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Vestibulo-ocular reflex as predictor of cerebral death in comatose patients

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Abstract

Objective: Our goal was to establish the role of VOR – vestibular ocular reflex - in predicting cerebral death in comatose patients.

Patients and Methods: Prognosis study based on three concurrent cohorts of comatose patients of known etiology followed until the ultimate outcomes: recovery, vegetative state or death. Sixty comatose patients (Glasgow scale 8 or less) with known causes were studied: 49 males and 11 females; 7 to 83 years old. The cold water vestibular stimulation was performed at the bedside by irrigation with 0o Celsius saline in the external auditory canal during one minute. The reflex was considered present when both eyes deviated toward the stimulated side (19 patients group 1); present but abnormal for irregular unconjugated eye movements (11 patients group 2) or absent (30 patients, group 3).

Results: Group 1 had total recovery in 42%, partial recovery in 37% and cerebral death in 21%. These results were 9%, 18% and 73% for group 2, respectively and group 3 had 100% cerebral death. The difference was statistically significant between groups 1 and 2, 3 ($p<0,05$ Fischer exact test and X^2 test).

Conclusion: Absence of VOR predicted 100% of cerebral death and VOR present normal predicted 21% of cerebral death in the comatose patients we studied.

Keywords: vestibular-ocular reflex, comatose patients, cerebral death.

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INTRODUCTION

There has been much recent public discussion on brain death. Effective resuscitation techniques are now so widely available that most doctors who practice in an acute care hospital are faced with the problem at some time. Misapprehensions as to the criteria for diagnosis and legal situations concerning brain death are common[1]. The importance of early recognition of brain death in the context of cadaveric organ transplantation is obvious. Even when the question of transplantation does not arise early recognition of the hopeless situation after death of the brain is important to shorten the period of uncertainty for victim's families and to prevent the waste of limited community resources[1].

There is also understandable reluctance from medical practitioners to pronounce death on the basis of irreversible loss of brain function rather than on the more obvious grounds of cardio-respiratory arrest. As we become better at maintaining cardio-respiratory function, the need for recognizing the hopeless situation becomes greater. Legally, a definition of death based on irreversible cessation of brain function has already been proposed by the Australia Law Reform commission, and such statutes have been assumed in other parts of the world[2].

Reluctance to diagnose brain death has led to demand for objective clinical investigation to support clinical judgment. The first such test to be used was the electroencephalogram (EEG) and no more than a year had passed before it became obvious that while EEG criteria could be helpful at times, in many situations the test was superfluous[3]. Radiology has been used to demonstrate absence of cerebral blood flow, but it is an invasive test which is rarely justified[1]. So it became crucial to diagnose brain death on clinical grounds paying particular attention to the history to establish the irreversibility of the patient's comatose condition. In this way, the simple bedside tests like the classical neurological examination such as observation of the posture, pupil size, pupillary reflex to the light and the response to pain, often gives us limited information about the brainstem function in comatose patients, notably in deep coma. In 1910, Rosenfeld demonstrated a close relationship between the results of the cold water caloric test – the vestibular-ocular test (VOT) – and the consciousness[4]. After that only a few reports have investigated the prognosis of comatose patients by means of the VOT.

This study was performed in order to evaluate the role of VOT in predicting cerebral death in patients who were comatose from various causes in the intensive care unit of the Hospital de Base do Distrito Federal, Brasília, Brazil.

PATIENTS AND METHOD

This study was submitted to and approved by the Brasília Department of Health Ethics Committee. The legal responsible for the patient was contacted and signed a consent term.

This is a prognosis study by means of three concurrent comatose patient's Cohorts. The first Cohort included patients with VOR present and normal (Group 1), the second was composed by patients with VOR present and abnormal (Group 2) and the third had patients with the VOR absent (Group 3) according to the definitions outlined below.

The subjects of the study were 60 comatose patients with known causes admitted for treatment at the Department of Critical Care – Neurosurgery and Neurology divisions - in the Hospital de Base do Distrito Federal, Brasília, Brazil, between March and October 2007. All these patients were in deep coma and were under mechanical ventilation. The definition of deep coma adopted in this study is the stage of Glasgow scale less than 8 and no reaction to pain or any other stimuli. The patients could be under sedation. Patients with history of acoustic trauma, chronic otitis media, ototoxic drug use, otologic surgery as well as neurological drug induced coma were excluded from this study. We also excluded from the analysis patients with lack of follow-up.

