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

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

Patients

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Table of Contents

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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

Statistics released in 2014 by the American Heart Association suggest that survival to hospital discharge following cardiac arrest and resuscitation is unlikely. In fact, 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). With these abysmal statistics, it stands to reason that all available interventions should be utilized. Targeted temperature management has become a mainstay within hospital systems in an effort to improve neurological function in patients who have suffered a cardiac arrest. Proponents further suggest that implementation improves survival to hospital discharge. Claims such as these deserve thorough investigation, understanding, and efficient implementation.

 Through literature review and assessment of available guidelines I proposed to evaluate the probable neuroprotective mechanism, and investigate current recommendations for implementation. I further proposed to evaluate the efficacy of targeted temperature management in preserving neurological function to hospital discharge and beyond.

Statement of the Problem

Targeted temperature management is generally a poorly understood intervention in medicine. It is believed to confer benefit to survival and neurological outcome, though the mechanism by which this benefit occurs is still under research. The magnitude of potential benefit also remains under scrutiny, partially due to the statistical and ethical difficulties of assigning control groups and normalizing patient variables across populations. Finally, the method of TTM induction remains somewhat poorly standardized. Assessment into the methods

and procedures of several studies may yield data on the most effective and efficient method and target temperature 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?

Research methods

To acquire relevant research PubMed, Clinical Key, Cochrane review and Google Scholar were referenced. Further insight into the efficacy, implementation and current guidelines of targeted temperature management was gained through search of Dynamed. 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.

Studies focusing on the use of targeted temperature management for neurological conditions without cardiac arrest were removed from the search criteria due to lack of applicability to this study. Articles that failed to demonstrate usable experimental result (i.e. expert opinions, letters to the editor, implementation guides, etc.) were removed from the pool of applicable references.

As this study has a broad scope pertaining to the mechanism and efficacy of targeted temperature management publications for adults as well as children were included. Furthermore, studies performed both on in-hospital cardiac arrest (IHCA) as well as out-of-hospital cardiac arrest (OHCA) were included. This allows greater ease of applicability of targeted temperature management across all aspects of healthcare and may shed light onto its effect both in a highly controlled ED/ICU environment as well a poorly controlled out of hospital scenario. This also increases the sample populations assessed through this literature review, making the ability to generalize outcomes more likely.

LITERATURE REVIEW

Pathophysiology of Targeted Temperature Management

Fan et al. (2017) study utilized a rat model to assess hippocampal neuronal mitochondria to assess apoptosis following ROSC. They hypothesize that reperfusion injury following cardiac arrest causes an increase in protein DRP-1 upon mitochondrial surface resulting in increased CYT-C release. This results in loss of mitochondrial fission resulting in apoptosis. Results of the study show increased DRP-1 and CYT-C as well as morphological changes in mitochondria in all cardiac arrest groups vs control groups ($P < 0.05$). This lends credence to the hypothesis that cardiac arrest causes increased expression of DRP-1 and CYT-C due to neuronal apoptosis. Further statistical difference was found between normothermic and hypothermic groups with hypothermic subjects expressing less DRP-1 and CYT-C indicating fewer neurons undergoing apoptosis due to reperfusion injury ($P < 0.05$). The overall neurological deficit and survival rates were also assessed and statistically significant improvements were noted to both in the TTM cardiac arrest group vs the normothermic cardiac arrest group (36% survival vs 64% survival.

No P values noted). This indicates overall improvement in survivability and function as well as

decreased mitochondrial and neuronal apoptosis.

Hackenhaar et al. (2017) performed a study focused on reactive oxygen species

development due to the influx of oxygen following ROSC. The study relied upon data collected

through implementation of a TTM program at Conceicau hospital in Brazil. Participants were

randomly assigned to normothermia or hypothermia depending upon the availability of a room

capable of allowing TTM to occur upon admission to the ICU. While not an ideal method for

designing a study, the authors did perform statistical analysis upon the two cohorts and found no

statistical significance in variables or cohort profile. As such, a good deal of generalizability can

be gleaned from assessment of this study. Venous blood samples were taken to assess the

quantities of reactive oxygen species and markers as well as analyze the development of

erythrocyte antioxidants. The study found that TTM was effective in decreasing the quantity of

reactive oxygen species as well as moderating electrolyte imbalance that often occurs as a result

of reperfusion injury to systemic organs as demonstrated by the levels of S100B brain injury

biomarker ($P < 0.05$). Furthermore, an increase in erythrocyte anti-oxidant values were noted,

allowing a greater protective effect to develop ($P < 0.05$ when assessing SOD, GPx, GST, and

