Improved Prognosis After Using Mild Hypothermia to Treat Cardiorespiratory Arrest Due to a Cardiac Cause: Comparison With a Control Group

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Introduction and objectives. Patients who survive a cardiac arrest have a poor short-term prognosis in terms of mortality and neurological function. The use of mild hypothermia has been investigated in only a few randomized studies, but appears to be effective for treating these patients. The aim of this study was to investigate the effect of this treatment on survival and neurological outcomes.

Methods. We compared mild hypothermia and usual treatment in patients who had experienced a prolonged cardiac arrest due to ventricular fibrillation or tachycardia and who showed signs of neurological damage. Patients were divided into 2 groups: a control group of 28 patients and a group of 41 patients who were treated with hypothermia. Patients were assessed at discharge and at 6 months.

Results. There was no significant difference between the 2 groups in baseline characteristics, including those of the cardiac arrest, or in the time to treatment. At discharge, neurological status was good in 18 patients (43.9%) in the hypothermia group but in only 5 (17.9%) in the control group (risk ratio =2.46; 95% confidence interval, 1.11-3.98; P=.029). At 6 months after discharge, neurological status was found to be good in 19 patients (46.3%) in the treatment group and 6 (21.4%) in the control group (risk ratio =2.16; 95% confidence interval, 1.05-3.36; P=.038). The effect of hypothermia may have been affected by various confounding factors.

Conclusions. Our findings demonstrate that hypothermic treatment after cardiac arrest prolonged by ventricular fibrillation or tachycardia helps improve the prognosis of anoxic encephalopathy.

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Mejora del pronóstico tras parada cardiorrespiratoria de causa cardiaca mediante el empleo de hipotermia moderada: comparación con un grupo control

Introducción y objetivos. Los pacientes que sobreviven a una parada cardiaca tienen mal pronóstico vital y neurológico a corto plazo. La hipotermia moderada se ha ensayado en escasos estudios aleatorizados y parece ser eficaz en el tratamiento de estos pacientes. Nuestro objetivo es mostrar el impacto de esta estrategia en la supervivencia y en el estado neurológico.

Métodos. Hemos comparado hipotermia frente a tratamiento habitual en pacientes tras parada cardiaca prolongada por fibrilación o taquicardia ventricular y con signos de daño neurológico, para lo que se establecieron un grupo control de 28 pacientes y otro grupo de 41 pacientes tratados con hipotermia. Los pacientes fueron evaluados al alta y a los 6 meses.

Resultados. No se encontraron diferencias significativas entre los grupos al comparar las características basales, las características de la parada y los tiempos de asistencia. Al alta tenían una buena situación neurológica 18 (43,9%) pacientes del grupo de hipotermia y 5 (17,9%) del grupo control (riesgo relativo [RR] = 2,46; intervalo de confianza [IC] del 95%, 1,11-3,98; p = 0,029). A los 6 meses del alta, se encontraban en buena situación neurológica 19 (46,3%) pacientes del grupo tratado y 6 (21,4%) del grupo control (RR = 2,16; IC del 95%, 1,05-3,36; p = 0,038). El efecto de la hipotermia puede verse afectado por diversos factores de confusión.

Conclusiones. Nuestros resultados ponen de manifiesto que el tratamiento con hipotermia después de parada cardiaca prolongada por FV o TV contribuye a mejorar el pronóstico de la encefalopatía anóxica.

ABBREVIATIONS

CPR: cardiopulmonary resuscitation.
CRA: cardiorespiratory arrest.
EMD: electromechanical dissociation.
MH: mild hypothermia.
VF: ventricular fibrillation.
VT: ventricular tachycardia.

