



Prehospital Immediate Therapeutic Hypothermia in Galicia: Results and Next Steps

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Abstract

Introduction: Despite mild therapeutic hypothermia (TH) being recommended as a post-resuscitation care by current international resuscitation guidelines, recent evidences have questioned its role. Our objective was to assess the results of immediate TH at the pre hospital level by the Galicia's Emergencies Medical Service (GEMS) in order to know the potential impact on patient's outcome.

Methods: Observational retrospective study. Patients older than 18 years with a witnessed out-of-hospital cardiac arrest (OHCA), and with recovering of spontaneous circulation (ROSC) after advanced cardiopulmonary resuscitation (CPR) provided by sanitary personnel of the GEMS, between 2005 and 2013 were eligible. The survival and brain function at hospital discharge and one year after OHCA were assessed comparing the patients treated with immediate after ROSC pre hospital mild TH with patients receiving standard care.

Results: One hundred ninety one patients were included, 94 (49.2%) with shockable rhythm (VF); 56 (29.3%) received TH; 36 of them (64.3%) with VF. Survival at hospital discharge and 1-year after OHCA was 55.4% and 51.8% in the TH group, versus 28.9% and 22.9% respectively in control group ($p < 0.001$ both). Also, percentage of patients with CPC score 1-2 was higher in the TH group: 80.6% vs. 56.4 at hospital discharge ($p < 0.05$) and 93.10% vs. 70.9% at one year follow-up ($p < 0.01$). TH was an independent predictive factor of long-term survival, both in VF (OR=3.83; 95% CI: 0.40-36.96) as in no-shockable rhythms (OR=3.50; 95% CI: 0.31-39.15).

Conclusions: In Galicia, immediate after ROSC pre hospital TH improved survival and functional status at short and long-term, independently of the first recorded ECG rhythm. Although limited, our data have been obtained from the real-life GEMS working conditions and should be considered in before radical modifications of CPR protocols.

Introduction

Despite the improvements in pre hospital and critical care management along the past decade [1], patients who remain unconscious after out-of-hospital cardiac arrest (OHCA) are at high risk of death or neurologic deficits [2]. Critical steps to improve outcome are early identification and cardiopulmonary resuscitation (CPR) by bystanders, early defibrillation, high-quality CPR, and post-resuscitation care including mild therapeutic hypothermia (TH) [3]. According to that, several Emergency Medical Services (EMS) have updated their protocols to implement early TH at the pre hospital setting [4,5].

In 2013, two large randomized clinical trials (RCT) questioned the results of TH, both at the pre hospital setting [6], and later at the hospital level [2]. Considering these results and until the update of international guidelines, the International Liaison Committee on Resuscitation (ILCOR), and the European Resuscitation Council (ERC) made two statements regarding TH [7,8]. Since the controlled conditions of RCT sometimes are widely different from the real life, a caution should be maintained before the immediate translation of RCT's results to clinical practice, and in the evidence's review process,

the results observed under usual assistance conditions should be also considered. We assessed the effects of immediate pre hospital TH in terms of survival and functional outcome at short and long-term, when applied by the EMS of Galicia (GEMS).

Methods

In this retrospective observational study we included patients aged over 18 years with a witnessed out-of-hospital cardiac arrest (OHCA), who recovered spontaneous circulation (ROSC) after advanced cardiopulmonary resuscitation (CPR) provided by the GEMS health personnel. The data collection period was from January 1st 2005 to March 31st 2013, with an additional year of clinical follow-up.

The GEMS advanced life support ambulances include a physician and a nurse, as well as two emergencies medical technicians. After the 2005 and 2010 ILCOR recommendations [9,10] the GEMS implemented immediate TH after ROSC at scene, progressively adopting it in its mobile Units as the temperature targeted management (TTM) protocol was implemented in the referral hospitals. Such protocol includes advanced airway management, tight oxygenation control, hemodynamic stabilization [11], leads

electrocardiogram (ECG) to consider the suitability for angioplasty, and in those remaining comatose after ROSC and located in an area where continued TTM was assured, if no contraindication, immediate start of TH. Contraindications to TH are trauma, toxic products, drowning, uncontrollable bleeding, coagulopathy, thrombopenia, and coronary syndrome with S-T segment elevation, cardiac tamponade, accidental hypothermia with $T^a < 32^{\circ}\text{C}$, suspected aortic dissection, pregnancy, and multi-organic failure.