PON1antioxidant enzymes). This results in a decrease in reactive oxygen damage to

neurological structures and results in maintenance of the blood brain barrier (BBB).

Jahandiez, et al. (2017) performed further studies using rabbits to model cardiac arrest

and determine the efficacy of TTM in protecting multiple organs from reactive oxygen injury.

Rabbits were grouped into a control, sham, and experimental groups assessing; TTM, TTM plus

neuroprotective medications, and neuroprotective medications alone. As they are not within the

realm of this study the influence of the neuroprotective medications will not be discussed here.

The rabbits were anesthetized and placed on mechanical ventilation. Cardiac arrest was induced through asphyxia and allowed to continue for 15 minutes. The rabbits were then resuscitated and treated normothermically or hypothermically. Evaluation of mitochondrial samples from the heart as well as the brain demonstrated a decrease in mitochondrial pore opening which precedes apoptosis. This agrees with the Fan et al. (2017) study that assessed the enzymatic precursors DRP-1 and CYT-C that mediate mitochondrial induced neuronal apoptosis. This study also found decreased sensitivity of the mitochondria to calcium influx, further decreasing the likelihood of apoptosis ($P < 0.05$). Interestingly, serum creatine, troponin levels, and pupil reflex were preserved in comparison to control ($P < 0.05$). This indicates a global benefit to multiple organ systems, as well as preserved autonomic function. Serum markers of neurological damage were also significantly depressed compared to control ($P < 0.05$).

The porcine studies performed by Jieben et al (2017) give us perhaps the most in-depth assessment of the reperfusion damage suffered by the brain during and after cardiac arrest. 34 pigs were placed into normothermic or hypothermic treatment cohorts. All were anesthetized and placed into cardiac arrest followed by resuscitation. The subjects were humanely euthanized and brain samples were collected for evaluation at 24 hours post ROSC to determine the functional status of the BBB. This was performed microscopically as well as with injected contrast dye prior to euthanasia. Serum studies were also assessed to determine the presence of proteins signaling the destruction of epithelial tight junctions and adherens junctions that control membrane permeability in the BBB. The therapeutic hypothermia cohort demonstrated significant improvement in visual examination of neurological structures, improved post-arrest neurological functioning, and diminished serum biomarkers indicating epithelial destruction

(P = 0.23, P < 0.5, P < 0.1, respectively). This suggests maintenance of an effective BBB

prohibiting osmotic damage and damage caused by the development of reactive oxygen species

(ROS).

Jieben et al. (2017) further evaluated the effects of cardiac arrest in relation to

degradation of vascular endothelium. The authors hypothesize that decreases in angiopoetin-1

(ANG-1) and elevations of angiopoietin-2 (ANG-2), both growth hormones, act to destabilize

vascular endothelium following cardiac arrest. This would result in greater vascular permeability

increasing cerebral edema due to destruction of the BBB. In an effort to study this effect pigs

were sedated and randomly assigned to normothermic, hypothermic or sham categories. Sham

pigs acted as control, undergoing the same procedure without cardiac arrest or cooling. The

subjects underwent an 8-minute period of cardiac arrest before attempted resuscitation. Upon

ROSC pigs assigned to the hypothermic group were cooled to 33 degrees Celsius before being

rewarmed to 37 degrees. Normothermic subjects were allowed to self-thermoregulate. At 12

hours post-cardiac arrest the pigs underwent neurological examination followed by euthanasia

and tissue/serum sampling. The hypothermic cohort group demonstrated statistically significant

improvements in neurological functioning vs the normothermic group (P < 0.01). Furthermore,

their serum ANG-1 and ANG-2 demonstrated fewer irregularities suggesting minimized damage

to vascular endothelium (P < 0.1). Once again this demonstrates an intact BBB decreasing the

likelihood of neuronal damage due too loss of osmotic control and production of ROS.