INTRODUCTION

Survival following a cardiorespiratory arrest (CRA) outside of a hospital setting depends on the type of initial assistance received. It may reach 16%-32% in patients who receive immediate attention; if no such assistance is forthcoming, however, the survival rate is drastically reduced.[1] The heart rhythm disorder that leads to CRA also has a major influence on survival; this may reach 34% if the cause is ventricular fibrillation (VF), but may be no more than 6% if the cause is asystole caused by electromechanical dissociation (EMD).[2,3] The importance of reducing brain damage due to anoxia/reperfusion has led to the coining of the phrase "cardiocerebral resucistion"[4]; only 1.4% of survivors of an extra-hospital CRA remain free of neurological problems[5] and 64% may have serious sequelae.[6]

Two randomized clinical trials[7,8] and a number of observational studies[9-12] report the efficacy of mild hypothermia (MH) in improving the prognosis of patients with CRA in terms of mortality and neurological outcome.[13] In 2003, the International Liaison Committee on Resuscitation (ILCOR) published the indications for this technique.[14] In our coronary unit the MH protocol has been used since 2003 in patients in coma after a prolonged CRA of cardiac cause. The present work, which represents the first large study of its kind in Spain, reports our results with this therapy.

METHODS

Study Subjects

The present study was performed in our 11-bed coronary unit. The study population was made up of all patients who were admitted between January 2000 and May 2008 with a diagnosis of extra- or intra-hospital CRA.

To be included, patients had to show VF or ventricular tachycardia (VT) without pulse as the first recorded rhythm, and to have been subject to advanced cardiopulmonary resuscitation (CPR) measures with orotracheal intubation. The outcome of CPR had to have been successful and a stable rhythm obtained, the patient being admitted to the coronary unit in coma (Glasgow <8) owing to cerebral anoxia (other causes had to have been excluded, especially pharmacological and metabolic coma).

Patients not considered candidates for MH were those with comorbidities in the terminal stage or who from the outset were hemodynamically or electrically unstable (arrhythmic storm) and refractory to treatment leading to death in the 24 h following admission. Patients in cardiogenic shock treated by conventional means (fluid therapy, sympathomimetic amines, emergency coronary intervention, and intra-aortic balloon counterpulsation) were not excluded if stabilization was achieved.

To analyze the influence of MH on prognosis in terms of mortality and neurological function, 2 cohorts of patients were compared, one in which the members received MH, the other in which the members received standard treatment (control). The control group was composed of patients with no contraindication for MH under the conditions outlined above; comparisons between this and the MH treatment group were therefore possible.

Mild Hypothermia Protocol

The MH protocol requires cooling be performed as early as possible after any complementary tests the attending physician should deem necessary. Patients are sedated with midazolam and morphine chloride; myorelaxation is achieved with cisatracurium. Cooling is achieved using an isothermal blanket at 33ºC and bags of ice. If the core temperature is not reduced (monitored using a urethral catheter or Swan-Ganz catheter) physiological saline or Ringer's solution at 4ºC is administered. Body temperature is maintained at 33-34ºC for 12-24 h. Patient hemodynamics are monitored invasively. Re-heating is passive, with sedation and relaxation suspended when 36ºC is reached. Hypothermia can be suspended if any important clinical deterioration becomes apparent that might hinder the management of the patient.

Data Gathered

Patient baseline characteristics and medical attention times from the moment of arrest until the target temperature was reached were gathered retrospectively from clinical records. The condition of each patient at admission was recorded in terms of the Glasgow score, the APACHE II score, the presence of infarction, whether the patient was in a state of cardiogenic shock, the need for balloon counterpulsation, acute coronary perfusion

TABLE 1. Baseline Patient Characteristics and Characteristics of the Arrest

	Control Group	MH Group	P
Patients, n	28	41	
Men	23 (85.2)	35 (85.4)	.469
Age, years	61.7 (12.2)	58.3 (15.8)	.336
Diabetes mellitus	6 (21.4)	8 (19.5)	.867
Prior ischemic heart disease	8 (28.6)	10 (24.4)	.721
Prior myocardial infarction	6 (21.4)	4 (9.8)	.296
History of heart failure	6 (21.4)	4 (9.8)	.296
Intra-hospital arrest	5 (17.8)	3 (7.3)	.255
Time elapsed until first assistance, min	1.5 [0-10]	5 [0.5-10]	.860
Time elapsed until defibrillation, min	10 [5-15]	10 [8-15]	.542
Time from arrest until stable rhythm after CPR, min	26.5 [17.8-42]	30 [20-34]	.887
Time elapsed until arriving at hospital, min	57 [42-62]	54 [45-68]	.547

CPR indicates cardiopulmonary resuscitation; MH, mild hypothermia.
Values are expressed as number of individuals (valid percentage), mean (SD) or median (interquartile range).

