EMERGENCY MEDICINE

Openventio PUBLISHERS

ISSN 2379-4046 Open Journal http://dx.doi.org/10.17140/EMOJ-3-137

Review

*Corresponding author
Özgür Karcioglu, MD
Department of Emergency Medicine
University of Health Sciences
Istanbul Education and Research
Hospital, 34098 Fatih, Istanbul, Turkey
Tel. +90-505-5252399
E-mail: okarcioglu@gmail.com

Volume 3 : Issue 2
Article Ref. #: 1000EMOJ3137

Article History
Received: June 23rd, 2017
Accepted: July 21st, 2017
Published: July 24th, 2017

Citation
Karcioglu Ö. Therapeutic hypothermia in trauma management: New tricks for an old dog? *Emerg Med Open J.* 2017; 3(2): 30-37. doi: 10.17140/EMOJ-3-137

Therapeutic Hypothermia in Trauma Management: New Tricks for an Old Dog?

Özgür Karcioglu, MD*

Department of Emergency Medicine, University of Health Sciences, Istanbul Education and Research Hospital, 34098 Fatih, Istanbul, Turkey

ABSTRACT

Neurologic injury is the most common cause of death in patients with out-of-hospital cardiac arrest (OHCA). Targeted temperature management or therapeutic hypothermia (TH) is commonly recommended for survivors of cardiac arrest as a common final pathway of various mechanisms to alleviate the neurologic injury. Induced hypothermia can be separated into three phases: induction, maintenance and rewarming; and each phase produces several changes in normal physiology. The induction of mild to moderate TH to a target temperature 32 ºC to 34 ºC in the initial hours after cardiac arrest improves the neurologic outcome of resuscitated patients. However, recent studies failed to provide convincing data for the beneficial effects of TH in practice. The main focus for early management of severe traumatic brain injury (TBI) is to eliminate the hazards of secondary injury, especially hypotension and hypoxia, which are known to herald worse outcomes. The administration of mild TH has also been shown to improve neurological outcomes in severe TBI. Although, the exact mechanisms are still elusive, it is known that hypothermia exerts its effects in many pathways of injury in TBI. The utility of TH, in addition to treatment for cardiac arrest, is noted in the course of acute brain injuries. It should be noted that the evidence is not yet sufficient to recommend routine use of TH for TBI outside of research settings.

KEY WORDS: Therapeutic hypothermia (TH); Hypothermia; Trauma management; Targeted temperature management; Traumatic brain injury (TBI); Trauma.

ABBREVIATIONS: ATP: Adenosine triphosphate; BTF: Brain Trauma Foundation; GCS: Glasgow Coma Scale; ICP: Intracranial pressure; OHCA: Out-of-hospital cardiac arrest; ROSC: Return of Spontaneous Circulation; TBI: Traumatic Brain Injury; TH: Therapeutic Hypothermia.

INTRODUCTION

Neurologic injury is the most common cause of death in patients with out-of-hospital cardiac arrest (OHCA) and contributes to the mortality of in-hospital cardiac arrest.[1] Neural tissue is damaged in traumatic injury as well. Traumatic brain injury (TBI) may be classified based on severity, ranging from 'mild' to 'severe', most commonly based on the Glasgow Coma Scale (GCS). There are two injury phases in TBI. Primary injury occurs immediately at the time of impact, and includes the tear, shear or haemorrhage due to the acceleration-deceleration or rotational forces. The process triggers multiple biochemical cascades in hours or days, which is termed secondary brain injury. Evolution of secondary damage mechanisms has been studied many times in the experimental setting, and can be divided into three distinct phases: acute, sub-acute and chronic. In another point of view, these hazards include ischaemic, cytotoxic and inflammatory processes.

The immediate interventions in TBI comprise ensuring maintenance of perfusion of the brain with oxygenated blood. 'Airway, breathing, circulation' confers to this prioritization. Post-TBI cerebral ischaemia may occur due to a combination of mechanical vessel distortion,

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

hypotension, loss of cerebral blood flow autoregulation, insufficient nitric oxide or vasospasm.[2] Therapeutic hypothermia (TH) may offer the prospect of an extended window to restore the integrity of circulation, with the brain maintained in a protective, hypometabolic state.

The promising idea of 'human refrigeration' was advocated first for the management of TBI and brain tumours by Fay in the 1940's who reported its application in 124 cases.[3]

TH has been historically classified into: mild (34.5-36.5 °C), moderate (34.5-32 °C), marked (28-32 °C) and profound hypothermia (<28 °C).[4-6] Induced hypothermia can be separated into three phases: induction, maintenance and rewarming, eachphase produces several changes in normal physiology.