Chen et al. (2017) performed controlled studies using the microvascular endothelial cells

of laboratory rats to assess the mechanism of neuroprotection using TTM. The rats were

anesthetized and euthanized. Cortical samples were obtained, homogenized and centrifuged

before being purified to contain only microvascular epithelial cells. These cells were placed in

culture and cultivated before being placed into control, ischemia, and ischemia/TTM groups. The experimental cells were placed in a low oxygen environment (1% O2, 5%CO2, 94%N2) before being returned to normal oxygen concentrations. Microscopic examination showed increase in cellular apoptosis in experimental vs control groups, ($P < 0.0083$). However, the TTM group demonstrated a decrease in apoptotic epithelial cells ($P < 0.0083$). Examination of apoptosis related protein expressions was performed. Similar results to Fan et al. (2017) were obtained. Unlike Fan et al. (2017), which assessed CYT-C release Chen et al. (2017) assessed the CYT-C precursor Bax as well as the product of CYT-C action, caspase 3. These proteins were all elevated in experimental groups ($P < 0.05$), though to a lesser degree in the TTM cohort ($P < 0.05$). The apoptosis mediating enzyme Bcl-2 was noted to be decreased in the experimental groups ($P < 0.05$) but was significantly higher in the TTM cohort, ($P < 0.05$), providing increased protection from induced apoptosis. This suggests that TTM produces increased protection to microvascular endothelium inhibiting the degradation of the brain-blood barrier, protecting against cerebral edema.

Improvement in Survival and Cognitive Function Following Implementation of Targeted Temperature Management.

Fan, et al. (2017). undertook an animal study utilizing rats to determine the effects of TTM on hippocampal structures, particularly in relation to neuronal mitochondria. They hypothesize that reperfusion injury following cardiac arrest causes an increase in dynamin-1-like protein (DRP-1) upon mitochondrial surface resulting in increased CYT-C release. This results in loss of mitochondrial fission resulting in increased DNA damage, release of reactive oxygen species, and neuronal apoptosis. If widespread this neuronal apoptosis leads to progressively worsening neurological status and potentially brain death following return of spontaneous

circulation. Subjects were randomly assigned to normothermia or hypothermia as well as random assignments to undergo cardiac arrest and rats who would not. The rats were anesthetized and mechanically ventilated. Rats in the cardiac arrest group were placed into lethal arrhythmia utilizing an esophageal pacing wire. Chest compressions and defibrillation were initiated 5 minutes post-arrest induction. Upon ROSC, cardiac arrest subjects then underwent normothermia utilizing heat lamps, or underwent TTM utilizing ice and alcohol. Temperatures were measured rectally. Control groups underwent the same treatments but were spared cardiac arrest. Neurological assessment was evaluated in all groups at 72 hours. The overall neurological deficit and survival rates were assessed and statistically significant improvements were noted in the TTM cardiac arrest group vs the normothermic cardiac arrest group ($P = 0.05$, $P = 0.001$, respectively). This indicates overall improvement in survivability and cognitive function. Diminished DRP-1 levels in the TTM arrest group further suggest that TTM inhibits neuronal apoptosis by inhibiting mitochondrial degradation.

Moler at al. (2017) performed a study to determine the efficacy of TTM for pediatric patients who experience IHCA. It utilized an age grouped, randomized study to treat patients into either normothermia or hypothermia cohorts over the course of five years and in several hospitals across a wide geographical region. A total of 334 patients participated. Patient's cognitive abilities and survival were assessed at 12 months post cardiac arrest. No significant difference was found in survival, nor was there difference in cognitive function at the 12-month mark indicating a lack of efficacy in this population ($P = 0.56$, $P = 0.63$, respectively). The authors do note that pediatrics experiencing an OHCA may represent a different population due to lack of age related disease processes and biological degradation. Pediatric cardiac arrest was further likely caused by congenital conditions or acute, severe conditions. As adult cardiac arrest

is more frequently caused by chronic conditions. Due to biological dissimilarity, pediatric

results may not be generalizable to adult populations.

