CorSalud 2017 Oct-Dec;9(4):236-241

CorSalud

Cuban Society of Cardiology

Original Article

Cardiocentro ERNESTO CHE GUEVARA SANTA CLARA CUBA

Therapeutic hypothermia in resuscitated cardiopulmonary arrest

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: April 18, 2017
Accepted: May 18, 2017

Competing interests
The authors declare no competing interests

Acronyms
CPA: cardiopulmonary arrest
TH: therapeutic hypothermia

On-Line Versions:
Spanish - English

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ABSTRACT

Introduction: Applying hypothermia in the first hours to a comatose patient who has survived cardiopulmonary arrest helps minimizing brain injury and improves survival.

Objective: To determine the use-effectiveness of therapeutic hypothermia after cardiac arrest.

Method: Quasi-experimental research on hospitalized patients in the Intensive Care Unit at the «Hospital Arnaldo Milián Castro» in Santa Clara, Cuba, between January 2013 and September 2015. The sample consisted of 26 patients: 13 treated (study) and 13 non-treated (control). Variables studied were: age, sex, arrest scenario, comorbidities and Glasgow coma scale (on admission, during neurological recovery at 72 hours and at discharge).

Results: No significant differences were found between both groups. The average age was 63 and 57 years, respectively. Male (more than 60%) and out-of-hospital arrest location predominated. Higher incidence comorbidities were: high blood pressure, heart disease and diabetes mellitus; as well as initial Glasgow coma scale score of 3 in both groups, often greater than 50%.

Conclusions: Therapeutic hypothermia-treated patients presented fewer neurological complications and lower mortality, despite having, in most cases, an initial non-shockable rhythm and longer arrest time.

Key words: Cardiac arrest, Induced hypothermia, Therapeutics

Hipotermia terapéutica en el paro cardiorrespiratorio recuperado

RESUMEN

Introducción: La hipotermia, aplicada en las primeras horas a un paciente en coma que ha sobrevivido a un paro cardiorrespiratorio, tiende a minimizar el daño cerebral y mejora la sobrevida.

Objetivo: Determinar la efectividad del uso de la hipotermia terapéutica en el estado posparada cardíaca.

Método: Investigación cuasi experimental en pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Arnaldo Milián Castro de Santa Clara, Cuba, entre enero de 2013 y septiembre de 2015. La muestra quedó conformada por 26 enfermos: 13 intervenidos (estudio) y 13 no intervenidos (control), donde se estudiaron las variables: edad, sexo, condiciones de la parada, comorbilidades y escala de Glasgow (al ingreso, en recuperación neurológica a las 72 horas y al

Lecture presented to the II National Symposium on Sudden Cardiac Death and I Ibero-American Convention on Sudden Cardiac Death (December 6-9, 2016. Havana, Cuba).

egreso).
Resultados: No se encontraron diferencias significativas entre ambos grupos. La edad promedio fue de 63 y 57 años, respectivamente; predominaron el sexo masculino con más del 60%, el lugar extrahospitalario de la parada, la hipertensión arterial, la cardiopatía y la diabetes mellitus como comorbilidades de mayor incidencia, y Glasgow inicial de 3 puntos, en ambos grupos, con frecuencia mayor del 50%.
Conclusiones: Los pacientes tratados con hipotermia terapéutica presentaron menos complicaciones neurológicas y menor mortalidad, a pesar de presentar, en su mayoría, un ritmo inicial no desfibrilable y un tiempo mayor de parada.
Palabras clave: Paro cardíaco, Hipotermia inducida, Terapéutica

INTRODUCTION

Cardiopulmonary arrest (CPA) is the vital emergency par excellence and the end point for many life-threatening acute diseases. It is defined as sudden, unexpected and potentially reversible stoppage of spontaneous breathing and circulation with consequent loss of consciousness, apnea or gasping and pulseless electrical activity[1].

CPA is undoubtedly a major health problem and its survival rate varies depending on the region and country; since in many cases it is influenced by the organization and responsiveness of the emergency services, as well as the preparation and experience of personnel in the emergency services staff[2-5].

Cardiopulmonary resuscitation has a likelihood of immediate survival of 30-50% and survival at hospital discharge varies from 5-35%, with an average of 11-20%. In a study in Canada, survival at discharge was 5.1%[6].

