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RESEARCH ARTICLE

Donor Management: Is It Always Possible to Achieve Goals to Prevent Organ Dysfunction?

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ABSTRACT

Objective: Ensuring the hemodynamic stability of patients following catastrophic brain injury is a very challenging process. The organ transplantation rate increased significantly with donor management (DM) provided in accordance with the goals set for DM-goals (DMGs). However, the factors affecting the achievement of these goals are unclear.

Materials and Methods: We included adult patients diagnosed with brain death (BD), also who was subsequently given at least 24 hours of donor care between January 1st, 2011 and August 1st, 2023 in the study. The DMG scores of each patient were calculated at the time of BD-detection, twenty-four hours before, 2, 6, 12, and 24 hours after the brain-death-detection-time.

Results: Among 194 BD patients, 78 patients who received 24-hour donor care were included in the study. The DMG scores of patients with trauma were statistically higher than those of patients who had other reasons for BD (95% CI: [1.4–17]; p:0.014). The results showed a significant decrease at 24 hours after detection, while there was no change at 6 and 12 hours after BD-detection in DMG scores (p<0.001). Also, the results showed that while the higher mean arterial pressure (MAP) recorded at 6,12 and 24 hours after BD-detection during DM increased the rate of liver and kidney transplantation (95% CI, 16.3–34.8]; p<0.001, [95% CI, 9.3–28.8]; p<0.001, respectively). Moreover, the most common problems encountered before BD-detection were diabetes-insipidus (30%) and fever (23%).

Conclusion: Although more studies are needed to provide more effective DM and increase transplantation rates, more comprehensive criteria, including organ perfusion parameters, should be determined, and the MAP target should be increased without hesitation in the use of vasopressor drugs.

Keywords: Brain death, brain death detection, donor management, donor management goals

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INTRODUCTION

The majority of transplanted organs are procured from donors after the determination of brain death (BD).[1] Although organ transplantation is the only treatment for end-stage organ failure, the gap between the demand and supply of organ transplantation is widening every day.[2] Therefore, effective donor management is even more important. Determination of BD and donor management (DM) is one of the most challenging processes experienced by physicians. In the Hippocratic Oath, we declare that we should treat our patients to the best of our abilities and skills. However, BD is the state in which our abilities and skills are lost. It is a difficult process for physicians to accept that their patients will not get better with any current treatment. Simultaneously, they should determine the diagnosis of BD without delay, provide effective care for adequate organ perfusion, and prepare the family for this challenging process. You can not see the results of the treatments you performed, but you know that if you can maintain organ perfusion and achieve the specified goals, the patients who have organ failure will recover. DM is the part where your abilities and skills are sufficient. A recent study by Patel et al.[3] found that the organ transplantation rate increased significantly with DM provided in accordance with the goals set for donor management goals (DMGs) after the diagnosis of BD. The study results showed that when these DMG criteria are achieved, the number of organs transplant-

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ed increases to three or more, and intrathoracic organs such as the heart and lungs have the most significant effect on increasing transplantation rates. In addition, the same study has shown that the probability of delayed rejection is lower in grafts where these goals can be achieved, as well as the increase in the number of organs transplanted per donor.

Nowadays the increase in donor age and comorbidities, as well as the inability to expand the donor pool, have made current DM even more important. Therefore, in the current study, we examined the factors affecting the DMG criteria in order to provide more effective DM in the ICU.

