.

Variables:

- General characteristics: age, gender, body mass index, ABO blood type, history (diabetes, hypertension, alcoholism...), and cause of brain death (traumatic brain injury, ruptured brain aneurysm, or cerebrovascular accident).

- Clinical and subclinical signs:

+ Heart rate, mean systolic blood pressure (SBP), average temperature, urine output in 1 h (starting at the time of admission but before brain-death test and organ procurement).

+ Rate of cardiac arrest, hypotension (mean BP<70 mm Hg), use of vasopressors, diabetes insipidus (Seckl's criteria: urine >3 l per day, urine osmolality <300 mOsm/kg, blood sodium >145 mEq/l).

+ Status of bacterial and viral infections: pneumonia, bacteraemia (sepsis), hepatitis B, hepatitis C, etc.

+ Haematology - biochemistry: haemoglobin, prothrombin time, PT-INR index, the amount of blood and serum transfused during resuscitation, kidney function tests (urea, creatinine), liver enzymes (AST/ALT), bilirubin, and blood sodium and potassium levels.

- Rate of extended criteria donor (mostly according to Briceno criteria: donor >60 years, ICU stay >4 days, hypotensive episodes <60 mmHg >1 h, bilirubin >2.0 mg/dl, ALT >170 U/l and/or AST >140 U/l, the use of dopamine doses >10 µg/kg per min and peak serum sodium >160 mEq/l).

Data analysis: using SPSS 20.0 software.

Results

Table 1. General characteristics of donors.

Mean age	29.8±10.9 (18-69); age group <40 (81.6%)
Gender	Male/female: 7.17/1 (87.8%)
BMI (kg/m²)	21.11±2.24 (17.58-27.80)
ABO blood types	O/A/B/AB: 55.1/14.3/26.5/4.1 (%)
Medical history	Hypertension/alcoholism/diabetes: 2.04/4.08/2.04 (%)
Brain-dead cause	Head trauma/ruptured cerebral aneurysm/cerebral infarction: 89.8/8.2/2.0 (%)

Table 1 revealed that the average age of donors was 29.8±10.9 and the working age (18-69 years old) was the majority. The male-to-female sex ratio was 7.17/1, the average BMI was 21.11±2.24, and the most frequent brain-death cause was head trauma (89.8%).

Table 2. Clinical signs of the donors.

Index	At admission	Before brain-dead test	Before procurement	p-value
Heart rate (per min)	98.1±22.5	104.5±19.4	101.7±28.7	0.447
Mean SBP (mmHg)	87.1±16.9	85.5±12.3	88.3±24.5	0.834
Temperature (°C)	36.6±0.6	36.1±1.2	36.4±1.6	0.121
Amount of urine (ml per hour)	330.0±278.1	663.2±405.9	480.0±312.8	0.039

As shown in Table 2, the subjects were resuscitated well before procurement, haemodynamic indices and temperature were maintained at stable levels, and there was no statistically significant difference, however, the urine volume increased during resuscitation which represented the progression of diabetes insipidus (p=0.039).

Table 3. Clinical changes of the donors.

Systemic disorders	Number (n)	Ratio (%)
Cardiac arrest (n=49)	2	4.1
Hypotension (n=49)	11	22.45
Use of vasopressors (n=49)	46	93.9
Diabetes insipidus (n=35)	31	63.3
Hypothermia (n=48)	20	41.7

All cases of cardiac arrest and hypotension were well resuscitated and remained stable until aortic clamping (Table 3).

Table 4. Bacterial and viral infection's status of donors.

Bacterial and viral infections		Number (n)	Ratio (%)
Sepsis		1	2.0
Viral infection	Hepatitis B	0	0
	Hepatitis C	2	4.1

According to Table 4, there was 1 patient with sepsis with the following blood culture results: *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Actinobacteria baumannii*. There were 2 donors who had antibodies against hepatitis C, but no virus was found in their blood.

Table 5. Donor's haematology test results.

Index	At admission	Before brain-dead test	Before procurement	p-value
Haemoglobin (g/l)	120.73±27.80	114.06±17.00	105.72±14.41	0.014
White blood cells (G/l)	19.14±6.49	15.90±4.85	14.16±3.97	<0.001
Platelet (T/l)	174.42±69.53	127.41±86.05	121.01±55.70	0.004
Prothrombin (s)	15.22±2.17	17.02±3.18	15.92±2.65	0.009
PT-INR	1.27±0.20	1.77±2.37	1.34±0.23	0.005

The haemoglobin and platelet levels decreased significantly but remained within the target criteria during resuscitation. Prothrombin time and PT-INR were severely disturbed but were also adjusted to the target before organ procurement (Table 5).