Nurnberger et al. (2017) followed in the footsteps of the Circulation Improving

Resuscitation Care Trial (CIRCT) which attempted to evaluate the effectiveness of conventional

CPR vs automated band CPR devices. All raw data from the CIRCT concerning cardiac arrest

and survival was made available to the authors who used it to evaluate survival to discharge of

patients who receive TTM out of/in hospital, in hospital and those who receive no cooling

whatsoever. The results suggest that survival to discharge is statically superior in patients who

receive prehospital/in hospital TTM, followed by those who receive in-hospital cooling only ($P =$

0.006 and $P < 0.001$, respectively).

The Nurnberger (2017) study does suffer, however, as it relies upon the limitations

imposed upon the designers of the original study which recorded treatment with TTM only as

ancillary data. As a result, no specific information is available concerning the nature,

mechanism, location of the arrest, the presenting rhythm, or neurological function following

ROSC is available. The study further lacks standardized methods of TTM implementation which

eliminates the author's ability to control for variabilities in the manner and method of TTM use.

As a result, it is difficult to claim significant generalizability to this study. That being said, this

was a far-reaching study with approximately 1,800 valid participants, thus the statistical

significance offers useful and accurate data regarding the utility of TTM to promote survival to

discharge. While difficulty is present in validating generalizability of the data, it presents an

effective stepping stone, suggesting that TTM can be efficacious in survival to discharge.

A study performed by Perman et al. (2015) used retrospective analysis to determine the

effectiveness of TTM on patients who suffer both IHCA and OHCA but present with a non-

shockable rhythm. Historically, data on the efficacy of TTM in non-shockable rhythms has been mixed. This study evaluates 519 patients and performs cohort matching to ensure lack of bias. Results indicate that TTM is effective at producing greater survivability to hospital discharge as well as improved neurological functioning. The authors also matched additional cohorts to assess the efficacy of TTM on patients both in hospital and out of hospital. It was determined that both cohorts enjoyed improved neurological functioning and survivability to discharge regardless of the location of arrest vs those who did not receive TTM (P = 0.003, P = 0.001 respectively). The size of this study as well as its cohort matching to eliminate bias reinforces the validity of these results.

Jieben, et al. (2017) performed several porcine studies to evaluate changes to neurological structures and biomarker assays to assess the mechanism by which TTM produces effect. Jieben et al. (2017) further assessed the rates of survival and neurological outcomes of the subjects following cardiac arrest induction and resuscitation to determine the efficacy of TTM. The researchers anesthetized the subjects and induced cardiac arrest. Arrest was allowed to continue for 8 minutes before CPR and defibrillation was initiated. Upon ROSC, the subjects either underwent cooling to 33 degrees Celsius before being rewarmed to 37 degrees Celsius. The control subjects were left normothermic. At 12 and 24 hours post-cardiac arrest the pigs underwent neurological examination followed by euthanasia and tissue/serum sampling. The hypothermic cohort group demonstrated statistically significant improvements in neurological functioning vs the normothermic group in all cited studies utilizing several different variables (P < 0.01).

Method for Targeted Temperature Management Induction

Cariou et al. (2017) evaluated the use of TTM by utilizing literature review to determine expert guidelines and recommendations. This study was immensely far reaching and included the use of TTM for cardiac arrest, traumatic brain injury, bacterial meningitis, status epilepticus, and shock. Through use of literature review the panel of experts provide grade I evidence for the use of TTM following out of hospital cardiac arrest with a shockable rhythm (ventricular fibrillation or ventricular tachycardia) if the patient remains comatose following ROSC. The authors give expert opinion that out of hospital cardiac arrest should be treated similarly, though they admit that they have no strong data for or against this intervention. Grade II recommendations include the implementation of TTM in patients who present with non-shockable rhythms (pulseless electrical activity and asystole) and remain comatose. Grade II evidence further exists for maintenance of TTM between 32-34 degrees Celsius. Grade II evidence exists to avoid the use of therapeutic hypothermia in pediatric patients as it has not been shown to improve neurological outcome and may be associated with increased mortality. This is in agreement with the study by Moler et al. (2015) assessed previously.