MATERIALS and METHODS

Inclusion and Exclusion Criteria

In the present study, brain death is defined according to the 2010 American Academy of Neurology guidelines for adults.[4] We included adult patients admitted to ICU at our facility in a university hospital and diagnosed with brain death, also who were subsequently given at least 24 hours of donor care between January 1st, 2011, and August 1st, 2023 in the study. The scores of each patient were calculated according to the Donor Management Goals Five[3] (DMG5 shown in Table 1) criteria at the time of brain death detection, twenty-four hours before, 2, 6, 12, and 24 hours after the brain death detection time. According to DMG criteria, scores above four were called Group I, and those with scores of four and below at the time of brain death detection were called Group II. This retrospective observational cohort study ''Donor management; Is it always possible to achieve goals in an effort to prevent organ dysfunction?'' was approved on October/2023 (no: 2023-19/29) by the ethics committee of Bursa Uludag University Medical Faculty (IRB00004769, decision number: 2023-1/37). No study-related interventions were performed on human subjects in accordance with the Helsinki Declaration of 1975; our study was conducted retrospectively, and approval was obtained from all patients/patient relatives during admission to the ICU for their clinical status, laboratory, and radiologic examination results to be used for scientific publications without specifying the descriptive characteristics (name, surname, ID number) of the patients. The need for informed consent was, therefore, waived by the ethics committee.

Data Collection

Demographic data (age, sex) of patients, their comorbidities (The diagnosis of acute renal failure was made according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[5]), the scores of each patient were calculated according to the Donor Management Goals Five (DMG5) criterias[3] (Table 1) those with scores of at the time of brain death detection, twenty-four hours before, 2, 6, 12 and 24-hours after the brain death detection time. Those with a DMG5 score of four or less at the time of brain death detection were called Group I, and those with a score of five or more were called Group II.

Statistical Analysis

Continuous variables are expressed as the mean (standard deviation) or median (interquartile range) and n (%), depending ±on the normality of the distribution for continuous variables; the Kolmogorov–Smirnov test was used to test the normality of the distribution for continuous variables. A repeated measures ANOVA with a Greenhouse–Geisser correction determined the mean arterial pressure, vasopressor support, diuresis, blood glucose levels, partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2:P/F) ratio, and sodium between time points. Post hoc tests using the Bonferroni correction revealed which measurement differed. The binary logistic regression test was used to predict the categorical dependent variables. Data analysis was conducted with statistical package or social science (SPSS) statistical software (SPSS28.0: SPSS; Chicago, Il, USA), and $p<0.05$ and $p<0.0125$ (for Bonferroni correction) were considered to be significant.

RESULTS

Patient Population and Characteristics

Between January 1st, 2011, and September 1st, 2023, 194 patients were diagnosed with brain death in our univer-

Table 1. United network for organ sharing region 5 donor management goals

Donor management hoal	Target range
Mean arterial pressure (mmHg)	60–110
Central venous pressure (mm Hg)	4–12
Ejection fraction (%)	≥50
Low-dose vasopressor*, no vasopressor used	≤ 1
Arterial blood gas (pH)	7.3–7.5
PaO_2: FiO_2 ratio	≥300
Serum sodium level (mEq/L)	≤155
Urine output (ml/kg/h) (4 hours)	≥0.5
Blood glucose level (mg/dL)	≤150

*: 10 µg/kg/min or less for dopamine; 10 µg/kg/min or less for norepinephrine. PaO_2/FiO_2: Partial-pressure-of-oxygen/fraction-of-inspired-oxygen

Table 2. The effects of causes of brain death, diagnosis time and patient characteristics on donor management goals

Variables	Group I DMG ≤4 (n=30)	Group II DMG> 4 (n=48)	p	95% CI lower bound	95% CI upper bound
Age (mean±SD)	41±3.6	50.1± 3.9	0.9	-0.8	0.07
Sex (male; n=47)	21	26	0.2		
BD diagnosis time after ICU admission (mean±SD, hour)	163±30	151±28.3	0.7	0.08	0.5
MAP at BD diagnosis time (mean±SD, mmHg)	80±4	81± 4	0.6	-0.6	0.3
MAP six hours after BD(mean±SD, mmHg)	74±4	75± 3	0.9	-0.5	0.6
MAP twelve hours after BD (mean±SD,mmHg)	66±6	72±5	0.4	-0.5	0.6
BD diagnosed with apnea test (n=44)	30	14	0.3		
P/F ratio at BD diagnosis time (mean±SD,mmHg/%)	268±115	265± 117	0.9	-0.4	0.5
Sodium levels at BD diagnosis time (mean±SD, mEq/L)	151±9	150± 12	0.9	-0.4	0.5
Total balance at BD diagnosis time (mean±SD, ml)	6452±7131	5177± 5433	0.4	-0.4	0.5
Creatinine at BD diagnosis time (mean±SD, mg/dL)	1.6±1.1	1.6± 1.4	0.9	-0.5	0.5
Blood glucose level (mean±SD, mg/dL)	172±62	171± 71	1	-0.5	0.5