TABLE 2. Condition at Admission

	Control Group	MH Group	P
APACHE II	22 [18-26]	21 [19-27]	.720
Glasgow	3 (3-7)	3 (3-7)	.236
STEMI	15 (53.6)	26 (63.4)	.414
Cardiogenic shock	7 (25)	17 (41.5)	.159
Need for sympathomimetic amines	12 (42.9)	19 (46.3)	.775
Need for intraortic balloon counterpulsation	6 (21)	11 (27)	.668
Infarctions treated with primary angioplasty	10 (66.7)	18 (69.2)	1
Infarctions treated with fibrinolysis	1 (6.7)	4 (15.4)	.636
STEMI without emergency reperfusion	4 (26.7)	4 (15.4)	.434
Left ventricular ejection fraction at admission (%)	36 (16)	37 (17)	.911

STEMI indicates ST elevation acute myocardial infarction.
Values are expressed as number of individuals (valid percentage), mean (SD) or median [interquartile range].

(angioplasty, fibrinolysis, or nothing) and via a cranial CT scan. The main aim of the study was to describe the neurological status of the patients at discharge and after six months using the Glasgow-Pittsburgh cerebral performance categories[15]: 1 – no sequelae, 2 – slight incapacity, although the patient is independent and no institutionalization is necessary, 3 – severe incapacity, the patient is not independent and needs to be institutionalized, 4 – persistent vegetative state, and 5 – death. As in earlier studies,[8,9] the first two steps on this scale were considered to represent a good neurological outcome, and the latter three a poor outcome.

Statistical Analysis

All collected data were subjected to descriptive statistical analysis, via frequency measurements (absolute frequencies and percentages) if the variables were qualitative, and via means and standard deviations or medians and interquartile range if quantitative. The magnitude of the effect of hypothermia was expressed in the form of relative risk (RR) and 95% confidence limits (95% CI). Univariate analysis of the quantitative variables was undertaken using the Student t test when their distribution was normal, and the Mann-Whitney U test when they were not. The qualitative variables were analyzed using the χ^2 or the Fisher exact test when the conditions required for the former test were not met. Interactions could not be evaluated in multivariate analysis owing to the small sample size. Logistic regression was therefore employed to determine whether the association between the intervention and the progress of patients at 6 months post-discharge was influenced by the baseline characteristics of the groups (confounding factors). From the collection of baseline variables shown in Tables 1 and 2, those with the potential to act as confounding factors were selected first in terms of their clinical and biological plausibility, and second in terms of the statistical criterion of Mickey et al,[16] excluding all those variables that in
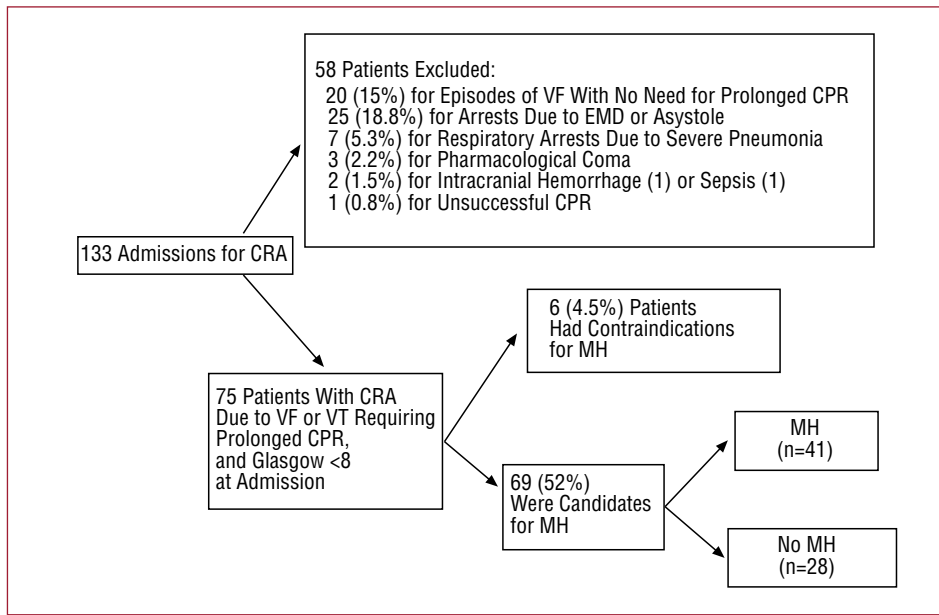
Figure 1. Flow diagram: selection of patients. EMD, electromechanical dissociation; VF, ventricular fibrillation; CRA, cardiorespiratory arrest; CPR, cardiopulmonary resuscitation; VT, ventricular tachycardia.

