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Review Article

CHESS-R: Post Cardiac-Arrest Hypothermia Evaluation for Patients with Shockable and Non-Shockable Rhythms – Retrospective Study

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Abstract

Background

Since the 2010 European Resuscitation Council (ERC) guidelines, it is recommended to apply Therapeutic Hypothermia (TH) to comatose patients after cardiac arrest (CA) and return of spontaneous circulation (ROSC). There is no evidence and these recommendations are based on expert opinions.

Objectives

To test if patients with a non-shockable initial rhythm (NSIR) should receive TH.

Methods

This was a retrospective data analysis including patients from 2007-2012. Inclusion criteria: all patients over 18 with out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA) without telemetry and outside of the operating room or Intensive Care Unit (ICU).

A neurological examination was performed on admission and every following morning. Outcomes were evaluated 6 months after discharge and dichotomized into good (Cerebral Performance Category (CPC) = 1 or 2) and poor (CPC = 3, 4 or 5).

Results

121 patients with a shockable initial rhythm (SIR) and 55 patients with NSIR received TH. 25% of all NSIR patients had a good outcome, as well as 54 with SIR. TH significantly ($P<0.001$) improved the outcome globally. The ratio good/bad outcome was 2.73 in the NSIR group with TH and 3.63 without TH. The rations for the SIR group were 1.24 and 4.02 respectively. Both ratios had no significant difference ($P=0.904$ and $P=0.073$), however the SIR group's difference was closer to a significance ($P=0.073$).

Conclusion

Contrary to the ERC recommendations, TH has no benefit for NSIR patients. We therefore advise no to cool them. Further prospective studies are needed.

Keywords: Cardiopulmonary Resuscitation; Cardiac Arrest; Non-Shockable Initial Rhythm; Shockable Initial Rhythm; Outcome; Hypothermia

Introduction

Sudden cardiac arrest is still a major cause of death [1]. Since therapeutic hypothermia (TH) has been introduced as a standardized therapy for resuscitation survivors, prognosis has improved significantly [2-4]. Since 2010 the European Resuscitation Council (ERC) has recommended to cool all comatose patients after cardiac arrest, even patients with a non-shockable initial rhythm (NSIR) even though the pilot studies were only done on patients with a shockable initial rhythm (SIR) [5]. However there is no evidence and these recommendations are solely based on expert opinions.

Objectives

The aim of our study was to evaluate the benefit of TH for patients with a NSIR in a retrospective study.

Methods

Our study was performed in the intensive care unit (ICU) of xxx. It was a retrospective data analysis of all patients in the years 2007-2012.

The main inclusion criterion was coma after cardiac arrest with ROSC. Patients needed to be 18 years or older. The patients also needed to survive the first night in the ICU.

Exclusion criteria were patients with Do-not-resuscitate/-do-not-intubate orders after initial cardiopulmonary resuscitation (CPR) and patients with in-hospital cardiac arrests in the operating room, the catheterization lab, on an ICU or with telemetry.

CPR was performed by Emergency Medical Services (EMS) on scene with a doctor trained in emergency medicine or by the in-hospital cardiac arrest team according to the 2005 European Resuscitation Council (ERC) guidelines [6] which were gradually replaced by the 2010 ERC guidelines [5]. All data concerning the cardiac arrest and CPR were collected from the EMS reports or the hospital resuscitation protocol. Ventricular fibrillation, pulseless ventricular tachycardia and a shock by an automatic external defibrillator were considered shockable initial rhythms (SIR). Pulseless electrical activity and asystole were considered non-shockable rhythms (NSIR).

Treatment in the ICU included invasive and non-invasive monitoring, echocardiography, haemodynamic support, mechanical ventilation, renal replacement therapy, glucose control, computed tomographic imaging, electro-encephalogram and urgent cardiac catheterization according to the 2005 and 2010 ERC guidelines [5,6]. Only patients with a shockable initial rhythm automatically received TH as a standardized treatment. The decision to apply TH to patients with a non-shockable initial rhythm was made by the attending physician. All patients with TH received analgesia, sedation and if necessary muscle relaxation. They were cooled with cold (4°C) intravenous 0.9% sodium chloride infusions and external cooling for 24 hours to a target temperature of 32-34°C. Paralysis and sedation were reduced or discontinued at the earliest possible time after hypothermia treatment had been completed. The Acute Physiology and Chronic Health Evaluation (APACHE) II score [7] was evaluated directly on admission to the ICU and every day post-ROSC. All data concerning post-resuscitation care was collected from the ICU charts.

