

Experience with Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest

Experiencia con hipotermia terapéutica en el paro cardíaco extrahospitalario

RICARDO LEVIN^{MTSAC}, MARCELA DEGRANGE^{MTSAC}, JACKSON KENNEDY, RAFAEL PORCILE^{MTSAC}, ALEJANDRO BOTBOL[†], NORBERTO BLANCO, JOHN BYRNE

ABSTRACT

Background: Out-of-hospital cardiac arrest (OHCA), one of the leading causes of death in the industrialized world, has a very low survival rate and high incidence of unfavorable neurological outcome among survivors, which have remained stable over the last three decades. The most recent clinical studies have proposed the usefulness of therapeutic hypothermia to reduce mortality and severity of unfavorable neurological outcome in OHCA survivors.

Objectives: The aim of this study was to evaluate the mortality and neurological status of comatose patients resuscitated from OHCA treated with therapeutic hypothermia, consider the indications and coronary angiography findings, and detect the complications associated with hypothermia.

Methods: Patients resuscitated from OHCA treated with therapeutic hypothermia were included in the study. The procedure consisted of cooling for 24 hours at a target temperature of 33°C followed by rewarming at 0.25°C/hour. The indications and coronary angiography findings were analyzed. The presence of metabolic disorders, arrhythmias, infections and bleeding were also evaluated. A p value <0.05 was considered statistically significant.

Results: The cohort consisted of 213 patients. In-hospital survival was 51.2% (n=109) and 46% of these cases (n=96) were discharged with favorable neurological status. Patients with shockable rhythms presented higher survival rates compared with those with non-shockable rhythms (58.2% vs. 37.7%; p=0.007). Coronary angiography was performed in 147 patients (69%) after a mean interval of 3.5 hours: 121 patients (82.3%) presented significant coronary artery disease and 69 patients (58%) had total occlusions. One-hundred and seven patients underwent percutaneous coronary intervention; among these patients 43 (40.2%) died during hospitalization and 61 (58.6%) deaths were reported among those who did not undergo coronary angiography or interventional procedure (p=0.005). The most common complications were hypokalemia (87.6%) and sinus bradycardia (66.7%).

Conclusions: The use of therapeutic hypothermia was associated with in-hospital survival >50% and favorable neurological outcome in 46.1% of cases. Mortality was lower in patients undergoing percutaneous coronary intervention. Hypokalemia and sinus bradycardia were the most common complications.

Key words: Cardiac Arrest - Cardiopulmonary Resuscitation - Therapeutic Hypothermia

RESUMEN

Introducción: El paro cardíaco extrahospitalario (PCEH), una de las principales causas de mortalidad en el mundo occidental, se asocia con una muy baja sobrevida hospitalaria y con un número elevado de secuelas neurológicas entre los sobrevivientes, sin modificaciones significativas en el pronóstico en las últimas tres décadas. Estudios clínicos más recientes plantearon la utilidad de la hipotermia terapéutica en la reducción de la mortalidad y el grado de deterioro neurológico en sobrevivientes de un PCEH.

Objetivos: Evaluar la mortalidad y el resultado neurológico de pacientes comatosos resuscitados de un PCEH tratados con hipotermia terapéutica. Considerar las indicaciones y los hallazgos de la cinecoronariografía y detectar complicaciones asociadas con la hipotermia.

Material y métodos: Se incluyeron pacientes resuscitados de un PCEH tratados bajo hipotermia terapéutica, que consistió en una fase de enfriamiento a 33 °C, un mantenimiento durante 24 horas y recalentamiento a 0,25 °C/hora. Se analizaron las indicaciones y los hallazgos de la cinecoronariografía. Se evaluaron complicaciones metabólicas, arrítmicas, infecciosas y hemorrágicas. Se consideró significativo valor de p menor de 0,05.

Resultados: De los 213 pacientes incluidos, la sobrevida hospitalaria fue de 109 pacientes (51,2%), de los que 96 (46,1%) presentaron al egreso buena recuperación neurológica. Se observó mayor sobrevida en pacientes con ritmos pasibles de desfibrilación respecto de aquellos con ritmos no pasibles de desfibrilación (58,2% vs. 37,7%; p = 0,007). Se derivaron (3,5 horas en promedio) a cinecoronariografía 147 (69%) pacientes, de los cuales 121 (82,3%) mostraron enfermedad significativa, observándose en 69 (57%) oclusión coronaria completa. Ciento siete pacientes fueron sometidos a angioplastia; 43 (40,2%) de ellos fallecieron durante la internación frente a 61 (58,6%) óbitos entre los no intervenidos o no estudiados (p = 0,005). Entre las complicaciones, las más frecuentes resultaron la hipopotasemia (87,6%) y la bradicardia sinusal (66,7%).

