Prognosis Following Seizures After Successful Cardiopulmonary Resuscitation In A Tertiary Hospital: A Retrospective Cohort Study

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ABSTRACT

Background

Neurologic outcomes following a cardiac arrest is reported to be detrimental and survivors face significant neurologic disability attributed to the diffuse cerebral damage from anoxia. Accurate prognostication is challenging.

Objective

To determine the prognosis of patients who had seizures after arrest.

Methods

This is an analytic, retrospective cohort study of adult patients that had successful resuscitation after cardiac arrest. The final sample size was 97. Comparison of the clinical outcomes was done using univariate and multivariate analysis. Multiple logistic regression was utilized. Level of significance was set at α-0.05.

Results

Post-arrest seizures increased the odds of dying up to 9 times. Age increases the odds of dying; among patients aged 65 years old and above, the odds are increased to 17 times, while among those aged 35 years old and above, the odds are up to 12 times. Presence of an intact brainstem response in the first 72 hours after arrest have 96% lower odds of dying compared to those who have none.

Conclusion

Patients with post-arrest seizures have higher morbidity and mortality rates. Patients with seizures that occur early after cardiac arrest have poorer prognosis and higher chances of death brought about by additional insults to an already damaged brain. Older patients have poorer prognosis. Preserved brainstem function seem to be a protective factor which can be a reflection of the degree of preserved brain activity despite anoxia.

Keywords: *post-arrest seizures, anoxic brain injury, post-arrest myoclonus, prognosis*

INTRODUCTION

Background

Neurologic outcomes after successful resuscitation following a cardiac arrest have been previously reported to be detrimental with low survival rates and to those who may have survived face significant neurologic disability attributed to the diffuse cerebral damage from anoxic injury.[1] Advances in past cardiac arrest care utilizing targeted temperature treatment had been reported to have improved survival and minimal disability.[2,3,4]

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Accurate prognostication after cardiac arrest is often challenging. Neurologists are frequently consulted to provide expert opinion on the chances of a meaningful recovery. Criteria for a poor outcome should have a high degree of certainty before being used routinely in clinical practice.[5] To be able to predict neurologic outcome in patients who had successful resuscitation after an arrest will have significant economic and ethical implications. Previous studies have reported in general that the presence of myoclonic seizures after anoxic injury is marker of poor prognosis.[6] One study reported improved outcome in patients with post-hypoxic myoclonus after cardiopulmonary resuscitation after hypothermia.[1] The presence of a withdrawal motor response within 48 hours post-arrest may be a feature that predicts a good prognosis after cardiac arrest.[5,]

Despite seminal advances in intensive care and cardiovascular therapy over the past several decades, brain injury continues to be the leading cause of disability after cardiac arrest. Care of these patients can be challenging, and it requires a great deal of medical resources and expense.[7] Since more aggressive and advanced treatments for post-cardiac arrest care have been more available, determining the prognosis of patients who have had seizures after successful cardiopulmonary resuscitation will have important socio-economical and ethical impacts in determining aggressiveness of treatment for these patients.

METHODS

STUDY DESIGN

This is an analytic, retrospective cohort study of adult patients that had successful resuscitation after cardiac arrest at The Medical City from January 2014-January 2019. All adult post-cardiac arrest in-patients directly admitted or referred to the Adult Neurology Service of The Medical City during said timeframe were included for chart review. Patients were identified using screening of the charts that would satisfy the inclusion criteria of all post-arrest patients with successful resuscitation; daily census; and computerized search for the following keywords: *post-arrest, status post cardiac arrest, post-arrest seizures, hypoxic-ischemic encephalopathy, post-hypoxic myoclonus, post-hypoxic seizure* at the medical records section. Patients were then classified as those who had seizures and those who did not have seizures.

SETTING

The study was conducted in an 800-bed capacity tertiary hospital. The hospital is accredited by the Joint Commission of International Accreditation (JCI) that ensures high quality health-care service to the patients. It is the first institution in the Philippines capable of conducting therapeutic hypothermia as standard of care among post-arrest patients. The Intensive Care Unit of this hospital is manned by certified Critical Care Specialists/Neurocritical Care intensivists. The study has been approved by the Institutional Review Board of The Medical City in Pasig City, Philippines.

