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The Neuroprotective Effects of Targeted Temperature Management on Post-Cardiac Arrest Patients

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Abstract

- Novel methods of ensuring survival following cardiac arrest and resuscitation are of supreme importance to the medical community. Targeted temperature management (TTM) has become increasingly utilized pre-hospital, in emergency departments, and within intensive care units to increase the likelihood of survival to hospital discharge. TTM has further been used to attempt to improve neurological functioning. The efficacy and mechanism behind TTM remains poorly understood. In several patient populations it also remains unproven. The purpose of this study is to assess the physiological mechanism, survival, neurological recovery and methodology of TTM use and implementation.
- Literature review was utilized to assess the physiological mechanism by which TTM elicits its neuroprotective effects. Statistics on neurological outcomes and survival rates were further examined. Finally, the proposed method to safely and efficiently induce and maintain TTM in appropriate patients was also assessed through literature review.
- TTM was found to improve survival and neurological functioning in adults suffering cardiac arrest both in-hospital and out-of-hospital. No improvement has been noted in studies on pediatric patients, thus TTM is not indicated in pediatric patients. Animal studies demonstrate a decrease in cerebral edema and mitochondrial apoptosis of neuronal cells with TTM application. Serum biomarkers of brain injury and disfunction of the endothelial lining constituting the brain blood barrier (BBB) have also been found to be decreased in patients undergoing TTM. Finally, serum assay of antioxidants demonstrates a decrease in oxidative damage and increase in antioxidant protection following reperfusion.

Introduction

- Patients who underwent an out-of-hospital cardiac arrest (OHCA) had a 12% likelihood of surviving to discharge (Chan, Mcnally, Tank & Kellerman, 2014), and the likelihood of retaining good neurological function is 8.5% (Buick et al., 2018).
- Targeted temperature management has become a mainstay within hospital systems to improve neurological function in patients after cardiac arrest
- Proponents further suggest that implementation improves survival to hospital discharge.
- The probable neuroprotective mechanism, improvements in survival and neurological functioning, and recommendations for implementation were assessed through literature review.

Statement of Problem

- Targeted temperature management is a poorly understood intervention. It is believed to confer benefit to survival and neurological outcome, though the mechanism is still under research. The magnitude of potential benefit to survival and neurological functioning also remains under scrutiny. Finally, the method of TTM induction remains poorly standardized. Assessment into the methods and procedures of several studies may yield data on the most effective and efficient method to confer the greatest benefit to survival and neurological function.

Research Questions

- By what proposed mechanisms does targeted temperature management improve survivability and neurological functioning following cardiac arrest and resuscitation?
- Do studies evaluating the benefit of targeted temperature management demonstrate statistically significant improvements in survival to hospital discharge as well as improvements in cognitive function following resuscitation?
- What is the currently agreed upon method of inducing targeted temperature management and what is its ease of implementation?

Methods

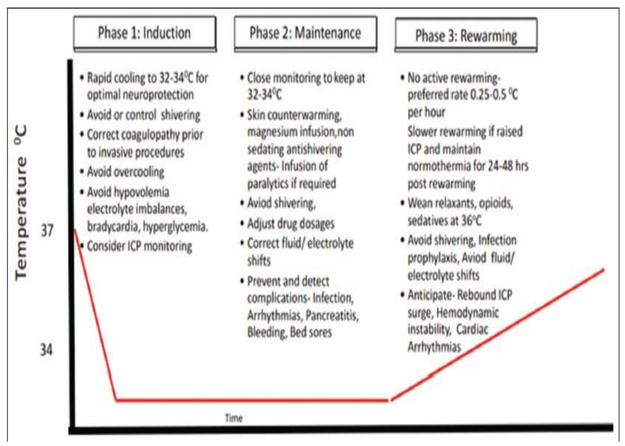
- To acquire relevant research PubMed, Clinical Key, Cochrane review and Google Scholar were referenced.
- Search terms included; targeted temperature management, therapeutic hypothermia, cardiac arrest, return of spontaneous circulation (ROSC) and neurological. These terms were used in several combinations to obtain appropriate research materials.
- Dynamed and the American Heart Association (AHA) were further assessed for recommendations on patient selection, implementation, and methodology behind TTM
- Studies performed both on in-hospital cardiac arrest (IHCA) as well as out-of-hospital cardiac arrest (OHCA) were included to assess the use of TTM prehospital. Furthermore, TTM use in pediatric patients as well as in shockable and non-shockable rhythms was assessed through literature review.

