Predicting Outcome after Cardiopulmonary Arrest in Therapeutic Hypothermia Patients: Clinical, Electrophysiological and Imaging Prognosticators

Prognóstico após Paragem Cardio-Respiratória em Doentes Submetidos a Hipotermia Terapêutica: Factores Clínicos, Electrofisiológicos e Imagiológicos

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ABSTRACT

Introduction: Predicting outcome in comatose survivors of cardiac arrest is based on data validated by guidelines that were established before the era of therapeutic hypothermia. We sought to evaluate the predictive value of clinical, electrophysiological and imaging data on patients submitted to therapeutic hypothermia.

Materials and Methods: A retrospective analysis of consecutive patients receiving therapeutic hypothermia during years 2010 and 2011 was made. Neurological examination, somatosensory evoked potentials, auditory evoked potentials, electroencephalography and brain magnetic resonance imaging were obtained during the first 72 hours. Glasgow Outcome Scale at 6 months, dichotomized into bad outcome (grades 1 and 2) and good outcome (grades 3, 4 and 5), was defined as the primary outcome.

Results: A total of 26 patients were studied. Absent pupillary light reflex, absent corneal and oculocephalic reflexes, absent N20 responses on evoked potentials and myoclonic status epilepticus showed no false-positives in predicting bad outcome. A malignant electroencephalographic pattern was also associated with a bad outcome (p = 0.05), with no false-positives. Two patients with a good outcome showed motor responses no better than extension (false-positive rate of 25%, p = 0.008) within 72 hours, both of them requiring prolonged sedation. Imaging findings of brain ischemia did not correlate with outcome.

Discussion: Absent pupillary, corneal and oculocephalic reflexes, absent N20 responses and a malignant electroencephalographic pattern all remain accurate predictors of poor outcome in cardiac arrest patients submitted to therapeutic hypothermia.

Conclusion: Prolonged sedation beyond the hypothermia period may confound prediction strength of motor responses.

Keywords: Coma; Heart Arrest; Hypothermia.

RESUMO

Introdução: A determinação do prognóstico em sobreviventes comatosos de paragem cárdio-respiratória baseia-se em evidência adquirida sobretudo antes do advento da hipotermia terapêutica. O nosso objectivo é avaliar a capacidade preditiva de dados clínicos, electrofisiológicos e imagiológicos após a hipotermia terapêutica.

Materiais e Métodos: Análise retrospectiva e consecutiva de doentes que foram tratados com hipotermia durante os anos de 2010 e 2011. Foram obtidos dados relativamente ao exame neurológico, potenciais evocados somatossensitivos e auditivos, electroencefalograma e ressonância magnética crânio-encefálica, nas primeiras 72 horas após o evento. O *outcome* definido foi a escala *Glasgow Outcome Scale* dicotomizada em mau prognóstico (pontuações 1 e 2) e bom prognóstico (pontuações 3, 4 e 5).

Resultados: Estudados no total 26 doentes. Reflexos pupilares, corneanos e oculocefálicos abolidos, ausência de respostas N20 nos potenciais evocados somatossensitivos, estado de mal mioclónico e um padrão 'maligno' na electroencefalografia relacionaram-se com mau prognóstico, sem falsos-positivos (p = 0,05). Dois doentes classificados com bom *outcome* demonstraram respostas motoras ausentes ou em extensão nas primeiras 72 horas, originando uma taxa de falsos-positivos de 25% para este parâmetro (p = 0,008). Ambos requereram sedação até às 72 horas. A presença de isquémia na ressonância não teve relação significativa com o *outcome*.

Discussão: A abolição dos reflexos pupilares, corneanos e oculocefálicos, a ausência de respostas N20 nos potenciais evocados, estado de mal mioclónico e um padrão electroencefalográfico 'maligno' mantêm-se parâmetros de mau prognóstico válidos em doentes submetidos a hipotermia terapêutica.