CI: Confidence interval; DMG: Donor management goal; SD: Standart deviation; BD: Brain death; ICU: Intensive-care-unit; MAP: Mean-arterial-pressure; P/F: Partial-pressure-of-oxygen/fraction-of-inspired-oxygen; mEq/L: Milliequivalents per liter

sity hospital. Among them, seventy-eight patients who received donor care for 24 hours or more were included in the study. The average age of these patients was 47±17 years, and the average time from admission to the ICU to the diagnosis of brain death was 158±149 hours. The most frequent cause of brain death was stroke. Patient characteristics are shown in Table 2. Among 78 patients, relatives of 28 patients permitted donation. Six of them were found unsuitable for donation due to infection, and one died before donation could be performed (Fig. 1).

The Effects of Causes of Brain Death, Diagnosis Time and Patient Characteristics on Donor Management Goals

To understand the effect of the causes of brain death on the DMG score, the DMG scores at the time of 24 hours after brain death detection were compared, and it was found that the total scores of patients with trauma were statistically higher than those of patients who had stroke and CPR (95% CI: [1.4–17]; p:0.014)). However, there was no significant difference between DMG scores according to age, sex, and diagnosis time (p>0.05 for all) see Table 2.

Changes in the Achievement of Donor Management Goals Over Time

A 2×2×2×2×2 mixed-design analysis of variance (ANOVA) was conducted to determine the effects of time on DMG scores. The results showed a significant decrease at 24 hours after brain death, while there was no change at 6 and 12 hours after brain death in DMG scores (p<0.001). Comparisons of the components of the DMG score revealed that mean arterial pressure (MAP) decreased over time despite vasopressor support, while diuresis, blood glucose levels, P/F ratio, and sodium did not change over time (p=0.039).

Pharmacological Treatments, Fluid Balance, and Nutrition

We found no significant differences between GroupI and Group II according to pharmacological treatments (esmolol, steroid, vasopressor drugs, mannitol, desmopressin, and low molecule weight heparin) at brain death diagnosis time (p>0.05 for all).

Problems Encountered in Donor Care

It was determined that the most common problems encountered before the brain death determination were diabetes insipidus (30 %) and fever (23 %). However, no relationship was found between the problems and age, sex, or cause of brain death (p>0.05 for all).

Apnea Test Versus Ancillary Test

Contrary to our expectations, performing apnea testing or ancillary tests for the diagnosis of brain death did not affect DMG scores (p>0.05).

Factors Affecting Donated Organs

Since heart and lung transplants are not performed in our center, we do not have information about the organs removed by other teams. Therefore, in this study, only statisti-

