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Study of resuscitated in- and out-hospital cardiorespiratory arrest patients undergoing therapeutic hypothermia

Estudo de pacientes reanimados pós-parada cardiorrespiratória intra e extra-hospitalar submetidos à hipotermia terapêutica

ABSTRACT

Objective: To determine the characteristics of patients undergoing standard institutional protocol for management of resuscitated patients after a cardiac arrest episode, including therapeutic hypothermia.

Methods: This was a retrospective analysis of 26 consecutive patients admitted following cardiac arrest, between January 2007 and November 2008.

Results: All cases underwent therapeutic hypothermia. Average age was 63 years, and the patients were predominantly male. Cardiac arrest event was out-of-hospital in 8 cases, in the emergency room in 3 cases, in the wards in 13 cases and in the operation room in 2 cases. The cardiac arrest rhythm was ventricular fibrillation in seven patients, asystolia in 11, pulseless electrical activity in 5 cases, and was undetermined in 3 patients. The interval between the cardiac arrest and return of spontaneous circulation was 12 minutes (SD ± 5 min). The time to reach the target temperature was 5 ± 4 hours, the hypothermia time was 22 ± 6 hours and time to rewarming 9 ± 5.9 hours. Fourteen patients died in the intensive care unit, a 54% mortality, and three patients died during the in-hospital stay, a 66% in-hospital mortality. There was statistically significant reduction in hemoglobin (p<0.001), leukocytes (p=0.001), platelets (p<0.001), lactate (p<0.001) and potassium (p=0.009), values and increased C reactive protein (p=0.001) and INR (p=0.004) after hypothermia.

Conclusions: The creation of a standard operative protocol for therapeutic hypothermia in post cardiac arrest patients management resulted in a high use of therapeutic hypothermia. The clinical results of this protocol adapted from randomized studies are similar to the literature.

Keywords: Hypothermia; Heart arrest; Intensive care

INTRODUCTION

Cardiorespiratory arrest (CRA) is the most frequent cause of global brain ischemia. Between 400,000 and 460,000 cases are seen every year in the USA.[1] Between 7 and 10% of the patients initially resuscitated after out-of-hospital cardiac-cause CRA survive, and are discharged from the hospital with good neurological outcome[2] and 18% after in-hospital CRA.[3]

Return of spontaneous circulation (ROSC) following CRA leads to the post-cardiorespiratory arrest syndrome. Nevertheless the advances in therapies for patients surviving to a CRA event, in the last 50 years few changes in patients' survival were seen. These patients mortality,

in an article published in 1953, was 50%,[4] and in 2006 the National Registry of Cardiopulmonary Resuscitation, after analyzing 19,000 adults and 500 children, presented a 67 and 55% mortality, respectively.[4]

Post-CRA management may reduce early hemodynamic instability and multi-organ failure mortality, and late mortality for brain injury.[5] Most of post-CRA deaths are seen within the first 24 hours after ROCS.[6]

Post-cardiorespiratory arrest syndrome is characterized by cardiovascular, neurological, respiratory, renal and metabolic systems impairment.[7] In two prospective controlled randomized clinical trials performed in Australia[8] and in Europe[9], benefit was proven for hypothermia induction for 12 and 24 hours, respectively, in patients who remained in coma after ROCS. In these trials, published in 2002, hypothermia was compared to normothermia following CRA.