Conclusiones: El empleo de hipotermia terapéutica se asoció con una sobrevida hospitalaria superior al 50%, con buen resultado neurológico en el 46,1%. Entre los pacientes sometidos a angioplastia se apreció un descenso de la mortalidad. La hipopotasemia y la bradicardia sinusal fueron las complicaciones más frecuentes.

Palabras clave: Paro cardíaco - Resucitación cardiopulmonar - Hipotermia terapéutica

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Address for reprints: Dr. Ricardo Levin - Portela 2975 - CABA - e-mail: rllevin@gmail.com

Universidad Abierta Interamericana, Buenos Aires Argentina
Vanderbilt University Medical Center, Nashville, Tennessee, USA
^{MTSAC} Full Member of the Argentine Society of Cardiology

[†] To apply as Full Member of the Argentine Society of Cardiology

Abbreviations

BIS Bispectral index
TH Therapeutic hypothermia

IV Intravenous
OHCA Out-of-hospital cardiac arrest

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) represents one of the leading causes of death in the industrialized world, with an annual incidence of 400,000 new cases per year in the United States. It is associated with a very low hospital survival rate <10% as reported by some contemporary series and high incidence of unfavorable neurological outcome among survivors. These outcomes have remained stable over the last three decades. (1, 2)

In 2002, two randomized, controlled clinical trials proposed the usefulness of therapeutic hypothermia (TH) to reduce mortality and the severity of unfavorable neurological outcome in OHCA survivors hospitalized after spontaneous circulation had been restored but who remained unconscious. (3, 4)

We analyzed a contemporary series of OHCA survivors to determine in-hospital survival and neurological recovery in patients treated with TH, analyze the complications associated with this therapy and evaluate the use of coronary angiography and percutaneous coronary intervention.

METHODS

Population

The study included patients >18 years consecutively admitted to the cardiac critical care unit in two university hospitals between May 1, 2007 and August 1, 2012. The patients had been resuscitated from a non-traumatic OHCA, spontaneous circulation had been restored but they remained

unconscious. In patients treated with benzodiazepines or morphine-derived analgesics, the specific antagonists were administered before deciding the inclusion in the protocol. The protocol was continued if coma persisted.

Patients with the following conditions were excluded: absence of evident unfavorable neurological outcome (Glasgow score >9), evidence of neurological damage before OHCA, traumatic cardiac arrest or OHCA due to infection or intoxication, hypothermia at admission (body temperature < 34 °C), history of terminal disease or coagulation disorders and pregnant women. Patients with a residual effect after the administration of benzodiazepine or morphine-derived antagonists were also excluded from the study.

Therapeutic hypothermia protocol

The provision of therapeutic hypothermia consisted of three well defined phases: induction, maintenance and rewarming.

The induction phase consisted of dropping the body temperature to a target value of 33 °C using saline infusion (30 ml/kg) at 4 °C and placing ice packs on the patient's axilla, groin and neck. At the same time, a controlled cooling device based on external circulation of cold water (Arctic Sun Temperature Management System, Medivance, Inc, Louisville, CO, USA) was prepared (Figure 1) to maintain target temperature (controlled by a temperature probe within the Foley catheter) for 24 hours (maintenance phase) after which the patient was actively rewarmed at 0.25°C/hour (rewarming phase).

All the patients were admitted with endotracheal intubation to the cardiac critical care unit, received mechanical ventilation and were connected to a bispectral index (BIS) monitor to measure the depth of anesthesia. Sedation was in-