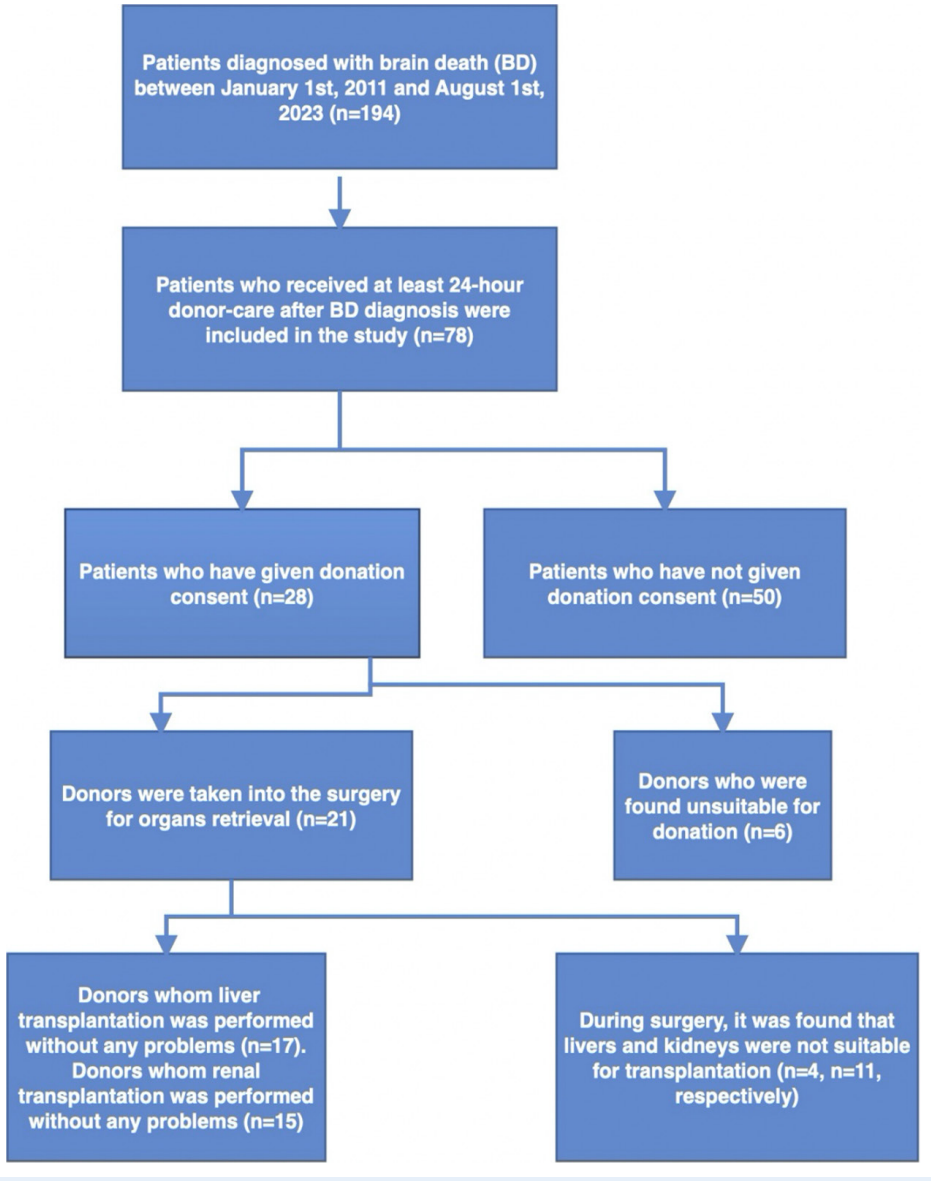

Figure 1. Flowchart

cal data for liver and kidney transplantations are reported. The results showed that while the higher MAP and P/F ratio recorded at 6,12 and 24 hours after brain death detection during DM increased the rate of liver transplantation ([95% CI, 16.3–34.8]; p<0.001, [95% CI, 60.2–268.4]; p=0.006, respectively), the higher MAP levels significantly increase the rate of kidney transplantation ([95% CI, 9.3–28.8]; p<0.001). Transplantation rate and MAP changes are shown in Figure 2. However, no relationship was found between the solid organ transplantation rate and age, sex, total DMG measurements, sodium level, vasopressor support, and diuresis (at the 24th hour of DM). (p>0.05 for all).