univariate analysis returned an association with the response reflected by a value of *P*>.20. Given the limitations posed by the sample size, adjustment for the effect of MH on the prognosis at six months post-discharge was performed variable by variable. The results are expressed as RR and 95% CI. The RR was calculated from the odds ratio (OR) provided by logistic regression using the formula $RR=OR/[(1-P_0)+(P_0\times OR)]$,[8,17] where P_0 is the incidence of "good neurological outcome" (Glasgow-Pittsburgh cerebral performance category 1-2) in the control group. An RR of >1 shows that MH improves the chances of a good neurological outcome at 6 months.[8,9] The guidelines of the STROBE[18] initiative were used in the presentation of results.

RESULTS

Patient Selection

During the study period, 133 patients with a diagnosis of extra- or intra-hospital CRA were admitted to our unit. Of these, 20 (15%) were excluded who presented with episodes of VF with successful cardioversion without the need for prolonged CPR, 25 (18.8%) whose first recorded rhythm was EMD or asystole, 7 (5.3%) with respiratory arrest due to severe pneumonia, 3 (2.2%) in pharmacological coma with Glasgow >8 once the effects of the sedatives were eliminated, 2 (1.5%) in which CPA was associated with extracardiac causes (1 intracranial hemorrhage, 1 sepsis), and 1 patient in whom a stable rhythm could not be achieved. Of the 75 remaining patients, those who were not candidates for MH according to the stated criteria were excluded: 5 (3.7%) died

within 24 h in a state of refractory cardiogenic shock, and one with advanced lung cancer. Of the final 69 patients included in the study, 41 (59.4%) received MH (all after 2003 except for one in 2002). Of the remaining 28 patients(controls), 21 (75%) were admitted between 2000 and 2003, and 7 (25%) later, overlapping in time with the patients subjected to MH. However, none of the controls showed any contraindications for MH; the treatment received depended on the criterion of the attending physician and his/her familiarity with the MH technique. Figure 1 shows a flow diagram for the selection of the patients.

