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The Neuroprotective Effects of Targeted Temperature Management in 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 begun increasingly utilized pre-hospital, in emergency departments, and within intensive care units to increase the threshold for 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 methodological behind TTM.
- Literature review was utilized to assess the physiological mechanism by which TTM elicits its effects. TTM elicits its effects 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 dysfunction of the endothelium, 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 repetition.

Methods

- To acquire relevant research PubMed, Clinical Key, Cochrane review and Cochrane databases were utilized.
- Search terms included: targeted temperature management, therapeutic hypothermia, cardiac arrest, return of spontaneous circulation (ROSC) and these terms were used in several combinations to obtain appropriate research materials.
- Dynamed, and the American Heart Association (AHA) were further assessed for associated recommendations on patient selection, implementation, and methodology behind TTM.
- Stöckl, M. et al. (2017) found in-hospital cardiac arrest (OHCA) as well as out-of-hospital cardiac arrest (OHCA) were included to assess the use of TTM pre-hospital. Furthermore, TTM use in pediatric patients as well as in vulnerable 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 TTM. Finally, serum assay of antioxidants demonstrates a decrease in oxidative damage and increase in antioxidant protection following repertition.
  - Ji et al. (2017) further evaluated damage to vascular endothelium. The serum and nerve damage as well as serum endothelial cell markers suggesting minimal damage to vascular endothelium (p < 0.1).
  - Chen et al. (2017) controlled studies using endothelial cells of laboratory rats. Ischemic cells in the group demonstrated a decrease in apoptosis (p < 0.003). 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).
  - Merger 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 TTM (p = 0.006).
  - Moller et 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 = 0.05).
  - 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 survival to discharge regardless of the location of arrest (p = 0.001 respectively).
- Method of implementation
  - Casamento et al. (2016) utilized review of patient records to assess varying procedures of TTM. They also noted a decrease in temperature at 12 hours to 36 degrees in 33.6% of patients undergoing TTM at 33.4–36.5 degrees or TTM at 36 degrees. Greater likelihood of complications was found in the 33.4–36 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).

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, Drp-1 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.
- Immediate implementation noted in survival, and in neurological functioning as measured by autonomic reflexes and operationally defined observation for 24-72 hours post-reanimation in animal studies. Improvement in survival and neurological outcome has also been noted in retrospective assessment of patient records.
- The benefit of TTM to survival and neurological outcome is supported in patients with a non-shockable cardiac rhythm. Perns, Gassner, and Erbersdobler (2015) found statistical significant improvements in patient survival with TTM vs normothermia when the initial presenting rhythm is non-shockable. (29% vs 15%, P = 0.01). Continued assessment found patients are more likely to be discharged neurologically intact if TTM is utilized following resuscitation in pediatric patients.
- The studies do not currently support the use of TTM in pediatric patients after asystole arrest (p < 0.05). Plausible mechanisms to the difference may be attributed to the different causal factors for pediatric cardiac arrest.
- Efficacy 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. Prehospital and/or in-hospital implementation time to TTM application is likely to diminish the potential benefit.