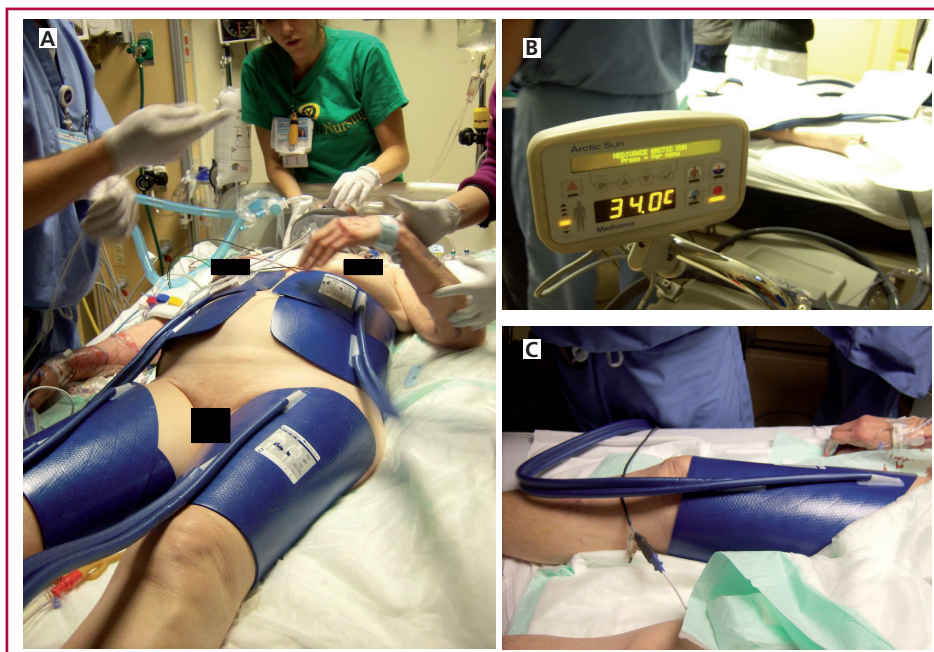


Fig. 1. Components of the Arctic Sun cooling and rewarming device based on external circulation of water. **A.** Placement of body components. **B.** Device console with temperature display screen. **C.** Components of lower extremities.

duced by the intravenous (IV) administration of midazolam, 2 mg every 5 minutes initially and 0.125 mg/kg/h thereafter, and fentanyl at 100 μ g/h in continuous infusion, titrating to obtain a bispectral index BIS >50. Vecuronium (neuromuscular blocking agent) was administered IV at 0.1 mg/kg/h as needed. A mean arterial pressure goal of more than 75 mm Hg was chosen and norepinephrine was used as vasoactive agent initially in patients with no signs of hypovolemia (central venous pressure >12 mm Hg). If target blood pressure was not achieved with a dose of 20 μ g/h norepinephrine, vasopressin was associated at a dose of 0.04 U/h. The vasoactive drugs were infused through a central line.

Complications were evaluated and classified as:

- Metabolic complications: hyperglycemia (blood glucose level >180 mg/dL), acidosis (pH <7.30), hypokalemia (K <3.5 mEq/L) and hypomagnesemia (<2.5 mg/dL).
- Infections: pneumonia (clinical features plus radiological findings) and sepsis (systemic inflammatory response syndrome plus documented infection).
- Hemorrhage: new gastrointestinal bleeding, brain hemorrhage or bleeding requiring blood transfusion.

Hemodynamic complications and arrhythmias: bradycardia, atrioventricular blocks and atrial fibrillation.

In-hospital mortality was defined as death occurring for a primary cause within 30 days of the admission date or during hospitalization.

Neurological recovery was defined according to the Pittsburgh Cerebral Performance Category (CPC) scale (Table 1). (5)

Coronary angiography and percutaneous coronary intervention

The indication of coronary angiography and percutaneous coronary intervention was evaluated, as well as the moment the procedures were performed. The indication depended on the preference of the attending physicians. The angiographic findings and the indication of revascularization and its complications were also analyzed.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean and standard deviation. The chi square test was used to compare categorical variables, and confidence intervals for OR were determined. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 statistical package.

Ethical considerations

The study protocol was approved by an institutional Ethics Committee. A family member or a patient's guardian gave informed consent for the patient to participate in the study.

RESULTS

The cohort consisted of 213 patients. The general characteristics, history of diseases of the study population and the information related with OHCA and TH initiation and management are described in Table 2.

