REVIEW ARTICLE

Targeted Temperature Management; Review of Literature and Guidelines; A Cardiologist's Perspective

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ARTICLE HISTORY

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Abstract: ***Background***: Out of Hospital Cardiac Arrest (OHCA) remains not an uncommon occurrence in USA and the rest of the world. However, the survival to discharge following an episode of OHCA in adults is still very disappointing at around 10%. Several areas of improvement including education of general public in early Cardio Pulmonary Resuscitation (CPR) by bystander, chest compression first, and improvement of Emergency Medical response time have had a positive effect on the outcomes and survival but still much needs to be done. Recently, new data has emerged with regards to post resuscitation care and mild induced hypothermia (now preferably called; Targeted Temperature Management {TTM}) and several advances have been made.

Conclusion: The purpose of this review is to summarize and compare the most recent guidelines and also provide a practical approach to TTM especially with regards to the field of cardiology.

Keywords: Out of hospital cardiac arrest, cardio pulmonary resuscitation, emergency medical response, targeted temperature management, post resuscitation care.

1. INTRODUCTION

Out of Hospital Cardiac Arrest (OHCA) is a not an uncommon occurrence in the general United States population with an estimated annual incidence of 7307 events per year in pediatric population and 110.8 events per 100,000 adult population [1]. Which roughly translates into 374,000 episodes of OHCA in the US adult population [1]. Despite improvement in delivery of health care, the survival to hospital discharge post OHCA remains abysmal at 10.5% in adults >18 years, 23.5% for children 13 to 18 years, 16.6% for children >1 to 12 years, and 6.2% for infants [1]. However, there has been a concerted effort by several organizations and also at at community level to improve the efficiency and response time by Emergency Medical Services. In addition, there have been recent trials which have specifically focused on post resuscitative care including targeted temperature management and new data have emerged. The International Liaison Committee on Resuscitation (ILCOR) issued an advisory statement on temperature management in 2015 and this was followed by American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [2, 3]. This review summarizes and compares these recommendations along with the European guidelines and also provides a practical overview of the process of targeted temperature management especially with regards to the cardiologists. In this review, the term Targeted Temperature Management (TTM) will be used to refer to mild induced therapeutic hypothermia as suggested by the most recent guidelines.

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2. CURRENT GUIDELINES

The 2015 ILCOR Advisory statement gave specific recommendations about the following 3 questions: should induced mild hypothermia be used in post cardiac arrest syndrome, when should it be instituted and for how long?

With regards to the first question whether TTM be used in the following 3 scenarios were described [2].

For patients with OHCA and initial shockable rhythm (*i.e.* Ventricular fibrillation or pulseless ventricular tachycardia), when compared to no TTM, the pooled Relative risk (RR) reduction was 0.75 (95% Confidence Interval {CI} 0.61-0.92) and 0.73 (95% CI, 0.60-0.88) for mortality and for poor neurological or functional outcome at 6 months or at hospital discharge respectively [4, 5].

While for OHCA survivors with initial non-shockable rhythm, the adjusted pooled Odds Ratio (OR) was, 0.90; (95% CI, 0.45-1.82) [6-8].

On the other hand, for in hospital cardiac arrest (IHCA), the evidence to support use of TTM was less impressive with an adjusted OR for mortality of 1.11; (95% CI, 0.81-1.54) and for poor neurological outcome of (adjusted OR, 1.08; 95% CI, 0.76-1.5) [9].

Based on the above review of evidence they gave a strong recommendation for OHCA and shockable rhythm, a

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weak recommendation for OHCA and non-shockable rhythm and weak recommendation for IHCA of any rhythm.

They however broadened the range for TTM from 32-34 degree Celsius to 32-36 degree Celsius in keeping with a large randomized controlled trial comparing 33 *vs* 36 degree temperature targets which found no difference between the two temperature groups [10].

The 2015 American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, however, gave a Class I, Level of evidence (LOE) B-R (randomized) for shockable rhythm OHCA; a Class I, LOE C-Expert Opinion (EO) for non-shockable and in-hospital cardiac arrests [3]. They agreed with ILCOR Advisory statement and also broadened the temperature range to 32°C to 36°C during TTM (Class I, LOE B-R).

While the European guidelines simply endorsed the ILCOR Advisory statement [11].

With regards to the 2nd question of how soon after cardiac arrest TTM be initiated the following recommendations were made:

Based on the review of randomized control trials pre-hospital cooling with rapid infusion of normal saline compared to no cooling was not associated with improved neurologic outcomes outcome (RR, 1.00; 95% CI, 0.95–1.06) [2]. Nor was there a mortality benefit (RR, 0.98; 95% CI, 0.92–1.04). However, the rearrests and occurrence of pulmonary edema were found to be significantly increased in the pre-hospital cooling arm (RR, 1.22; 95% CI, 1.01–1.46), and (RR, 1.34; 95% CI, 1.15-1.57) respectively [2, 12]. Based on these data, all three guidelines recommended against the routine use of pre-hospital cooling with rapid infusion of intravenous fluids. However, the effects of cooling in pre-hospital setting using methods other than rapid infusion of intravenous fluids are yet to be investigated.