TH is practised mainly in the treatment of adult cardiac arrest and neonatal hypoxic-ischemic encephalopathy. Some evidence indicate that hypothermia could be useful in neurologic injuries, such as stroke, subarachnoid hemorrhage and TBI. The administration of mild TH has been shown to improve neurological outcomes and can prevent severe brain damage after OHCA.[7,8]

Different mechanisms of effect have been postulated for TH in mitigating the hazards of hypoxia and ischemia in the tissues and the organism as a whole. TH decreases the metabolic rate to restore the supply and demand of O_2, attenuates excitotoxicity, limits inflammation, prevents energy adenosine triphosphate (ATP) depletion, reduces free radical production and also intracellular calcium overload to avoid apoptosis.[6]

Dating back to the pioneer studies of Fay, nearly 75 years of basic and clinical evidence support therapeutic value of induced hypothermia.[3,6] However, its availability in the management trauma is not studied in depth. Hypothermia has long been viewed as a threat to trauma victims and thought to be associated with increased mortality. Nonetheless, some recent reports pointed out beneficial effects in selected situations.

RATIONALE FOR USE: ANIMAL STUDIES

Hypothermia was shown to potentiate the activation of various molecular mechanisms which are involved in cell survival pathways. This promising finding occurred specifically in the pre-synaptic mossy fibres in the stratum lucidum of the hippocampus, which indicates an important role of hypothermia in cell survival.[9] One of the mechanisms that postulate the protective effect of hypothermia against hazards of TBI is attenuation of the expression of various pro-inflammatory cytokines taking part in the pathogenesis of TBI such that Interleukin-1β (IL-1β), IL2, IL6 and TGFβ-2.[10,11]

A study showed that IL-10 production was reduced in rat microglia cultures under hypothermic conditions, suggesting that the neuroprotective effects of hypothermia may paradoxically involve the suppression of anti-inflammatory cytokines as well.[12] Cooling also suppressed the X-linked inhibitor of apoptosis protein cleavage thus promoting its binding onto caspases and inhibiting the protease activity.[13] Using an ischaemia-reperfusion model, Kobayashi et al[14] screened 24,000 genes using high density oligonucleotide microarray and found that the expression of 33 genes were temperature-dependent. Hypothermia has an impact on a range of protein kinases involved in cellular transcription regulation. This leads to a diminution of necrosis, and a secondary reduction in the inflammation that would otherwise contribute to the cycle of secondary injury.

In a recent study Moffatt et al[15] conducted a systematic review and culminated data on 327 animals cooled to ≤20 °C after hemorrhagic shock in these trials. Evidence regarding profound hypothermia suggests that this form of resuscitation modality could be beneficial to the patients with hemorrhagic shock. Animal studies, as a whole, demonstrate a clear benefit of the use of TH in the management of TBI. Although, the exact mechanisms are still elusive, it is known that hypothermia exerts its effects in many pathways of injury in TBI.

Cooling modulates production of a range of inflammatory mediators implicated in secondary brain injury. Chen et al[16] assayed levels of six of these in a swine model of lethal haemorrhage, applying cardiopulmonary bypass with ahyperkalaemic perfusion fluid after 30 minutes of haemorrhage. Animals that were cooled demonstrated reduced serum levels of pro-inflammatory IL-6, compared to normothermic animals. Levels of a protective heat shock protein, Heat-shock protein-7 (HSP-70), and an anti-inflammatory cytokine, IL-10, were found to be elevated in the cooled animals. Other inflammatory cytokines released by activated microglia and astrocytes in the context of injury include IL-1β, IL-18 and TNF-α, and modulation of this response is observed in hypothermia.[17]

The Theoretical Rationale for Cooling

Hyperthermia must be avoided following cardiac arrest. Failure to control a patient's core temperature is associated with the development of fever and worse neurologic outcome.[7,8,18,19] According to an observational study of 151 patients, the risk of death increases for each degree over 37 °C during the first 48 hours after cardiac arrest (odds ratio [OR] 2.26; 95% CI 1.24-4.12).[18] Under the concept of cardiocerebral resuscitation, patients with return of spontaneous circulation (ROSC) following OHCA should receive post-resuscitation care including urgent mild TH and cardiac catheterization.[20]

Cooling can be beneficial according to well-demonstrated clinical principles. First, intracranial hypertension is a firm predictor of neurological deterioration and increased mortality in head injury.[21] Secondly, cooling has been demonstrated to control intracranial pressure (ICP).