Conclusão: A necessidade de sedação nestes doentes pode diminuir a capacidade prognóstica das respostas motoras.

Palavras-chave: Coma; Hipotermia Induzida; Paragem Cárdio-Respiratória.

INTRODUCTION

Therapeutic hypothermia (TH) is a well-established treatment for patients surviving cardiac arrest (CA). Decreased brain damage from hypoxic-ischemic encephalopathy and increased survival has been demonstrated in randomized clinical trials.[1-4]

Predicting outcome during the first days after the arrest has been a challenging task for intensivists and a preoccupation for the patient's relatives. The American Academy of Neurology has issued a practice parameter, based on evidence from several trials, that establishes accurate clinical and electrophysiological predictors to assist in decision-making regarding continuum of life-supporting measures[5]. Absent pupillary light reflexes (PLR), absent corneal reflexes and absent or extensor motor responses within 72 hours after CA are the clinical parameters and absent N20 responses on somatosensory evoked potentials (SSEPs) and

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serum neuron-specific enolase (NSE) > 33 ng/ml at days 1 to 3 and the presence of myoclonic status epilepticus within 24 hours all predict poor outcome in non-hypothermic patients.[6-8]

There are few data on the predictive value of these clinical and electrophysiological parameters in patients submitted to hypothermia. Recent studies have tried to address this issue showing some conflicting results, especially regarding clinical data.

The goal of our study was to assess the false-positive rates of all these parameters and magnetic resonance imaging (MRI) on survivors of CA submitted to TH.

MATERIALS AND METHODS

We performed an observational study through a retrospective analysis of all consecutive patients admitted to our Medical Intensive Care Unit (ICU) in Lisbon, Portugal and treated with TH after in and out-of-hospital CA, during the years 2010 and 2011. At our ICU all patients with in and out-of-hospital CA over 18 years-old are treated with TH, as long as the following criteria are met: (1) no response to verbal commands after recovery of cardiac rhythm, (2) no more than 8 hours since the arrest until the beginning of therapy, (3) no known coagulopathy, (4) no terminal illness, (5) no sustained hypotension (systolic blood pressure < 80mmHg) and (6) no CA secondary to trauma, aortic dissection, intracranial hemorrhage or hypovolemic shock.

Patients meeting all the above criteria are treated with a 24-hour period of hypothermia to a target temperature of 33ºC, achieved through initial infusion of iced normal saline (at 4ºC) and external ice packs and maintenance using an external cooling device. Monitoring of target temperature is done by a central temperature device. Upon completion of this period rewarming, either passive or with an external device, is performed by a rhythm of 0.5ºC per hour. Sedation with propofol and alfentanyl is done for the 24-hour hypothermia period and an initial bolus of vecuronium is also administered for shivering prevention. Sedation is withdrawn in the rewarming period allowing neurological assessment to take place, unless it is required for other reasons.

According to our predefined institutional protocol, all patients perform a brain computerized tomography (CT) scan at hospital admittance to screen for the presence of structural brain injury. Initial brain edema is also looked for. Somatosensory and auditory evoked potentials (AEPs), MRI and electroencephalogram (EEG) are obtained during the first 72 hours from admittance. Neurological examination is performed in all patients at the admission, at 24, 48 and 72 hours and at discharge by certified and experienced intensivists or neurointensivists. Verbal response, motor response, PLR, corneal and oculocephalic (OC) reflexes are registered. Myoclonic jerks and myoclonic status epilepticus are also identified, characterized and registered.

For the purpose of this study, demographics, location of CA (in or out-of-hospital), type of arrhythmia, time to return of spontaneous circulation (ROSC), need for vasopressors, neurological findings, imaging findings, EEG patterns, SSEP and AEP results and administration of sedatives (dosage and duration) were collected.