The TH is provided by rapid infusion of cold (4°C) saline serum with the goal of 34°C central temperature. Sequential temperature measurements were made before the beginning and after every dose of 500 ml of saline. If in any of the tests was below 33°C , the infusion was interrupted, checking it every 10 minutes and restarting the infusion when over 34°C . The need of sedation and analgesics was considered for all the patients, as well as the muscle relaxation to avoid shivers. The total period of hypothermia was 24 hours; after that the rhythm of rewarming was $0.25^{\circ}\text{C}/\text{hour}$.

The variables recorded were: age, sex, medical history, who witnessed the OHCA (witness, health staff, emergency team), time elapsed from onset of OHCA up to CPR, time elapsed from loss of consciousness up to ROSC, initial provider of the CPR (witness, emergency team), the first recorded ECG rhythm, post-resuscitation treatments applied (with or without TH). The main outcome was the survival at hospital discharge and one year after the OHCA, and the secondary outcome was the brain function evaluated with the Cerebral Performance Categories, at the hospital discharge and one year after the OHCA. Patients in good cerebral condition were those scored in categories one and two in the CPC scale assessment [12-14].

The GEMS makes a continuous quality control, including the follow-up from the beginning (first call received in the ECC) up to the final result, including in case of OHCA, the follow-up until twelve months after the date of the event. This process has been authorized previously for the responsible of the Sanitary System, and is developed according to the terms established by law [15].

Statistical analysis: Data are presented as mean \pm standard deviation for continuous variables and numbers and percentages for categorical variables. Wilcoxon signed-rank test was used to compare distributions of continuous outcome measures. Groups were compared using χ^2 test and Mann-Whitney U test. P values less than 0.05 were considered significant. Multiple logistic regression analysis assessed the factors associated with survival; adjusted Odds ratio (OR) and the 95% CIs were calculated. The heterogeneous distribution of the initial ECG rhythm was considered as a confounding factor, and was included in the multivariate analyses. SPSS software version 22 was used for all analyses.

Results

191 patients were included, 149 men (78.0%) and 42 women (22.0%), with an average age of 61.3 (SD 15.7) years. 56 patients were treated with TH (29.3%); their mean age was 61.8 (SD 14.8) years, and 80.4% were male. The remaining 135 subjects (70.7%), aged 61.0 (SD 16.1) years, and 77.0% male, constituted the control group (Table 1).

| | TH1 N (%) | Controls (SC2) N (%) | P value |
|---|--------------|-------------------------|---------|
| N | 56 (29.3) | 135 (70.7) | |