In 2009 Tokutomi et al[22] conducted a comparison study on ICP and biochemical parameters in patients cooled to 35 °C (compared with historical controls cooled to 33 °C). They conc-

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

luded that cooling patients to 35 °C is safe and the ICP reduction effects of 35 °C hypothermia are similar to those of 33 °C hypothermia.

Patients who are not neurologically intact following resuscitation from cardiac arrest should have their temperature managed. The only absolute contraindication for temperature management is an advanced directive that proscribes aggressive care or a medical scenario for which such care is not appropriate. TH should not be used in patients with active non-compressible bleeding, but TTM (targeted temperature maintained ≤36 °C) in this population is reasonable. Either TH or TTM may be used in pregnant or hemodynamically unstable patients, and those receiving coronary catheterization or thrombolytics.[23,24] Fever prevention is recommended in all cardiac arrest patients without an advanced directive proscribing the necessary interventions.[18,19]

Induced Hypothermia in Traumatic Brain Injury

Hypothermia has long been used in subarachnoid hemorrhage (SAH) (more than a half century) when it was used as a neuroprotective measure against bleeding or ischemia during aneurysm repair surgery. The usefulness of mild TH has also been studied in patients with severe TBI.[25-29] Table 1 demonstrates properties of the outstanding human studies that were reviewed in the present study.

Table1: Main Characteristics of the Outstanding Human Studies that were Explained and Reviewed in the Present Study.

Investigator(s)	Sample size	Objectives	Results
Clifton et al[25]	46	Effect of TH *versus* standard management in severe non-penetrating brain injury	TH resulted in improved neurologic outcome with minimal toxicity in severe head injury.
Marion et al[26]	84	Neurologic recovery at 3 months and at 6 months in severe TBI	Treatment with moderate TH for 24 hours in patients with severe TBI hastened neurologic recovery and may have improved the outcome
Aibiki et al[27]	26	To examine the levels of thromboxane B2 and 6-keto prostaglandin F1 alpha production in arterial and internal jugular bulb sera in patients with TBI.	Moderate hypothermia may reduce prostanoid production after TBI, there by attenuating an imbalance of thromboxane A2 and prostaglandin I2
Jiang et al[28]	87	To investigate the protective effects of long-term (3-14 days) mild TH (33-35 °C) on outcome	Long-term mild TH significantly improves outcomes in patients with severe TBI.
Shiozaki et al[29]	91	To determine whether mild TH is essential in the treatment of severe TBI with low-intracranial pressure	Mild TH should not be used for the treatment of severe TBI with low ICP because this therapy conveys no advantage over normothermia in such patients.
McIntyre et al[31]	Systematic review of 12 trials	Toexplore the effects of depth, duration, and rate of rewarming after discontinuation of TH on mortality and neurologic outcome in TBI	TH may reducerates of mortality and poor outcome in TBI. Outcomes were influenced, by depth and duration of TH and rate of rewarming after discontinuation of TH.
Peterson et al[32]	Systematic review of 13 trials	Effects of TH on mortality, favorable neurologic outcome, and adverse effects in adults with TBI	Findings support previous findings that TH constitutes a beneficial treatment of TBI in specific circumstances.
Sadaka and Veremakis[33]	Systematic review of 18 trials	Effect of TH in patients with TBI on ICP	A significant reduction of ICP was noted in all of the patients
Clifton et al[34]	392	Effect of early TH (2-5 h) *versus* normothermia in the course of severe TBI.	No impact on the neurologic outcome is observed.
Clifton et al[35]	232	To assess whether very early induction of TH improves outcome in severe TBI	Did not confirm the utility of TH as a primary neuro protective strategy in severeTBI
Dunkley and McLeod[36]	Systematic review of 8 trials	To demonstrate the efficacy of TH in adult patients with TBI	TH had increased benefits in patients with haematoma-type injuries as opposed to those with diffuse injury and contusions. TH should recommence if rebound intracranial hypertension is observed.
Maekawa et al[38]	148	Benefits of TH in patients with severe TBI	Tight hemodynamic management and slow rewarming, together with prolonged TH did not improve the neurological outcomes or risk of mortality compared with strict temperature control
Hifumi et al[39]	129	Compare the effectiveness of the two TH regimens in severe or critical trauma	The fever control group had a significant reduction of TBI-related mortality compared with the TH group. Fever control may be considered instead of TH in patients with TBI.
Sydenham et al[40]	systematic review of 23 trials (1614 randomised patients)	To estimate the effect of mild TH for TBI on mortality and long-term functional outcome complications	There is no evidence that hypothermia is beneficial in the treatment of TBI. TH may be effective in reducing death and unfavourable outcomes for TBI, but significant benefit was only found in low-quality trials.
Jiang et al[41]	215	To compare the effect of long-term *versus* short-term mild TH on the outcome of severe TBI patients	Prolonged TH (5 days) was more effective than conventional TH (2 days) in reducing the number of patients with poor neurological outcomes.
Adelson et al[42]	115	To assess whether TH for 48-72 h with slow rewarming improved mortality in children with TBI	Hypothermia for 48 h with slow rewarming does not reduce mortality after pediatric severe TBI.

