Effects of Therapeutic Hypothermia in Critically Ill Patients, Post Cardiopulmonary Arrest

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Authors’ contributions

This work was carried out in collaboration between both authors. Author AIA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AIA and CF managed the analyses of the study. Author AIA managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Cardiac arrest (CA), which occurs outside hospital conditions, is one of the leading causes of death in developed countries and remains responsible for high mortality and morbidity even after successful resuscitation. Hypothermia Therapy (TH) is one of the available therapeutic options aimed at minimizing one of the mechanisms responsible for Post Cardio Respiration Syndrome (PCRS), brain injury arrest after a cardiopulmonary arrest.

Objective: The aim of this study is to clarify the significance of TH after cardiac arrest, in critically ill patients.

Material and Methods: A bibliographic review of the literature, mobilizing the descriptors "Therapeutic hypothermia", "Post cardiopulmonary arrest" and "Critically ill patients". Ten conceivable databases were selected, between 2014-2020, and seven studies were included for analysis.

Results and Discussion: It was found that there are some controversial results. Studies comparing the effects of TH with normothermia have shown similar results regarding neurological recovery, although TH may reduce oxidative damage in some studies. Three of the studies show...
some beneficial effects, but one shows that these effects will only be beneficial in younger years, in the shortest possible time to ROSC and at the rhythm of CA in ventricular fibrillation. One of the studies showed no beneficial effects on the use of TH.

**Conclusion:** It can be concluded that although part of the clinical practice has existed for more than a decade and recommendations for use in all patients after ROSC exist, there is considerable controversy and questions about various aspects of implementation. There are still some questions to answer. However, some studies also show good effects of TH (32°-34°) and normothermia (36°).

**Keywords:** Therapeutic hypothermia; postcardiopulmonary arrest; critically ill patients.

1. INTRODUCTION

The critical patient is composed of an inconsistent sample not uniform of people who require complex care and constant monitoring due to different aggressions, which usually requires a hospital stay at an Intensive Care Unit (ICU). Cardiac arrest (CA) is associated with very high mortality and causes neurological dysfunction in survivors [1]. CA is a devastating condition and associated with a mortality rate of more than 90% [2]. Even after successful return of spontaneous circulation (ROSC) about 80% of patients remain comatose and the majority of deaths after ROSC are due to neurological injuries [3]. Suffering a CA can be a life-changing experience with significant impact on daily life. Many of those who survive have a wide range of later neurological impairments [4]. It has been shown that even a brief CA lasting only a few minutes can permanently change the affected individual, including reduced cognitive function in relation to emotions and memories [5]. In 1803 a Russian resuscitation model was described in which patients were covered with snow and waited for ROSC. Almost twelve years later, in the campaign of Napoleon Bonaparte about Russia, Baron Larrey used hypothermia to preserve injured limbs and as an anaesthetic during amputations. More than a century later, in 1937, Dr. Temple Fay cooled a patient to 32°C for 24 hours to slow the growth of neoplastic cells, and in 1940 Smith and Fay studied the physiological effects of hypothermia on cancer patients.

TH is recommended for patients who remain in a coma after successful resuscitation. TH for patients who remain in coma after resuscitation from CA improves both survival and neurological outcomes [6,7] (Swedish Council of Cardiopulmonary Resuscitation-CPR, [8]).

A decrease in brain metabolism from TH could be one of the most important mechanisms of neuroprotection [9,10,1]. Since 2003, International Liaison Committee on Resuscitation (ILCOR) TH recommends treatment for all with CA who restore their spontaneous circulation [11]. It is a part of the follow-up treatment according to CA according to the current protocol for advanced cardiac life support of American Heart Association/American College of Cardiology [12]. A Cochrane review published in 2012 also reported the benefits of TH. There is disagreement about what the target temperature should be, when TH should be initiated, which CA victims should receive treatment, and so on. Since the pathophysiology for neurological injuries is similar according to CA regardless of the rhythm or location of the cardiac arrest, the decision to initiate TH should be made on an individual patient basis, taking into account the aetiology of the cardiac arrest, the time prior to initiation of CPR, the duration of CPR prior to ROSC, and the overall prognosis based on the underlying comorbidities [8,13,14].

Targeted Temperature Management (TTM) with a target of 32°C to 36°C (moderate therapeutic hypothermia) is currently equally advocated for all patients with coma following successful resuscitation after cardiac arrest. However, study results published in 2013 did not show conclusive effects of this treatment in the 19% of patients who had cardiac arrest with a non-shockable rhythm (asystole or pulseless electrical activity), and the use of hypothermia in this situation subsequently decreased [15,16].