Characteristics of the CRA and Condition of Patients at Admission

Table 1 shows the baseline characteristics of the patients and the characteristics of the CRA suffered. Table 2 describes the clinical situation of the patients at admission. No significant differences were seen between the baseline characteristics of the patients who underwent MH and those of the control group. Nonetheless, the control group had a larger percentage of patients with ischemic heart disease, who were diabetics, who had suffered a prior infarction and episodes of heart failure, while the MH group had a greater percentage with acute ST elevation myocardial infarction (STEMI), and cardiogenic shock. Since the small sample size limited the detection of any significant differences, all baseline variables were analyzed as potential confounding factors for inclusion in logistic regression analysis.
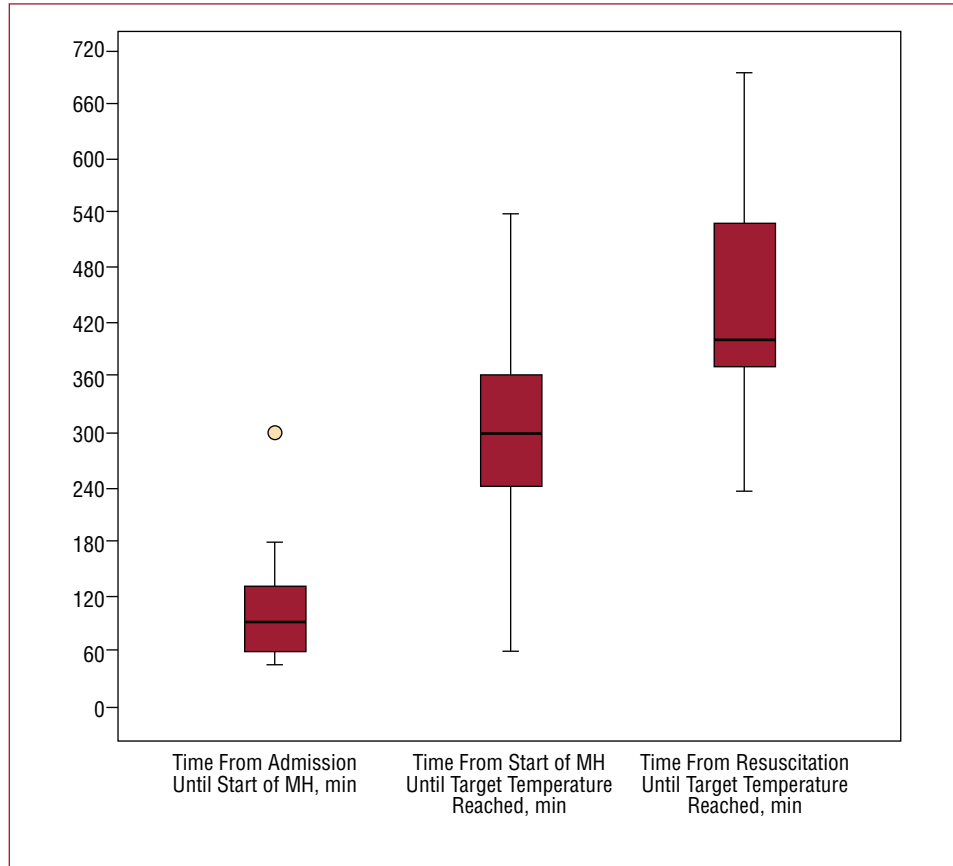
Figure 2. Distribution of the time periods elapsed with regard to the hypothermia procedure. Values are medians, Tukey first and fourth hinges, and maximum and minima not considered anomalous (whiskers).

Assistance Times and Induction of Hypothermia

Table 1 shows the different assistance times recorded, while Figure 2 shows the different time periods elapsed with regard to the MH procedure. The time elapsed until the beginning of assistance procedures was defined as the total time in arrest during which no assistance was received, irrespective of the persons providing that assistance (these were untrained persons in 29% of cases). Before undergoing MH, 19 (46.3%) patients were subjected to emergency coronary angiography, with primary angioplasty in 18 (43.9%) cases. Three (7.3%) underwent a brain CT scan. The mean time elapsed between admission and reaching the target temperature in patients subjected to emergency coronary angiography was 391.1 (139.9) min compared to 355.5 (140) min in the patients not subjected to this procedure (P=.419). The target temperature was reached in all patients; the need to suspend hypothermia arose in no patient.