Literature Review

- Pathophysiology
  - Fan et al. (2017) utilized a rat model to show increased DRP-1 and CYT-C as well as morphological changes in mitochondria in all cardiac arrest groups ($P < 0.05$) suggesting decreased mitochondrial induced neuronal apoptosis ($P < 0.05$).
  - Hackenhaar et al. (2017) performed a study focused on reactive oxygen species (ROS) development. TTM was effective in decreasing reactive oxygen species($P < 0.05$)
  - Jahandiez, et al. (2017)) performed studies using rabbits to model cardiac arrest. A decrease in mitochondrial apoptosis was noted ($P < 0.05$).
  - Jieben et al (2017) performed a series of porcine studies assessing the effects of TTM. The TTM cohort demonstrated improvement on examination of neurological structures, and diminished serum biomarkers indicating epithelial destruction ($P < 0.05$). Jieben et al. (2017) further evaluated damage to vascular endothelium. The serum ANG-1 and ANG-2 of the TTM cohort demonstrated fewer irregularities suggesting minimized damage to vascular endothelium ($P < 0.1$)
  - Chen et al. (2017) performed controlled studies using endothelial cells of laboratory rats. Ischemic cells in the TTM group demonstrated a decrease in apoptosis ($P < 0.0083$). The CYT-C precursor Bax as well as caspase 3 were elevated to a lesser degree in the TTM cohort ($P < 0.05$).
- Survival and cognition improvements
  - Fan, et al. (2017) performed an experiment performing TTM on lab rats. Improvements were noted in the TTM group in survival and neurological function. ($P = 0.05$).
  - Nurnberger et al. (2017) utilized data obtained from the Circulation Improving Resuscitation Care Trial (CIRCT). The results suggest that survival to discharge is superior in patients who receive prehospital/in-hospital TTM ($P = 0.006$).
  - Moler at al. (2017) performed a study to determine the efficacy of TTM for pediatric patients who experience IHCA. No significant difference was found in survival, nor was there difference in cognitive function ($P = 0.56$, $P = 0.63$, respectively).
  - Perman et al. (2015) used retrospective analysis to determine the effectiveness of TTM who present with a non-shockable rhythm (Asystole/PEA). Both cohorts enjoyed improved neurological functioning and survivability to discharge regardless of the location of arrest ($P = 0.003$, $P = 0.001$ respectively).
- Method of implementation
  - Casamento et al. (2016) utilized review of patient records to assess varying magnitudes of TTM. Patients underwent TTM at 32-34 degrees, or TTM at 36 degrees. Greater likelihood of complications was found in the 32-34-degree group ($P = 0.01$). They also note an increased discharge to home rate in the 36-degree group ($P = 0.02$).
  - Yuan et al. (2017) performed a porcine study on the effects of early versus delayed administration of TTM. CPC scores demonstrated improved neurological function in the early TTM group ($P < 0.012$).
  - Kirkegaard et al. (2017) assessed the use of TTM for 24 vs 48 hours. No difference was noted for favorable neurological outcome or survival to discharge ($P = 0.33$, $P = 0.19$). The likelihood of adverse effects was higher in the 48-hour cohort. ($P = 0.03$).
  - Aschauer, Sterz, Laggner, and Behringer (2012) assessed the cost-effectiveness of TTM. Total costs per 100 patients was found to be between 3.7, and 4.1 million euro. A cost-effectiveness ratio of 3.827 euro per QALY was discovered.

Discussion

- Animal studies performed by Fan et al. (2017) and Chen et al. (2017) demonstrate inhibition of mitochondrial induced cellular apoptosis through alteration of mediators of mitochondrial pore opening such as CYT-C, Caspase-3 and Bax.
- Further protection is offered due to the increase in anti-apoptotic factors such as Bcl-2. This interferes with neuronal apoptosis as well as ensuring the continued function of microvascular endothelium. As a result, further injury due to damage to the BBB and subsequent free radical damage and cerebral edema was prevented.
- There is a clear benefit to survival and neurological recovery when TTM is applied to adults undergoing IHCA and OHCA with an initially shockable rhythm.
- Improvements were noted in survival, and in neurological functioning as measured by autonomic reflexes and operationally defined observation for 24-72 hours post-resuscitation in animal studies Improvement in survivability and neurological outcome has also been noted in retrospective assessment of patient records.
- The benefit of TTM to survivability and neurological outcome is supported in patients with a non-shockable cardiac rhythm. Perman, Grossestreuer, Douglas, Wiebe, Carr, Abella (2015) found statistical significant improvements in patient survival with TTM vs normothermia when the initial presenting rhythm is non-shockable. (29% vs 15%, $P = .001$). Continued assessment found patients are more likely to be discharged neurologically intact if TTM is utilized following resuscitation in PEA/Asystole (OR 2.1; 95% CI 1.01-4.36).
- The studies do not currently support the use of TTM in pediatric patients due to lack of efficacy. This may be due to the different causalities in pediatric cardiac arrest.
- Earlier application of TTM is associated with improved likelihood of neurological improvement. TTM application prior to ED arrival however, is controversial. TTM appears to elicit its effects during reperfusion. Prolonged cardiac arrest, or prolonged time until TTM application is likely to diminish the potential benefit.



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Clinical Applicability

- TTM is most effectively accomplished by rapidly decreasing core body temperature to 32-36 degrees Celsius, though fevers and shivering are more common on the lower end of this spectrum. As such, a moderate approach to TTM may be safer and require fewer interventions such as antipyretics and sedation.
- Dynamed recommends rapid induction to target temperature 32-36 degrees C for 24 hours followed by rewarming over 12-24 hours. The Yuan et al. (2017) study further suggests that earlier implementation is effective in preserving neurological function.
- Per the American Heart Association, TTM should be induced in patients who remain unresponsive following OHCA with ROSC and a presenting shockable rhythm. TTM may be considered for patients who remain comatose following ROSC with non-shockable rhythms or following IHCA. Core body temperature should be decreased to 32-34 degrees Celsius and maintained for 24 hours
- The AHA does not currently endorse routine pre-hospital cooling methods
- TTM can be readily applied in rural ER practice and maintained for transport to a higher level of care by EMS, decreasing the time to therapeutic effect
- An endovascular, esophageal, bladder or rectal temperature probe should be placed for continuous core temperature monitoring.

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