PARTICIPANTS

The study included adult post-cardiac arrest patients admitted at The Medical City from January 2014 to January 2019. All post-arrest patients underwent therapeutic hypothermia as standard of care. They were classified as to those who had frank seizures after cardiac arrest and to those who did not. Patients with another medical condition with limited life expectancy like advanced stage of malignancy and patients with progressive brain illnesses like brain tumors or neurodegenerative diseases were excluded.

VARIABLES

Functionality from discharge will be classified according to the Cerebral Performance Category Scale 8 as follows:

Table 1. Cerebral Performance Category Scale

Scale	Definition
1	Good cerebral performance; conscious, alert, able to work, might have mild neurologic deficit
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life.
3	Severe cerebral disability; conscious dependent on others for daily support because of impaired brain function.
4	Coma or vegetative state
5	Dead: brain death

Prognosis will be determined via outcome trichotomized as (1) Good outcome with CPC scale 1-2, (2) Bad outcome CPC scale of 3-4, and (3) Deceased with CPC score of 5 14 . Age was trichotomized into 18-34 years old, 35-64 years old and 65 years old. All EEG recordings used the Nicolet one EEG machine. EEG findings were classified and dichotomized as (1) Malignant: burst suppression, status epilepticus and unreactive EEG and (2) Benign: reactive EEG and with epileptiform discharges.[10]

DATA SOURCES/ MEASUREMENT

All eligible patient charts were reviewed based in inclusion criteria. The following data were collected through manual chart review: age, sex, co-morbidities like hypertension, diabetes mellitus, neurologic disease, heart disease, lung disease, kidney and liver disease, timing of seizures, brain stem response, functional outcome, length of hospitalization and duration of seizures.

STUDY SIZE

Sample size was computed based on the comparison of death among post-arrest patients with and without seizure, assuming that those patients with seizures proportion of death is 81.8%, and those with seizures is 50% 9 . An alpha error of 5% and power of 80% was computed, the sample size calculated was 27 per group or 54 for two groups. The final sample size required was 97 after controlling for 4 more variables in the analysis.

STATISTICAL METHODS

Descriptive analysis of the data was done. For qualitative variables, frequency distributions were calculated and presented by cross-tabulations. For the quantitative variables, the mean, median, standard deviation and range was estimated. Comparison of the clinical outcomes in terms of dependency and prognosis among post-arrest patients with and without seizures was done using univariate and multivariate analysis. Chi-square test was used in the univariate analysis and relative risk and the 95% confidence interval was calculated. Multiple logistic regression was utilized with the level of significance at α- 0.05.

RESULTS

Table 2 shows the results of the frequencies and distribution amongst post-arrest patients clinical characteristics and their outcome. Elderly patients had poorer prognosis as majority of them died (68.2%). Most of those who had good outcomes were those aged between 18-34 years old. There was no significant difference between gender in terms prognosis. Majority of post-arrest patients had hypertension, diabetes mellitus and heart problems. Though most of the patients who died had neurologic problems (77.8%) and heart problems (73.1%) as co-morbidities, all co-morbidities had no significant difference in terms of mortality. Most of post-arrest patients had out-of-hospital arrest and these resulted in poor functional outcome with 62.3% dying. Functional outcome was better in patients with in-hospital arrest (19.4%) versus those with out-of-hospital arrest (14.8%). Provision of basic life support (BLS) upon arrest resulted in lower mortality (30.8%) compared to those who did not receive BLS (67.9%). There was a significantly better functional outcome in patients who received BLS (67.9%) compared to those who did not (14.3%). Presence of seizures post cardiac arrest had a significant effect of having poor