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

TBI is the most common cause of death in young population. Acute care of TBI comprise mainly elimination of the risk of secondary injuries, namely, hypoxia, hypotension, and hyperthermia. TH is seen as a critical intervention following acute neurologic injury, although most of the researches have yielded inconclusive results concerning efficacy so far. In the case of TBI, clinical trials have shown conflicting results, despite almost uniform efficacy seen in preclinical experiments. In head and spinal trauma, mild cooling may help to limit secondary injury. More preclinical and clinical research is needed to better define whether there could be a role for induced hypothermiain the case of spinal cord injuries.[30]

Several systematic reviews suggested that the best results were elicited with the treatment mode in which mild TH had been maintained for >48 h, and that the rate of rewarming had been very slow.[31,32] A systematic review by Sadaka et al[33] culminated data from 13 randomized clinical trials and 5 observational studies regarding effects of intracranial hypertension in those with TBI using TH. A significant reduction of ICP was noted in all of the patients.

"The National Acute Brain Injury Study: Hypothermia (NABIS: H)" was a prospective, multicenter, randomized trial which enrolled 392 patients with 16 to 65 years of age with coma following TBI conducted in 2001.[34] The patients were randomly assigned to be treated with hypothermia (33 °C initiated within 6 hours after injury), maintained for 48 hours by means of surface cooling, or normothermia. They concluded that the procedure is not effective in improving outcomes in patients with severe TBI. Nonetheless, subsequent analyses identified several factors that might improve the effects of mild TH for treating patients with TBI in clinical settings. Authors suggested that hypothermia was not induced quickly enough to produce a benefit in normothermic patients, and that rewarming patients who arrived hypothermic was detrimental.

Ten years later, NABIS: H II was performed as a randomised, multicentre clinical trial of young patients with severe TBI who were enrolled within 2.5 h of injury at six sites in the USA and Canada.[35] Patients were either cooled to 33 °C for 48 h and then gradually rewarmed or treated at normothermia. This trial did not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe TBI. Nonetheless, exploratory subgroup analyses revealed that in patients with surgically removed hematomas the hypothermia group had better outcomes, while in patients with diffuse brain injuries there was no significant difference in outcomes.

Very recently, Dunkley and McLeod have culminated data from eight peer-reviewed studies and concluded that TH had increased benefits in patients with haematoma-type injuries as opposed to those with diffuse injury and contusions.[36] It also suggests that cooling should be reconsidered if rebound intracranial hypertension ensues. They postulated that TH can have a positive impact on patient outcome, but more research is required.

Early after penetrating brain injury (PBI). Regional cerebral oxygen tension and consumption significantly decreased in the ipsilateral cortex in the PBI group compared with the control group.[37] At the same time point, glucose uptake was significantly reduced globally in the PBI group compared with the control group.

The guideline of the Brain Trauma Foundation (BTF) constructed the base for a meta-analysis of eight relatively comparable RCTs, and pointed out a significant risk reduction of mortality (RR 0.51; 95% CI 0.33-0.79) and favourable neurological outcomes (RR 1.91; 95% CI 1.28-2.85) when hypothermia was maintained longer than 48 hours.[32] This was in accord with the findings of McIntyre et al[31]. These results prompted BTF to issue a Level III recommendation for the use of hypothermia in TBI in adult patients.