Based on this evidence, the International Liaison Committee on Resuscitation (ILCOR) included this therapy among its recommendations for post-cardiorespiratory arrest patients, including patients with ROCS post-CRA out-of-hospital, for 12 to 24 hours, when the arrest rhythm was ventricular fibrillation (VF). Although there is no evidence so far, also included patients with other arrest rhythms, and those occurring in-hospital.[10]

The mechanism how hypothermia is beneficial is not fully understood. In normal brains, the oxygen request is reduced by 6% for each 1ºC drop above 28ºC. It reduces reperfusion-related chemical reactions, such as oxygen free radicals production, excitatory amino-acids release, and calcium interchange leading to mitochondrial damage and apoptosis.[10]

However, although hypothermia is a recommended therapy for this group of patients, it is not a fully used measure among us. In January and February 2007 it was prepared and issued a Standard Operational Procedure (SOP) for guiding the management, increase treatment compliance and reduce the variability for this therapy use in the Hospital Mater Dei at Belo Horizonte, MG, Brazil. This study objective was to identify the results after the hypothermia protocol introduction in patients with cardiorespiratory arrest out of the intensive care unit (ICU). Additionally, it aimed to determine the issues influencing the hypothermia time, time to hypothermia, time to rewarming, and laboratory results in patients undergoing therapeutic hypothermia.

METHODS

Aiming identify the epidemiology and outcomes of cardiorespiratory arrest patients management, we retrospectively analyzed all patients admitted post-CRA with any out-of-ICU rhythm, who remained in coma after ROSC and undergoing therapeutic hypothermia from January 2007 to November 2008 in the Hospital Mater Dei – Belo Horizonte (MG, Brazil) ICU.

The patients were managed according to the Unit adopted hypothermia protocol. For data collection, the Hospital Mater Dei – ICU database was used. This study was approved by the hospital's Research Ethics Committee.

Protocol

The protocol complied with the POP-M-UTI-032 guidelines, discussed in January 2007 and published in February 2007.[11]

To prevent delay in the therapeutic start, the bed was previously prepared with a thermal cushion with esophageal temperature sensor. All patients underwent initial resuscitation aiming to aggressively correct hypotension, hypovolemia, hypoxemia, and hypoglycemia. Continued sedation with midazolam and fentalyl was started, and continued curarization with continued cisatracurium infusion or pancuronium bolus. Patients with an indication for coronary catheterization, were immediately submitted to this procedure.

The target temperature was 32 to 34ºC, reached with 30 mg/kg NaCl 0.9% or Ringer Lactate infusion at 4 to 8ºC,[12] ice applied to skin folds and use of the thermal cushion until the target temperature was reached. If the temperature was not reached, the cold intravenous infusion was repeated after 4 hours.

The patients were invasive arterial pressure monitored for hemodynamic control and serial blood tests collection (arterial blood gas, lactate, coagulogram, complete blood counts, ions). A central venous line was established for volume tests and vasopressors and inotropic agents administration, as necessary. Swan Ganz catheter monitorization was used at the intensivist physician discretion.

Trans-thoracic echocardiogram and laboratory tests review was performed for all patients. The temperature was maintained at the target for 12 to 24 hours.

Rewarming was started with resetting the thermal

cushion temperature + 0.5ºC per hour, until reaching 36ºC. Neuromuscular blockers were kept during the rewarming and prophylactic antithermics for 48 hours.

Statistical analysis

Descriptive analysis was performed for all variables. Continuous variables were expressed as mean ± standard deviation and median (minimum – maximum). Normality was checked with the Shapiro-Wilk test. For comparison of the means, for independent and normal variables, the t Student test was used for independent samples. In case of non-normality, the medians were compared using the Mann-Whitney test. For pairwise comparison of more than two groups, the variance analysis model (ANOVA) for repeated measures was used in case of normality, and the Friedmann test in case of non-normality. To identify the differences detected in the ANOVA, a Tukey multiple comparisons test was used. In the Friedmann test, the Dunn test for multiple comparisons was used. The significance level was 0.05.

Due to the small sample size, the variable "outcome" was recoded, becoming dichotomized: one of the categories as non-survivors and the other as survivors.

The statistics softwares used for the analysis were GraphPad Prism 4 for Windows and SPSS 12.0 for Windows.