Geocadin et al. (2017) performed a literature review to determine the efficacy of therapeutic hypothermia for both shockable and non-shockable cardiac rhythms. They further attempt to assess the efficacy of prehospital initiation of cooling methods as well as the possible benefits of several pharmacologic agents. Clear benefit of TTM is gleaned through literature review upon both survival to discharge and neurological functioning when the presenting rhythm is shockable. No clear evidence for or against TTM is noted for non-shockable rhythms (RD 6%, 95% CI 3%-9%). They advise that TTM may improve functional neurological outcome and survival when the presenting rhythm is asystole or pulseless electrical activity, granting it an

evidence rating of C. They have found no benefit to the induction of TTM prehospital (level A recommendation after literature review of several class I studies). The authors further suggest that, as the nature of TTM's neurological mechanism of action is yet unknown the ideal timeline for implementation is indefinite. Regarding the addition of neuroprotective agents such as xenon, nimodipine, lidoflazine, selenium, thiopental, etc. no benefit to neurological outcome or survivability is found. When considering the adverse effects of these medications, risk-benefit analysis clearly favors risk. As such this publication advises against the addition of these medications to a comatose patient following cardiac arrest.

Gueret, Bailitz, Sahni, & Tulaimat (2017). focused on the implementation and efficacy of John H Stroger Hospital's TTM protocol. Of note is the interdisciplinary method of development and implementation the hospital used to ensure the appropriateness of TTM as well as staff adherence to policy. It goes on to detail the steps undertaken to ensure proper education of the hospital staff. Regarding efficacy, the Gueret et al. (2017) study focused upon both OHCA and IHCA as well as both shockable and non-shockable rhythms. Using the hospital's records, they were able to select population samples from prior to TTM implementation to act as a control. This study failed to demonstrate statistical significance across both survivability and neurological outcome both when discussing OHCA and IHCA as well as regarding the presenting rhythm. The authors admit that this is likely due to the small sample sizes and low power due to homogenous and unifocal population and location. While P-values remained low the actual percentages of survival and neurological functioning were consistent with improvements to patients noted in larger studies with greater statistical power. This is particularly true when discussing OHCA and patients with shockable initial rhythm. As such it

is likely that the inability to demonstrate statically significant improvement lies not in the hospital's results, but in the size and scope of the study itself.

Casamento et al. (2016) utilized review of patient records in two hospital ICUs in New Zealand and Australia. All patients were over 18 and were comatose and ventilated following OHCA or IHCA. Patients were grouped through retrospective analysis of the treatments they underwent during their hospital stay. Patients either underwent TTM at 32-34 degrees for 24 hours followed by passive rewarming, or TTM at 36 degrees for 28 hours, followed by warming to no more than 37 degrees for 36 hours, then <37.5 degrees until 72 hours post cardiac arrest. 138 patients were found that matched criteria split into the two treatment cohorts with 69 subjects apiece. Greater complications including shivering, fever and need for sedation were found in the 32-34-degree group ($P < 0.001$, $P = 0.01$, $P < 0.001$ respectively). They also note an increased discharge to home rate with significance in the 36-degree group suggesting greater efficacy and safety utilizing the 36-degree protocol ($P = 0.02$). Of particular note, this study did not directly evaluate neurological outcomes by any metric. They further failed to follow up with patients to determine survival duration or neurological function post-discharge. However, it can be supposed that the increased likelihood of discharge directly to home carries with it the assumption that these patients retained enough cognitive function to function effectively independently. Thus, some measure of cognitive benefit can be inferred. The study also failed to evaluate differences between the location of arrest, time to intervention, or presenting rhythm.

