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Prevalence and factors associated with the diagnosis of brain death

Prevalência e fatores associados ao diagnóstico de morte encefálica

Prevalencia y factores asociados con el diagnóstico de muerte cerebral

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Abstract: Objective: to evaluate the prevalence of brain death and its associated factors. **Method:** cross-sectional study with data from the records of neurocritical patients and potential organ donors between 2018 and 2019, being analyzed by descriptive statistics and multivariate multinomial logistic regression. **Results:** the prevalence of brain death in followed-up patients was 46.6%, predominantly men, adults, with traumatic brain injury (44.3%) as cause of death. Factors associated with brain death were: Glasgow Coma Scale score (RRR=0.30; p=0.001), vasoactive drug use (RRR=7.55; p=0.000) and Hemorrhagic and Ischemic stroke (RRR=2.14; p=0.031). **Conclusion:** there was a high prevalence of brain death. The use of vasoactive drugs, the Glasgow Coma Scale score and the diagnoses of Hemorrhagic and Ischemic stroke were associated with the evolution to the condition.
Descriptors: Brain Death**;** Critical Care; Glasgow Coma Scale; Neurology; Tissue and Organ Procurement

Resumo: Objetivo: avaliar a prevalência de morte encefálica e os fatores associados. **Método:** estudo transversal com dados dos registros de pacientes neurocríticos e potenciais doadores de órgãos entre 2018 e 2019, sendo analisados por meio de estatística descritiva e regressão logística multinomial multivariada. **Resultados:** a prevalência de morte encefálica nos pacientes acompanhados foi de 46,6%, predominando homens, adultos, com Traumatismo Cranioencefálico (44,3%) como causa da morte. Os fatores associados à morte encefálica foram: *score* da Escala de Coma de Glasgow (RRR=0,30; p=0,001), uso de droga vasoativa (RRR=7,55; p=0,000) e Acidente Vascular Cerebral Hemorrágico e Isquêmico (RRR=2,14; p=0,031). **Conclusão:** houve uma alta prevalência de morte

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encefálica. O uso de droga vasoativa, o *score* da Escala de Coma de Glasgow e os diagnósticos de Acidente Vascular Cerebral Hemorrágico e Isquêmico mostraram-se associados à evolução para o quadro.
Descritores: Morte Encefálica; Cuidados Críticos; Escala de Coma de Glasgow; Neurologia; Obtenção de Tecidos e Órgãos

Resumen: **Objetivo:** evaluar la prevalencia de la muerte cerebral y sus factores asociados. **Método:** estudio transversal con datos de los registros de pacientes neurocríticos y potenciales donantes de órganos entre 2018 y 2019, siendo analizado por estadísticas descriptivas y regresión logística multivariada multinomial. **Resultados:** la prevalencia de la muerte cerebral en pacientes de seguimiento fue del 46,6%, predominantemente hombres, adultos, con lesión cerebral traumática (44,3%) como causa de muerte. Los factores asociados con la muerte cerebral fueron: la puntuación de la Escala de Coma de Glasgow (RRR-0,30; p-0,01), el consumo de drogas vasoactiva (RRR-7,55; p-0,000) y el accidente cerebrovascular hemorrágico e isquémico (RRR-2,14; p-0,031). **Conclusión:** hubo una alta prevalencia de muerte cerebral. El uso de drogas vasoactivas, la puntuación de la Escala de Coma de Glasgow y los diagnósticos de accidente cerebrovascular hemorrágico e isquémico se asociaron con la evolución a la afección.
Descriptores: Muerte Encefálica; Cuidados Críticos; Escala de Coma de Glasgow; Neurología; Obtención de Tejidos y Órganos

Introduction

Brain death (BD) is characterized by the loss of brain and brainstem functions irreversibly. The diagnosis is made with the aid of two clinical examinations, performed by different and trained physicians, in addition to a complementary examination, being characterized by aperceptive coma, absence of brainstem reflexes and apnea.[1-2] The neurological condition can be assessed using the Glasgow Coma Scale (GCS), which defines the level of consciousness by observing the ocular, motor and verbal response, and was updated in 2018 with the addition of pupillary assessment to correlate the severity of traumatic neurological damage. It is based on a numerical value, being an instrument widely used for the evaluation of patients.[3-4]

The diagnosis of BD is mandatory and its notification is compulsory, and the organ responsible for receiving these notifications is the Notification, Capture and Distribution of Organs Central in each state.[5] From the notification and opening of the BD Protocol, the patient is considered a potential organ donor, and the process of communication with the family about the diagnosis of BD is initiated.[6] Currently, the organ donation should be performed after the consent of first or second degree relatives or by the partner of the deceased.[7]

Given the technological advances, nowadays, it is possible to maintain the patient's body in BD, providing hemodynamic support, such as ventilatory and cardiac, enabling organ donation.[8] The team needs to know this care, since an effective care can result in higher transplant results.[9] In Brazil, in 2019, 11,400 potential donors were reported, with neurological causes responsible for 85% of deaths, including Traumatic Brain Injury (TBI) and Cerebrovascular Accident (CVA), the main ones.[10]

Studies addressing BD allow greater understanding of the subject.[11-12] In this context, it was questioned, with this research, what is the prevalence of BD in neurocritical patients accompanied by an Organ Searching Organization (OSO) and the factors that influenced this outcome? In this context, the present study aimed to evaluate the prevalence of brain death and associated factors.