2.1. Definition of Comatose

OHCA patients after Return of Spontaneous Circulation (ROSC) who remain comatose *i.e.* who are unable to fully follow all verbal commands, should be considered for TTM [13]. However, one usually encountered clinical dilemma is, that patient may not be appropriately following verbal commands within few minutes of ROSC, but after a certain interval, most patients do show some improvement in neurologic status even prior to institution of TTM. The question then becomes whether to institute TTM or not. The Guidelines however, don’t specifically address this question but the 2 most important trials excluded patients if they could follow verbal commands, thus, common sense would dictate that the patient’s most recent neurologic status rather than immediate post ROSC neurologic status should dictate whether TTM should be instituted or not [4, 5].

2.2. Contraindications to TTM

Although there are very few true contraindications to TTM, they include intracranial bleeding, severe sepsis, excessive bleeding to refractory hypotension and pregnancy [13].

2.3. Duration of Hypothermia

The ILCOR Advisory statement recommended TTM for at least 24 hours post arrest as was the trial design of the two largest trials [5, 10].

2.3.1. Temperature Management Post Rewarming

For Patients who are managed with TTM post arrest fever will usually not occur until after 48-72 hours [3]. However, post rewarming, fever can be observed in 41-52% of patients [14, 15] and there is observational data that suggests that fever post arrest can be associated with poor outcomes [16, 17]. Hence, the AHA guidelines gave a Class IIB, LOE C-LD (limited data) for actively preventing fever in post rewarming period in the unconscious patients and the most practical method may be to leave the equipment used for TTM in place longer than the duration of TTM [3].

2.3.2. Technique of TTM

The process of TTM can broadly be divided into three distinct phases: induction, maintenance and rewarming [18].

2.3.3. Induction

In this phase the goal is to drop the mean core temperature to the target temperature using various external or internal cooling methods.

2.3.4. Choosing the Target Temperature

Previously AHA Guidelines and European Resuscitation Council (ERC) guidelines had suggested a target temperature of 32◦ to 34◦ C [19]. However, a large randomized controlled trial showed no difference in outcomes when using 33◦C versus 36◦C targets [9]. Therefore, the ILCOR advisory committee, AHA and ERC have accordingly broadened the range for TTM to 32◦ to 36◦ C. However, choosing the target temperature should include clinical information like presence of high risk for bleeding, like a post Percutaneous Coronary Intervention (PCI) patient, who could be cooled to a higher target temperature to minimize risk of bleeding. On the other hand, patients with evidence of seizures or cerebral edema etc. could be cooled to a lower temperature.

2.4. How to Cool

Different methods have used and shown to be effective. The most commonly used ones with their pros and cons are enumerated below:

1. Cooling by ice packs or wet towels: cheap and effective in decreasing the core temperature but maintenance of hypothermia is difficult and requires excessive diligence on part of the nursing staff [20-23]. Also rewarming is unreliable.
2. External air or water circulating cooling pads or blankets: easy to apply reliable temperature control [24].
3. External water circulating cooling pads with gel coating [25, 26].
4. Intravascular cooling by way of a large bore central venous access which circulates cool saline through different sized balloons in the venous circulation which removes heat from blood by conduction and brings down the core temperature [27-30].

5. Evaporative trans nasal cooling : this can be started before the return of ROSC [8-10].
6. Extra Corporeal Membrane Oxygenation (ECMO): rarely used for just this purpose but if patient is maintained on ECMO for clinically required hemodynamic support then it can also be used to monitor and regulate core temperature [31, 32].

Of the above mentioned methods cooling by gel coated pads with circulating water and invasive methods like cooling with intravascular cooling catheters are more commonly employed and will be described below in detail.

Cooling by gel coated water circulating adhesive pads as depicted in the Fig. (**1**), offers special advantages. Studies have shown that it is as effective as conventional methods in reducing the core temperature [33]. One randomized controlled study actually showed that the number of patients who reached core temperatures below 34 degrees was higher for Artic Sun® than conventional cooling methods although not statistically significant [25]. It also reliably maintains the core temperature and also provides more reliably rewarming [18]. The cons include additional cost associated with system. The prototype for this in US is Artic Sun®5000 (Brad medical, Denver, Colorado, USA) and ZOLL'S STx™ (Asahi Kasei/Zoll medical corporation, San Jose, California, USA) Surface Pad System. Another potential concern for these external cooling pads is a patient with skin injury or burns or very obese patients.