RESULTS

Twenty six patients admitted to the Hospital Mater Dei ICU from January 2007 to November 2008 following a cardiorespiratory arrest (CRA) episode were analyzed. The patients were in average 63.0 ± 18 years old, median 64.5 (19-91) years. The male gender was predominant, accounting for 92.3% cases. The cardiorespiratory arrest was out-of-hospital in 8 cases, in the emergency department in 3 cases, and during in-hospital stay (out of ICU) in 13 cases, and in the surgery room in 2 cases. The heart rhythm was ventricular fibrillation in 7 patients, asystolia in 11, pulseless electrical activity (PEA) in 5 patients, and undetermined rhythm in 3 patients. The time between the cardiac arrest and return of spontaneous circulation was, in average 12.0 ± 5.0 minutes. The time to the target temperature, from the admission, averaged 5.0 ± 4.0 hours. Hypothermia time averaged 22.0 ± 6.0 hours. Rewarming took 9.0 ± 5.9 hours. Admission lactate was average 6.0 ± 3.7. Blood glucose was averaged 133.0 ± 17.0 mg/dL (Table 1).

Table 1 – Site of cardiac arrest and the post-cardiac-arrest rhythm

	N	%
CRA site		
Ward/Room	13	50
Surgery room	2	8
Out-of-hospital	8	31
Emergency dept.	3	12
Total	26	100
Arrest rhythm		
PEA	5	19
Asystolia	11	42
VF	7	27
Unknown	3	12
Total	26	100

CRA – cardiorespiratory arrest; PEA - pulseless electric activity; VF – ventricular fibrillation.

The post-hypothermia outcomes are shown in table 2. Nine patients were discharged from the ICU, and from these, five were discharged from the hospital. Two were transferred to other institutions and two remain in-hospital. Fourteen patients died in the ICU, a 54% in-ICU mortality, three died during the stay in the ward, mounting 66% in-hospital mortality.

Table 2 – Outcome

Outcome	N	%
ICU/Hospital discharge	5	19
ICU Discharge/Transference	2	8
ICU Discharge/Ward	2	8
ICU Death	14	54
Out-of-ICU Death	3	12
Total	26	100

ICU – intensive care unit.

The arrest rhythm was variable among the survivors. In the patients who were discharged from the ICU, the CRA rhythm was VF in 5 patients, asystolia in 2, PEA in 1, and unknown in 2 patients. The site of CRA among survivors was: 3 at the ward, 1 at the emergency department, 3 out-of-hospital and 2

Table 3 – Hours to hypothermia, hypothermia time, and rewarming time versus outcome

Variable	Outcome	N	Mean ± SD	Median (IQ)	Statistics	P value
Time from CRA/ hypothermia(hours)	Survivors	9		9 (5-12)	24.5*	0.005
	Non-survivors	17		4 (0.5-6)		
Hypothermia time(hours)	Survivors	9	20.4 ± 2.9		-1.2**	0.235
	Non-survivors	17	23.4 ± 6.9			
Time to rewarming (hours)	Survivors	9		5 (4-12)	53.5*	0.291
	Non-survivors	16		7.5 (6.0-14.7)		

CRA – cardiorespiratory arrest; SD – standard deviation; IQ – minimum-maximum. *U Mann-Whitney statistics for medians comparisons due to non-parametrical distribution. **t Student test for means comparisons due to normal distribution.

Table 4 – Laboratory profile versus time: admission, during hypothermia and after rewarming

Variable	Admission	During hypothermia	After rewarming (48 hours)	P value
Hemoglobin	11.7 ±3.2 (26)	11.5±3.0 (26)	10.6±2.4 (26)	<0.001#*
RCP	38.5 (8.5-145.3) (22)	83.0 (43-152) (24)	151.0 (105.5-204.5) (25)	0.001&*
Leucocytes	15.8 (12.3-21.2) (24)	10.9 (8.4-15.7) (26)	10.0 (8.7-13.2) (25)	0.001&*
Platelets	210.1 ± 78.1 (25)	162.7± 72.9 (26)	145.5 ± 69.9 (25)	<0.001#*
Creatinine	1.7± 1.7 (25)	1.3 ± 0.9 (25)	1.3 ± 0.8 (25)	0.317#
Potassium	4.1 ± 1.1 (26)	3.5 ± 0.7 (25)	4.0 ± 0.8 (26)	0.009#*
SvO$_2$	73 ±12.8 (10)	75.8± 10.1 (18)	73.7±10.1 (16)	0.655#
Lactate	6.2±3.7 (26)	3.0 ± 3.4 (24)	1.9±1.3 (24)	<0.001#*