Progress During Hospitalization

No significant differences were seen between the control and MH patients with respect to the length of hospital stay (median, 11 [4-30] days vs 11 [7-19] days; P=.95). However, a trend was apparent, with 7 (25%) of the control patients spending over 30 days in hospital compared to 5 (12.2%) of the MH patients (P=.205). The median duration of orotracheal intubation was 7 (3-11) days in the control group compared to 4 (2-7) days in the MH group (P=.068). The most common infectious complication was nosocomial pneumonia, which was suffered by 13 (46.4%) of the control patients and 16 (41%) of the MH patients (P=.66). Electroencephalograms and evoked N20 neurosensory potentials were performed as deemed required in patients showing initially torpid neurological progress (15 [55.6%] patients in the control group vs 19 [46.3%] in the MH group; P=.457). These tests returned a "poor prognosis" or "result compatible with severe anoxic encephalopathy" for 14 (50%) in patients in the control group and 16 (39%) in the MH group (P=.366).

Final Diagnosis

The final diagnosis was STEMI in 41 (59.4%) patients, non-STEMI (NSTEMI) in 4 (5.8%), chronic ischemic cardiomyopathy in 8 (11.6%), dilated
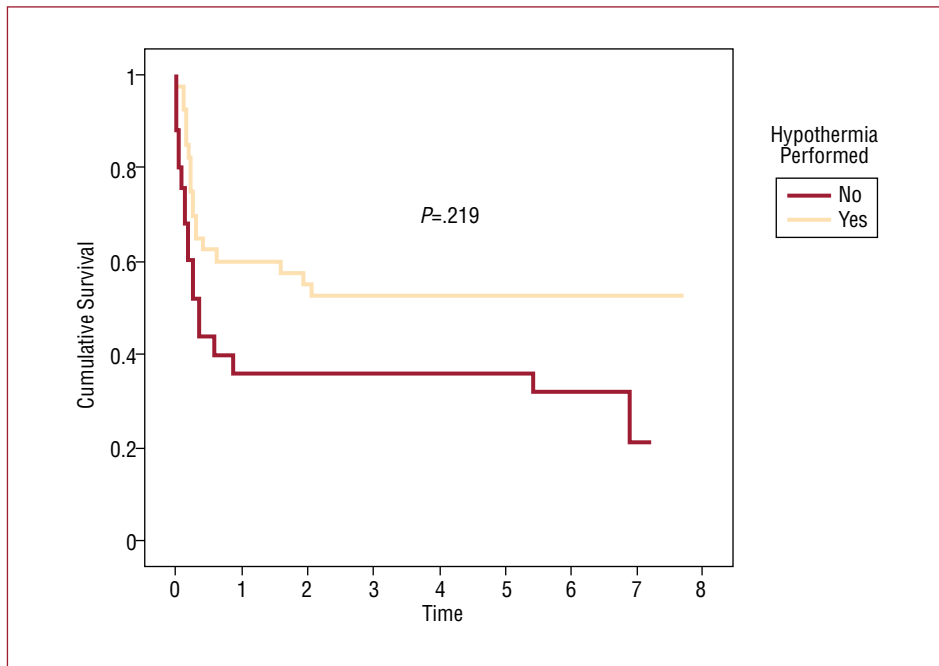
Figure 3. Kaplan-Meier survival curves.

cardiomyopathy in 4 (5.8%), long QT syndrome in 2 (2.3%), hypertrophic obstructive cardiomyopathy in 1 (1.4%), and severe hypopotassemia with QT prolongation and polymorphic VT due to proximal tubulopathy in 1 (1.4%). No etiological diagnosis was arrived at in 7 (10.1%) patients, 6 of whom died during their stay in hospital, and one of whom was discharged in a persistent vegetative state.

Survival and Neurological Prognosis

A total of 23 (56.1%) patients in the MH group survived until discharge compared to 11 (39.3%) in the control group (RR=1.43; 95% CI, 0.84-2.44; P=.17). At 6 months, 21 (51.2%) patients of the MH group and 9 (32.1%) of the control group remained alive (RR=1.59; 95% CI, 0.86-2.95; P=.116). Figure 3 shows the Kaplan-Meier survival curves; no significant differences were seen despite the marked trend in favor of MH treatment (P=.219).