Table 6. Amount of blood products transfused during resuscitation.

Blood products	Number (n-%)	Amount of transmission (ml)		
		Minimum	*Maximum*	*Mean*
Red blood cells (ml)	28/49 (57.1%)	250	3200	1026.79±604.69
Platelets (ml)	2/49 (4.1%)	250	500	375.00±125.00
Plasma (ml)	21/49 (42.9%)	200	1350	551.25±315.44

In 57.1% of cases, red blood cells were transfused preoperatively, the average volume of infusion was 1026.79 ml, and only 2 cases required platelet transfusion with an average volume of 375 ml (Table 6).

Table 7. Biochemical test results.

Index	At admission	Before brain-dead test	Before procurement	p-value
Na (mmol/l)	141.86±8.12	153.30±10.58	149.35±10.37	<0.001
Ure (mmol/l)	5.96±2.94	5.49±3.44	4.49±3.07	0.166
Creatinine (µmol/l)	102.16±65.18	94.46±36.74	82.77±23.86	0.234
AST (U/l)	104.89±181.48	71.32±74.98	52.64±41.18	0.168
ALT (U/l)	62.04±83.48	45.97±59.27	39.17±45.13	0.307
Total Bil (µmol/l)	13.97±8.63	18.50±9.21	17.39±9.33	0.108
Directed bil (µmol/l)	3.21±1.70	5.23±3.36	5.38±3.23	0.01
Albumin (g/l)	30.91±6.72	26.58±5.01	31.14±8.61	0.007

In Table 7, blood sodium levels increased significantly during resuscitation compared with the time of admission ($p<0.001$) corresponding to diabetes insipidus. The mean ALT/AST increased, but within the resuscitation target, and this index tended to improve during resuscitation.

Table 8. Liver characteristics of donors on ultrasound and computerized tomography.

Characteristics		Ultrasound	Computerized tomography
Number		46/49 (93.9%)	4/49 (8.16%)
Liver parenchyma	Normal	44 (95.7%)	4 (100%)
	Cirrhosis	0	0
	Steatosis	2 (4.3%)	0
	Liver trauma	0	0
Anatomical variation of hepatic artery		0/46	0/4
Anatomical variation of portal vein		0/46	0/4
Bile duct dilatation		0/46	0/4

Ultrasound is the main test to examine the organs before surgery (Table 8).

Table 9. Criteria for selection of liver donors.

Donor's selective criteria		n	%
Standard criteria		22	44.90
Extended criteria	Age >60	1	2.04
	ICU stay >4 days	3	6.12
	SBP <70 mmHg lasting at least 1 h	1	2.04
	Hepatitis C	2	4.08
	Blood sodium >160 mmol/l	16	32.65
	AST >170 U/l and/or ALT >140 U/l	6	12.24
	Sepsis	1	2.04
	BMI>28, Hb <70 g/l, ICU >7 days, Dopamine >10 µg/kg/min, total Bilirubin >34 mmol/l, PaO_2 <80 mmHg, liver steatosis >30%	0	0

44.90% of donors were within the ideal standard. In the extended standard group, the highest rate was electrolyte disorders (32.65%) (Table 9).

Discussion

In our study, the average age of donors was 29.8±10.9 years, the lowest was 18 years old, the highest was 69 years old, and up to 81.6% of the donors had the ideal age of under 40 years old (Table 1). The average age in our study was much lower than other studies around the world. The mean age of organ donors in Korean and French populations in the statistics of Son and Khiem (2016) [8], Jung, et al. (2015) [10] were 48 and 58, respectively. We chose donors at a young age, mainly under 40, because liver transplantation has only been developed in Vietnam for about 10 years and a qualified result from the quality of the transplant is needed. In general, age will partially

affect liver volume, liver perfusion, and a mild increase in fibrosis [11].

The proportion of male brain-dead donors accounted for 7.17/1 more than 87.8% in our study (Table 1) and this can be explained by the fact that most of the organ donors at Viet Duc University Hospital had brain death caused by traumatic brain injury, which is predominate in males. Research by He, et al. (2005) [12] on the epidemiology of traumatic brain injury at Viet Duc University Hospital showed that the male rate accounted for 79.4%. Research by Son and Khiem (2016) [8] on liver donors in Strasbourg (France) showed that the proportion of men accounted for only 54.1%, much lower than in our study, and this difference was explained by the cause of brain death with the highest rate in Strasbourg being by cerebrovascular accident (62.2%) - a disease with an equal prevalence between the two genders. However, this result also showed that the cause of brain death due to stroke in our country has not been paid enough attention.