Table 2. Qualitative Data

	Deceased N (%)	Bad Outcome N (%)	Good Outcome N (%)	P-value
Age Interval				0.135
18-34 yrs old	5(35.7)	4(28.6)	5(35.7)	
35-64 yrs old	26(66.7)	9(23.1)	4(10.3)	
65 yrs old and above	30(68.2)	7(15.9)	7(15.9)	
Gender				
Male	43(67.2)	13(20.3)	8(12.5)	0.304
Female	18(54.5)	7 (21.2)	8(24.2)	
Comorbidities				
Hypertension	40(64.5)	12(19.4)	10(16.1)	0.896
Diabetes Mellitus	31(68.9)	9(20.0)	5(11.1)	0.373
Lung Problem	2(40)	2(40)	1(20)	0.487
Heart Problem	19(73.1)	4(15.4)	3(11.5)	0.452
Kidney / Liver Disease	7(63.6)	2(18.2)	2(18.2)	0.971
Neurologic Problem	14(77.8)	3(16.7)	1(5.6)	0.279
Location of Arrest				
In hospital	23(63.9)	6(16.7)	7(19.4)	0.689
Out of hospital	38(62.3)	14(23)	9(14.8)	
BLS provided				
Yes	**4(30.8)**	**5(38.5)**	**4(30.8)**	**0.036**
No	57(67.9)	15(17.9)	12(14.3)	
Post-arrest Seizures				
Present	**40(83.3)**	**5(10.4)**	**3(6.2)**	**<0.001**
Absent	21(42.9)	15(30.6)	13(26.5)	
EEG Finding				
Malignant	28(66.7)	11(26.2)	3(7.1)	0.457
Benign	32 (59.2)	11(20.4)	11(20.4)	
Brain stem response within first 72 hours				
Present	**6(18.2)**	**13(39.4)**	**14(42.4)**	**<0.001**
Absent	55(85.9)	7(10.9)	2(3.1)	

functional outcome where 83.3% died and only 6.2% had good functional outcome. There was no significant difference in terms of functional outcome in patients with Benign EEG findings versus those with Malignant EEG findings. An intact brain stem response in the first 72 hours of arrest was also found to be significantly different in terms of outcome where an absent brainstem response was associated with high mortality (85.9%).

Table 3 shows the subgroup analysis done on patients who have had post-arrest seizures. The time of seizure onset was found to have significance in terms of outcome. Ninety-six percent of post-arrest patients who had seizures in less than 30 minutes from arrest time died and no patient had a good outcome. There was a decreasing trend in terms of death when the seizure onset occurred at a much later time. Recurrence of seizures after

Table 3. Post-arrest Seizure Subgroup Analysis

	Deceased N (%)	Bad outcome N (%)	Good outcome N (%)	P-value
Time of seizure from arrest				**0.026**
<30 minutes	24 (96)	1(4)	0(0)	
31-60 minutes	9(90)	1(10)	0(0)	
61 minutes-24 hours	4(66.7)	1(16.7)	1(16.7)	
>24 hours	3(42.9)	2(28.6)	2(28.6)	
Seizure during Hypothermia				
Present	**36(90)**	**3(7.5)**	**1(2.5)**	**0.013**
Recurrence of Seizure after Hypothermia				
Present	21(91.3)	1(4.3)	1(4.3)	0.341
Absent	19(76)	4(16)	2(8)	
Number of AEDs used				
3 and below	32(76.2)	6(14.3)	4(9.5)	0.401
More than 3	8(88.9)	1(11.1)	0(0)	

hypothermia was not significant in terms of outcome. The number of AEDs was not significantly associated with functional outcome of post-arrest seizure patients.

The Odds-Ratio of death among post-arrest patients are shown in Table 4. The presence of a neurological problem was associated with the highest odds of dying by 2.5 times compared to those who do not have a neurologic problem. Age was noted to have a significant effect on the mortality of post-arrest patients where those aged 35-64 years old and 65 years old and above increased the odds of dying by 13 times more than those aged 18-34 years old. Provision of BLS upon arrest was noted to be protective, decreasing the odds of dying by 78% compared to those who were not given BLS.

Intact brainstem response in the first 72 hours also decreased the odds of dying of up to 59% compared to those who had absent brainstem responses. The presence of post-arrest seizures significantly increased the odds of dying by 6 times compared to those who had no seizures post-arrest.