2. MATERIALS AND METHODS

A bibliographic review of the literature is one of the research methods used in the practice of evidence-based research, and its purpose is to collect and summarize research findings on a particular topic [17,18].

In the period between May and July 2020, a protocol has been developed to identify studies of interest for this work, consisting of a search in the search engines: Ebsco and B-ONline, and in

A search strategy using the following descriptors was used to identify relevant studies: Therapeutic hypothermia AND Post cardiopulmonary cardiac arrest AND Critically ill patients.

3. RESULTS

Seven articles have been selected for the study, which follow in Table 1.

Table 1. Description of selected studies and main results of the investigations

<table>
<thead>
<tr>
<th>Study</th>
<th>Author(s)/ Year</th>
<th>Main Results</th>
</tr>
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<tbody>
<tr>
<td>E1: &quot;Therapeutic Hypothermia in Critically Ill Patients: A Systematic Review and Meta-Analysis of High Quality Randomized Trials&quot;</td>
<td>Jun Hyun Kim, Adám Nagy, Alessandro Bellettii, Giuseppe Biondi-Zoccai, Valery V Likhvantsev, Giovanni Landoni; 2020 [19]</td>
<td>Study shows that TH (32-35°C) is associated with higher mortality in critically ill patients and no difference in good neurological outcome compared to normothermia. It could be concluded that although there is still the possibility that TH is beneficial in a given setting, it is better to avoid routine use of TH outside the settings specified in the international guidelines.</td>
</tr>
<tr>
<td>E2: &quot;Therapeutic Hypothermia Reduces Oxidative Damage and Alters Antioxidant Defenses after Cardiac Arrest&quot;</td>
<td>Fernanda Hackenhaar, Tássia Medeiros, Fernanda Heemann, Camile Behling, Jordana Putti, Camila Mahl, Cleber Verona, Ana Silva, Maria Guerra, Carlos Gonçalves, Vanessa Oliveira, Diego Riveiro, Silvia Vieira, Mara S. Benfato; 2017 [20]</td>
<td>It was possible to verify that mild TH was used for harm reduction, and it could also reduce oxidative damage, in post-CA. Study aimed to compare oxidative damage and antioxidant defense in patients treated with controlled normothermia with mild TH during Post cardiac arrest. Study consisted of 31 patients treated with controlled normothermia (36°C) and 11 patients treated with 24h mild TH (33°C), victims of in- or out-of-hospital CA. It was concluded that hypothermic and normothermic patients have similar biomarkers for brain injury, but hypothermia reduces malondialdehyde and protein carbonyl levels, markers of oxidative damage. Study suggests that a mild TH reduces oxidative damage and alters antioxidant defenses in patients following CA.</td>
</tr>
<tr>
<td>E3: &quot;Therapeutic Hypothermia After Cardiac Arrest&quot;</td>
<td>Wulfran Bougouin, Florence Dumas, Alain Cariou; 2017 [21]</td>
<td>-It was possible to compete on two levels of targeted temperature management (33°C or 36°C) and found no difference in survival or neurological function. Even in the 36°C group, natural temperature development was not allowed, but the temperature was actively controlled to prevent fever. -Although the authors of the results recall that recent guidelines advocate a strategy of targeted temperature management (maintaining a temperature between 32°C and 36°C) for comatose patients with return of spontaneous circulation after cardiac arrest.</td>
</tr>
<tr>
<td>E4: &quot;Predictors of death among cardiac arrest patients after therapeutic hypothermia: A non-</td>
<td>Catarina Ruivo, Célia Jesus, João Morais, Paula Viana; 2016 [22]</td>
<td>-Patients who survived, had a lower mean age, a shorter PC-ROSC time and a predominant initial rhythm of ventricular fibrillation -It was found that the effectiveness of TH was apparently related to a younger age, a defibrillating</td>
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</table>
Study | Author(s)/ Year | Main Results
--- | --- | ---
E5: “Cooling the body after resuscitation following cardiac arrest” | Arrich J, Holzer M, Havel C, Müllner M, Herkner H; 2016 [23] | Study showed that when we compared people whose body was cooled to 32°C to 34°C after resuscitation with people whose body was not cooled at all, we found that 63% of people who were cooled would suffer no or only minor brain damage, while only 33% of people who were not cooled would suffer no or only minor brain damage. -In addition, the effect of refrigeration had an important effect on easy survival, with or without brain damage: 57% would survive if their body was refrigerated, compared to 42% if their body was not refrigerated at all. -It was found that there were no serious side effects, but cooling the body was associated with an increased risk of pneumonia and an increased risk of low blood potassium levels.