Maekawa et al[38] conducted a multicenter controlled Brain-Hypothermia (B-HYPO) Study- in patients with severe TBI (GCS 4-8). The randomized controlled trial was designed in Japan to compare the neurological outcomes between TH (32-34 °C) and strict temperature control (35.5-37 °C) for patients with TBI between 2002 and 2008. There were no significant differences in the likelihood of poor neurological outcome or mortality between the two groups. One year later, Hifumi et al[39] performed a *post-hoc* study to re-evaluate data based on the severity of trauma as abbreviated injury scale (AIS) 3-4 or AIS 5 and compare Glasgow Outcome Scale score and mortality at 6 months. The fever control group demonstrated a significant reduction of TBI-related mortality compared with the MTH group (9.7% *vs*. 34.0%, p=0.02) and an increase of favorable neurological outcomes (64.5% *vs*. 51.1%, p=0.26) in patients with AIS 3-4, although the latter was not statistically significant.

Marion, conducted a study that randomized 82 patients and compared Glasgow Outcome Scores at 3, 6, and 12 months in 1997.[26] They found no difference in mortality, but more patients in the hypothermia group had better outcomes. Analysis by initial severity level revealed that the benefit occurred in the patients who were less severely injured (with initial GCS scores of 5 to 7) while there was no statistically significant benefit in patients who were more severely injured (those with lower GCS of 3 or 4).

A systematic review of 22 randomized controlled trials of mild-to-moderate hypothermia (32 to 35 ºC) following TBI noted a small but significant decrease in the risk of death (RR 0.76, 95% CI 0.60-0.97) or poor neurologic outcome (RR 0.69, 95% CI 0.55-0.86) among more than 1,300 patients treated, but noted that significant benefit was seen only in low quality trials.[40] The time-dependent effect of hypothermia was evaluated by Jiang et al. for TBI.[41] This randomized study of 215 patients with severe TBI demonstrated that prolonged hypothermia (5±1.3 days) was more effective than conventional hypothermia (2±0.6 days) in reducing the number of patients with poor neurological outcomes. Cooling blankets were used in both patients arms to reach 33-35 °C of rectal temperature. In a more recent

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

multicenter, multinational, randomised controlled trial on induced hypothermia, Adelson et al[42] hypothermia for 48 h with slow rewarming does not reduce mortality of improve global functional outcome after paediatric severe traumatic brain injury.

Hypothermia can be administered either early after injury and prior to intracranial pressure elevation, in which case it is termed "prophylactic," or as a treatment for refractory intracranial pressure elevation, typically referred to as "therapeutic."

Guidelines: BTF has published guidelines to highlight and mitigate effects of TBI in humans in 2016 and cited "prophylactic hypothermia"as a Level IIB recommendation - i.e., low-quality body of evidence.[43] They mentioned that "early (within 2.5 h), short-term (48 h post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury".

The Pediatric TBI Guidelines provided the knowledge and background for standard management of children following severe TBI and highlighted that there are very few clinical studies to date.[44] Despite the lack of clinical data in children, TH may be considered in the setting of refractory intracranial hypertension.

Treatment of intracranial pressure may be considered at a threshold of 20 mmHg.

Level II—Moderate hypothermia (32-33 °C) beginning early after severe TBI for only 24 hrs duration should be avoided;
Level II—Moderate hypothermia (32-33 °C) beginning within 8 hrs after severe TBI for up to 48 hrs' duration should be considered toreduce intracranial hypertension;
Level II—If hypothermia is induced for any indication, rewarming at a rate of _0.5 °C per hour should be avoided;
Level III—Moderate hypothermia (32-33 °C) beginning early after severe TBI for 48 hrs duration may be considered.[45]

Hypothermia induction should be started as soon as possible to minimize neurologic damage. Infusing cold fluids, e.g., Ringer's lactate >25 ml/kg at 4°C, is the easiest and most effective method for inducing hypothermia.[46]

Fever worsens outcome after stroke and probably severe head injury, presumably by aggravating secondary brain injury.[47] Current approaches emphasize maintaining normothermia through the use of antipyretic medications, surface cooling devices, or even endovascular temperature management catheters. However, this approach has not been systematically tested with regard to clinical outcome. Similarly non-induced hypothermia has been associated with an increase in mortality after TBI.[48]

Induced hypothermia has been a proposed treatment for TBI based upon its potential to reduce ICP as well as to provide neuroprotection and prevent secondary brain injury.[34] On the other hand, some systematic reviews and meta-analyses found similar but more borderline benefits for death and neurologic outcome as well as an increased risk for pneumonia.[31,34,49-51] Two trials of hypothermia therapy in children with TBI have shown no improvement in neurologic or other outcomes; one showed a non-significant increase in mortality.[42,52]

McIntyre et al[31] conducted a systematic review of all randomized controlled trials of TH for at least 24 hours compared to normothermia in victims of TBI.[31] They concluded that TH may reduce the risks of mortality and poor neurologic outcome in adults with TBI. Outcomes were influenced, however, by depth and duration of hypothermia as well as rate of rewarming after discontinuation of the procedure.