A neurological consultation service evaluated all patients at least twice. For most patients, especially patients with a prolonged wake-up time, CT scans and EEGs were performed. Decisions to limit care were made together with the family and the neurological consultation service.

The neurological outcome was evaluated at discharge either directly from the ICU, the acute care hospital or a rehabilitation facility. Surviving patients were either contacted directly or via their attending general practitioner at least 6 months after the resuscitation in order to re-evaluate their results and permission to use their data was obtained. The outcome was assessed independently from the attending physicians and categorized according to the cerebral performance categories (CPC) [8]. All patients were dichotomized in a good and poor outcome. A CPC score of 1–2 was considered a good neurological outcome and a CPC of 3–5 a poor outcome.

A basic neurological examination was performed by trained intensive care nurses during every shift (three shifts per day) and by an intensive care physician twice a day. Motor response on day 3 post-ROSC was considered absent if the Glasgow Motor Score was 1 (makes no movements) [9].

Since our study is a retrospective data analysis, all patient data is anonymous. No additional blood samples were taken and therefore an institutional review approval for this investigation was not required by the local ethics committee.

Statistical Analysis

Continuous data are given as a mean and standard deviation for normally distributed data and respectively as median and range for asymmetrically distributed data. Categorical variables are given as counts and percentages. Differences in continuous data were analyzed using the unpaired t test. For categorical variables we used the Chi-Square test. Statistical analysis was performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered to indicate statistical significance.

Results

In the years 2007-2012, 177 patients (76.3% male, mean age 62 ± 14 years) were treated with TH (Table 1). Nearly all patients (92.7%) were OHCA survivors, and 74.6% had a witnessed cardiac arrest. Bystanders initiated CPR in 61.4% of all cases. During CPR, two thirds of all patients had a shockable initial rhythm (68.8%). The cumulative adrenaline dose administered during CPR was 4.2 mg ± 4.7.

Table 1. Basic patient characteristics.

		Hypothermia applied?				Significance
		No		Yes		
		Outcome		Outcome		
		Bad	Good	Bad	Good	P
Out of hospital resuscitation	No, n (%)	0 (0)	0 (0)	9 (5.1)	4 (2.3)	0.13
	Yes, n (%)	36 (20.3)	16 (9.0)	53 (29.9)	59 (33.3)	
Witnessed	No, n (%)	11 (6.2)	3 (1.7)	22 (12.4)	9 (5.1)	0.006*
	Yes, n (%)	25 (14.1)	13 (7.3)	40 (22.6)	54 (30.5)	
By-stander CPR	No, n (%)	11 (6.3)	3 (1.7)	30 (17.0)	24 (13.6)	0.213
	Yes, n (%)	25 (14.2)	13 (7.4)	31 (17.6)	39 (22.2)	
Initial rhythm?	Not shockable, n (%)	11 (6.3)	3 (1.7)	30 (17.0)	11 (6.3)	<0.001*
	Shockable, n (%)	25 (14.2)	13 (7.4)	31 (17.6)	52 (29.5)	
Cumulative Adrenalin during CPR, mg		4.7 ± 4.0	1.7 ± 2.6	6.4 ± 5.4	4.1 ± 6.8	0.020*

Outcome

Of all 177 patients, 79 regained consciousness. Of those patients, 65 had a good cerebral performance (CPC=1) and 13 were moderately impaired (CPC=2). Therefore, 78 patients (44.1%) achieved a good neurological outcome according to our dichotomization. All 68 patients had a good neurological outcome at hospital discharge as well as 6 months afterwards.

6 patients regained consciousness but had a severe neurological impairment. Two patients were in a persistent vegetative state and 91 had died at the time of our neurological outcome assessment. Overall, 62 patients (55.9%) had a poor outcome at discharge as well as 6 months after discharge.

Baseline Characteristics

We detected several differences in patients with a good outcome compared to those with a poor outcome (Table 2): Patients with a favorable outcome were younger (P=0.007). Sex had no influence on the outcome (P=0.430).