The primary outcome was neurological function as measured by the Glasgow Outcome Scale (1 - death; 2 - vegetative state; 3 - severe disability; 4 - moderate disability; 5 - good recovery with good functional outcome) at the time of discharge and at 6 months. For the purpose of this study we divided these results into two categories: poor outcome (corresponding to grades 1 and 2) and good outcome (corresponding to grades 3, 4 and 5). No surrogate outcomes were defined.

EEG

EEG results were classified in two categories: benign and malignant patterns, according to data published in previous studies.[9-16] Malignant patterns included a non-reactive background, burst-suppression, generalized suppression and non-responsive status epilepticus. A non-responsive status epilepticus was considered when aggressive therapy with antiepileptics was administered for 24 hours or more and no improvement was observed. Interpretation was done by experienced and certified neurophysiologists. Classification into benign and malignant patterns was done retrospectively based on the neurophysiologist's interpretation and according to the bibliography consulted.

Evoked Potentials

Cortical N20 responses were assessed bilaterally. Auditory potentials were obtained in all patients. Interpretation of the results was performed by a certified neurophysiologist and classification into good or bad outcome categories was done retrospectively based on the neurophysiologist's interpretation and according to the bibliography consulted.

MRI

Imaging results were descriptive and major patterns such as cerebral edema, cortical ischemia, generalized ischemia, hemorrhage, deep structures ischemia and normal findings were identified. Interpretation of the results was done by certified neuroradiologists. For data analysis we considered only two categories: normal MRI and ischemic MRI (defined as the presence of acute ischemic lesions on the cortex, basal ganglia, cerebelar cortex or subcortical white-matter attributed to anoxia), and this classification was done retrospectively based on the neurorradiologist's description.

Statistical analysis

Comparisons for outcome were performed using Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. We analyzed the following variables: age, gender, initial cardiac arrest rhythm, time to ROSC, local of arrest, PLR, corneal reflex, OC reflexes, motor response, presence of myoclonic status, SSEP, AEP, EEG pattern, presence of ischemic lesions on MRI and need for vasopressors. Associations between variables and outcome were assessed using univariate logistic regression

considering a *p* value of $p < 0.05$. False-positive rates (FPR) were calculated for all parameters showing a $p < 0.05$ and defined as 1-specificity, for poor outcome were, using 95% confidence intervals (CI). Tests were two-sided and a *p*-value <0.05 was considered statistically significant. Analysis was performed using SPSS v. 18.0.

This study was approved by the local ethics committee and a waiver for informed consent was obtained.

RESULTS

Thirty consecutive patients receiving TH were studied. Two received TH for elevated intracranial hypertension due to brain trauma and were excluded. Other 2 patients died within the first 24 hours and were excluded for lack of data. Twenty-six patients received TH for CA, 22 were men (85%) and 4 were women (15%). Median age was 54 (range 24-89 with a standard deviation (SD) of 18). Fourteen patients (54%) died during hospitalization and 18 patients (70%) were dead by 6 months. No permanent vegetative state was observed at 6 months. No patients were lost to follow-up.

Age, gender, time to ROSC, place of arrest, AEP, the presence of ischemia on MRI, the need for vasopressors and the type of the initial cardiac rhythm at the arrest did not influence outcome in a statistical significant way. Absent PLR, absent corneal reflexes, absent OC reflexes, motor response no better than extension, myoclonic status, absent N20 responses and a malignant EEG pattern obtained within 72 hours of arrest all predicted poor outcome (table 1).

Besides motor response, no other parameters had false positive results. Motor response no better that extension had a FPR of 25%. Two out of 8 patients with no motor response or extension had a good outcome at 6 months (table 2).

Only 4 patients required sedation beyond the hypothermia period. We analyzed the relationship between prolonged sedation and motor response and no statistical correlation was achieved (OR = 1.7, 0.2 - 19.4, $p = 0.57$). Of the 3 patients requiring prolonged sedation and showing motor responses no better than extension, 2 recovered awareness at 6 months.