Method

This is a cross-sectional study, based on access to the OSO database of the municipality of Petrolina, Pernambuco (PE). OSO is an institution responsible for the search, identification, maintenance and collection of donors for transplant purposes.[13]

The study population involved neurocritical patients and potential organ donors admitted to public and private hospitals accompanied by OSO. The collection was carried out by one of the researchers of the study, a student in the health area trained by the advisors in order to obtain homogeneous information. A collection instrument was used, constructed by the authors, to search the data in the database of records made in spreadsheets of daily activities of the OSO, provided by the institution. The collection period took place between September 2019 and February 2020. All records of neurocritical patients whose GCS was equal to or less than seven and who were hospitalized in the years 2018 and 2019 were included. Records of patients who did not present the results of GCS evaluations and information on the clinical outcome were excluded.

The study variables involved sociodemographic and clinical information of patients such as: gender, age, GCS, vasoactive drug (VAD) use, use of sedation prior to protocol opening, sedative drug, cause of hospitalization, nature of the hospitalization, follow-up time, clinical outcome, family interview, protocol closing time, implementation of the donation and reason for non-effectiveness.

Initially, descriptive statistics were performed through frequency distribution and measures of central tendency and dispersion as mean and standard deviation (SD) for patients diagnosed with BD. The associated factors were analyzed using the multinomial logistic regression model. Therefore, the cause of death (BD and cardiorespiratory arrest - CRA) was adopted as a dependent variable compared to patients who evolved to clinical improvement of the condition, which is the reference category. The multivariate model was generated by the stepwise method of variable selection, considering the inclusion criterion the p value of 0.20, thus obtaining an adjusted model. The effects of the explanatory variables were verified by the relative risk ratio (RRR). A 95% confidence interval and significance of 5% were adopted.

The data were organized in a database in the Microsoft® Office Excel 2013 software and then processed by the statistical program Stata 14.0. The research respected the ethical precepts involving research with human beings required by Resolution of the National Health Council nº 466/2012 and was approved by the Ethics and Research Committee of the Integrated Health Center Amaury de Medeiros of the University of Pernambuco, under opinion nº 3,605,843 on August 26, 2019.

Results

A total of 416 patients were followed by the OSO in 2018 and 2019, of which 194 (46.6%; CI95% 41.9-51.5) evolved to BD, 100 (24.0%; CI95% 20.2-28.4) for CRA and 122 (29.3%; CI95%25.1-33.9) had clinical improvement. Regarding the 194 patients in BD who comprised the study, the

majority were male (63.9%), with a mean age of 41.7 (SD: 17.3). The main hospitalization diagnoses were TBI (44.3%) and Hemorrhagic Cerebrovascular Accident (HCVA) (41.8%).

The mean GCS of these patients was 3 (SD 0.4) and most were hospitalized in public hospitals (93.8%). Patients were followed by the OSO team for an average of 2.6 days (SD 1.9) (Table 1).

Table 1 – Sociodemographic and clinical characteristics of patients with brain death monitored by OSO. Petrolina, 2018 – 2019.

Sociodemographic Variables	n	% or mean±SD*	CI95%†	
Age	194	41.7 ± 17.3	39.2	44.1
Gender				
Female	70	36.1	29.6	43.1
Male	124	63.9	56.9	70.4
Cause of hospitalization				
Cranioencephalic Trauma	86	44.3	37.4	51.4
Hemorrhagic Cerebrovascular Accident	81	41.8	35	48.9
Ischemic Cerebrovascular Accident	6	3.1	1.4	6.8
Ischemic Hypoxic Encephalopathy	9	4.6	2.4	8.7
Clinical Causes	8	4.1	2.1	8.1
Neurological Malformations	1	0.5	0.1	3.6
Neoplasia	3	1.6	0.5	4.7
GCS‡	194	3 ± 0.4	3	3.1
OSO Follow-up time (days)	194	2.6 ± 1.9	2.3	2.8
Hospital Nature				
Private	12	6.2	3.5	10.6
Public	182	93.8	89.4	96.5

Note: * standard deviation; † confidence interval of 95%; ‡ Glasgow Coma Scale.