Table 2. Outcome by significant patient characteristics.

		Hypothermia applied?				Significance
		No		Yes		
		Outcome		Outcome		
		Bad	Good	Bad	Good	P
Sex	Female, n (%)	13 (38.3)	4 (11.7)	16 (32.0)	9 (13)	0.430
	Male, n (%)	23 (32.6)	12 (17.1)	46 (23.0)	54 (37.0)	
Age on admission, years		67 ± 12	54 ± 15	64 ± 15	61 ± 14	0.007*

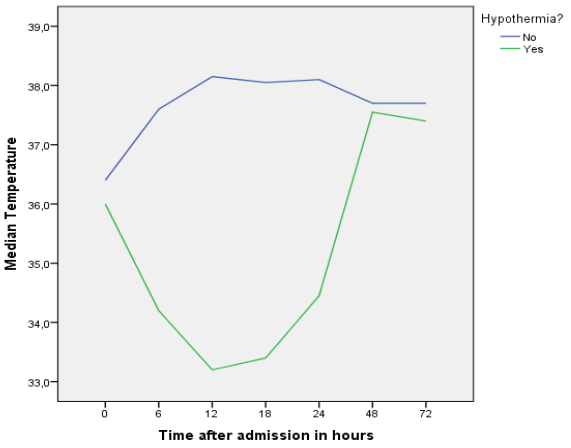

Figure 1. Temperature by Hypothermia regime.

A non-shockable initial rhythm (P<0.001) was associated with a poor outcome. The Temperature profile of both TH and non-TH groups is displayed in Figure 1.

Differences in the Outcome

The outcome was improved by applying TH to all patients (Table 3).

Table 3. Outcome by hypothermia and rhythm.

		Hypothermia applied?				Significance
		No		Yes		
		Outcome		Outcome		
		Bad	Good	Bad	Good	P
Initial rhythm?	Not shockable, n (%)	11 (6.3)	3 (1.7)	30 (17.0)	11 (6.3)	<0.001*
	Shockable, n (%)	25 (8.2)	13 (7.4)	31 (17.6)	52 (29.5)	

Of all 55 patients with a NSIR, 14 had a favorable outcome (25.5%). The ratio good/bad outcome was 2.73 when TH was applied and 3.63 when TH was not applied (Table 4). TH did not significantly improve the outcome for patients with a non-shockable initial rhythm.

Table 4. Outcome by initial rhythm with ratios.

		Outcome				Ratio		Significance
		Bad Outcome		Good Outcome		TH	No TH	
		Hypothermia applied?		Hypothermia applied?		Good/	Good/	
		No	Yes	No	Yes	Bad	Bad	P
Initial rhythm	Not shockable, n (%)	11 (20%)	30 (54.5)	3 (5.5)	11 (20%)	2.73	3.63	0.904
	Shockable, n (%)	25 (20.7)	31 (25.6)	13 (10.7)	52 (43.0)	1.24	4.02	0.073

Of all 121 patients with a SIR, 65 had a good outcome (53.7%). The ratio good/bad outcome was 1.24 when TH was applied and 4.02 when TH was not applied. TH did improve the outcome, although it was barely not significant (P=0.073).

Out-of-Hospital-Resuscitations

We also analyzed the sub-group of OHCA with successful ROSC since care is generally different in the two locations because of operational issues if nothing else (location, available personnel, down time, etc). 92.6% of all patients were OHCA survivors (Table 5). A witnessed cardiac arrest influenced the outcome positively as well as the initial rhythm and applied hypothermia. Sex, by-stander CPR or reaching the target temperature (as long as hypothermia is attempted)are no significant influences. Fever after hypothermia could influence the outcome negatively (only barely not significant but with strong tendencies).

Predictors of Outcome

As a further point of study, we also examined patients on day 3 after ROSC (Table 5). A missing motor response (Glasgow Coma Scare Motor response (GCS-M) = 1) was associated with a bad outcome (P<0.001). Out of all 75 patients without motor response, only 9 had a good outcome. Of all 127 patients with a motor response, 63 had a bad outcome and 64 a favorable outcome. This was true for patients with and

without hypothermia. However, this was due mainly to the patient group where no TH was applied. In this group, out of 72 patients with a motor response, 60 had a bad outcome (Specificity 27%). In the TH group, out of 55 patients with a motor response, 52 had a good outcome (Specificity 95%).

