

Research Article

The effects of therapeutic hypothermia in patients in ROSC (Return of Spontaneous Circulation): Appropriate or ineffective treatment? A literature critical review

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Abstract

Background: the methods of resuscitation fight sudden cardiac arrest, also provide for the treatment of prehospital therapeutic hypothermia as one of the attempts to increase survival and decrease the debilitating neurological outcomes.

Aim: this literature review aims to assess whether this practice is effective or inappropriate.

Materials and methods: The literature search focused on the scientific work that has considered the use of pre-hospital therapeutic hypothermia in adults after sudden cardiac arrest non-traumatic were examined 12 electronic databases and 7 international journals, they were not imposed time limits and were considered all the research designs in English and Italian.

Assessing the significance of the internal and external validity, it was achieved through checklists specific than the study design.

Results: from literature, have found 400 articles, of which 371 are not relevant or not consulted or double publications including 29 scientific papers in the first assessment.

In the second assessment, they were included six studies: 4 randomized control trials, an observational research a systematic review and meta-analysis.

Limitations: in scientific papers considered, shows some unevenness such as diversity on how outcome evaluation, the neurological damage, the time to onset of hypothermia, body temperature on target and on methods to detect it.

Discussion: the work examined show no statistically significant differences between the group of patients who underwent hypothermia than untreated; However, in a study that considered cardiac arrest patients with non-shock able rhythms, some results emerge clinically relevant than the mitigation of neurological anoxic damage.

Background

Cardiac arrest is the highest clinic emergency that can show up in front of the EMT. The European incidence rate is tested around 41 per 100.000 person/years [1], while in North America reaches a value of 52 per 100.000 person/years [2].

The global out-of-hospital cardiac arrest survival rate remains between 9 and 11% [3].

At the hospital discharge, we can find a better survival rate, settled around 21%, in those cases supported by ventricular fibrillation or pulseless ventricular tachycardia [4].

The out-of-hospital treatment is structured around the quick detection of the cardiac arrest status, the sudden alert of the EMT, the early defibrillation, chest compressions, artificial ventilation and the performance of A-CPR.

In the last years, induced hypothermia for patient successfully resuscitated, with a resumption of sustained perfusing cardiac activity associated with significant respiratory effort after cardiac arrest, but still remaining in a coma status is a practice that has widely taken hold.

This group of patients, named “in return of spontaneous circulation” (ROSC), were the first subjects treated with controlled therapeutic hypothermia, assuming that this treatment could improve neurological outcome (reducing the post-anoxia-cerebral damage) and survival of patients after cardiac arrests.

The biological mechanism that leads the lowering of body temperature to generate neuro protective effects is not completely known, but the hypothesis is that decreasing the body temperature of a single grade (°C) will produce a slowing of 6% of cellular metabolism and of oxygen request [4,5].

The American Heart Association Guidelines of 2005 [6], 2010 [7]

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and the European Resuscitation Council (ERC) recommendations of 2015 [8] suggest the use of therapeutic hypothermia both in ROSC patients with arrhythmic pulse (evidence of 1st class, B level), and in patients with non-shockable rhythms (evidence of 2nd class, B level).

Moving from these premises, in 2010 the International Liaison Committee on Resuscitation Council [9] and European Resuscitation Council [5] proposed some recommendations that led EMT of many countries to implement the method suggested not only on the field and during the transportation of patients to hospital, but also after admission.

There are many different issues to be evaluated in this clinical-caring approach.

The first question refers to the target body temperature that has to be reached. There are three levels grouped in three categories: mild (between 33 and 35°C), moderate (between 28 and 32°C), severe (lower than 28°C) [4].

This process in turn articulates in three moments, which are induction, target temperature maintenance and patient re-heating [5].

Although experimentations have been effected on animals, the large number of the studies realized on human has referred to the light and moderate methods.

There are different methods to check body temperature, usually invasive techniques, and accordingly they are employed in hospital circle, while the measurements of body surface (axillary, groin and others) result inadequate [4-7].

Another aspect to be considered is about the timing of cooling patients to reach the target temperature.

In ROSC patients, the objective is to start the hypothermic treatment as soon as possible, to continue and maintain it in hospital in order to reach a range between 32 and 34°C within 12 hours and keep it up to 24 hours [3-5,7].

The speed of cooling should be 1.5°C per hour [5].

Attention must be kept to devices employed to induce a controlled lowering of body temperature. They are many and different, but usually the ones used out of hospital are quick infusion of isotonic hydroelectrolytic intravenous solutions at 4°C, or adhesive pads producing cooling effects, or frozen bars to position around the patient [3-5,7].

Goals

In the first guide lines of clinical practice, given the positive results of the first studies that were showing a decrease of death and debilitating neurological outcomes, was emphasized the chance to set the patients in controlled therapeutic hypothermia.

Successively, other studies questioned this method, considering it inefficient compared to the improvement of the outcomes.