Patients who survive cardiopulmonary arrest suffer from a general ischemia-reperfusion injury called post-cardiopulmonary arrest syndrome which can lead to poor neurologic outcome or even death. This syndrome triggers a cascade of harmful inflammatory reactions in the body which may last for many days[7].

Treatment aimed at minimizing the inflammatory response and cell death in the reperfusion period may improve clinical outcomes after CPA. One of the few proven in-hospital treatment strategies is induced hypothermia (IH)[8].

In Cuba, with the cardiac arrest descriptor, there were no studies or records related to in/out hospital survival after CPA, and no results on the use of TH have been published. Therefore, we set out to determine how effective the use of TH is in post-CPA patients hospitalized in the Intensive Care Unit.

METHOD

A quasi-experimental research was carried out in patients hospitalized in the Intensive Care Unit at the *Hospital Arnaldo Milián Castro* in Santa Clara, Cuba, between January 2013 and September 2015.

A total of 26 patients divided into 2 groups were studied:

1. Intervened group (study) who were induced hypothermia, suitable for our environment and previously validated in another investigation, consisting of 13 patients.
2. Historical control group who met the same criteria as that intervened. They were statistically compared to demonstrate their homogeneity.

The following variables were studied: age, sex, stoppage conditions, comorbidities and Glasgow scale (on admission, during neurologic outcome at 72 hours and at discharge). The latter was measured in both groups, at the beginning and end of their outcome. Monte Carlo techniques were used in every analyzes, to estimate exact probabilities, given the small sample size.

RESULTS

Table 1 shows there were no significant differences between both groups in terms of age, arrest duration, sex, arrest location, comorbidities, initial rhythm and Glasgow on admission, so the sample is homogeneous. There were only significant differences regarding the time of CPA (p=0.008), and shockable initial rhythm (p=0.039) favoring the non-intervened group, which means that, such group

Table 1. Behavior of the epidemiological and clinical variables in both groups.

Variable		Study		Control		t-Student	p
Age ($\bar{\chi}$±SD)		63.0±11.52		57.92±14.45		0.990	0.332
Arrest duration ($\bar{\chi}$±SD)		14.77±9.52		6.77±2.98		2.891	0.008
		N°	%	N°	%	χ^2	p
Sex	Female	5	38.5	3	23.2	0.722	0.673
	Male	8	61.5	10	76.8		
Arrest location	Out-of-hospital	10	76.8	9	69.2	0.000	1.000
	In-hospital	3	23.2	4	30.8		
Comorbidities	HBP	9	69.2	9	69.2	0.000	1.000
	Ischemic HD	5	38.5	5	38.5	0.000	1.000
	Diabetes mellitus	7	53.8	4	30.8	1.418	0.234
	Valvulopathy	1	7.7	0	0.0	0.000	1.000
	Dilated cardiomyopathy	1	7.7	1	7.7	0.000	1.000
Initial rhythm	Shockable	6	46.2	11	84.6	4.248	0.039
	Non-Shockable	7	53.8	2	15.4		
Glasgow on admission	3	7	53.8	8	61.5	4.219	0.129
	4 – 5	1	7.7	4	30.8		
	6 – 7	5	38.5	1	7.7		

HD, heart disease; SD, standard deviation; HBP, High blood pressure; CPA, Cardiopulmonary arrest.

theoretically should have a better prognosis compared to the study group, since these two variables are directly related to the prognosis.

Tables 2 and 3 show the comparison of the outcome in both groups, according to the Glasgow Scale score on admission and at 72 hours. In the intervened group, where TH was applied (**Table 2**), it is observed that 10 patients improved, with an average increase in the Glasgow score of 5 points, none worsened and 3 remained the same. In the non-intervened group (**Table 3**) can be seen that only 4 patients improved, 7 remained the same and 2 worsened. The 4 patients who improved only increased one point on the Glasgow scale.

In the study group 10 patients (76.8%) were discharged alive from the Intensive Care Unit while only 3 (15.4%) in the control group (**Table 4**), who had a mortality of 84.6%, with a highly significant statistical difference (p=0,005).

Neurologic outcome according to the GOS scale (Glasgow Outcome Scale) showed high mortality in the control group (84.6%), compared with 23.2% in the study group (**Table 5**), which also showed significant differences (p=0,007).

Table 2. Analysis of the Glasgow coma scale follow-up in the study group.