Table 5 shows the multivariate analysis of the study. In this test, we can note that the presence of post-arrest seizures increased the odds of dying up to 9 times compared to those who did not have seizures considering that both brainstem response and age variables were kept constant. Age was also significantly associated with mortality. Again, provided that seizures and brainstem response variables were kept constant, the odds of dying amongst patients aged 65 years old and above was up to 17 times, while in those aged 35 years old and above, there was an increased odds of dying of up to 12 times. This means that the elderly population were more likely to expire compared to those who were
younger be it that both had seizures, and both had intact brainstem response. The presence of an intact brainstem response in the first 72 hours after arrest give up to 96% lower odds of dying compared to those who had no

Table 4. Multiple Logistic Regression

Risk Estimate

	P value	Odds Ratio	95% Confidence Interval	
			Lower	Upper
Sex	0.132	1.93	0.816	4.551
Age 35-64years old	**0.035**	**12.58**	**1.189**	**132.915**
Age >65 years old	**0.033**	**13.39**	**1.230**	**144.683**
Diabetes Mellitus	0.185	1.756	0.762	4.049
Hypertension	0.473	1.364	0.584	3.184
Heart Problem	0.169	1.99	0.741	5.325
Neurologic Problem	0.123	2.51	0.758	8.318
Kidney/Liver problem	0.897	1.10	0.296	4.011
Pulmonary Disease	0.302	0.39	0.062	2.457
Location of Arrest	0.751	1.15	0.489	2.691
BLS provided	**0.013**	**0.22**	**0.063**	**0.785**
Hypotension after ROSC	0.22	1.71	0.724	4.011
Brainstem Response	**<0.001**	**0.41**	**0.14**	**0.125**
Post-arrest Seizures	**<0.001**	**5.78**	**2.304**	**14.491**

Table 5 Multivariate Analysis

	P value	Odds Ratio	95% Confidence Interval	
			Lower	Upper
Post-arrest seizures	**0.003**	**8.66**	**2.102**	**35.649**
Age 34-64 years old	**0.021**	**11.84**	**1.462**	**95.792**
Age >65 years old	**0.013**	**16.56**	**1.817**	**150.845**
Brainstem Response	**<0.001**	**0.036**	**0.009**	**0.144**

brainstem responses after arrest when the variables of age and post-arrest seizures were kept constant.

DISCUSSION

Neurologic outcome after successful resuscitation following cardiac arrest has been previously reported to be detrimental with low survival rates and those who survived face significant neurologic disability attributed to the diffuse cerebral damage from anoxic injury.[1]

Studies that explore prognosis of post-arrest patients have no report on the effect of age in terms of functional outcome. It has been that reported that there is no significance in age in terms of functional outcome among post-arrest patients but no elaboration as to which age would have higher chances of having poor outcome or death.[11,12] In our study, elderly patients had poorer prognosis, for majority of the elderly patients died and most of those who had good outcomes were younger patients. This study was comparable to previously reported findings where hypertension and heart disease were the most common co-morbidities associated with poor outcome among post-arrest patients.[1,11] Majority of post-arrest patients had out-of-hospital arrest with poor functional outcome. Bouwes et. al. also reported similar results wherein 86.7% of those who had out-of-hospital arrest had poor outcomes, and 48% eventually dying one month after cardiac arrest. those who received BLS had lower mortality rates at 30.8% compared to those who did not receive BLS at 67.9%. There was also significantly better functional outcome in patients who received BLS compared to those who did not.

Post-arrest seizures had a significant effect on outcomes with 83.3% of those who had seizures eventually dying, only 6.2% had good functional outcome. Knight et al reported similar results with 81.8% of mortality during hospitalization and 100% mortality within 30 days of post-arrest patients with seizure though the sample size was low at 33. Bisshops et al mentioned that 53.7% of patients with clinical myoclonus had poor outcomes. Benign EEG patterns were associated with good functional outcome compared to those with Malignant EEG patterns. However, EEG recordings amongst patients in this study were not done at a fixed time from arrest or were intermittently performed depending on the availability of the machine and/or the decision of the attending neurologist. Continuous EEG of at least 48 hours from arrest is necessary to increase sensitivity of detecting electrographic seizures in comatose patients[9] . The presence of a brain stem response in the first 72 hours of arrest was found to be significantly different in terms of outcome. Different studies have also reported the effect of brainstem response in terms of prognosis on post-arrest patients; it has been mentioned that patients with absent corneal and pupillary light reflexes 1-2 days after rewarming have 100% non-survivability while another study reported 54% bad outcome and 80.6% unfavorable outcome.[10,14,11] Although the absence of a brainstem response in the first 24 hours could not be directly linked to having a poor outcome as an absence of brainstem response during this time can be due to hypothermia, it was said to be a robust indicator of poor prognosis at 72 hours.[14] This stresses the importance of the clinical neurologic examination as a mandatory and necessary tool to substantiate prognostication or poor recovery.