RCP – reactive C protein; SvO$_2$ – venous oxygen saturation. Results expressed as mean ± standard deviation or median (min-max). In parenthesis, the number of patients in who the test was obtained. Friedman test or ANOVA.
*significant.

at the surgery room.

Analyzing the variable hours to hypothermia, hypothermia time and time to rewarming versus the dichotomized outcome, it was found a significant difference in outcomes for the median hours to hypothermia. Survivor patients had a longer median [9 (5-12)] than those who died (p=0.005) (Table 3). For hypothermia time and time to rewarming no significant difference was identified.

Regarding the hemodynamic variables, in average the patients used 0.47 ± 0.90 mcg/kg/min norepinephrine; during the out-of-hypothermia time this value was 0.33 ± 0.21 mcg/kg/min, while during hypothermia 0.47 ± 0.26 mcg/kg/min were required. Mean blood pressure during hypothermia was 87.0 ±4.3 mmHg, and out-of-hypothermia 83.0 ± 6.8 mmHg. The heart rate was 79.0 ± 5.0 bpm during hypothermia, and 87.0 ± 4.0 bpm out of this period. Mean cardiac output during hypothermia was 2.70 ± 0.44 L/min, while out of hypothermia it was 3.20 ± 0.66 L/min.

Only two patients required vasopressin (7.7%). In 15 patients (58%) dobutamine was used. Pulmo-nary artery catheter monitoring was used in 14 patients (54%).

Mean blood glucose was 133 mg/dL (SD ± 17).

Laboratory values were analyzed such as hemoglobin, leucocytes, platelets, reactive C protein, international normalized ratio (INR), creatinine, lactate, potassium, pH, bicarbonate and zero time SvO$_2$ during hypothermia (24 hours) and by 48 hours to identify this treatment related changes. The table 4 shows the values found for each variable. A significant difference was found in the means versus time for the variables hemoglobin, C reactive protein, leucocytes, platelets, INR, potassium and lactate.