Substantial variability among studies in the depth and duration of hypothermia, as well as the rate of rewarming limit the ability to draw conclusions from these studies. A newer trial examined the potential benefit of TH when initiated within two

Table 2: Emergent and Intensive Care Management of Patients with TBI *via* Induced Hypothermia.

Step	Why necessary?	Notes-pitfalls
Tight control of serum glucose	Hyperglycemia is associated with excitotoxicity, neuronal membrane damage and sepsis	There is a decrease in insulin sensitivity and insulin secretion. Hyperglycemia should be treated with I.V. insulin therapy and close monitoring
Monitor cardiac rhythm	Avoid arrhythmia.	Ventricular arrhythmias are seen more commonly in severe hypothermia.
Electrolyte disorders	Hypokalemia and hypomagnesemia	Can cause arrhythmias, muscle weakness and altered mental status
Monitor blood parameters	pH, coagulation markers, electrolytes, renal andhepatic function. Drug metabolism may be distorted, thus drug levels should also be studied.	
Care for potential infective sources	Provide good oral hygiene, monitör IV lines, administer respiratory therapy and keep suctioning. Gut lumen washout and administration of non-absorbable antibiotics through the nasogastric (NG) tube in patients cooled for three days or longer (PKHT)	
Slow rewarming	(<=0.1°C/ hour) and halt or reverse the rewarming in response to prolonged ICP spikes. Monitor for hyperkalaemia.	Rewarming at a rate of >0.5°C per hour should be avoided.

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

to five hours of TBI in a selected group of younger patients and found no benefit of treatment on mortality or neurologic outcomes.[35] Given the uncertainties surrounding its appropriate use, some authors put forth that TH treatment should be limited to clinical trials, or to patients with elevated ICP refractory to other therapies.[40,44,53] Table 2 describes emergent and intensive care management of patients with TBI *via* induced hypothermia.

CONCLUSION

Although, the exact mechanisms are still elusive, it is known that hypothermia exerts its effects in many pathways of injury in TBI. TH has a potential to improve outcomes in trauma and specifically, TBI when applied early to gain time for intervention to restore the circulation, and as a way of preventing secondary injury. It should be noted that the evidence is not yet sufficient to recommend routine use of TH for TBI outside of research settings.

CONFLICTS OF INTEREST

Author mention that there is no conflict of interest in this study.

REFERENCES

1. Coppler PJ, Marill KA, Okonkwo DO, et al. Concordance of brain and core temperature in comatose patients after cardiac arrest. *Ther Hypothermia Temp Manag*. 2016; 6(4): 194-197. doi: 10.1089/ther.2016.0010

2. Sahuquillo J, Vilalta A. Cooling the injured brain: How does moderate hypothermia influence the pathophysiology of traumatic brain injury. *Curr Pharm Des*. 2007; 13(22): 2310-2322. doi: 10.2174/138161207781368756

3. Fay T. Observations on prolonged human refrigeration. *N Y State J Med*. 1940; 40: 1351-1354.

4. Tisherman SA, Rodriguez A, Safar P. Therapeutic hypothermia in traumatology. *Surg Clin North Am*. 1999; 79(6): 1269-1289. doi: 10.1016/S0039-6109(05)70077-3

5. Nagel S, Papadakis M, Hoyte L, Buchan AM. Therapeutic hypothermia in experimental models of focal and global cerebral ischemia and intracerebral hemorrhage. *Expert Rev Neurother*. 2008; 8(8): 1255-1268. doi: 10.1586/14737175.8.8.1255

6. Andresen M, Gazmuri JT, Marín A, Regueira T, Rovegno M. Therapeutic hypothermia for acute brain injuries. *Scand J Trauma Resusc Emerg Med*. 2015; 23: 42. doi: 10.1186/s13049-015-0121-3

7. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002; 346(22): 549-556. doi: 10.1056/NEJMoa012689

8. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002; 346(8): 557-563. doi: 10.1056/NEJMoa003289

9. Atkins CM, Oliva AA, Jr., Alonso OF, et al. Hypothermia treatment potentiates ERK1/2 activation after traumatic brain injury. *Eur J Neurosci*. 2007; 26(4): 810-819. doi: 10.1111/j.1460-9568.2007.05720.x

10. Kinoshita K, Chatzipanteli K, Vitarbo E, et al. Interleukin-1beta messenger ribonucleic acid and protein levels after fluid-percussion braininjury in rats: Importance of injury severity and brain temperature. *Neurosurgery*. 2002; 51(1): 195-203.