Glasgow 1 *vs* Glasgow 2	Nº	Average range
Negative ranges	0[a]	
Positive ranges	10[b]	5.00
Even	3[c]	
Total	13	

[a] Glasgow 2 < Glasgow 1
[b] Glasgow 2 > Glasgow 1
[c] Glasgow 2 = Glasgow 1

Table 3. Analysis of the Glasgow coma scale follow-up in the non-intervened group.

Glasgow 1 vs Glasgow 2	Nº	Average range
Negative ranges	2[a]	2.00
Positive ranges	4[b]	1.00
Even	7[c]	
Total	13	

[a] Glasgow 2 < Glasgow 1
[b] Glasgow 2 > Glasgow 1
[c] Glasgow 2 = Glasgow 1

Table 4. State at discharge in both groups.

State at discharge	Study Group		Control Group	
	N°	%	N°	%
Alive	10	76.8	2	15.4
Deceased	3	23.2	11	84.6
Total	13	100.0	13	100.0

χ^2=9.905; p=0.005

Table 5. Relation of neurologic outcome in both groups.

Glasgow Outcome Scale	Groups			
	Study		Control	
	N°	%	N°	%
Deceased	3	23.2	11	84.6
Neuro-vegetative	5	38.4	1	7.7
Favorable outcome	5	38.4	1	7.7
Total	13	100.0	13	100.0

χ^2=9.905; p=0.007

DISCUSSION

In a review of 6,369 patients where 3452 were intervened (study group), the mean age was 62 and 64 years for the study and control groups, respectively; male sex predominated in over 60% of patients in both groups, and comorbidities were similar in both, hence heart disease, hypertension and diabetes were most prevalent[9]. These results coincide with those of our research.

Most studies[10,11] show that the most frequent initial rhythms are those Shockable with an average of 70-75%, as well as better results in terms of these patients' survival.

Reinikainen *et al.*[12] in a large study consisting of 3958 patients and a design similar to ours, showed that Glasgow at admission has not shown differences, nor is it considered a predictor of mortality, nor of neurological damage.

Attempts have been made to establish clinical prognostic values primarily based on pupillary light reflex and Glasgow coma scores. Although presented false positives, there is a high possibility of poor outcome when these indicators do not improve after 72 hours, and are much more sensitive from the sixth day, according to the revision published by Morgenegg and Oddo[13], especially if accompanied of myoclonias, where almost 100% of poor neurologic outcome and death are predicted in most patients.

Survival after an out-of-hospital arrest depends on the type of initial assistance, and can reach 16-32% in witnessed cases with immediate assistance, but greatly decreases if not[14].

Hörburger *et al.*[11] led a study between 1991 and 2008, with 3952 patients diagnosed with CPA. Excluded 3124 who did not meet the hypothermia criteria, to make the sample homogeneous, which left 828 patients: 361 in the historical control group and 467 assigned to the TH group. This investigation found as main results an intact neurologic outcome in 55% of patients with TH, vs. 42% of historical control group, and a mortality of 67% vs. 48%, respectively, without finding significant differences in terms of age and sex; where shockable rhythm was the most frequent (74%)[11,15].

In an international multicenter clinical trial, where patients were randomized to 33 or 36ºC, survival at the end of the trial was 50% for the group assigned at 33ºC and 48% for the 36ºC. There were no differences between the diverse subgroups of age, sex, resuscitation time, initial rhythm, shock state upon admission and size of the participating site. It is important to consider that the 33 ºC group remained significantly more days on mechanical ventilation, so these patients were less likely to have awakened before the predetermined assessment of prognosis than 36 ºC group (44% vs. 52%; p=0.03). It is also known that the lower the temperature at which the

patient is subjected, the longer he takes to awaken; in addition, the most serious patients were assigned to the 33ºC group, which bias the investigation[16].

Hypothermia has been gaining acceptance because of its importance in the improvement of survivors of cardiac arrest and until now it is the only therapy that has been shown to reduce mortality and improve neurological outcomes. Therapeutic hypothermia must be started quickly when there are supporting criteria. Hospital should prioritize the establishment of hypothermia protocols and systems to enable their implementation in a coordinated and effective way[17].

CONCLUSIONS

Patients treated with therapeutic hypothermia presented better neurologic outcome and lower mortality, despite mostly presenting a non-shockable initial rhythm, and a longer stoppage time. The implementation of therapeutic hypothermia has not yet been widespread as much as is recommended, despite what has been shown by studies carried out in other parts of the world and being an important recommendation of the resuscitation guidelines for post-cardiac arrest care since 2010.

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