Most patients in brain death (76.3%) used VAD, and 10.3% used sedation prior to the opening of the BD protocol, the most used being Fentanyl® associated with Midazolam® (85.7%). The mean protocol closing time was 7.8 hours (SD 7.9).

Regarding organ donation, most families (57.2%) authorized to carry it out after the interview and, of these, 53.1% were realized donations. Among the main reasons for its non-effectiveness, medical contraindication (50.6%) and family refusal (41.8%) (Table 2).

Table 2 – Characterization of brain-dead patients followed by OSO. Petrolina, 2018 – 2019.

Characterization Variables	n	% or mean±SD†	CI95%‡	
VAD*				
No	46	23.7	18.2	30.3
Yes	148	76.3	69.7	81.8
Sedation prior to opening the protocol				
No	174	89.7	84.5	93.3
Yes	20	10.3	6.7	15.5
Sedative Drug				
Fentanyl® + Midazolam®	18	85.7	61.3	95.8
Others	3	14.3	4.2	38.7
Family Interview				
Refusal	38	19.6	14.5	25.8
Acceptance	111	57.2	50.1	64.5
Notifications	45	23.2	17.7	29.7
Protocol closing time (in hours)	194	7.8 ± 7.9	6.7	8.9
Donation effectuation				
No	91	46.9	39.9	54.0
Yes	103	53.1	46.0	60.1
Reason for non-effectiveness				
Family Refusal	38	41.8	31.9	52.3
Medical Contraindication	46	50.6	40.2	60.8
Lack of logistics for organ procurement	7	7.7	3.7	15.5

Note: * vasoactive drug; † standard deviation; ‡ confidence interval of 95%.

Analyzing the factors associated with the diagnosis of BD in patients followed by OSO, it was observed that an increase of one point in the GCS score represents a reduction in the chance of death by BD (RRR 0.30; p - value = 0.001) and CRA (RRR 0.46; p - value = 0.000). Patients who used VAD were more likely to die both by BD (RRR 7.55; p-value = 0.000) and by CRA (RRR 2.78; p - value = 0.001) compared to patients who evolved to clinical improvement.

Regarding the diagnosis of hospitalization, patients who had as cause the HCVA and ischemic cerebrovascular accident (ICVA) were more likely to die due to BD (RRR 2.14; p - value = 0.031) compared to those who presented clinical improvement. It was not associated with

patients who evolved to death by CRA (p > 0.05). Age, gender and days of hospitalization were not significant in the analysis (p > 0.05) (Table 3).

Table 3 – Factors associated with the diagnosis of brain death in patients followed by OSO. Petrolina, 2018-2019.

	Encephalic Death				CRA*			
	RRR†	p-value	CI95%‡		RRR†	p-value	CI95%‡	
Age	0.99	0.544	0.98	1.01	1.00	0.645	0.99	1.02
Gender								
Male	0.90	0.753	0.48	1.71	0.95	0.891	0.47	1.91
Female	1.00				1.00			
GCS§	0.30	0.001	0.15	0.59	0.46	0.000	0.30	0.70
VAD‖								
Yes	7.55	0.000	4.20	13.57	2.78	0.001	1.48	5.21
No	1.00				1.00			
Hospitalization Days	1.08	0.353	0.92	1.26	0.90	0.418	0.70	1.16
Diagnosis of hospitalization								
ICVA**/HCVA††	2.14	0.031	1.07	4.29	1.91	0.085	0.91	3.99
Other causes	1.00				1.00			

Note: * cardiorespiratory arrest; †relative risk rate; ‡ confidence interval of 95%; § Glasgow Coma Scale; || vasoactive drug; ** ischemic cerebrovascular accident; †† hemorrhagic cerebrovascular accident.

Discussion

The 194 cases analyzed between 2018 and 2019 represented approximately 19.4% of the reported cases of BD in the state of Pernambuco through the two years.[10,14] The sociodemographic profile and the main causes of death evidenced in the present study presented, at the same time, agreement and divergence in relation to the literature. Regarding gender and age, most were men and in adulthood, corroborating the national profile. However, regarding the causes, the CET followed by the HCVA prevailed, diverging from the scenario in national territory, in which the main cause of BD was CVA, followed by CET.[10]

A 2014 study conducted in the same region of Pernambuco of the present study showed that most cases of CET were associated with automobile accidents.[11] This may explain the fact

that most cases are male, because men are generally more involved in these accidents.[15] A study aimed at evaluating the profile of potential donors and effective donors showed that, among traumatic causes, the most affected sex was male, and that non-traumatic causes, such as HCVA, are related to bad lifestyle habits and chronic diseases.[16]