At discharge, 18 (43.9%) patients of the MH group and 5 (17.9%) of the control group (RR=2.46; 95% CI, 1.11-3.98; P=.029) showed a good neurological status (Glasgow-Pittsburgh categories 1 or 2). Six months after discharge this was true of 19 (46.3%) in the MH group and 6 (21.4%) in the control group (RR=2.16; 95% CI, 1.05-3.36; P=.038), with a significant improvement seen in 1 patient in each group. Information on the progress of all patients was available.

Effect of Hypothermia, Adjusted for Potential Confounding Factors

Adjustment was made for the following potential confounding factors: age, history of diabetes mellitus, prior ischemic heart disease, time until defibrillation, total arrest time, STEMI as the cause of arrest, APACHE II on admission, Glasgow score on admission, and cardiogenic shock. As expected, adjustment for a more serious condition at admission, such as APACHE II or longer total arrest led to MH having a non-significant effect on prognosis. Adjustment for other important factors, such as age or time until defibrillation, led to MH having an effect at the limit of significance (Table 3).

DISCUSSION

At out unit, MH has been used with patients admitted for cardiac arrest due to VF or VT since 2002, and under protocol since 2003. The technique is, however, little used in Spain; indeed, the present study is the largest from Spain to be published to date.

In agreement with previous randomized trials,[7,8,13] the results of the present retrospective analysis show that MH may be beneficial in terms of neurological prognosis and survival. The present results also contribute towards confirming the usefulness of MH

TABLE 3. Relative Risk (Non-Adjusted and Adjusted) of a Good Neurological and Functional Outcome (Pittsburgh Cerebral Performance Category 1-2) Compared to a Poor Outcome (Pittsburgh Cerebral Performance Category 3-5) (MH Group Compared to control Group) at 6 Months Post Discharge

Effect of Mild Hypothermia	RR (95% CI)	P
Non-adjusted	2.16 (1.05-3.36)	.038
Adjusted for age	2.08 (0.98-3.31)	.055
Adjusted for diabetes mellitus	2.25 (1.07-3.48)	.034
Adjusted for a history of ischemic heart disease	2.21 (1.02-3.47)	.044
Adjusted for time until defibrillation	2.37 (0.99-3.72)	.052
Adjusted for total time of CRA	2.30 (0.83-3.75)	.080
Adjusted for STEMI	2.27 (1.10-3.47)	.030
Adjusted for Glasgow at admission	2.55 (1.17-3.79)	.023
Adjusted for APACHE II at admission	1.99 (0.78-3.43)	.131
Adjusted for cardiogenic shock	2.25 (1.09-3.45)	.031

95% CI indicates 95% confidence interval; CRA, cardiorespiratory arrest; RR, relative risk; STEMI, ST elevation acute myocardial infarction.

within the context of routine daily practice[11] in a wide range of less strictly selected patients, including those admitted in cardiogenic shock[12] and those with CRA having an origin in factors other than ischemic heart disease.[19] The 39.3% intra-hospital mortality among the present control patients is comparable to that reported by Bernard et al[7] (32%), that indicated for a historic cohort by Belliard et al[9] (36%), as well as in other registries.[2] It should be remembered, however, that this survival following a CRA is only seen in the most favorable context, ie, arrest due to witnessed VF and immediate attention. The prognosis becomes much less favorable when one of these conditions is not met, in fact even with the smallest delays in defibrillation.[20,21]

Currently, the only therapeutic measures of demonstrated benefit (within a context of full medical attention for critical patients) with respect to survival and neurological progress following a CRA, are MH, defibrillation as early as possible,[22,23] and primary angioplasty when the CRA is due to an acute myocardial infarction.[24,25]

The effectiveness of MH with respect to minimizing anoxic damage to the central nervous system has led some authors to question the validity of the variables conventionally used to provide a neurological prognosis after a CRA[26,27]: certainly, MH is one of the main factors improving prognosis. Given the lack of data on how often this technique is used in Spain, the results of Abella et al[28] from 2005 are of particular interest: 87% of doctors interviewed (cardiologists or emergency medicine specialists at a sample of reference centers) had never made use of MH in patients in whom such therapy was indicated. The under-use of this technique is widely recognized and the inclusion of a cooling protocol in clinical practice guidelines has been proposed.[29]