Yuan et al. (2017) performed a porcine study on the effects of early versus delayed administration of TTM. The subjects were anesthetized and cardiac arrest was induced through electrical stimulation. Resuscitation was attempted after 8 minutes of cardiac arrest. Following ROSC, the subjects either received no TTM, received chilled normal saline immediately. or

received chilled saline at one-hour post-ROSC. The subjects were assessed using the cerebral

performance category (CPC) scale. Serum and brain samples were collected following

euthanasia. CPC scores demonstrated improved neurological function in the early hypothermia

group found vs the non-hypothermia group ($P < 0.01$) as well as in the delayed hypothermia

group ($P < 0.012$). Microscopic examination of neurological cells demonstrated preservation of

the BBB in the early and late hypothermia groups vs control ($P < 0.007$, $P<0.026$, respectively).

The early hypothermia cohort further showed minimal ischemia without necrosis to brain

structures vs significant degeneration in the other cohorts.

Sonder et al. (2017) studied several commercially available cooling devices to determine

the speed of induction as well as the amount of time spent within the target temperature ranges.

The study was retrospective with ten ICU units and three ED units in Philadelphia. 140 patients

were identified as suffering an OHCA or IHCA with the application of TTM. Endovascular

cooling and the application of cooling gel pads were found to be superior to the application of

topical cooling blankets in regard to time within target temperature without variation. ($P < 0.01$).

Furthermore, cooling rate using endovascular techniques was quicker using endovascular cooling

catheters vs gel pads and cooling blankets at 2.06 degrees Celsius / hour (plus or minus 1.12

degrees Celsius / hour. $P < 0.05$ for gel pads, $P < 0.01$ for cooling blankets). The time from

cardiac arrest to the initiation of cooling was lowest in the cooling blanket cohort, however the

author notes that several patients were accepted as transfers from other hospitals and had

endovascular or gel cooling devices placed, following acceptance. This would account for a

significant increase in the time from cardiac arrest to cooling induction. No transferred patients

were found to be present in the cooling blanket cohort.

Goury et al. (2017) assessed the efficacy of a novel esophageal cooling device (ECD). The ECD takes the place of a nasogastric or orogastric tube. Surrounding the suction catheter is a secondary set of exchange lumens that connect to a chiller pumping cold saline. Contact with the lumen provides internal cooling to target temperature rapidly. The study reports an average decrease in core temperature of 0.26 degrees Celsius per hour with effective maintenance at target temperature with minimal deviation. Goury et al. (2017) further state that endoscopy revealed no, or minor trauma in 93.5% of the assessed patients. They further suggest that no trauma suffered could be directly linked to the ECD use.

Stockl et al. (2017) performed analysis on the use of neuromuscular blockade to decrease the incidence of shivering in patients undergoing TTM. They established a double-blind study creating a control group that would receive appropriately dosed rocuronium in response to shivering vs an experimental group that would receive continuous rocuronium. Results demonstrated a decrease in the likelihood of shivering when patients receive continuous neuromuscular blocking agents ($P < 0.01$). The study further demonstrates a decreased need for sedation and analgesia in the continuous group ($P < 0.01$). A more rapid resumption of consciousness and decrease in the length of hospital stay was also noted. ($P < 0.04$, $P < 0.03$ respectively). No differences between survival and neurological outcome was observed.

Kirkegaard et al. (2017) assessed prolonged use of TTM over 48 hours vs the standard 24 hours. Patients were randomly selected from 10 university hospitals across Europe. 355 patients were enrolled in the study. Patients were cooled to 33 degrees Celsius for 24 hours in the control group, or 48 hours in the experimental group. At six months post discharge no difference was noted for favorable neurological outcome ($P = 0.33$). No difference was noted in survival at

discharge either (P = 0.19). The likelihood of adverse events including, but not limited too; seizures, hypotension, arrhythmia, or renal failure were more present in the 48-hour cohort. (P = 0.03).

Aschauer, Sterz, Laggner, and Behringer (2012) assessed the costs of 398 patients undergoing TTM in Austria to determine the cost-effectiveness of TTM following cardiac arrest. These costs included; hospitalization, cooling procedures, rehabilitation and placement of implantable cardiac defibrillator. Total costs per 100 patients was found to be between 3.7, and 4.1 million euro. The researchers further assessed CPC following discharge to determine quality-adjusted life year (QALY). A cost-effectiveness ratio of 3.827 euro per QALY was discovered. This suggests that possible benefit of TTM is favorable when cost-benefit ratios are assessed, particularly due to the life altering nature of the possible benefit to the patient.