11. Truettner JS, Alonso OF, Dietrich WD. Influence of therapeutic hypothermia on matrix metalloproteinase activity after traumatic brain injury in rats. *J Cerebr Blood Flow Metabol*. 2005; 25(1): 1505-1516. doi: 10.1038/sj.jcbfm.9600150

12. Matsui T, Kakeda T. IL-10 production is reduced by hypothermia but augmented by hyperthermia in rat microglia. *J Neurotrauma*. 2008; 25(6): 709-715. doi: 10.1089/neu.2007.0482

13. Qiu L. Hypothermia in traumatic brain injury – A literature review. *J Intens Care Soc*. 2011,12 (3); 201-214. doi: 10.1177/175114371101200307

14. Kobayashi MS, Asai S, Ishikawa K, et al. Global profiling of influence of intra-ischemic brain temperature on gene expression in rat brain. *Brain Research Rev*. 2008; 58(1): 171-191. doi: 10.1016/j.brainresrev.2008.03.001

15. Moffatt SE, Mitchell SJB, Walke JL. Deep and profound hypothermia in haemorrhagic shock, friend or foe? A systematic review. *J R Army Med Corps*. 2017. pii: jramc-2016-000723. doi: 10.1136/jramc-2016-000723

16. Chen Z, Chen H, Rhee P, et al. Induction of profound hypothermia modulates the immune/inflammatory response in a swine model of lethalhemorrhage. *Resuscitation*. 2005; 66(2): 209-216. doi: 10.1016/j.resuscitation.2005.01.021

17. Morino T, Ogata T, Takeba J, Yamamoto H. Microglia inhibition is a target of mild hypothermic treatment after the spinal cord injury. *Spinal Cord*. 2008; 46(6): 425-431. doi: 10.1038/sj.sc.3102163

18. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med*. 2001; 161(16): 2007-2012. doi: 10.1001/archinte.161.16.2007

19. Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation*. 2013; 84(8):

1062-1067. doi: 10.1016/j.resuscitation.2013.03.038

20. Ewy GA, Bobrow BJ. Cardiocerebral resuscitation: An approach to improving survival of patients with primary cardiac arrest. *J Intensive Care Med*. 2016; 31(1): 24-33. doi: 10.1177/0885066614544450

21. Juul N, Morris GF, Marshall SB, et al. Marshall LF. Intracranial hypertension and cerebral perfusion pressure: Influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. *J Neurosurg*. 2000; 92(1): 1-6. doi: 10.3171/jns.2000.92.1.0001

22. Tokutomi T, Miyagi T, Takeuchi Y, Karukaya T, Katsuki H, Shigemori M. Effect of 35 degrees C hypothermia on intracranial pressure and clinical outcome in patients with severe traumatic brain injury. *J Trauma*. 2009; 66(1): 166-173. doi: 10.1097/TA.0b013e318157dbec

23. Nielsen N, Hovdenes J, Nilsson F, et al; Hypothermia Network. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand*. 2009; 53(7): 926-934. doi: 10.1111/j.1399-6576.2009.02021.x

24. Skulec R, Kovarnik T, Dostalova G, Kolar J, Linhart A. Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome. *Acta Anaesthesiol Scand*. 2008; 52(2): 188-194. doi: 10.1111/j.1399-6576.2007.01510.x

25. Clifton GL, Allen S, Barrodale P, et al. A phase II study of-moderate hypothermia in severe brain injury. *J Neurotrauma*. 1993; 10(3): 263-271. doi: 10.1089/neu.1993.10.263

26. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med*. 1997; 336(8): 540-546. doi: 10.1056/NEJM199702203360803

27. Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2production after traumatic brain injury in humans. *Crit Care Med*. 2000; 28(12): 3902-3906.