E6: “Therapeutic hypothermia after cardiac arrest: outcome predictors” | Rodrigo Leão, Paulo Ávila, Raquel Cavaco, Nuno Germano, Luís Bento; 2015 | Research shows that sixty-seven patients were enrolled in the study, 12 of whom had good neurological results. -Ventricular fibrillation and electroencephalographic theta activity were associated with increased survival and improved neurological outcomes. -Study showed that although there is a belief that reaching the target temperature early improves neurological prognosis, in this study, earlier reaching the target temperature was associated with increased mortality and poorer neurological outcomes.

E7: “Therapeutic hypothermia after cardiac arrest” | Abdullah Alshimemeri, 2014 [24] | This study shows that prognosis following out-of-hospital cardiac arrest is generally poor, which is may due to the severity of neuronal damage. -Finds that the use of TH has gradually occupied an important role in managing neuronal injuries in some cases of cardiac arrests. Some clinical trials conducted in comatose post-resuscitation cardiac arrest patients within the last decade have shown induced hypothermia to be effective in facilitating neuronal function recovery. -The study reveals that some evidence has emerged from clinical trials that demonstrates the efficacy of induced hypothermia in restoring neuronal function and reducing mortality associated with cardiac arrest. -To optimize treatment outcomes, however, patient recruitment should be carefully conducted to minimize risks of hypothermia-associated complications.

4. DISCUSSION

More than 50 years ago, Peter Safar, in describing what we now know as the ABCs of cardiopulmonary resuscitation, included the induction of hypothermia in patients who showed no signs of neurological recovery within 30 minutes [25]. Improving outcomes for patients who are resuscitated after cardiac arrest but remain in coma has been challenging. This fact runs through all studies. The protective effects of hypothermia were first studied and described in...
the late 1950s and then seem to have been forgotten for about 20 years before intensive care physicians revived interest in this therapy. Accordingly, the use of mild to moderate hypothermia for critically ill patients, especially for brain injured patients, has gained interest to limit the extension of initial brain lesions [26]. This can be achieved by various methods and targeted temperatures. Moderate TH is currently recommended to improve neurological outcomes in adults with persistent coma following resuscitated cardiac arrest outside the hospital. However, the efficacy of moderate TH in patients with non-shockable rhythms (asystolic or pulseless electrical activity) is under discussion [27,16]. These facts are consistent with studies E4 and E6. CA survivors suffer from a global ischemia reperfusion injury [28] which can lead to poor neurological outcome and death. This syndrome triggers a cascade of harmful inflammatory reactions in the body that can last for several days. Treatment aimed at minimizing the inflammatory response and cell death in the reperfusion period can improve the outcome after cardiac arrest. Results in all studies.

One of the few proven inpatient treatment strategies is the induction of therapeutic hypothermia (TH). Defined as a reduction of body temperature to 32°C to 34°C [28]. The main protective effect of TH is to reduce global cerebral damage through multifactorial pathways, body and brain metabolism in general, apoptosis, influx of Ca2+ into the cell, intra- and extracellular acidosis, accumulation of the exotoxic neurotransmitter glutamate, release of glycine, inflammation, nitric oxide production and free radical production; as in studies E2, E5 and E7.

The term "targeted temperature management" (TTM) has emerged as the most appropriate term for interventions used to achieve and maintain a certain temperature level for each individual [29,30]. Facts confirmed by the E1, E2 and E3 studies Studies E1, E2, E3, E4 and E6 show that the level of target temperature can vary depending on the situation. TTM can be used to prevent fever (E3), maintain normothermia or lower the core temperature. TTM is widely used in intensive care units (ICUs) as a primary neuroprotective method to protect against neuronal injury or degeneration in the central nervous system. However, its indications are associated with varying degrees of evidence based on inhomogeneous or even contradictory literature. Our aim was to conduct a systematic analysis of the literature in order to edit national guidelines [31,32,29].

