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TARGETED TEMPERATURE MANAGEMENT FOR CARDIAC ARREST

Evidence Based Medicine Guideline

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SUMMARY
Therapeutic hypothermia or targeted temperature management (TTM) following cardiac arrest has been shown to attenuate neurologic damage and improve survival. Recent evidence has shown similar outcomes between cooling the patient to 32-34°C for 24 hours and maintaining normothermia. No significant benefit has been found for the use of therapeutic hypothermia to 32-34°C. The optimal target temperature following cardiac arrest remains unknown.

RECOMMENDATIONS

- **Level 1**
  - **Targeted temperature management (TTM) of 32-36°C for at least 24 hours should be implemented in comatose patients with out-of-hospital cardiac arrest (OHCA) with initial shockable rhythm.**
- **Level 2**
  - **TTM of 32-36°C for at least 24 hours should be implemented in comatose patients with OHCA with initial non-shockable rhythm**.
  - **Avoid prehospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after return of spontaneous circulation (ROSC).**
- **Level 3**
  - **TTM of 32-36°C for at least 24 hours should be implemented in comatose patients with in-hospital cardiac arrest (IHCA).**

INTRODUCTION

Therapeutic hypothermia or TTM has been suggested as a potentially neuroprotective intervention for many years. Animal studies have shown therapeutic hypothermia acts via multiple pathways to delay cell death. It reduces cellular metabolic demand, excessive accumulation of cytotoxins and oxygen free radicals, preservation of the blood brain barrier, continuation of ATP stores, and restitution of the microcirculation (1,2). To date, TTM has been shown to be effective in two specific indications: neonatal hypoxic-ischemic injury and following adult cardiac arrest. It remains unknown whether therapeutic hypothermia / TTM should be applied to populations outside of these proven indications (3).

Therapeutic Hypothermia and Cardiac Arrest

Out-of-hospital cardiac arrest (OHCA) is associated with poor survival and poor neurological outcomes. Cerebral reperfusion results in the generation of free radicals and other mediators that trigger chemical cascades resulting in further damage to the brain (1). Although there is relatively good evidence of benefit in comatose patients with out-of-hospital ventricular fibrillation or tachyarrhythmia from a cardiac cause, there is limited data regarding other initial rhythms and non-cardiac causes of arrest. Additionally, there are limited studies regarding the optimal target

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

temperature and duration for therapeutic hypothermia. The current American Heart Association guidelines are as follows:

> "We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used (*strong recommendation, moderate-quality evidence*). Whether certain subpopulations of cardiac arrest patients may benefit from lower (32°C–34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this. We recommend Targeted Temperature Management (TTM) as opposed to no TTM for adults with out-of-hospital cardiac arrest (OHCA) with an initial shockable rhythm who remain unresponsive after return of spontaneous circulation (ROSC) (*strong recommendation, low-quality evidence*). We suggest TTM as opposed to no TTM for adults with OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC (*weak recommendation, very-low-quality evidence*). We suggest TTM as opposed to no TTM for adults with in-hospital cardiac arrest (IHCA) with any initial rhythm who remain unresponsive after ROSC (*weak recommendation, very-low-quality evidence*). In making these recommendations, we place a higher value on the potential for increased survival with good neurologic outcome as compared with the possible risks (which appear to be minimal) and the cost of TTM. We emphasize that the mortality after cardiac arrest is high and the treatment options are limited. Although the evidence for TTM compared with no temperature management is of low quality, it is the only post-ROSC intervention that has been found to improve survival with good neurologic outcome. We have, therefore, made our recommendation strong in spite of the low-quality evidence." (4)

LITERATURE REVIEW

A 2018 systematic review and meta-analyses conducted by Kalra et al. aimed to determine if there is a benefit to TTM in the pre-hospital and in-hospital setting. They compared hypothermia vs. normothermia groups in 5 randomized controlled trials which showed no difference in the rates of all-cause mortality and favorable neurological outcome (5). Similarly, they reported no difference in all-cause mortality and favorable neurological outcomes in the pre-hospital vs. in-hospital groups. The authors concluded TTM with therapeutic hypothermia may not improve mortality or neurological outcomes in post cardiac arrest patients and the application of therapeutic hypothermia should be re-evaluated.

In order to evaluate TTM after intraoperative cardiac arrest, Constant et al. performed a multicenter retrospective study of 101 patients that underwent emergent surgery and developed either asystole, pulseless electrical activity, or ventricular tachycardia/fibrillation (6). The 30 patients that received TTM had an increased risk of infection, but not arrhythmia, bleeding, or metabolic/electrolyte disorders. In addition, TTM was not significantly associated with better 1-year functional outcome among those successfully resuscitated.

Leao et al. conducted a 2-year prospective study to determine outcome predictors in post cardiac arrest patients who underwent hypothermia protocol (7). 69% were OHCA. The main causes of cardiac arrest were acute myocardial infarction and respiratory failure. Twenty-five patients had ventricular fibrillation, 26 had asystole, and 10 had pulseless electrical activity. The authors found that VF was associated with better neurological prognosis among patients who received therapeutic hypothermia. There was no difference in mortality or neurological outcome when treatment was initiated outside the hospital vs. in-hospital. Lower time to reach target temperature was associated with higher mortality and worse neurological outcomes.