DISCUSSION

Donor Management Goals have been recommended by the Organ Procurement Organizations (OPOs) for DM in ICU. [3] Recent studies suggested that meeting a set number of DMGs as part of a bundle during both the donor hospital and OPO phase of care has been associated with significantly more organs per donor and improved graft outcomes. [2,6–9] However, to our knowledge, no article has been published investigating the factors affecting DMGs to provide more effective DM. In our study, we investigated the reasons why we could not achieve these goals through donors with low DMG values. As a result of our investigation, it was

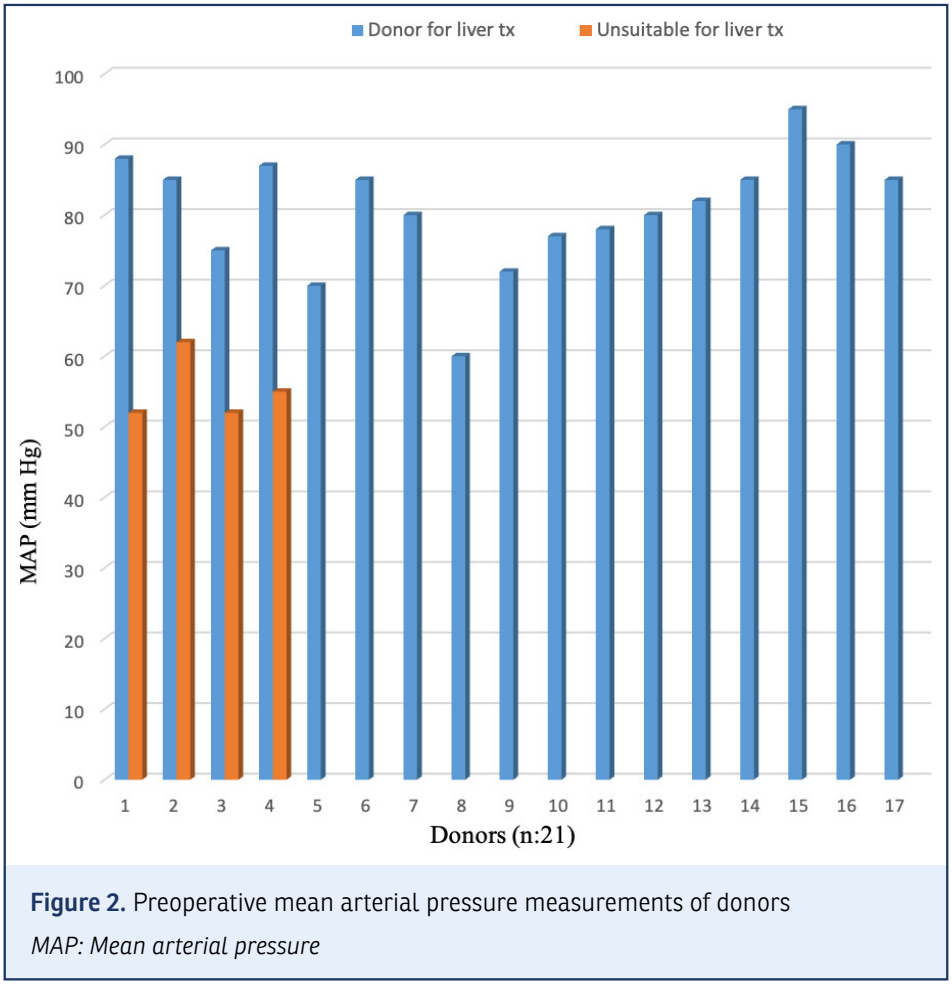

Figure 2. Preoperative mean arterial pressure measurements of donors

MAP: Mean arterial pressure

found that DMG scores with donors who had trauma were statistically higher than those of patients who had stroke and CPR, despite there being no difference in their ages. We think that this is because in trauma cases with brain death, there is isolated head trauma, and, in other cases, there is usually multiple organ failure.

Donor management exclusively toward organ resuscitation, which can be defined as an effort to prevent organ dysfunction. This effort includes providing optimal circulating intravascular volume, normalizing electrolyte and metabolic imbalances, and maintaining hemodynamics to promote adequate perfusion and prevent organs from hypoxia.[10] Therefore, to achieve all these goals, you should use many pharmacological agents. So, can these goals be achieved under all circumstances with medical treatments? Do these goals become more difficult to achieve as time goes on? Our study showed that six and twelve hours after the time of diagnosis of brain death, the DMG score maintained its score at the time of detection, while after 24 hours, the score decreased significantly despite pharmacological treatment.