| | | | |
|--|----------------|----------------|--|
| Age (years) (mean+SD3) | 61.8+14.8 | 61.0+16.1 | n.s.4 |
| Sex (men) | 45 (80.3) | 104 (77.0) | n.s. |
| Shockable rythm | 36 (64,3) | 58 (42.9) | <0.05 |
| Medical history | | | |
| Chronic heart failure | 4 (7.1) | 8 (5.9) | n.s. |
| Previous AMI | 13 (23.2) | 24 (17.8) | n.s. |
| Ischemic heart disease | 17 (30.4) | 34 (25.2) | n.s. |
| Previous cardiac arrhythmia | 10 (17.9) | 23 (17.0) | n.s. |
| Arterial hypertension | 23 (41.1) | 53 (39.3) | n.s. |
| Previous TIA or stroke | 4 (7.1) | 11 (8.1) | n.s. |
| Diabetes mellitus | 7 (12.5) | 21 (15.6) | n.s. |
| Asthma or COPD | 6 (10.7) | 14 (10.4) | n.s. |
| Previous percutaneous coronary intervention | 6 (10.7) | 14 (10.4) | n.s. |
| Previous coronary-artery bypass grafting | 6 (10.7) | 13 (9.6) | n.s. |
| Witnessed OHCA5 | 46 (82.1) | 98 (72.6) | n.s. |
| By-stander CPR | 20 (43.5) | 52 (53.1) | n.s. |
| % Cases with time from OHCA to onset of CPR less than 15 min | 52 (92,9) | 123 (91.1) | n.s. |
| Time from loss of consciousness to ROSC (mean+ SD) | 25.2+13.2 | 23+14.8 | n.s. |
| Percutaneous coronary intervention | 5 (8.9) | 10 (7.4) | n.s. |
| Coronary-artery bypass grafting | 3 (5.4) | 8 (5.9) | n.s. |
| Survival at hospital discharge | 31 (55.4) | 39 (28.9) | <0.001 |
| CPC 1-26 at hospital discharge | 25 (80.6) | 22 (56.4) | <0.05 |
| 1-year survival | 29 (51.8) | 31 (23.0) | <0.001 |
| CPC 1-2 one year after OHCA | 27 (93.1) | 22 (71.0) | <0.01 |
| Shockable rhythm and survival - Hospital discharge - 1-year after OHCA | 23/36 22/36 | 27/58 23/58 | OR7 (95% CI)8 2.03 (0.86-4.77) 3.83 (0.40-36.96) |
| Non-shockable rhythm and survival - Hospital discharge - 1-year after OHCA | 8/20 7/20 | 12/77 8/77 | OR (95% CI)8 3.61 (1.22-10.70) |

| | | | |
|--|--|--|----------------------|
| | | | 3.50 (0.31-39.15) |
|--|--|--|----------------------|

Table 1: Clinical characteristics and outcomes of the patients

TH1: Mild therapeutic hypothermia; SC2: Standard care; SD3: Standard deviation; n.s.4: Not significant ($p > .05$); OHCA5: Out-of-hospital cardiac arrest; CPC 1-26: % patients categorized as 1 or 2 in the Cerebral Performance Categories scale assessment; OR7: Risk ratio; 95% CI8: Confidence interval at 95% level

In the TH group, 36 (64%) had a shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) whereas in the control group this figure was 58 (43%). The data corresponding to the medical history, time elapsed from loss of consciousness to ROSC, presence of witnesses, initial CPR, survival and the functional situation of the survivors at hospital discharge and after one year is shown in Table 1.

The logistic regression model was statistically significant, $(4) = 26.302$, $p < .001$. The model explained 29.5% (Nagelkerke) of the variance in survival at hospital discharge rate and correctly classified 72.2% of cases. Those patients who received therapeutic hypothermia were 3.82 times more likely to be alive at hospital discharge than patients who did not, with medium effect size (Table 2). TH was a survival factor at short and long-term, independently of the first recorded rhythm. The OR and intervals of confidence at 95% are shown in Table 1.

| Outcome | U | Cohen's d |
|--------------------------------|-----------|-----------|
| Survival at hospital discharge | 2779.5*** | -0.55 |
| CPCa | 2603.0*** | 0.65 |

Table 2: Mann-Whitney test for independent samples to compare the impact of hypothermia in main and secondary outcome

Note: *** $p < 0.01$. (a) CPC level measured at hospital discharge

Discussion

Currently, TH is part of the standard post-resuscitation care for unconscious patients who recovered after OHCA [1,12,16-18] as a consequence both of the 2005 and 2010 CPR International guidelines [9,10], as well as for the improvement of the results in survival. Recently, two large RCT revealed that immediate TH after ROSC at the pre hospital setting [6], or after the admission at the hospital [2] did not improve the results assessed in terms of survival and brain function, when compared respectively to TH at hospital setting or normothermia. These data challenge the current EMS protocols and might induce a radical change in CPR guidelines.

In order to know our results in our usual working conditions, we assessed the results of immediate TH after ROSC in case of OHCA in our setting and extended the follow-up period to one year. Our main finding is that TH, when applied immediately after ROSC at the scene in case of OHCA tripled survival independently of the first ECG rhythm detected. Our findings are consistent with similar studies developed by other EMS both in VF [6,20] as in no-VF rhythms [20].