A stable donor's systemic status is an important factor in optimising the graft's function. In our study, the average heart rate fluctuated between 98-104 beats per minute, the mean blood pressure of above 80 mmHg was maintained relatively constantly, and there was no difference between these values at the time of admission, the time of brain-death test, and before organ procurement (Table 2). The results were within the haemodynamic stability criteria for brain-dead donors per the 2007 Paris Organ Transplantation Conference [13]. This demonstrates that brain death resuscitation is effective in maintaining haemodynamics. During the resuscitation process, we recorded 11 cases (22.45%) with hypotension, but they were all resuscitated well afterwards and maintained haemodynamically stable until organ removal (Table 3). In order to maintain haemodynamic stability during resuscitation, most subjects must take vasopressors and the rate of vasopressors in our study was 93.9%. Our results on heart rate-average blood pressure, rate of haemodynamic disturbances, as well as the rate of vasopressor use are similar to those of [14], but on an in-depth study on resuscitation. The author analysed in more detail the different time points from the time the patient was admitted to the hospital to the time of organ removal thereby showing that the rate of haemodynamic disturbances at the time of admission was the highest at 21.3%, and the rate of using vasopressor at the highest point was 100%.

A dysfunctional hypothalamus after brain death leads to impaired thermoregulatory function. Hypothermia increases diuresis, interferes with coagulation, increases the risk of arrhythmias, and increases the risk of infection [15]. In our study, the average temperature was kept relatively constant during the resuscitation process and ranged from 36.00 to 37.2^{o}C, and the difference in temperature between the time points from admission to before surgery was not statistically significant (Table 2). Our average temperature was similar to the study of Dung (2019) [14] (36.41±1.31^{o}C). During the resuscitation process, we also actively implemented measures to prevent hypothermia such as warming and supplying warm fluids.

Diabetes insipidus is very common in subjects with brain-death due to damage to the posterior pituitary hypothalamus [16]. In Kazemeyni and Esfahani's study (2008) [17], the rate of diabetes insipidus in brain-dead subjects was 70.2%, and our statistics show similar results with a rate of 63.3% (Table 3). In addition, our results also showed that the mean urine volume during resuscitation and before organ procurement significantly increased compared to hospital admission (p=0.039) (Table 2). This demonstrates that despite the resuscitation, hypothalamic damages are always progressive in brain-dead people.

Infection is a common condition in subjects with brain-death because of severe systemic conditions, coordinative damages, and long hospital stays with invasive therapies. A study by [8] recorded that 6.76% of brain-dead subjects had sepsis and their livers were still taken for transplantation. Our study recorded 1 case of bacteraemia in which antibiotics were used according to the antibiogram (Table 4). The rest were given prophylactic antibiotics during resuscitation. Sepsis is not a contraindication for organ donation with appropriate preoperative and postoperative antibiotics along with adjustment of immunosuppressive regimens for recipients after surgery. However, there are reports that lead to mixed opinions when there are recipients with hepatic artery occlusion as the cause is believed to be the result of bacteraemia caused by *E. coli* of the donor [18, 19].

There is a great deal of evidence that there were no differences in survival between the two groups of grafts taken from anti-HCV-positive donors and anti-HCV-negative donors. People previously infected with the hepatitis C virus in the blood are considered a contraindication for liver donation. However, in the new era of antiviral hepatitis C drugs, even brain-dead donors with the hepatitis C virus in their blood can be considered for liver transplantation to non-hepatitis C-infected recipients, and of course were treated with anti-hepatitis C drugs after transplantation [20]. Our study recorded 2 cases with positive anti-HCV tests, however, no virus was detected in the blood count and both grafts were transplanted to subjects with hepatitis C (Table 4). That was a reasonable selection of liver donors in the context that the organ resources are always lacking and need to be utilised to the fullest extent while ensuring the safety of the recipients.

Hypernatremia is a common condition in brain-dead people, which is a consequence of diabetes insipidus. Hypernatremia is also a common concern in brain-dead donors because some studies have suggested that it affects graft function and increases graft mortality. It is hypothesized that high levels of sodium in donor blood lead to increased osmotic pressure, cellular oedema, and exacerbation of cellular injury upon reperfusion. In our study, the average sodium concentration at the time of the brain-death test and before surgery was 153.30 mmol/l and 149.35 mmol/l, respectively, and the ratio of sodium max >160 mmol/l was 32.65% (Table 7). Our results are the same as in the study of Totsuka, et al. (1999) [21] with an average blood sodium concentration of 153.5 mmol/l and of Magus, et al. (2010) [22] with a maximum blood sodium concentration >160 of 36%. Our study also showed that blood sodium at the time of the brain-death test and before organ procurement was both high and significantly increased compared with at the time of hospital admission (141.85 mmol/l) with $p<0.001$. Thus, despite intensive resuscitation, blood sodium disorder still worsens corresponding to the state of diabetes insipidus.