Table 5. Predictors of Outcome and by initial Temperature.

		Hypothermia applied?				Significance
		No		Yes		P
		Outcome		Outcome		
		Bad	Good	Bad	Good	P
Motor response on day 3	No motor response, n (%)	22	3	44	6	<0.001*
	Motor response, n (%)	6	12	3	52	
Initial Temperature, °C		37,2	32,3	35,6	35,9	0.057

The initial temperature also differed in both groups. Patients with TH had a higher initial temperature with 35.7°C compared to patients without TH with 34.8°C. These differences were not significant (P=0.057).

Discussion

Even though Therapeutic Hypothermia has been a successful treatment concept for comatose patients after cardiac arrest and ROSC, it remains unclear if this treatment is beneficial to all patient groups. Multiple studies have shown that it improves survival and the neurological outcome in patients who had an initially shockable rhythm. Therefore it is a level I recommendation and should be applied to all patients fulfilling treatment criteria. It should also remain an ERC recommendation for advanced life support after cardiac arrest.

It has been unclear if it is a good treatment option for patients with an initially non-shockable rhythm. The ERC recommended treating these patients with TH as well, although it was only a level V recommendation (expert opinion). Nevertheless further studies were needed to evaluate the treatment recommendations.

According to our study, applying TH to patients with a NSIR brings no benefit – neither in survival nor in the short and long-term neurological outcome. Therefore we would not recommend applying TH to patients with a NSIR. Nevertheless, before these recommendations should be applied a prospective randomized study with enough power to disprove any treatment benefits should be performed.

TH has a benefit in survival and neurological outcome – short and long-term. It also brings some unwanted side effects. It is know that TH has an influence on hemostaseology and increases bleeding complications [10,11].

When TH is applied, established predictors such as pupillary and corneal reflexes on day 1 are not valid anymore [12,13]. Biomarkers such as NSE > 33 µg/l are also not predictors with a 100% Specificity when TH is applied [14-17]. A combination of an elevated Neuron Specific Enolase and S-100B can be used to predict a bad outcome. However a motor response on day 3 after ROSC is the most reliable predictor to predict a favorable outcome[16]. We also showed that a GCS-M of 1 is a reliable predictor of a bad outcome with a specificity of 88%. In our patient group, a GCS-M > 1 was no reliable predictor of a good outcome (Sensitivity 50%). When TH is applied, it can be used to predict a good outcome (Sensitivity 95%). End-of life decisions should not be made before 72h post-ROSC [18,19]. Longer wake-up durations should be expected when TH is applied19. All newly created algorithms for predicting the outcome when TH is applied, can be used for these patients [20-23].

However, when no TH is applied – as we would recommend after performing this study – a favorable outcome should not be predicted with this marker (Sensitivity 27%). If TH is not applied anymore, the previously established predictors can be used again [12,22,23].

Limitations

Our study of course has some limitations: Some data are missing due to the clinical nature of our study without a standardized study protocol. It is also possible that since all examinations and results were available to the treating physicians, they might have based some of their clinical decisions on these results. This systematic bias is due to the retrospective observational type of study.

Conclusion

Our study suggests that the ERC guidelines to cool all comatose patients after cardiac arrest with ROSC regardless of their initial rhythm does not benefit patients. Even though it may not be harmful when applying TH to patients with a NSIR, it does not significantly improve their survival neither their short- nor long-term neurological outcome.

A prospective randomized study with enough power to disprove any treatment benefits should be performed.

Conflict of Interest

There is no conflict of interest.

Summary

Why this topic is important? - The ERC guidelines of 2010 are solely based on expert opinion and real data is needed to support or contradict these opinions.

What does this study attempt to show? - The impact of Therapeutic Hypothermia (TH) on patients with both a shockable and non-shockable initial rhythm (SIR and NSIR).

What are the key findings? - TH does not improve the outcome in the NSIR group.

How is patient care impacted? – TH should not be applied to patients with NSIR anymore, further studies are required however.

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