In our study, both groups (TH and no-TH) were similar in relation with age, sex, characteristic of first witness, rate of bystander CPR, and time elapsed from the onset of OHCA till the first attempt of CPR. A

major limitation was the heterogeneous distribution of the initial ECG rhythm, with a higher rate of shockable rhythms in TH group ($p < 0.05$). However, after the multivariate analysis of the probability survival, the TH showed up as an independent predictive factor, both at hospital discharge as to one year after OHCA, with an OR between 2.0 and 3.8 (Table 1).

When the data of survival are compared with other published studies (Table 3), in case of shockable rhythms treated with TH, our results are similar to those obtained by Kim et al. (2014) (61.1 vs. 62.6%), but in case of non-shockable rhythms ours survival is higher (35.0 vs. 19.2%). In contrast, in the control group the survival observed by Kim et al. (2014) is higher in case of shockable rhythm or not (Table 3). We must emphasize that in that RCT, both groups received TH, the experimental at the pre hospital setting, and the controls after hospital admission [6]. When non-shockable rhythms are analyzed, our survival rates are similar to those found by Don et al. [20] both in TH (35.0 vs. 30.3%) as in controls (10.4 vs. 13.6%), but far away from the rates over 50% in TH, detected by Holzer et al. (2002) and Bro-Jeppesen et al. in small samples of patients [20] (Table 3).

| Design | N | Follow-up | % Survival (TH vs. no TH) | % CPC 1-21 (TH vs. no TH) |
|---------------|-------------------------|-----------|---|--------------------------------|
| RCT | VF2: 583 no-VF3: 776 | Discharge | VF: 62.6 vs. 64.2 no-VF: 19.2 vs. 16.3 | 57.5 vs. 61.8 14.4 vs. 13.4 |
| Retrospective | 534 (no-VF) | 30 days | 50.0 vs. 38.5 | 28.5 vs. 25.3 |
| Retrospective | 44 (no-VF) | Discharge | 53.8 vs. 23.8 | - |
| Retrospective | 28 (no-VF) | Discharge | 20.0 vs. 23.1 | 20.0 vs. 30.7 |
| Retrospective | 30 (no-VF) | 4 days | - | 26.6 vs. 33.3 |
| Retrospective | 313 | Discharge | 30.3 vs. 13.6 | 11.5 vs. 8.9 |
| Retrospective | VF: 97 no-VF: 94 | 1 year | VF: 61.1 vs. 39.6 no-VF: 35.0 vs. 10.4 | 58.3 vs. 25.9 33.3 vs. 9.1 |

Table 3: Main studies assessing the results of the mild therapeutic hypothermia initiated at the pre hospital setting

% CPC 1-21: % patients categorized as 1 or 2 in the Cerebral Performance Categories scale assessment. VF2: Shockable rhythm. no-VF3: No-shockable rhythm.

In the brain function assessment by means of CPC scale [5,11,14,19,20], we found a significantly better result in TH group compared with controls at hospital discharge ($p < 0.05$) as well as one year after OHCA ($p < 0.01$).

Our results are relevant and reveal the results in the real-life conditions of an EMS, including the follow-up to 1-year after OHCA, a period not covered by other studies [2,6,20].

A further limitation of our study is the retrospective design, that makes difficult the control of several and relevant factors involved, even more if we consider the results of the two RCT mentioned [2,6] so we must keep cautious about attributing our results only to the TH. Finally, the differences found in the brain function, could not be

related exclusively with the TH, due not only to the heterogeneous distribution of initial rhythm in both groups, but also by the limited sample size.

Conclusions

In our pre hospital setting, immediate TH after ROSC contributed to a significant improvement of the long-term survival to OHCA with good brain function, independently of the first ECG rhythm detected. The new guidelines should consider not only the results of RCT developed in controlled conditions, but also the results obtained after the implementation of protocols in real-life.

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