One-hundred and nine patients (51.2%) survived during hospitalization. At discharge, 76 (69.7%) patients were in CPC 1, 20 (18.3%) in CPC 2, 5 (4.5%) in CPC 3, 5 (4.5%) in CPC 4 and 3 (2.8%) in CPC 5. During hospitalization, 104 patients died; 56 (53.8%) initially presented a shockable rhythm (ventricu-

Table 1. Pittsburgh cerebral performance category scale

CPC 1: Good cerebral performance. Conscious, alert patient, without neurological deficit or mild deficits (nonincapacitating hemiparesis, mild dysphasia or minor cranial nerve abnormalities)
CPC 2: Moderate cerebral disability. Moderate neurological dysfunction. Conscious patient, who may have hemiplegia, seizures, ataxia, dysarthria, dysphasia or permanent memory or mental changes. Sufficient cerebral function for independent activities of daily life (dressing, traveling by public transportation, and preparing food).
CPC 3: Severe cerebral disability. Conscious patient, but dependent on others for daily support at an institution or with exceptional family effort. He presents at least limited cognition. This category includes a wide range of cerebral abnormalities ranging from ambulatory patients with severe memory disturbance or dementia, precluding independent existence, to prostrate, paralytic patients able to communicate only with the eyes, as in the locked-in syndrome.
CPC 4: Coma, vegetative state. Unconscious patient, unaware of surroundings. No verbal or psychological interaction with the environment.
CPC 5: Brain death. Certified brain death or death by traditional criteria.

lar tachycardia or ventricular fibrillation) versus 38 (36.5%) patients with non-shockable rhythms (bradycardia, asystole or pulseless electrical activity) and 10 patients (9.61%) presented other rhythms.

When survival rate and initial rhythm were compared, patients with shockable rhythms presented higher survival rates [58.2% (78/134 patients)] compared with those with bradycardia or asystole [37.7% (23/61 patients) (p=0.007, CI 0.23-0.81)]. A non-significant trend was observed in other initial rhythms [44.4% (8/18 patients)] (p=0.007, CI 0.63-4.86).

One-hundred and forty seven (69%) patients underwent coronary angiography within the first 6 hours after hospitalization (average: 3.5 hours) due to ST-segment elevation in 124 (84.4%), new left bundle branch block in 17 (11.6%) and ST-segment depression in 6 (4.1%) cases. In 121 (82.3%) patients, coronary angiography revealed significant coronary artery disease: 69 (57%) patients presented total occlusion of a coronary artery, 47 (38.8%) had a severe lesion (>70% occlusion) in at least one coronary artery, while 5 (4.1%) patients had normal coronary arteries. One-hundred and seven patients underwent percutaneous coronary intervention and 132 stents were implanted.

Among the patients undergoing percutaneous coronary intervention, 43 (40.2%) died during hospitalization and 61 (58.6%) deaths were reported among those who did not undergo coronary angiography or an interventional procedure (p=0.005, OR 0.2865-0.8577).

The adverse events observed during TH are detailed in Table 3.

Table 2. General characteristics of the population and factors associated with cardiac arrest

Characteristic (n total=213)	n (%)
Age, years	61.2 ± 7.3
Male sex	184 (86.4)
Hypertension	137 (64.3)
Smoking habit	95 (44.6)
Diabetes	73 (34.3)
History of cardiac surgery	23 (10.8)
History of percutaneous coronary intervention	91 (42.7)
History of myocardial infarction	67 (31.5)
Site of cardiac arrest	
Street	97 (45.5)
Work place	104 (48.8)
Home	12 (5.6)
Initially attended by witnesses	198 (92.9)
Initially attended by emergency personnel	15 (7.1)
Initial recorded rhythm VT/VF	134 (62.9)
Initial recorded rhythm bradycardia, asystole or pulseless electrical activity	61 (28.6)
Other initial recorded rhythm	18 (8.5)
Time to circulatory recovery, min	10.3 ± 4.2
Time to hypothermia, min	143.6 ± 21.3

Among the 104 deceased patients, the primary cause of death was cardiac in 40 (38.5%) cases, neurological in 36 (34.6%), infectious (sepsis with multiorgan failure) in 22 (21.2%) and respiratory in 5 (4.8%) patients. In 6 (5.8%) cases, the family decided to discontinue vital support.

DISCUSSION

In our series, the main findings demonstrate that patients resuscitated from OHCA in whom spontaneous circulation had been restored but remained unconscious presented in-hospital survival >50% with a high rate of neurological recovery after TH. This greater survival was observed in patients undergoing early coronary angiography and percutaneous coronary intervention compared with those who were not intervened. The use of hypothermia was associated with an important number of complications.

Survival was greater in patients with initial shockable rhythms compared with other type of rhythms.