DISCUSSION

Claims of targeted temperature management's improvements in survival to hospital discharge and improvements in neurological outcomes appear well founded. In adult patients with initially shockable rhythms that remain comatose after ROSC, the data supports this assertion. Sizeable literature review and outcome studies, including the Nurnberger et al. (2017) and Perlman et al. (2015) studies demonstrate statistically significant improvement in survival to discharge as well as improved neurological functioning.

While outcome and literature review studies provide a good base of information, greater information is obtained through proper experimental design. The porcine, rabbit, and rat studies provide phenomenal experimental design and the ability to assess the biological and physiological processes affected by cardiac arrest, resuscitation and TTM. The ability to assign

control, sham, and experimental groups and perform dissection and assessment of subjects post-experiment without the ethical implications present in patient-centered studies provides results with the least bias and greatest control of confounding variables. 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. This prevents further injury due to loss of the blood brain barrier and subsequent free radical damage and cerebral edema following reperfusion.

The animal studies further provide insight into survival and neurological benefits. Improvements were noted in survival post-arrest and improvements in retained neurological functioning as measured by autonomic reflexes and operationally defined observation for 24-72 hours post-resuscitation. Indeed, a rat model by Fan et al. (2017) showed increases in survival to 2 hours with TTM vs normothermia (64% vs 34% respectively with a P-value of <.05). The authors also found improvements in neurological functioning. Two studies by Jieben et al. (2017) found similar neurological results. While failing to find a difference in cardiac arrest survival, evaluation using the overall performance category, cerebral performance category, or neurological deficit score was found to improve in cardiac arrest with TTM (P values of < 0.05 and < 0.01, respectively).

The assertion that TTM improves survivability and neurological outcomes is only somewhat supported in patients with a non-shockable cardiac rhythm upon encounter. 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). Cariou et al. (2017) provides a large amount of information by performing meta-

analysis on several studies and assessed many variables to create a comprehensive review and

recommendation for the use of TTM. The panel suggests considering TTM as a decrease in

mortality was discovered (RR 0.86, 95% CI 0.76-0.99). They do however note that neurological

outcomes remain unchanged between TTM and normothermia. The authors also note that the

studies analyzed often provided contradictory results leading to a suggestion to consider TTM vs

a strong recommendation. One could suppose that the admittedly weaker evidence for TTM in

non-shockable rhythms could derive from the processes that cause a non-shockable rhythm to

develop. Namely, prolonged cardiac arrest. In these instances, prolonged hypoxia could feasibly

lead to irreparable brain injury or death regardless of the effect TTM has. Indeed, this appears to

be the case as studies of the physiology behind TTM suggest its neuroprotective effect takes

place during reperfusion as well as inhibiting the development of cerebral edema. If the arrest is

prolonged, neuronal damage stemming from hypoxia is likely to be widespread enough that any

improvement in maintenance of the BBB and prevention of ROS production becomes a moot

point.

       The studies do not currently support the use of TTM in pediatric patients. Several

possibilities are present as to the lack of effect. Of particular note is the likelihood that pediatric

cardiac arrest is unlikely to be due to sudden arrhythmia or chronic condition. Pediatric cardiac

arrest is far more likely to be the result of congenital condition, respiratory failure, or traumatic

injury. In these instances, survival is less likely to be the result of care following ROSC. Instead

it will most likely be due to the severity of trauma or condition as well as the efficacy of

resuscitative efforts themselves. Pediatric patients are physiologically and metabolically

different from adults. Conventional wisdom would suggest that most studies on adult

populations would generalize poorly to pediatric patients due to these differences.

In conclusion, TTM demonstrates statistically significant improvements to patients who

undergo cardiac arrest and resuscitation in both survival to hospital discharge as well as retained

cognitive functions. This benefit is less pronounced in patients whose initial cardiac rhythm is

non-shockable or when the time to initiation of TTM is prolonged. While the likelihood of

benefit is diminished, the relative safety, magnitude of benefit on activities of daily living, and

cost-effectiveness of the intervention is adequate to recommend the treatment for appropriate

patients.