As shown in Table 3, the shorter the interval between arrest and seizure occurrence, the poorer the outcome. It was previously reported that the presence of seizures in post-arrest patients is an ominous sign of poor prognosis. However, there was no reported study on the effect of the interval between arrest and occurrence of seizures on clinical outcome. The theory was supported by animal studies, is that post-arrest myoclonus

can come from both the cortex and the brain stem. In post-anoxic injury, the cerebral cortex is heavily damaged and increased metabolic activity brought about by seizures may cause additional insults on the already damaged brain.[13] In this study, it is hypothesized that earlier seizure occurrence is attributed to a more dismal prognosis. Presence of seizures during hypothermia have significant effect on death rates with 90% of those who had seizures during hypothermia eventually dying. Although some studies have postulated that hypothermia may be helpful in decreasing the metabolic demand of neurons by inhibiting occurrence of seizures and improving its outcome when initiated, in this study seizures during hypothermia were still associated with higher mortality.[2,3,5,9] Males had twice the odds of dying compared to females but was not statistically significant similar to a previous study.[14] The provision of BLS was noted to be a significant protective factor for death amongst post-arrest patient in up to 88% where attempts to restore the circulation to the brain helped prevent irreversible damage brought about by anoxia. Brainstem response was also another protective factor in up to 59% of the study population. Post-arrest seizures were a significant risk factor with the odds of dying increased in up to 6 times compared to those who did not have seizures. In patients of the same age group and intact brainstem response, the presence of frank seizures alone significantly increased the odds of dying up to 9 times compared to those without seizures. This means that the added neuronal injury brought about by seizures is a significant aggravating factor in post-arrest patients.

CONCLUSION

Patients with post-arrest seizures have higher morbidity and mortality rates. Patients with seizures that occur early after cardiac arrest have poorer prognosis and higher chances of death (up to 9 times higher) brought about by additional insults to an already damaged brain. Previous studies have not reported the effect of age on post-arrest patients and post-arrest patients with seizures. Older patients have poorer prognosis despite successful resuscitation and intervention compared to young adults. Preserved brainstem functions 72 hours post-arrest seems to be a protective factor which can be a reflection of the degree of preserved brain activity despite anoxia.

GENERALIZABILITY

Neurologic outcomes and prognosis after anoxic injury are difficult to determine even with the advent of more advanced resuscitative efforts. The neurological exam remains an important diagnostic tool as it can determine the presence of an intact brainstem functions, which have been shown to be a good measure of preserved brain activity despite anoxia. Clinical seizures, especially those occurring very early after arrest are indicators of eventual mortality. Younger patients have better chances of survival compared to older patients.

RECOMMENDATIONS

The Investigators recommend prospective studies of post-arrest seizure patients including follow up of their functionality at 30 days after discharge. Studies of post-arrest seizure patients with continuous EEG recording is also suggested. The investigators also suggest devising prognosticating criteria among post-arrest patients and validation of said criteria that would include the age, timing of seizure from arrest and brainstem responses as they have been shown to have significant risks and protective factors on post-arrest patients.

LIMITATIONS

There were no follow ups after patient discharge so there was no way of evaluating if patients with poor functional outcome at discharge could eventually improved over time. EEG recordings were done intermittently based on availability of the EEG machine, and not done at specific time

points. No continuous EEG recordings were done, and most EEG determinations were done hours after a frank seizure episode.

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DECLARATION OF COMPETING INTERESTS

The Authors declare no conflict of interest.

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