Out-of-hospital cardiac arrest is an important and prevalent condition (400,000 cases per year in the United States or 1,000 events per day; 40,000 to 50,000 cases per year in our country) with very high mortality. Lombardi et al. reported a survival rate of 1.4%, while Dunne et al. estimated it in 0.3%. It is also an important cause of disability among survivors, with an incidence of severe unfavorable neurological outcome ranging from 50% to 100%, including persis-

Table 3. Complications associated with hypothermia

Complication	n (%)
Hypokalemia	186 (87.3)
Low magnesium levels	58 (27.2)
Hyperglycemia	65 (30.5)
Pneumonia	22 (10.3)
Sepsis	44 (20.6)
Bleeding	37 (17.4)
Seizures	5 (2.3)
Bradycardia	153 (71.8)
Sinus bradycardia	142 (66.7)
First-degree atrioventricular block	5 (2.3)
Second-degree atrioventricular block	3 (1.4)
Third-degree atrioventricular block	1 (0.5)
Need of temporary pacemaker	2 (0.9)
Atrial fibrillation	17 (8)
Use of inotropic agents	94 (44.1)
Use of vasopressors	179 (84)
Use of vasodilators	44 (20.6)
Intraaortic balloon pump	23 (10.8)

tent coma and brain death. (6-9)

In 2002, two randomized, controlled studies reported, almost simultaneously, the favorable effects of applying scheduled and systematic TH in comatose survivors from OHCA. (3, 4)

These randomized studies, together with other uncontrolled series, produced a change of concept, and TH became the standard treatment with a precise indication in comatose survivors from OHCA when the event was due to a shockable rhythm. (10, 11)

Unfortunately, and despite the recommendations, the number of resuscitated patients who are appropriately treated with TH is generally limited. In 2007, Bianchin et al. reported that only 16% of intensive care units in Italy used TH, while the results of a new survey performed by Gasparetto et al. in 2010 showed that 45% of the intensive care areas were not using it. (12, 13)

In our series, results of hospital survival >50% and neurological recovery in nearly 70% of treated patients in CPC 1 and 2 could be incorporated to those reported by investigators proposing a wide application of this technique in comatose survivors from OHCA. In addition, among the 147 patients who underwent immediate coronary angiography, an important percentage of total occlusion (Figure 2) or severe lesions were reported. Therefore, percutaneous coronary intervention was performed in 107 cases, establishing the difference in survival with patients who did not undergo coronary angiography or an interventional procedure.

The International Liaison Committee on Resuscitation (ILCOR) recommends the importance of de-

termining the etiology of OHCA. Considering that in patients with ST-segment elevation without cardiac arrest, immediate coronary angiography reduces the incidence of death and reinfarction and that acute coronary syndromes are the main cause of OHCA, coronary angiography and percutaneous revascularization, a time dependent strategy, seem to be reasonable in this scenario, particularly when the electrocardiogram is suggestive of a coronary event. (10, 11, 14)

In the same line, Spaulding et al. described that 71% of 84 patients resuscitated from OHCA and referred to immediate coronary angiography presented significant coronary artery occlusion with total occlusion in 48% of cases. In the Arizona SHARE (Save Hearts in Arizona Registry and Educations) Registry, only 20% presented a non-cardiac cause of cardiac arrest. (15, 16)

However, the indication of coronary angiography with eventual intervention in survivors from OHCA is complicated for several reasons. Firstly, there is limited evidence because OHCA has been invariably excluded in studies evaluating percutaneous coronary intervention and it is uncertain if the implementation of TH could interfere with angioplasty. The possibility of higher incidence of complications after TH as arrhythmias, vasospasm, hemodynamic instability or bleeding after a percutaneous coronary intervention requiring subsequent antiplatelet treatment is also a cause of concern. Despite these doubts, several authors suggest that both procedures can be safely performed simultaneously, and the implementation of one method should not delay the implementation of the other. In this sense, the American Heart As-

sociation and the European Resuscitation Council recommend patient transfer to the catheterization laboratory after resuscitation from OHCA of presumable cardiac etiology, independently of the presence of previous symptoms or electrocardiographic findings. (10, 11, 14-18)