Elevating liver enzymes in brain-dead donors is often a consequence of trauma, hypoxia, anaemia, haemodynamic instability, and sometimes toxicity and drug side effects. In our study, the mean values of AST and ALT increased slightly and tended to decrease over time to near normal levels (52.64 U/l and 39.17 U/l respectively) at times before organs procurement (Table 7). There were only 6 cases where maximum AST and ALT levels increased higher than the standard values for the ideal donor (AST >170 U/l and/or ALT >140 U/l) (Table 9). This result was different from the study of Magus, et al. (2015) [23] with the percentage of donors with ALT >500 U/l up to 7%. This difference is mainly caused by the donors in this study having a relatively large proportion of asphyxiation (anoxia), and this group often had elevated liver enzymes.

Total bilirubin levels greater than 34 µmol/l are considered an exaggerating factor [24]. In our study, the mean bilirubin concentration was in the normal range (from 13.97 to 18.59 µmol/l), there was no difference between during the time from hospital admission to organ removal, and there were no cases of bilirubin concentration exceeding the ideal standard (Table 7-9). Our average bilirubin concentration was similar to the study of Carpenter, et al. (2019) [25], however, this study had 7.6% Bilirubin cases within the extended criteria. This can also be explained because the cause of brain death in this study was more than 20% asphyxiation and 44.6% stroke. Stroke subjects often have a high average age with systemic diseases such as diabetes and dyslipidaemia affecting liver quality, while asphyxiation is the cause of hypoxia in the liver.

The implementation of preoperative imaging facilities were used to evaluate the imaging features of the transplant organ for surgery such as liver volume, anatomical variations of the hepatic hilum, and liver steatosis [26]. All of our subjects had at least one preoperative imaging method to evaluate the morphological characteristics of the organs, which was mainly abdominal ultrasound, however, only 4 cases (8.16%) were imaged with a CT scan. Accordingly, in 100% of subjects no liver damage was detected (parenchyma and hepatic hilum components) on ultrasound or computed tomography while 2 cases (4.17%) had grade I liver steatosis images on ultrasound. Compared with macroscopic results from surgery and pathology, the sensitivity of ultrasound on the diagnosis of liver steatosis was 2/13 (15.38%) and the specificity was 2/2 (100%). We could not find any studies in the English literature that used ultrasound to assess the liver status of brain-dead donors before surgery. At centres in France, CT scans of the whole body are often applied to assess both brain death and the status of the organs to be removed. The study of Tache, et al. (2016) [27] showed that abdominal CT excluded two donors that had severe liver steatosis (>60%), and found that 10% of the donors had anatomical variations of the hepatic arteries. However, in our study, the liver donors were mainly traumatized at a younger age, thus the role of preoperative screening with imaging tools was reduced. The use of ultrasound for screening is also reasonable as bedside ultrasound helps to limit the need to move, which aggravates the whole-body condition.

The consideration of clinical features was completed so that we can choose a reasonable liver donor. In the first stage, we selected the ideal donor according to Feng's criteria (age <40 years, brain death due to trauma, haemodynamic stability, no liver steatosis, no chronic liver disease as well as communicable diseases) [28]. However, over time, when the demand for transplants remained very high and we mastered the techniques of organ procurement and transplantation as well as resuscitation, we gradually began using donors at an expanded standard. Based on Bricano's expanded criteria combined with some other updated studies [5, 29, 30], we selected an extended criteria to apply to our research. Accordingly, 55.10% of donors were in the expanded criteria, with the highest rate being hypernatremia (32.65%) followed by elevated liver enzymes (12.24%) (Table 9). Our study results are consistent with the study of Gruttadauria, et al. (2008) [29] with the proportion of subjects with ideal criteria also approximately 50%. However, this study also had statistics on the rate of risk factors of which the highest percentage was the electrolyte disorder (32.65%). This result was consistent with the characteristics of the cause of brain death differ between developed and developing countries with mainly young subjects having brain death due to traumatic brain injury.

Conclusions

There are many variations in the clinical and subclinical signs of the body as well as homeostasis in brain-dead donors of which the most prominent are changes in haemodynamics, temperature, urine output, complete blood count, blood clotting, and blood sodium levels. These are all factors that are included in the criteria to consider the selection of a liver donor. Resuscitation to limit these changes helps to obtain more organ resources as well as a good quality liver transplant.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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