The need of digging into this subject with a view to elaborate recommendations ad hoc is the ground for this literature critical review.

Materials and methods

Methodology used to formulate the research question refers to PICO model.

The problem studied refers to the efficiency of pre hospital therapeutic hypothermia.

The therapeutic treatment was focused around the pre hospital application of pads or cooling bars and/or infusion of isotonic hydro electrolytic intravenous solutions at 4°C in ROSC adult patients.

The comparison consisted of patients in ROSC but treated with therapeutic hypothermia only after their arrival in A&E unit, or never treated.

The outcome looked for concerned both survival rate and the reduction of neurological deficit from post-anoxia damage.

The research design of the studies included were: randomized and controlled studies, clinical trials, sytematic review and meta-analysis, guide lines, all the prospective observational and retrospective studies.

In the first evaluation, no limits were given to the publishing date of the articles, bibliography, otherwise, concentrated between October 2014 and October 2015.

Electronic database consulted are: PubMed, Cumulative Index to Nursing and Allied Healt Literature (CINAHL), TRIP database, Evidence, Clinical Evidence, Cochrane library, Joanna Briggs Institute Library, Registered Nurses Association of Ontario (RNAO), National Guideline Clearinghouse (NGC), New Zealand guidelines Group (NZGG), National Institute for Health and Care Excellence (NICE).

For the above-mentioned, search string was created with Medical Subjects Heading (Mesh) terms: “Prehospital” AND “Therapeutic” AND “Hypothermia”.

For Italian literature were consulted: L’Infermiere, Italian Journal Emergency Medicine (ITJEM), Emergency Care Journal (ECJ), Scenario, Professioni Infermieristiche, Assistenza Infermieristica e Ricerca (AIR), Sistema Nazionale Linee Guida (SNLG), Evidence.

For the aforesaid magazines (excepted ECJ), search string was: Ipotermia terapeutica preospedaliera.

For ECJ, keywords used were:” Prehospital Therapeutic Hypothermia”.

From this literature review, 400 articles of search have emerged of which 345 have been discarded because not pertinent, 24 because double publications and 2 were not accessible.

To a first evaluation, the articles considered valid have been 29 (Table 1).

For the collection of scientific works has been used the computer program “Microsoft Excel” 2007.

In second appeal, critical analysis has been used to notice potential bias, and it was realized through three different check lists.

For the systematic review has been used the Quality of Reporting of Meta-analyses (QUOROM) statement10 scheme.

Randomized Controlled Trials (RCT) was verified with Jadad scale method 11.

Observational studies as case-control and cohort studies have been

Table 1. PICO Methodology.

Problem	Is the pre-hospital therapeutic hypothermia in patients with ROSC effective?
Intervention	Patient treated with therapeutic hypothermia before their arrival in hospital
Comparison	Patient non-treated with therapeutic hypothermia before their arrival in hospital
Outcomes	Increase of survival rate and decrease of post-anoxia neurological negative outcome

checked with the list contained in the Newcastle-Ottawa scale 12.

The blind criteria of the studies hasn't been considered as it was ethically and deontological inapplicable to the examined subject.

Measures of statistic summary found in the reviewed and included studies for their comparison have been: association such as odds ratio (OR), relative risk (RR), hazard risk (HR), for those statistically significant, P value (significant at 0,05%), to check on the hypothesis chi-square test (χ^2), to measure comparative dispersion, standard deviation (DS) and the confidence interval (set at 95%) and eventually percentile values have been used.

Results

The research articles found were 400. After a first consideration regarding the relevance related to the research question end excluded double publications, only 29 scientific works proved validity.

After a second analysis using evaluation check lists to detect bias (Newcastle-Ottawa scale, Jadad score, QUORUM) 6 paperwork have been selected (Table 2).

Table 3 collects all the main results of six studies included in this review.

In the first RCT [13], 118 patients in ROSC after aritmic cardiac arrest and set in therapeutic hypothermia using infusion of saline at 4°C have been compared with 116 patients in the same conditions , but non-treated with therapeutic hypothermia.

At discharge, no statistically relevant differences have been noted regarding an improvement of the outcome.

In the second RCT 14, considering patients in ROSC with non-shockable rhythms of craniological cause, the 82 patients treated with pre-hospital hypothermia showed a better outcome at the discharged compared to the 81 non- treated.

A third RCT [15] conducted in Europe and Australia that enlisted 950 patients divided in two groups of which the first one (counting

476 people) was put under hypothermic therapy, and the other one (counting 474 people) was used as control group, no differences were noted neither regarding survival rate, nor about neurological outcomes.

The fourth work, conducted in USA [16], enlisted 1359 patients with heart failure and resuscitated by paramedics, 688 of which set in hypothermia with hydro electrolytic infusion at 4 °C. Compared with the control group no differences were noted neither regarding survival rate nor about post anoxia neurological outcomes.