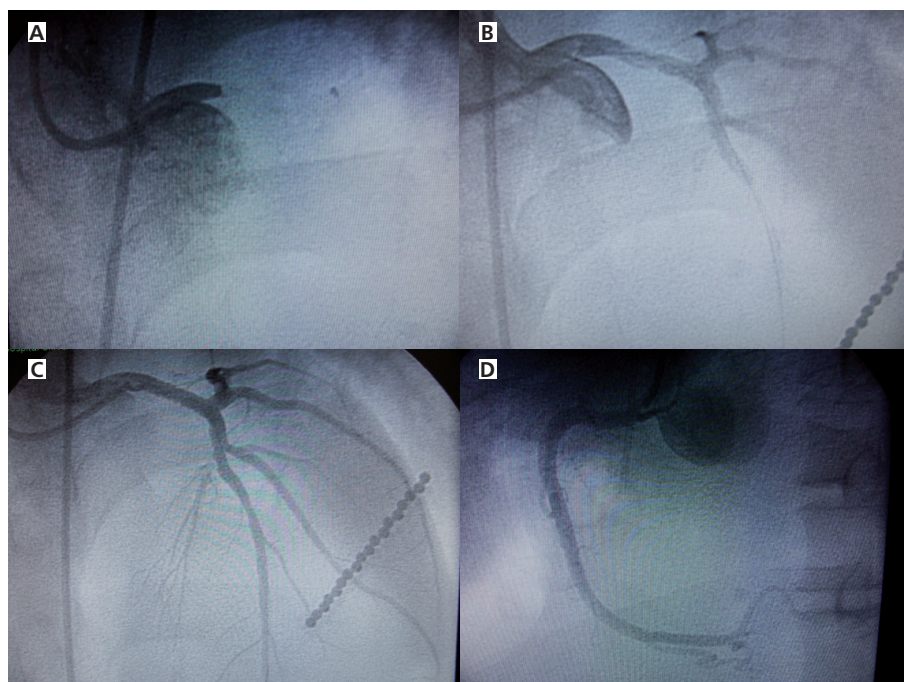
Despite its benefits, TH can be associated with adverse effects, mainly due to the physiological abnormalities produced by cooling (and subsequent re-warming) of body temperature. In our series, the most common adverse effects were metabolic complications and arrhythmias.

Among the former, hypokalemia was the rule, and was present in 87.6% of cases. In agreement with our results, Mirzoyev et al. described a significant decline in serum potassium during cooling (from 3.88 to 3.17 mmol/L) in 94 sequential patients with OHCA undergoing TH, with a nadir at 10 hours after cooling onset and recovery during the rewarming phase. In 2002, Bernard et al. reported low potassium levels in patients treated with hypothermia at admission in the critical care area as well as after 6 and 12 hours. (4, 19)

Hyperglycemia was observed in 30.5% of patients. Bernard et al. had reported increased glucose levels in patients undergoing TH compared with those with normal body temperature from admission to discharge, and they associated this finding with reduction in insulin levels and higher insulin resistance produced by hypothermia. (4)

Bradycardias, in particular sinus bradycardia, occurred in 71.8% of patients in our series and is due to depressed automaticity of pacemaker cells in-

Fig. 2. Coronary angiography. **A.** Left main coronary artery with 100% stenosis. **B.** Angioplasty of the left main coronary artery. **C.** Final result. **D.** Right coronary artery without lesions.



duced by hypothermia. This result is similar to that of Batista et al. who characterized sinus bradycardia as a common (in 30% of his population) and benign condition. In the same line, an interesting study performed by Thomsen et al. in Denmark, identified sinus bradycardia as an independent marker of favorable outcome as patients treated with hypothermia who developed sinus bradycardia presented lower mortality. (18, 20)

The incidence of coagulation disorders and infections was significant in our study and in the published literature. (21)

Despite our series included an important number of patients resuscitated from OHCA treated with TH and many of them underwent coronary angiography and percutaneous coronary intervention, the present study lacks a control group and included patients with initial shockable and non-shockable rhythms. The high prevalence of male sex could represent a bias. Although the outcome was better in patients treated with hypothermia that had shockable rhythms and in those who underwent coronary angiography, we cannot rule out other factors, such as clinical presentation, duration of cardiac arrest or myocardial revascularization, which could have contributed to this association.

CONCLUSIONS

In a population of OHCA survivors admitted after spontaneous circulation had been restored but remained unconscious, TH was associated with survival similar to the one described in the literature with favorable neurological outcome in patients with an initial shockable rhythm. Mortality was lower in patients undergoing coronary angiography and percutaneous coronary intervention but other factors could also have some influence in these outcomes. Bradyarrhythmias and metabolic complications were the most common adverse effects observed.

Conflicts of interest

None declared. (See author's conflicts of interest forms in the web / Supplementary Material)

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