In a study by Lascarror et al. [16], two retrospective case studies indicated beneficial effects of hypothermia on both neurological outcomes and survival of these patients (E4, E5 and E7), two studies showed no effect (E1, E2 and E3) and two indicated harm (E6). This uncertainty needs to be clarified as non-shockable rhythms are now prevalent in patients with cardiac arrest and are associated with a poor prognosis, with only 2 to 15% of patients having good neurological outcomes compared to almost 65% of patients having cardiac arrest with shockable rhythms.

Neumar et al. [28] point out that increased use of TH as part of a standardized, targeted treatment protocol for post-ROSC care improves survival rates after outpatient cardiac arrest. Regardless of the cooling method chosen, TH is easily feasible and without serious side effects or complications associated with mortality. The E6 study is against this because it shows that earlier target temperature achievement led to increased mortality and poorer neurological outcomes. There are not only positive effects on the brain, but several studies also point to a possible benefit of TH for the heart. Although TH has been shown to be beneficial only for patients with initial ventricular fibrillation, most centers also use it for comatose survivors with other initial rhythms when active treatment is decided upon, as in the E4 study. There is still some controversy; the optimal target temperature, timing and duration of cooling have not yet been defined [33], as shown in studies E1, E2, E3, E4 and E7.

TH as a very important question, which has become even more difficult after the introduction of TH, is when and how comatose patients can be predicted [33,34]. Too early a prognosis may lead to too early discontinuation of treatment in patients with a potential for successful survival. Thus, in the first 2 days after cardiac arrest, there are no clinical predictors for a poor outcome [33,28]. Once treatment is initiated with TH, the focus must be on optimizing the standardized post-ROSC treatment as recommended and following the predefined plan. If patients do not wake up immediately, we must bear in mind that this may take time, especially if sedatives and opiates have been used for many days. Although the scientific evidence is limited, the recommended time to initiate an active prognosis...
in still comatose patients after discontinuation of sedation seems to be 72 hours after reaching normothermia [33]. Somatosensory evoked potential, measurement of neuron-specific enolase (in blood), electroencephalography and neurological clinical examination are the prognostic tools with the best scientific evidence [33,28].

The E5 and E7 studies indicate that TH is a simple technique that can be performed in an intensive care unit, is cheap and the only one capable of altering the neurological prognosis of patients with cardiac arrest, so there is no reason not to use it on a large scale, as Pinto [30] points out in his advertisement. On the other hand, Polderman [35] mentions that TH suppresses the inflammatory response and thus increases the risk of infection. Ensure proper hand hygiene and careful care to prevent hospital-acquired infections such as catheter-associated bloodstream infections, ventilator-acquired pneumonia (VAP) and catheter-associated urinary tract infections. Patients with hypothermia are susceptible to aspiration and VAP because hypothermia impairs the function of the respiratory genitals and reduces gastric motility. This situation is in order for the E5 study.

In a study conducted by Busch and Soreide [36], a lower age and shorter time to ROSC as well as the time span according to the implementation guidelines were associated with good results. The results are consistent with study E4, as the best results were directly related to younger age and shorter time to ROSC between CA and ROSC.

With regard to the results of the analyzed studies, it can be concluded that this study of TTM induction is a new and novel approach that improves neurological outcomes in unconscious adult patients with cardiac arrest; however, studies on the complications of hypothermia or on different induction methods are limited and further studies are needed.

5. CONCLUSION

The use of TTM in the currently recommended form improves the results in comatose cardiac arrest survivors compared to a lack of temperature control. To date, we have not established the time of onset, specific temperature targets, or duration of TTM that have a definitive effect. Nurses play a crucial role in the prevention, detection and treatment of adverse effects and complications of therapeutic hypothermia. Nearly all adverse effects can be prevented or treated in an intensive care setting.

The care of patients receiving therapeutic hypothermia can be very complex and require intensive nursing supervision. Many require multiple vasopressors, antiarrhythmics, insulin therapy and electrolyte replacement. Other concurrent supportive treatments may include an intra-aortic balloon pump, continuous renal replacement therapy, and prone positioning of the patient.

Increased use of TH as part of a standardized, targeted treatment protocol for resuscitation aftercare improves survival rates after ambulatory cardiac arrest. Although TH has been shown to be beneficial only for patients with initial ventricular fibrillation, it is also used in the majority of centers for comatose survivors with other initial rhythms when active treatment is decided. A combination of TH, coronary angiography and PCI is associated with the best results. We definitely need more studies on this difficult but important aspect of follow-up treatment at CA.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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