The fifth study [17] is about a cohort-retrospective monocentric study comparing 56 patients in ROSC treated with cooling pads to induct pre hospital controlled hypothermia, with 54 patients treated just the same but in hospital; authors can't highlight any difference in the neurological outcome between the two groups.

The last scientific work considered is a systematic review with meta-analysis [18] that, comparing the six trials in which 715 patients were studied, showed no statistically significant differences between the pre hospitals hypothermically treated group and the control group.

Discussion

This literature review was done with the aim of verifying the possibility of a better survival rate and a mitigation of neurological anoxic damage with the use of pre hospital controlled hypothermia by EMT in adult patients in ROSC.

Bibliography research that uphold this review included 6 trials of which 4 RCT, a cohort-retrospective study and a systematic review with meta-analysis.

Totally, 3134 patients have been checked of which 1562 enlisted in the treated group and 1572 in the control group.

Therapeutic hypothermia was inducted trough hydro electrolytic infusion at 4°C , in three studies have been used not invasive devices too , and in the systematic review was included a trial in which hypothermia was inducted through nasal administration of cooling substances.

Target temperature was set at 33.9°C (DS \pm 0.77).

For all the studies, the outcomes considered were the presence of post anoxic neurological results after hypothermic treatment and five studies saw the survival rate too.

In some cases, a further analysis was made regarding prognosis related to cardiac rhythm (arrhythmic or other).

In all the works, no significant differences have been noted between the treated group and the control group related to neurological outcomes, and for the authors that have checked them even in the survival rates no differences emerged.

Only in a single work patients with cardiac arrest presenting a non-shockable rhythms (flatlined or electromechanical dissociation – EDM) of cardiological cause and treated with pre-hospital controlled hypothermia with low temperature fluids infusion, would show a better neurological outcome, but the difference between the experimental group and the control group doesn't show any statistically significant difference (P=0.146).

Limits

The considered researches show some uneven aspects such as differences of methodology in the evaluation of the outcome, of neurological damage, of the hypothermia timing of induction, of the

Table 2. Scientific works found.

Database	Found	Not Applicable	Double	Not Accessible	Considered
PUBMED	217	198			19
TRIP	114	92	16	1	5
NICE	57	48	6	1	2
CINAHL	3	1	1		1
COCHRANE	1				1
EVIDENCE	0				
CLINICAL EVIDENCE	0				
JOANNA BRIGGS	1	1			0
CLERINGHOUSE	1	1			
RNAO	0				
NEW ZEALAND	2	2			0
SLNG	0				
SCENARIO	4	2	1		1
L'INFIRMIERE	0				
ITJEM	0				
ECJ	0				
PROF INF	0				
AIR	0				
EVIDENCE	0				
	400	345	24	2	29

Table 3. Scientific works included in this revision.

	Study design	Patients population	N°of patient treated with pre-hospital hypothermia	N°of patient non treated with pre-hospital hypothermia	Methods to induce therapeutic hypothermia	Target Temperature	Outcome differences between two groups
Bernard <i>et al.</i> 2010 [13]	RCT	Patients in ROSC with arrhythmic CCA	118	116	Fluids infusion at 4°C	34,4–35,2	No
Bernard <i>et al.</i> 2012 [14]	RCT	Patients in ROSC with non arrhythmic CCA	82	81	Fluids infusion at 4°C	34,4–35,7	Better outcome at discharge and in the treated group with cardiac arrest from cardiac causes
Nielsen <i>et al.</i> 2013 [15]	RCT	Patients in ROSC with arrhythmic CCA	476	474	Fluids infusion at 4°C and body surface devices	33	No
Kim <i>et al.</i> 2014 [16]	RCT	Patients in ROSC (all types of CCA)	671	688	Fluids infusion at 4°C	34	No
Uray <i>et al.</i> 2014 [17]	Coorte retrospective	Patients in ROSC (all types of CCA)	56	54	Body surface devices	33,9	No
Hunter <i>et al.</i> 2014 [18]	Systematic review and meta-analysis	Adult patients in ROSC from non-traumatic CCA	358	357	Fluids infusion at 4°C and body surface, intranasal and inhaling devices.	32-34	No

target body temperature and methods to check it.

The above-mentioned restrictions lead us to hope for other scientific research to be more stringent to erase the doubts about the effectiveness and appropriateness of hypothermic treatment in patients in ROSC.

Conclusions

During the last years, some studies have been realized with different research design regarding pre-hospital therapeutic hypothermia in patients presenting sudden cardiac arrest.

Despite the above-mentioned limitations of the works reviewed, no differences rise concerning the survival rate and neurological post anoxic damage between patients treated with hypothermia and non-treated patients.

One single research showed a significant improvement of neurological outcome in patients with non-aritmic cardiac arrest.

Results obtained from this literature review cast considerable doubt on the wisdom of real effectiveness of the considered treatment.

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Conflict of interest

Authors state the absence of any conflict of interest.

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