Vasopressor drugs can be used in almost all donors whose intravascular volume replacement is not sufficient to keep the mean arterial pressure above a certain value. Guidelines recommend dopamine, the preferred catecholamine, especially for cardiac graft survival because of theoretical concerns that norepinephrine may increase pulmonary capillary permeability, induce mesenteric and coronary vasoconstriction, and increase left ventricular afterload.[10–12] Therefore, low-dose dopamine has been used as the first-line vasopressor drug given vasoactive and inotropic effects, immunomodulatory properties, and its role in decreasing cellular injury by scavenging reactive oxygen species (ROS).[10,13,14] Currently, there is not enough evidence to recommend dopamine over other vasopressors preferentially.[14] Similar to the findings from other studies, we found no significant differences between DMG scores according to vasopressor drug types or their dosages.

Maintaining hemodynamic stability becomes even more difficult during the process of BD, which is characterized by physiological instability.[15] Organ dysfunctions develop in

poorly managed donors, and successful organ transplantation does not occur.[10,13,14] Due to catastrophic brain damage, most potential donors present with similar problems, such as life-threatening arrhythmia and diabetes insipidus (DI).[14] The most common electrolyte disorder is hypernatremia, which is mostly caused by DI.[16,17] In our study, it was determined that the most common problems encountered before the determination of brain death were diabetes insipidus and central fever. We think that the reason for this situation is the disruption of the hypothalamic-pituitary axis before brain death occurs. Since volume losses and capillary permeability caused by DI increase over time after brain death, mean arterial pressure may not be increased even if the vasopressor dose is increased. However, no relationship was found between the problems and age, sex, or cause of brain death.

The most important problem surrounding BD is how to determine the irreversible absence of brain functions. The apnea test, which indicates the absence of brainstem response to carbon dioxide levels, shows irreversible coma.[18] The apnea test can be performed on donors who are hemodynamically stable and have had a sufficient waiting period.[18] However, when performing the apnea test, you must separate the donor from the ventilator, which may cause hypoxia in the organs. Contrary to our expectations, performing apnea testing or ancillary tests for the diagnosis of brain death did not affect DMG scores.

In the previously mentioned study by Patel et al.,[3] it was emphasized that the viability of intrathoracic organs increased when DMG criteria were met. In our study investigating the transplantation rate of liver and kidneys, we found that organ viability was mostly dependent on the MAP measured before donation. Despite the growing consensus on DMGs, we believe that to increase transplantation rates for the liver and kidneys, we need to determine more comprehensive criteria that include organ perfusion parameters and set the MAP target higher.

Limitations

Randomized controlled trials could not be conducted in BD and DMGs due to ethical problems. The current study, like other studies with donors, has some limitations. Since heart and lung transplants are not performed in our center, we do not have information about intrathoracic organ prognosis. Having included kidney and liver donors by a single university tertiary ICU limited the generalizability of our findings. The short observation period after brain death determination may have also affected our results. However, this is the first study ever performed on DMGs and effecting factors in BD patients.

CONCLUSION

In summary, BD patients with trauma have often access to DMGs than with other BD reasons. However, it is not possible to reach DMGs 24 hours after the determination of brain death, even with pharmacological treatment. Although more studies are needed to provide more effective DM and increase transplantation rates, more comprehensive criteria, including organ perfusion parameters, should be determined, and the MAP target should be increased without hesitation in the use of vasopressor drugs. Still, it gave us hope to see that we can achieve these goals in the ICU with pharmacological treatment, even within a certain period, regardless of age and comorbidities.

Disclosures

Ethics Committee Approval: The study was approved by the Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee (No: 2023-19/29, Date: 10/10/2023).

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