The GCS score evidenced in the present study indicated a greater severity of the neurocritical patients followed up. Patients with scores 3 and 4 have higher mortality rates when compared to higher scores.[4] The recommended score for the opening of the BD protocol is equal to three.[6]

The time of follow-up of the patient by the OSO team from observation to confirmation of death was within the expected, in the same way that the time of the protocol was relatively short. In the first case, the minimum time of hospitalization and observation in the hospital should be respected to start the procedures for confirming BD, except for individuals with ischemic hypoxic encephalopathy, in which the minimum time is extended to 24 hours.[1]

Regarding the time for executing the protocol, the minimum time between one clinical examination and another for its confirmation is one hour in patients over two years of age and for younger patients, an interval of six or 24 hours is required.[1] Most patients were hospitalized in public hospitals, a fact that may be directly related to the high-complexity reference service in traumatology and neurology in the region being public,[17] added to the fact that about 80 to 90% of the population of Pernambuco does not have coverage of supplementary health care.[18]

The use of VAD was predominant in this study, reinforcing the severity of cases, since, for hemodynamic resuscitation of the potential donor, there is a strong recommendation from the Brazilian Association of Intensive Care Medicine, after volume expansion. These drugs are frequently used in intensive care units (ICU) because they act in the cardiovascular system and regulate vital functions, and may be necessary due to physiological changes in BD, but should be adequate to the therapeutic response in each situation to achieve hemodynamic stability.[19-20]

Regarding the use of sedation, a lower proportion of the cases analyzed made use. The use of sedation in the ICU has the role of reducing stress response and providing comfort, and the level and depth of sedation are related to hospitalization time and mortality.[21]

The most used sedation was Fentanyl® associated with Midazolam®, with Fentanyl® being a fast-acting and efficient sedative and analgesic used to potentiate benzodiazepines, such as Midazolam®, which is characterized as a hypnotic producer of drowsiness.[22] These two drugs are commonly used in intensive care centers.[23] For the determination of BD, some procedures are necessary, such as the exclusion of treatable factors that may confuse its diagnosis, and the suspension of the use of sedatives.[24]

Medical contraindication was the main reason that prevented organ donation, followed by family refusal. Currently, the latter was the main reason for the non-effectiveness of organ donation in Brazil, representing 40% of the reasons in 2019.[10] A study conducted in Rio Grande do Sul, with the objective of understanding the motivations for the families' decision regarding donation, showed that refusal was associated with several factors, such as the non-acceptance of death in the situation of unexpected illness and the lack of expression in life about this position, making decision-making more difficult.[25]

Among the factors associated with the diagnosis of BD and death from CRA in relation to those who presented clinical improvement, the GCS score proved relevant, because the higher its score, the greater the chance of survival. A low GCS score is a factor of severity, being associated with negative clinical outcomes in neurocritical patients.[26] Despite the limitations of the GCS, it can be considered an ally to indicate clinical outcome in neurological cases.[3]

The present study showed a significant association between the use of VAD and the evolution of the neurocritical patients, revealing that those who made its use were more likely to progress to BD and CRA in relation to those that improved clinically. It can be inferred that the use of VAD may be an indication of greater severity. The literature indicates, among other risk

factors, a relationship between the use of VAD and the negative clinical outcome in ICU patients, with a higher chance of progression to death.[27]

The diagnoses of ICVA and HCVA showed a significant relationship in the evolution to BD in relation to those that evolved to clinical improvement, although the highest frequency of causes of hospitalization was CET. The reason that CVA is an aggravating factor in the evolution to BD may be related to risk factors associated with the condition, such as Systemic Arterial Hypertension, obesity and smoking, among others.[12,28]

The present study found limitations in its execution due to the incompleteness of some information in some medical records, hindering the construction of the database.

Conclusion

The prevalence of BD represented almost half of the neurocritical patients followed up in the present study. Most of them were male, in adulthood, whose main diagnoses of the cause of death were CET and the HCVA. The use of VAD and the diagnoses of ICVA and HCVA are associated with the evolution to BD. Similarly, it reinforced that the GCS score was shown to be a predictor of severity. This finding reinforces, in clinical practice, the validity of the GCS for the evaluation of the neurocritical patients, suggesting greater attention by the professionals who follow up them. The fall of a point on the scale implied in severity and possible evolution to the diagnosis of BD.

Most families agreed to donate organs, but refusal was the second reason for preventing donations, which represented a relevant number in the study. The patient in BD is the main source of organs for transplants, being the commitment of all professionals and institutions involved important in all stages of the donation process, from identification and diagnosis to the time of family interview. This scenario allows increasing the implementation of the donation, since transplantation provides survival and quality of life to chronic patients, potential organ recipients.

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