Clinical Applicability

Staff training on TTM should stress the importance of identifying appropriate patients

based on ROSC and status as comatose. Procedurally, efficacy has been demonstrated in

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. Fewer complications

would in turn lead to improved patient outcomes. 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.

The American Heart Association has further guidelines for the implementation and

induction of TTM. Per the AHA, 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. This is largely in agreement with the method endorsed by Dynamed.

During cooling, blood pressure, oxygen saturation, glucose and potassium must be assessed and sedatives or paralytics must be used to combat seizure activity and shivering. Jain, Gray, Slisz, Haymore, Badjatia and Kulstad (2018) assessed current methods to prevent shivering. They posit that shivering may increase cerebral metabolic stress, interfering with the neuroprotective effect of TTM. As such they recommend a step-wise approach to shivering prophylaxis including regular NSAID dosing every 4-6 hours. Buspirone administration every 8 hours and IV magnesium as a continuous infusion may also be administered. Superficial warming to temperature receptors in the face and hands may further prevent shivering. Neuromuscular blockade with vecuronium is suggested should shivering develop, though the Stockl et al. (2017) study demonstrates that continuous infusion may be preferential due to decreased need for sedation and analgesia. Hospital stay may further be decreased by continuous vs bolus neuromuscular blockade.

The AHA recommends rewarming at 24 hours progressing at 0.25 degrees per hour until normothermic. Antipyretics may be used to prevent reflex hyperthermia following rewarming. These recommendations fit well into the recommendations described above, though the Casamento et al. (2016) study does suggest that TTM at 34-36 degrees Celsius may be as effective in regard to neurological outcome, and survival to discharge. This decrease in the magnitude of hypothermia may further prevent complications such as shivering, fever, and the need for sedation or analgesia from developing. The Kirkegaard et al. (2017) study is in

agreement with the AHA recommendation for 24 hours of TTM. It demonstrated no difference in survival or neurological function with prolonged TTM. TTM for 48 hours was further demonstrated to increase the likelihood of adverse effects.

Dynamed provides resources to assist in the method of implementing TTM. Within an emergency department or ICU, the patient should be sedated, intubated and ventilated. An endovascular, esophageal, bladder or rectal temperature probe should be placed for continuous core temperature monitoring. Cooling should be activated as rapidly as possible with the intention to decrease core temperature to 32-36 degrees Celsius. Surface cooling can be implemented rapidly using ice packs, cooling blankets or water circulation pads, though surface cooling may be more variable in temperature maintenance. Core cooling can be implemented using chilled normal saline or lactated ringers at 4 degrees Celsius until target temperature is reached, followed by maintenance infusion.

The Sonder et al. (2017) study demonstrated that esophageal or gel pad cooling methods provided for more rapid achievement of target temperature as well as a decreased likelihood of variability. This would be important as relatively minor shifts from 32-34 degrees Celsius would readily place the neurological system of a patient at risk of achieving euthermia, minimizing or negating TTM's therapeutic effect. While not assessed by Sonder et al. (2017), Goury et al. (2017) demonstrated the safety and efficacy of esophageal devices in providing TTM.

Application of TTM is considerably cost-effective per the Aschauer, Sterz, Laggner, and Behringer (2012) study, particularly in light of the benefits, and favorable risk to benefit ratio. Implementation has been shown to be performed adequately with several different commercially available methods. It has further been shown to demonstrate a benefit in terms of survival to discharge as well as in retained neurological capability. Due to its ease of implementation and

potentially life altering benefit it should be readily attempted in all appropriate patients in ED

and ICU. While not expressly indicated by the AHA studies demonstrating the effectiveness of

early application, such as the Yuan et al. (2017) study, have been performed. Initial attempts at

TTM following ROSC may be beneficial on appropriate patients when implemented prior to

arrival in the ED. This may be accomplished by trained medical personnel or by EMS in the

clinical environment. TTM is a versatile and reliable intervention due to the readily available

cooling devices, and the ease of TTM induction. As a result, TTM can be readily applied to

patients following ROSC in pre-hospital or clinical environments as well as in the ED and ICU.

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