The result of the caloric test was the predictive variable and was classified as present and normal when the patient showed conjugated deviation of the eyes to the side of the stimulus (Group 1). It was considered present and abnormal in patients that showed restricted conjugate deviation of the eyes, slow or irregular movements of the eyes, slight or occasional movements (Group 2). The reflex was considered absent in patients that showed no eye movements after the stimulus (Group 3).

The prognosis of the patients was recorded as recovery, vegetative state and death. Recovery means the state in which the patient is awake without any stimulation and has clear conscience. In the vegetative state patients respond to pain and loud voices and have spontaneous respiration but do not have clear conscience. Death is defined as the irreversible cardio-respiratory arrest and/or irreversible interruption of cerebral function including the brain-stem function as defined by the Brazilian Medical Council[5].

The features evaluated in the patient´s records were the etiology of the coma, level of conscience by Glasgow scale, use and type of sedative drugs. The cold water test was performed after excluding the presence of wax or blood clot in the external auditory canal by means of otoscopy. When necessary the external canal was cleaned at bedside. The cold caloric test was performed

using cold saline close to 0° Celsius. The patient's head was rested on a pillow at an angle of 30°, with the horizontal plane. About 50 ml of ice saline was introduced slowly for 60 seconds into the external auditory canal. After the stimulation, the eyes of the patients were manually opened by the examiner avoiding hindrance to the eye movements. These movements were recorded as above. The patients were followed up according to their records and the caloric test was repeated daily in groups 1 and 2 in order to detect any change from the initial result until the final outcome.

In Group 1 and 2 the sedation was kept. In Group 3, the patients had the test repeated at 6, 24 and 72 hours and the sedative drugs were discontinued. The series of examinations was interrupted when the patient showed reaction to the pain stimuli, became conscientious or died.

The outcomes of recovery, vegetative state and death were recorded and the relative risk for each outcome was analyzed for the confidence interval of 95% by the X^2 test and Fisher´s test and p was considered statistically significant when it was less than 0.05. The 3.4.2 Epi Info version was employed for statistic analysis.

RESULTS

There were 60 patients divided into three groups. Nineteen patients had VOR present and normal (Group 1), 11 patients had VOR present and abnormal (Group 2) and thirty patients had VOR absent (Group 3). Table 1 summarizes the demographic variables of the studied patients. Forty-nine patients were male and eleven were female. The mean age was 45 years old (range 7 to 83 years old ± 17.7 years). Twenty-eight patients had intra cerebral contusion or hematoma by brain injury, 18 patients had cerebral vascular accidents and fourteen patients were comatose by other causes such as: medullar traumatism, cardiac arrest, meningitis, hydrocephaly, hemorrhagic or septic shock. The follow up time ranged from 1 to 30 days. The mean follow up among the patients with VOR present was 8 ± 2.8 days and it was 5 ± 1.4 days in the group of patients with VOR absent.

Nineteen patients had the VOR present and normal (Group 1) and 16 were male. The age ranged from 12 to 70 years (mean 42 ± 2.8 years) (Table 1). Among these patients, 42% (n=8) recovered, 37% (n=7) had vegetative state and 21% (n=4) died (Table 2). Three out of four patients who died changed the VOR from normal to absent before death. The probability for recovery in this group was 4.63 times higher than for the patients with VOR present and abnormal but this was not statistically significant (p=0.06). The confidence interval for 95% was 0.66, 32.29 (Table 3).