DISCUSSION

The most relevant finding in our study is the FPR of 25% for motor response no better than extension in predicting a poor outcome. According to the American Academy of Neurology, in the pre-hypothermia era this clinical parameter could predict a bad outcome with a FPR of 0% (0 - 3).[5] Few studies have addressed this issue in the setting of TH and those who did report conflicting evidence. Three previous studies argue that motor responses within 72 hours might not be reliable in predicting outcome.[9,10,12] They concluded that false-positive rates might be relevant

Table 1 - Frequency of occurrence of demographics, clinical data, electrophysiological data, and MRI in patients with poor and good outcome at 6 months

	Poor outcome	Good outcome	*p*
Patients, n (%)	**18 (70)**	**8 (30)**	
Age, mean ± SD	61.6 ± 17.9	42.5 ± 8.7	0.060
Male gender, n (%)	15/18 (83)	7/8 (88)	0.641
Time to ROSC (min), mean ± SD	20.3 ± 18.1	17.5 ± 14.1	0.800
In-hospital CA, n (%)	9/18 (50)	1/8 (13)	0.081
Absent PLR, n (%)	8/18 (44)	0/8 (0)	0.028
Absent corneal reflex, n (%)	8/18 (44)	0/8 (0)	0.028
Absent OC reflexes, n (%)	9/18 (50)	0/8 (0)	0.016
Motor response no better than extension, n (%)	15/18 (83)	2/8 (25)	0.008
Presence of myoclonus, n (%)	8/18 (44)	0/8 (0)	0.028
Absent N20 responses, n (%)	7/12 (58)	0/5 (0)	0.041
Absent AEP, n (%)	3/12 (25)	0/5 (0)	0.324
Malignant EEG pattern, n (%)	8/11 (73)	0/4 (0)	0.026
Ischemia on MRI, n (%)	8/14 (57)	3/8 (38)	0.330
Need for vasopressors, n (%)	9/18 (50)	3/8 (38)	0.437
No V. Fibrilation, n (%)	12/18 (67)	5/8 (63)	0.587

ROSC - return of spontaneous circulation; CA - cardiac arrest; PLR - pupillary light reflex; OC - oculocephalic; AEP - auditory evoked potentials; EEG - electroencephalogram; MRI - magnetic resonance imaging; V. - ventricular

Table 2 - False positive rates of variables predicting bad outcome

Parameter	False-positive rate (CI at 95%)
Absent PLR	0.00 (0.00 - 0.08)
Absent corneal reflex	0.00 (0.00 - 0.08)
Absent OC reflexes	0.00 (0.00 - 0.08)
Motor response no better than extension	0.25 (0.12 - 0.41)
Myoclonus	0.00 (0.00 - 0.08)
Absent N20 responses	0.00 (0.00 - 0.16)
Malignant EEG pattern	0.00 (0.00 - 0.23)

False-positive rates for bad outcome (with 95% confidence intervals) given by 1-specificity; CI - confidence intervals; PLR - pupillary light reflex; OC - oculocephalic; EEG - electroencephalogram

and suggested that sedation is the major confounding factor. A more recent prospective study suggested that motor response maintains its predictive value in TH patients.[11] We found that both our patients who did well at 6 months and had a motor response no better than extension, required prolonged sedation beyond the TH period. Among those patients in whom sedatives were restricted to the TH period (first 24 hours), no false-positives were observed. Fugate et al[11] also report 2 patients in their hypothermia group with no motor responses who survived. Both were receiving sedatives and neuromuscular blocking agents around the time of assessment. These findings suggest that when sedation is restricted to the TH period, allowing an additional 48-hour period free of these medications until the third day of clinical assessment, motor response keeps its high prognostic value. Still, we recommend caution in using motor response in prognostication and suggest adding other clinical and electrophysiological parameters in decision-making.