For the variables hemoglobin and leucocytes there as a clearly statistically significant drop after hypothermia (p<0.001 and 0.001, respectively). For the reactive C protein variable, there was an increase after rewarming (p=0.001). A statistically significant drop in mean platelets (p<0.001), lactate (p<0.001) and potassium (p=0.009), and increased INR (p=0.004) were found. For better illustrating these differences, box-plots of these variables were prepared (Figure 1).
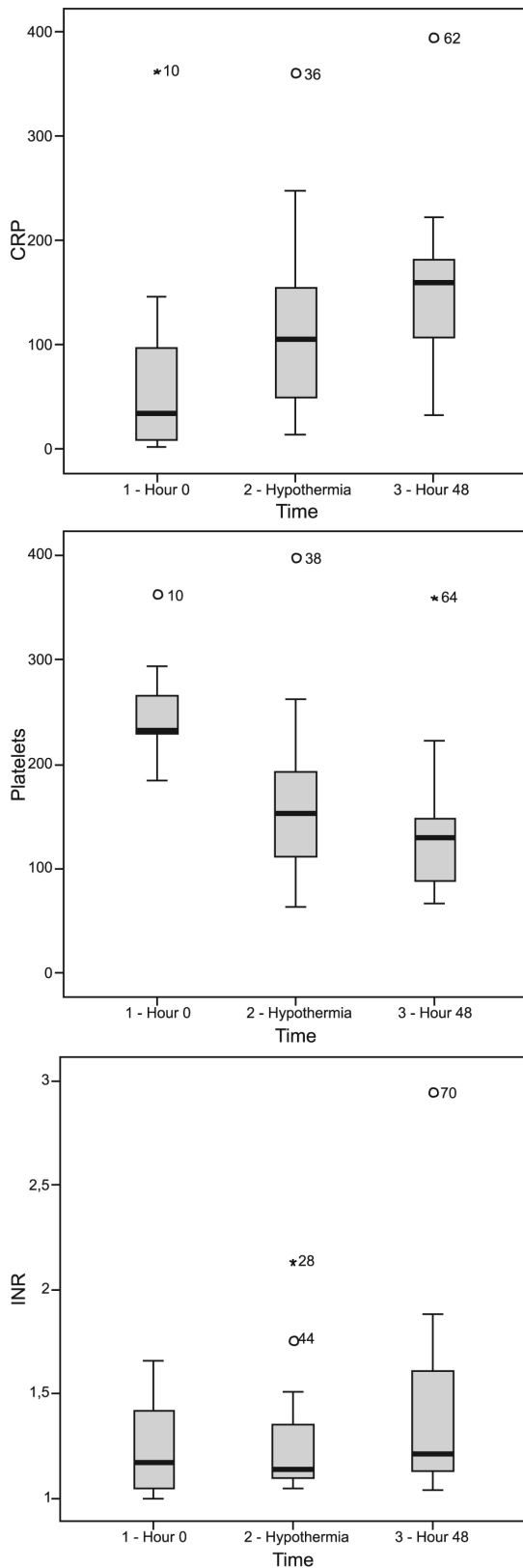
RCP = reactive C protein; INR = international normalized ratio.
Figure 1 – Laboratory data versus time (admission, hypothermia and after 48 hours).

DISCUSSION

CRA patients mortality remains very high.[1] In our series, the in-hospital mortality was 66%, coinciding with the figures by Nolan et al. in England where, after analyzing 28,958 cases for 10 years, the mortality was 71.4%.[10] In Canada, in a multicenter trial by Keenan et al., also in ICUs, a 66.5% mortality was seen among 2,760 patients.[13] In the USA, analyzing 1992-2005 patients above 65 years old, a in-hospital mortality of 81.7% was found, however with no statistically significant difference during the study period.[13]

Regarding the site of the CRA event, although only two patients came from the surgical room, both were discharged from the hospital, showing a better recovery trend among these patients, coinciding with data showing 43.9% survival by Nolan et al.[15], 34.5% by Sprung et al.[16], and 38% by Girardi et al.[17] These improved results may perhaps be related to CRA cases in monitored sites having better outcomes.

Implementation of CRA patients treatment protocols, as well as multidisciplinary approach, showed benefit for these patients' outcomes.[18,19] In this series we found results compatible with the literature,[8,9] reaching some goals such as time to the target temperature (5 hours), hypothermia time (22 hours) and rewarming time (9 hours). Regarding the relationship between time to hypothermia and death, in this series, paradoxically, lower mortality was found among patients taking longer to reach hypothermia (p=0.005), a result possibly attributable to the small sample size. However, additional studies are warranted to determine the therapeutic strategy, as data from both works are not homogeneous, with an average 8 hours in the European study[9] and 2 hours in the Australian[8] to the target temperature.