Eleven patients had VOR present and abnormal (Group 2). All patients in this group were males and the age ranged from 19 to 83 years (mean 55 ± 3.5

Table 1. Demographic variables of the patients

	Male No.(%)	Female No. (%)	Total No.	Age range Mean (SD), y	Etiology No. (%)
Group 1	16 (84.2)	03 (15.7)	19	12 – 70 Mean 42 ± 2.8	TBI* – 9 (47.4) CVA** – 4 (21.1) Others – 6 (31.6)
Group 2	11 (100)	00	11	19 – 83 Mean 55 ± 3.5	TBI* – 3 (27.3) CVA** – 5 (45.5) Others – 3 (27.3)
Group 3	22 (66)	08 (34)	30	7 to 67 Mean 35 ± 3.5	TBI* – 16 (53.3) CVA** – 9 (30) Others – 5 (16.7)

* Traumatic Brain Injury
** Cerebral-vascular Accident

Table 2. Ultimate outcomes (recovery, vegetative state and death) by the vestibular ocular test result

Vestibulo ocular reflex	Outcomes			Total %
	Recovery %	Vegetative state %	Death %	
Present normal (Group 1)*	42	37	21	100
Present abnormal (Group 2)	9	18	73	100
Absent (Group 3)	-	-	100	100

*Statistically different from Groups 2 and 3 (p<0.05 in both comparisons)

Table 3. Distribution of the patients with VOR present by the ultimate outcomes

VOR Present	Outcomes		Total No.
	Recovery No.	Vegetative State/ Death No.	
Normal No.	8	11	19
Abnormal No.	1	10	11

Relative Risk of Recovery 4.63 (IC 95% 0.66-32.29) and p= 0.06

Table 4. Distribution of the patients with VOR present by the ultimate outcomes

VOR Present	Outcomes		Total No.
	Death No.	Recovery/ Vegetative state No.	
Abnormal No.	8	3	11
Normal No.	4	15	19

Relative Risk of Death 3.45 (IC 95% 1.35-8.87) and p= 0.008

years). In this group, 73% (n=8) died, 18% (n=2) had vegetative state and only 9% (n=1) recovered (Table 2). Three patients changed VOR from abnormal to absent before dying. The risk for death in this group was 3.45 times higher than for the group with VOR abnormal and normal and this difference was statistically significant (p=0.008) (Table 4).

The probability of keeping in the vegetative state among patients who did not die was calculated for patients with VOR present and abnormal and it was 1.43 times higher than for the patients with VOR present and normal, but this difference was not statistically significant (p=0.5, IC 95% 0.54-3.75) (Table 5).

Table 5. Distribution of the patients with VOR present that did not die, by the ultimate outcomes

VOR Present	Outcomes		Total No.
	Vegetative state No.	Recovery No.	
Abnormal No.	2	1	3
Normal No.	7	8	15

Relative risk of vegetative state 1.43 (IC 95% 0.54-3.75) and p= 0.5

Among the thirty patients with VOR absent (Group 3), 22 were male and the age ranged from 7 to 67 years (mean 35 ± 3.5 years) (Table 1). All patients died in this group during the follow up and no one improved the VOR results before death. Table 2 shows the ultimate outcomes for all 60 patients related to the VOR test results at the first evaluation.

DISCUSSION

Cerebral death is consequent upon irreversible loss of brain stem function. Loss of cortical activity only tends to result in persistent vegetative states6. Tests of brain stem function are therefore more appropriate for the diagnosis of brain death than those of cortical function and there are numerous reports in the literature of prolonged survival in vegetative patients[1].

We have been reviewing the literature concerning the parameters, clinical signs and the evaluation of comatose patients trying to predict the ultimate outcome of these patients. There is no consensus in the literature regarding the criteria and procedures for predicting the recovery of the comatose patients. Most of the studies have controversies concerning the specificity of the tests used[7]. The Glasgow comatose scale has been used largely even though it is not appropriate for patients in deep coma under mechanical ventilation and sedation. It has low specificity and a high tendency for predicting poor prognosis when employed alone[8].

The signs commonly relied upon to establish the level of conscience are the responses to stimuli including painful stimuli, corneal reflexes. It was observed at times that these signs do not reflect the true level of conscience[9]. Nathanson et al[9] first proposed the value of vestibular stimulation, particularly the caloric test in six comatose patients for predicting the level of conscience at the time of the test. They reported four different results of the caloric test and correlated the test to the prognosis of the patients. For those authors the caloric test was more predictive of the ultimate outcome of comatose patients than simple clinical tests such as deep tendon reflex and corneal reflex.