PLR, corneal and OC reflexes and the presence of myoclonic status all showed no false-positives, which confirm these clinical parameters as good predictors even in hypothermic patients. These results are also confirmed by previous studies.[9-12]

N20 responses on SSEP also showed no false-positives. Although few studies in auditory evoked potentials have been done in predicting their prognostic reliability, we performed this test in all our patients and found that all our 3 patients with absent responses had poor outcomes. Despite this, no statistical significance was achieved in this test (p = 0.324) warranting the need for further studies.

On the EEG pattern no false-positives were seen. Our EEG classification was based on previous studies, though some suggest that classifying status epilepticus as a malignant pattern might withhold treatment that could otherwise improve patient outcome. In one study it has been suggested that an EEG pattern of status epilepticus in a subset of patients with good clinical parameters may have a favorable outcome.[17] Oddo suggested that EEG background reactivity should be assessed to determine if a patient may benefit from aggressive antiepileptic treatment. Status epilepticus on a reactive EEG background in the presence of other favorable clinical and electrophysiological prognosticators may yield a good outcome if treated early. Nevertheless, as seen in other series, a malignant EEG pattern invariably predicts bad outcome and we strongly support its use in prognostication.[10-12]

MRI findings were not reliable for predicting bad outcome. We acknowledge that our classification of imaging findings is probably insufficient. We did not quantify the amount of ischemic lesions and that may have interfered on results. A recent retrospective analysis used quantification of apparent diffusion coefficient (ADC) values on MRI to predict outcome.[18] They found that lower whole-brain median ADC values were significantly related to poor outcome. This may be a more objective and effective way of prognostication than simple observation and description of acute ischemic lesions as we did.

Finally, we observed that despite age and place of arrest did not achieve a significant statistical result, their p value is very close to 0.05, which may indicate a trend towards a difference. Younger patients had better outcomes than older ones, but we have no means through this study to find a plausible explanation. A further study relating age to cause of arrest and assessing a probable lower tendency to withdraw life-sustaining measures in younger patients may clarify this issue. In our patients out-of-hospital arrest seems to be more related to good outcome than in-hospital arrest. In another recent study Kory et al[19] found no differences in outcome between patients submitted to TH or not for in-hospital arrest, suggesting that this group may not benefit from the treatment. This was a small, retrospective study in which most patients had a non-shockable rhythm, which may explain the results. We found no significant differences in the type of rhythm of our patients between those who had in or out-of-hospital arrest, although there were more assystolies in those who arrested inside the hospital than those who suffered CA outside the hospital. We suggest that further studies should be conducted in order to identify subsets of patients who might or might not benefit from TH.

Our study has several limitations. First, its retrospective

nature may have a potential for bias. Second, its limited sample size makes it more difficult to detect important differences. Although it includes all hypothermic patients during a full 2-year period that were admitted to our institution, we could gather only 26 eligible patients since registries were not standardized before 2009. Third, it is a single-centre study, and despite our institution is a large urban, academic-medical center who serves an area around 1 million people, this may pose a problem of generalizability. Last and most importantly, a self-fulfilling prophecy might have influenced our results, since it is an observational study. Most patients who were thought to have a poor outcome were withdrawn from life-sustaining measures and died. The assumption of the outcome was based on the same variables that were being studied. This means that a variable will appear to be a very strong predictor of outcome if it was earlier considered as an important factor in determining a poor prognosis, not allowing patients to have a chance of recovery for the next 6 months. This is a very difficult hazard to overcome in observational studies like this one, since it was previously defined that these same variables should guide decision-making in this subset of patients.

CONCLUSION

Our findings suggest that PLR, corneal and OC reflexes, myoclonic status, bilateral absent N20 responses and a malignant EEG pattern within 72 hours of arrest yield a poor prognosis in CA patients submitted to TH. Caution should be taken when using motor responses as a prognostic parameter in TH patients, and should be interpreted in the context of sedative and paralytic medication. We support a multimodality approach (including clinical and electrophysiological data) regarding a decision of withdrawal of life-sustaining measures.

CONFLICT OF INTERESTS

Nothing to report

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