Fig. (1). Artic Sun gel coated water circulating cooling pads with the typical conformation of pads.

Cooling by invasive catheters requires placement of a large bore central venous line either in internal jugular, subclavian or femoral position. The most common brands include Coolgard ™ 3000/Alsius Icy heat Exchange catheter Thermal Regulating system (Alsius Corporation, Irvine, California, USA) and ZOLL Thermogard XP® Temperature Management System (Asahi Kasei/Zoll medical corporation, San Jose, California, USA). The catheters contain balloons through which cool saline goes in and cools the venous blood and the warm saline is removed. It is however a closed system so that the coolant does not enter the venous circulation of the patient. Most catheters in the market in addition to inlet and out let ports for the cooling fluid also have ports which can be used for central venous access Fig. (**2**). Cons include placing a large bore central venous catheter as well as small risk of catheter associated infection and thrombosis which is seen with any central venous catheter [18].

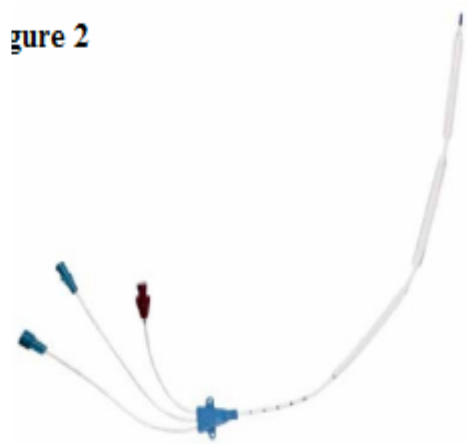

Fig. (2). Coolgard ™ 3000/Alsius Icy heat Exchange catheter Thermal regulating system with the inlet and out ports along with a third port for intravenous infusion.

2.4.1. Maintenance Phase

During this phase the target core temperature is maintained for least 24 hours.

2.4.2. Rewarming Phase

During this phase the core temperature is gradually raised roughly 0.25-0.5◦C/hour [34]. There can be significant electrolyte derangements and fluid shifts during the maintenance and rewarming phases. It has been shown that rebound hyperthermia in the post TTM phase is associated with poor outcomes [16, 17]. Therefore, it may be prudent to leave the equipment used for TTM in place a bit longer to potentially prevent this phenomenon. In addition use of prophylactic methods like scheduled acetaminophen or other anti-pyretics can be instituted but, such interventions have not be studied in randomized trials. The AHA 2015 guidelines give a Class IIb, (LOE C-LD; Limited data) recommendation for actively preventing fever in post TTM patients [3].

2.5. The Post Resuscitation Syndrome

It describes a condition following global body ischemia/reperfusion and it resembles systemic inflammatory syndrome in several ways including release of inflammatory mediators, cytokines and endothelial dysfunction [35-38]. There are several metabolic and electrolyte derangements which are quite frequently observed and which can get exaggerated with TTM like elevated lactic acid, hypokalemia, hypocalcemia and hypomagnesemia [10, 18, 39]. In addition there are also coagulation abnormalities which become more exaggerated with the institution of TTM and may increase susceptibility to bleeding [40, 41]. This becomes especially relevant in the setting of recent coronary intervention. So for a cardiologist taking care of patients with OHCA, it is quite essential to be familiar with these derangements as it may require adjustments of the medicine dosages like heparin infusion *etc*. Also the key branching point with regards to management of OHCA is the post Return of Spontaneous Circulation (ROSC) Electrocardiogram (ECG). If the ECG shows ST segment elevation or new Left Bundle Branch Block (LBBB) then there is at least observational data that immediate coronary angiogram and possibly primary Percutaneous Coronary Angioplasty (PTCA) could result in improved survival [42-44]. The guidelines agree on immediate coronary angiography in this particular situation. The AHA guidelines give a (Class I, LOE B-NR) recommendation while the European guidelines give a strong recommendation with limited low quality data [11]. On the other hand, if the post ROSC ECG does not show clear STEMI or LBBB or then proceeding with coronary angiography is advocated by some but randomized data is lacking. The PEARL Study which is actively recruiting patients to answer this specific question: whether immediate coronary angiography and if feasible PCI improves outcomes in non-STEMI OHCA patients when compared to no angiography [45].

CONCLUSION

In summary the OHCA is a not an uncommon occurrence and in some instances the precipitating factor or at least a contributing factor may be myocardial ischemia/ infarction in addition to several other non-cardiac causes. The ILCOR statement and American and ESC guidelines are consistent with regards to institution of TTM. However, they differ in the strength of recommendation. In any case, there seems to be a growing body of data which supports TTM in all cases of OHCA patients but the minimum target temperature to be achieved has now been changed to 36◦ in view of recent data.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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