Barrios et al.[10] and Poulsen & Zilstorff[11] have also demonstrated the correlation between the VOR absence and the incidence of death. In their studies all patients with absent VOR died. Mahapatra and Tandon12 found a good correlation between the VOR and the auditory brain stem responses (ABR) in predicting the ultimate outcome of comatose patients with severe brain trauma. In their study, 81% of patients with normal ABR versus 87% of patients with normal VOR recovered. Among the patients with VOR absent no one recovered. Among the 21 patients with abnormal ABR, 50% recovered, 25% died.

In our study we decided to establish three Cohorts based on the results of the caloric test and observe the ultimate outcomes in these groups. Among the 30 patients with VOR present, 19 showed normal result to the test (Group 1) and had better prognosis than the 11 patients with abnormal VOR (Group 2). In this group we observed the worsening of the VOR in 6 patients before death. The risk for death was 3.45 times higher in the group with VOR abnormal than in the group with VOR

normal and this difference was considered statistically significant. All patients with VOR absent died and no one changed the status of the VOR during the follow up. These results are in agreement with previous studies[9-12]. However Yagi and Baba[13] reported 86 deeply comatose patients who underwent caloric tests, 46 with VOR absent. Among these patients, 35 died, 7 had vegetative state and 4 recovered. The authors discussed the need for complementary examination such as the ABR for better prediction of the outcomes of patients in deep coma.

The fact that 100% of our patients with VOR absent died is not in agreement to the Yagi and Baba`s report[13]. We agree with them about the point that not all patients with VOR normal will have good prognosis and it is possible that a patient with VOR absent shows recovery during the follow up depending on the etiology of the coma. We believe that the recovery from deep coma depends on multiple factors and the tests that evaluate the brain stem function must complement each other.

The technological advance in the last century brought up the possibility to keep the cardiac function over the time after the diagnosis of brain death. In our study, this time ranged from 24 hours to 18 days. Hicks and Torda1 reported the maintenance of the cardiac function from 8 hours to 5 days. This is the time window to remove organs for transplantation. Therefore the precise diagnosis of brain death is essential in this field.

Relating to the etiologies of coma, Pallis14 reported that severe brain trauma and subaracnoid hemorrhage were the most prevalent causes of brain death and this is in agreement with our findings. In our series 53% of the patients had trauma and 30% cerebral-vascular accidents (Table 1).

Our results point out the convenience of the caloric test in the follow up of patients with deep coma and its use for predicting the ultimate outcomes in these patients. We strongly recommend the routine use of VOR not only for predicting the brain death but also for follow up of comatose patients. This simple practice may not only predict the status of the brain stem but also signal the convenience of beginning the protocols for brain death and availability of organs for transplantation.

The probability of recovery in group 1 was 4.65 greater than in group 2 and this approached statistical significance ($p=0.06$). The probability of vegetative state among those who survived was 1.43 times higher in group 2 than in group 1 but this was not statistically significant ($p=0.5$) We think the lack of significance in these comparison are due to small numbers in our cohorts.

Finally it is important to follow up the patients with normal VOT with daily tests because the reflex may become abnormal or absent heralding worsening of the coma and changing the initial prognosis.

CONCLUSIONS

The VOT is a simple, non invasive test that does not require complex equipments and is easy to learn that can be performed at the bed side in few minutes. Each labyrinth can be stimulated individually and the stimulus is highly reproducible and well tolerated by the patients. The test can be repeated several times and is useful for the follow up of comatose patients. Mechanical ventilation and sedation do not interfere with the test responses.

From our observations we can conclude that the patient with VOR present and normal has better prognosis. The VOR may change from normal to abnormal or absent during the follow indicating worsening of the comatose condition but changes in the opposite direction were not observed. Abnormal VOR was related to guarded prognosis and absent VOR predicted 100% death outcome in our patients.

VOT is a helpful tool in predicting brain death. The test must be performed at regular time intervals during follow up of patients in coma. Studies with larger numbers of patients are needed in order to establish sensitivity, specificity as well as positive and negative predictive values for VOT in predicting brain death in comatose patients.

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