Nevertheless these interesting results, it is important underlying several limitations in this study, as its retrospective design, limited number of patients and follow-up time, different CRA rhythms, which have intrinsically different results on mortality, and finally, different sites of the CRA event. All these features may significantly fade any signs eventually present in the analysis. Main complications in this therapy are infections, coagulopathies, arrhythmias and hyperglycemia.[20] In this series, increased INR and reduced platelet counts were seen after hypothermia, however no bleeding complication was seen. No patient had

blood transfusions during of after hypothermia (dada not shown). Regarding increased infection, statistically significant leucocytes and reactive C protein increases were found, however with no proven infection identified after this treatment Regarding hemodynamic variables, there is no literature evidence for the appropriate values in this patients' group regarding mean blood pressure, central venous pressure, venous central saturation and clearance of lactate. Thus, values considered appropriate are those defined by the early goal-directed therapy.[21,22] In this series, an increased norepinephrine requirement during hypothermia was identified (0.47 mcg/kg/min versus 0.33 mcg/kg/min), however with no harm to the mean blood pressure, heart rate, and a reduced heart output (3.2 and 2.7) as it was found by Bernard et al. in Australia.[8] Regarding lactate values, there was a clearance, with a statistically significant difference between admission and hypothermia and after rewarming times, evidencing that the pre-established goals were reached.

Glucose control is controversial. Van den Berghe et al.[23] showed reduced mortality when blood glucose was strictly kept between 80 and 110 mg/L, however in recent papers, Oksanen et al.[24] and Losert et al.[25] benefit was found when there was a moderate control between 100 and 144 mg/dL. In this study the mean blood glucose was 133 mg/dL, within the recommended values.

This therapy use is simple and easily performed, as the target temperature goals can be reached with 4ºC solution infusion and skin folds ice.[12,26] The thermal cushion and neuromuscular blocker would, then, be adjuvants, offering increased stability for temperature control, however when missing, they are not a limitation for this technique.

CONCLUSION

A Standard Operational Procedure (SOP) for the treatment of cardiac arrest patients resulted in an elevated adhesion. The main topic of this protocol, the application of therapeutic hypothermia showed results compatible with the pertinent literature. The apparent paradox of the relation of less time to obtain hypothermia and increased mortality needs to better addressed in a larger series. New reviews of the protocol should be done periodically to adapt it to the current literature.

RESUMO

Objetivo: Conhecer as características dos pacientes submetidos a um protocolo operacional padrão institucional de atendimento a pacientes reanimados após episódio de parada cardiorrespiratória incluindo a aplicação de hipotermia terapêutica.

Métodos: Foram analisados retrospectivamente 26 pacientes consecutivos após episódio de parada cardiorrespiratória de janeiro de 2007 a novembro de 2008.

Resultados: Todos os casos foram submetidos a hipotermia terapêutica. Idade média de 63 anos, predominantemente do sexo masculino. O local da parada cardiorrespiratória foi extra-hospitalar em 8 casos, pronto socorro em 3, durante internação fora da unidade de terapia intensiva em 13 casos e o bloco cirúrgico em 2 casos. O ritmo de parada foi fibrilação ventricular em sete pacientes, assistolia em 11, atividade elétrica sem pulso em 5 casos e não foi determinado em 3 pacientes. O intervalo entre a parada e o retorno à circulação espontânea foi de 12 ± 5 minutos. O tempo requerido para alcançar a temperatura alvo foi de 5 ± 4 horas, o tempo de hipotermia foi de 22 ± 6 horas e para o reaquecimento usaram-se 9 ± 5,9 horas. Catorze pacientes evoluíram a óbito na unidade de terapia intensiva, representando uma mortalidade de 54%, e três pacientes tiveram o mesmo desfecho durante a internação, determinando uma mortalidade intra-hospitalar de 66%. Houve redução estatisticamente significativa dos valores de hemoglobina (p <0,001), leucócitos (p=0,001), plaquetas (p<0,001), lactato (p<0,001) e potássio (p=0,009), e aumento de proteína C reativa (p=0,001) e RNI (p=0,004) após aplicação de hipotermia.

Conclusões: A elaboração de protocolo operacional padrão de hipotermia terapêutica para o tratamento de pacientes com parada cardiorrespiratória, utilizando-se das rotinas adaptadas de estudos randomizados, resultou em elevada aderência e seus resultados assemelham-se aos dados publicados na literatura.

Descritores: Hipotermia; Parada cardíaca; Cuidados intensivos

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