The effectiveness of MH in the treatment of CRA due to asystole, EMD or non-cardiac causes remains to be determined. Very few case reports exist that indicate clearly favorable results,[30] and in larger numbers of patients the results have been contradictory.[11,12] In addition, it still needs to be determined whether reaching the target temperature more quickly provides any benefit. The notion that this might be the case stems from observations mainly made in animal studies.[31,32] In the large clinical studies mentioned above,[7-9] large differences with respect to the moment when MH was begun, the time taken to reach the target temperature, and the length of time this is maintained did not seem have much effect, and certainly did not seem to reduce the effectiveness of the treatment. In the present work, the mean time elapsed between the recovery of a stable rhythm until reaching a core temperature of <34°C was notably shorter (median, 405 [360-420] min) than that reported by Belliard et al[9] (552 [380-665] min).

Different courses of action exist to rectify the potential loss of benefit associated with delay in cooling, including perfusion with 2 L of saline solution at 4°C,[33] or perfusion with Ringer's lactate serum before arriving at the hospital[34] or even during CPR.[35] There are also several ways of inducing MH with closed circuit intravascular devices.[36] A report involving a large number of patients in which these devices were used has been published,[37] the results suggesting that a more rapid arrival at the target temperature favors good neurological progress.

In the present work only 3 of the last patients seen were managed using these devices, which facilitate MH. With all probability, their more extended use would increase the use of therapeutic hypothermia in Spain. Finally, diffusion of the technique might be

expected to have a great influence on the prognosis of patients as well as have an important positive economic impact on health systems, as described in other contexts.[38]

Limitations of the Study

The present work suffers from the intrinsic limitations of all retrospective studies, but with accentuations in 3 areas. First, it was difficult to obtain precise data for the time elapsed until the beginning of CPR, until defibrillation was achieved, or the total time of CPR; none of these were directly measured. Second, there was an overlap from 2003 between patients subjected to MH and those with no contraindication for this technique but who in the end did not undergo such treatment; this gives rise to suspicions of a selection basis. The non-practicing of MH in such candidates depended on the familiarity of the attending medical teams with the technique, although since its implantation in our unit it has been increasingly used as experience has been gained. Thus, of all the candidates for MH in 2002, only 1 patient of 7 (14.4%) underwent such treatment, in 2003 the figure was 4 out of 8 (59%), in 2004, 9 out of 10 (90%), in 2005, 9 out of 9 (100%), in 2006, 2 out of 3 (66%), in 2007 10 out of 10 (100%), and between January and May of 2008, 6 out of 7 (87.5%). These data reflect the reality of implanting new procedures into conventional clinical practice. Finally, the third limitation is the improvement in the extra-hospital attention for CRA (especially the greater speed of arrival of assistance and the greater availability of defibrillators) that may have occurred over the last 8 years; this may have had a very positive effect with respect to the prognosis of these patients. In conclusion, in this work the non-adjusted effect of MH on prognosis at 6 months is similar to that reported by other authors.[7-9] Unfortunately, due to the sample size, no adequate adjustment for several potential confounding factors was possible. The adjustments that were possible, however, appear to show that some variables have an important influence (Table 3).

CONCLUSIONS

Mild hypothermia is a therapeutic technique that contributes towards an improvement in prognosis with respect to survival and neurological outcome in patients who have suffered a prolonged CRA due to VF or VT. Specific recommendations have been made regarding the use of this technique. Its effectiveness seems to be dependent on several factors, particularly the treatment received for the cause of the arrest (especially if this involves acute myocardial infarction), and the time elapsed before resuscitation procedures begin. It may therefore be a useful therapeutic alternative and perhaps even an essential part of the protocol that should be followed in patients presenting with CRA.[10]

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