Bernard et al. performed a randomized controlled trial to compare moderate hypothermia to normothermia after OHCA (8). All patients had ventricular fibrillation as the first recorded rhythm and remained comatose after return of spontaneous circulation. Hypothermia was initiated in the field by application of cold packs. Patients randomized to hypothermia were maintained at 33°C for 12 hours. At 18 hours, patients were actively rewarmed over 6 hours. Patients randomized to normothermia were maintained at 37°C. Seventy-seven patients were included in the study; 43 were treated with hypothermia. 49% of patients treated with hypothermia had a good outcome, defined as discharge to home or rehabilitation, compared to 26% of normothermic patients, resulting in an odds ratio for good outcome from hypothermia of 5.25. There was no reported difference in adverse effects.

The Hypothermia after Cardiac Arrest Study Group performed a multicenter, randomized, controlled trial to compare moderate hypothermia to normothermia after out-of-hospital cardiac arrest (9). All patients had ventricular fibrillation or non-perfusing ventricular tachycardia as the first recorded rhythm. Hypothermia was initiated upon hospitalarrival

with an external cooling device to a target temperature of 32-34°C, which was maintained for 24 hours, followed by passive rewarming. Patients randomized to normothermia were maintained at 37°C. 273 patients were included in the study; 136 were treated with hypothermia. 55% of patients treated with hypothermia had a good outcome, defined as Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability), compared to 39% of normothermic patients, resulting in a risk ratio of 1.4. Six-month mortality was 42% in the hypothermia group and 55% in the normothermia group, resulting in a risk ratio of 0.74. There was no reported difference in adverse effects.

A 2012 Cochrane Review of pooled data from the studies above, as well as an abstract and a feasibility study concluded that therapeutic hypothermia is beneficial in patients with OHCA, a presumed cardiac cause of arrest, and ventricular fibrillation or ventricular tachycardia as the first recorded arrhythmia (10-12). However, the sample size for asystole and non-cardiac causes of arrest were too small to draw significant conclusions.

Nielsen et al. performed a multicenter, randomized, controlled trial to compare hypothermia at 33-36°C (13). All patients had a GCS less than 8 and a first recorded rhythm other than asystole. Hypothermia was initiated after hospital arrival using a combination of external and intravascular cooling devices at the preference of the center and maintained for 28 hours, followed by rewarming at 0.5°C hourly. Evaluation at 180 days revealed no statistically significant difference in mortality or neurological outcome between the groups. A serious adverse event, such as seizure, infection, bleeding, cardiac arrhythmia, or electrolyte deficit, occurred in 93% of patients cooled to 33°C, compared to 90% of those cooled to 36°C, which was a statistically significant difference.

A 2016 Cochrane Review update that included the above study, as well as a study looking at hypothermia in conjunction with hemofiltration, found that recent studies did not provide additional data that required altering the conclusions of the 2012 review (14).

Baldursdottir et al. published a case series evaluating neurological recovery for all forms of asphyxiation (15). The case series looked at 14 patients treated with therapeutic hypothermia. Nine patients had a cardiac arrest, and all were comatose with a GCS of 3-5. Nine of fourteen survived with minimal neurological impairment. Of the five non-survivors, four had cerebral edema on the initial CT scan.

Targeted Temperature Management Checklist

- ☐ Admit to ICU
- ☐ Place patient on continuous pulse oximetry, telemetry, and EEG monitoring
- ☐ Initial labs: CBC, PT/INR, PTT, CMP, magnesium, phosphorus, ionized calcium, cortisol, lactate, ABG
- ☐ Maintain patient NPO
- ☐ Heparin for DVT prophylaxis
- ☐ Pepcid for GI prophylaxis
- ☐ Standard glucose management
- ☐ Apply Lacri-Lube to both eyes and cover with pads
- ☐ Apply the Bard® Arctic Sun in automatic mode to desired target temperature
    - Temperature should be taken with a rectal, esophageal, or bladder temperature probe
        - A bladder temperature probe should not be used in anuric patients
    - Target temperature should be reached within 1 hour
    - Monitor temperature hourly
- ☐ A heated humidification ventilator circuit should be set to 34°C
- ☐ Sedation should be maintained for a RASS of <1
- ☐ If the patient starts shivering, start fentanyl drip and PRN bolus to obtain a Bedside Shivering Assessment Scale < 1
    - If Fentanyl ineffective, add Propofol
    - If Fentanyl and Propofol ineffective, activate bolus rocuronium 50 mg IV initially and then start a drip titrated so that the patient does not shiver. Then stop the drip and bolus 50 mg as needed to prevent shivering.
- ☐ Serial labs every 6 hours:
    - K, Mg, iCa, Phos, ABG
    - Do not use standard electrolyte replacement protocols
        - Give 40 mEq KCl for K <3.4
        - Give 1 gm Mg for Mg <1.8
        - Give 1 gm CaCl for iCa < 0.9, check iCa Q4 while replacing
        - Give 10mMol NaPh for Ph < 2.5
- ☐ Start rewarming 24 hours after the initiation of hypothermia
    - Rewarm at 0.25°C to a target temperature of 37°C
- ☐ Wean off sedation after rewarming is complete

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