28. Jiang J, Yu M, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg*. 2000; 93(4): 546-549. doi: 10.3171/jns.2000.93.4.0546

29. Shiozaki T, Hayakata T, Taneda M, et al. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients withlow intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg*. 2001; 94(1): 50-54. doi: 10.3171/jns.2001.94.1.0050

30. Finkelstein RA, Alam HB. Induced hypothermia for trauma: current research and practice. *J Intensive Care Med*. 2010; 25(4): 205-226. doi: 10.1177/0885066610366919

31. McIntyre LA, Fergusson DA, Hébert PC, Moher D, Hutchison JS. Prolonged therapeutic hypothermia after traumatic brain injury in adults: A systematic review. *JAMA*. 2003; 289(22): 2992-2999. doi: 10.1001/jama.289.22.2992

32. Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: A systematic review and meta-analysis. *J Neurotrauma*. 2008; 25(1): 62-71. doi: 10.1089/neu.2007.0424

33. Sadaka F, Veremakis C. Therapeutic hypothermia for the management of intracranial hypertension in severe traumatic brain injury: A systematic review. *Brain Inj*. 2012; 26(7-8): 899-908. doi: 10.3109/02699052.2012.661120

34. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. 2001; 344(8): 556-563. doi: 10.1056/NEJM200102223440803

35. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): A randomised trial. *Lancet Neurol*. 2011; 10(2): 131-139. doi: 10.1016/S1474-4422(10)70300-8

36. Dunkley S, McLeod A. Therapeutic hypothermia in patients following traumatic brain injury: A systematic review. *Nurs Crit Care*. 2017; 22(3): 150-160. doi: 10.1111/nicc.12242

37. Gajavelli S, Kentaro S, Diaz J, et al. Glucose and oxygen metabolism after penetrating ballistic-like brain injury. *J Cereb Blood Flow Metab*. 2015; 35(5): 773-780. doi: 10.1038/jcbfm.2014.243

38. Maekawa T, Yamashita S, Nagao S, Hayashi N, Ohashi Y; Brain-Hypothermia Study Group. Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: A randomized controlled trial. *J Neurotrauma*. 2015; 32(7): 422-429. doi: 10.1089/neu.2013.3197

39. Hifumi T, Kuroda Y, Kawakita K, et al. Fever Control Management Is Preferable to Mild Therapeutic hypothermia in traumatic brain injury patients with abbreviated injury scale 3-4: A multi-center, randomized controlled Trial. *J Neurotrauma*. 2016; 33(11): 1047-1053. doi: 10.1089/neu.2015.4033

40. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Syst Rev*. 2009; (2): CD001048. doi: 10.1002/14651858.CD001048.pub4

41. Jiang JY, Xu W, Li WP, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab*. 2006; 26(6): 771-776. doi: 10.1038/sj.jcbfm.9600253

ISSN 2379-4046 http://dx.doi.org/10.17140/EMOJ-3-137

42. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): A phase 3, randomised controlled trial. *Lancet Neurol*. 2013; 12(6): 546-553. doi: 10.1016/S1474-4422(13)70077-2

43. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017; 80(1): 6-15. doi: 10.1227/NEU.0000000000001432

44. Adelson PD. Hypothermia following pediatric traumatic brain injury. *J Neurotrauma*. 2009; 26(3): 429-436. doi: 10.1089/neu.2008.0571

45 Kochanek PM. Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents-second edition. *Pediatr Crit Care Med*. 2012; 13(Suppl 1): S1-S82. doi: 10.1097/PCC.0b013e31823f435c

46. Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest–a feasibility study. *Resuscitation*. 2005; 64(3): 347-351. doi: 10.1016/j.resuscitation.2004.09.002

47. Andrews PJ, Sleeman DH, Statham PF, et al. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: A comparison between decision tree analysis and logistic regression. *J Neurosurg*. 2002; 97(2): 326-336. doi: 10.3171/jns.2002.97.2.0326

48. Konstantinidis A, Inaba K, Dubose J, et al. The impact of nontherapeutic hypothermia on outcomes after severe traumatic brain injury. *J Trauma*. 2011; 71(6): 1627-1631. doi: 10.1097/TA.0b013e3182159e31

49. Georgiou AP, Manara AR. Role of therapeutic hypothermia in improving outcome after traumatic brain injury: A systematic review. *Br J Anaesth*. 2013; 110: 357-367. doi: 10.1093/bja/aes500

50. Harris OA, Colford JM Jr, Good MC, Matz PG. The role of hypothermia in the management of severe brain injury: A meta-analysis. *Arch Neurol*. 2002; 59(7): 1077-1083. doi: 10.1001/archneur.59.7.1077

51. Henderson WR, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ. Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis. *Intensive Care Med*. 2003; 29(10): 1637-1644. doi: 10.1007/s00134-003-1848-2

52. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008; 358: 2447-2456. doi: 10.1056/NEJMoa0706930

53. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. III. Prophylactic hypothermia. *J Neurotrauma*. 2007; 24(Suppl 1): S21-S25. doi: 10.1089/neu.2007.9993