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ROLE OF THERAPEUTIC HYPOTHERMIA IN IMPROVING OUTCOME AFTER TRAUMATIC BRAIN INJURY : A SYSTEMATIC REVIEW

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Abstract

Introduction: *A nondegenerative and noncongenital brain injury caused by external mechanical forces can cause permanent or temporary harm to cognitive, physical, and psychosocial functions and change or diminish awareness. Traumatic brain injury can cause cerebral edema and ICP increase, worsening the lesion. Cellular death can occur minutes to hours after an injury, although negative effects can last 72 hours or more. Therapeutic hypothermia (HT) can lower ICP and protect neurons, improving patient prognosis and lowering mortality.*

The aim: *This article showed role of therapeutic hypothermia in improving outcome after traumatic brain injury.*

Methods: *This study demonstrated compliance with all requirements by comparing itself to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards. Therefore, the experts were able to ensure that the study was as current as feasible. For this search strategy, publications published between 2013 and 2023 were considered. Several online reference sources, including Pubmed and SagePub, were utilized for this purpose. It was determined not to consider review pieces, previously published works, or works that were only partially completed.*

Result: *In the PubMed database, the results of our search brought up 112 articles, whereas the results of our search on SagePub brought up 107 articles. The results of the search conducted for the last year of 2013 yielded a total 59 articles for PubMed and 38 articles for SagePub. In the end, we compiled a total of 28 papers, 19 of which came from PubMed and nine of which came from SagePub. We included seven study that met the criteria.*

Conclusion: *HT has not reduced, but may have increased, mortality in TBI patients in some high-quality studies. However, TBI patients with elevated ICP may benefit from hypothermia as therapy rather than as prophylaxis when initiated within 24 hours.*

Keyword: *Hypothermia; Intracranial preassure; Traumatic brain injury*

INTRODUCTION

Traumatic brain injury (TBI) is a nondegenerative and noncongenital event in the brain caused by external mechanical forces that allows permanent or temporary damage to cognitive, physical and psychosocial functions with conditions of change or decrease in consciousness.[1] Trauma is the leading cause of death in people aged <45 years and more than half of these deaths are the result of head injury. The American Trauma Society (ATS) states that approximately 500,000 Americans are hospitalized each year after brain trauma. Approximately more than 75,000-90,000 above died at a young and healthy age.[2]

The epidemiology of brain trauma is inaccurate because there are different definitions and classifications. The incidence of head injuries in the United States is estimated at 180-220 cases per 100,000 population.[3] As many as 10% of these traumas are fatal and result in nearly 550,000 people being hospitalized each year in the United States with head trauma. Head injuries account for 40% of deaths from acute injuries in the United States. Every year there are 200,000 victims who suffer brain injuries and need to be hospitalized and 1.74 million people who suffer minor head injuries who need assistive devices due to temporary disability for at least 1 day.[4,5]

Head injuries can cause complications for sufferers, including cranial complications and systemic complications. Cranial complications are complications that may occur in patients with TBI, including: cerebral edema, intracranial hypertension, infection, calcium ion toxicity and vasospasm. Systemic complications, especially ischemic, include hypoxemia, hypotension, hypertension, hyperglycemia, and hypoglycemia. This means that TBI must be managed immediately and well.[6] Optimal management of head injury patients begins with early and appropriate triage.[7–9]

The occurrence of cerebral edema and subsequent elevation of intracranial pressure (ICP) can be observed as a consequence of traumatic brain injury, hence potentially intensifying the severity of the lesion. Cellular demise may transpire within a span of minutes to hours subsequent to an injury, whereas deleterious consequences may persist for a duration of 72 hours or beyond. Therapeutic hypothermia (HT) has been shown to have the potential to decrease ICP and serve as a neuroprotective intervention, consequently safeguarding neuronal functionality and enhancing patient prognosis while reducing mortality rates.[10]

The use of HT in patients with TBI is a subject of ongoing debate and uncertainty in the academic community. The management of hypertension is supported by the results obtained from a significant number of experimental animals. Numerous studies have demonstrated that HT can enhance neurological results and mitigate mortality rates. Numerous studies have examined the efficacy of HT in patients with severe TBI and have found no significant improvement in outcomes compared to control groups. Furthermore, a multicenter trial with a substantial sample size has provided evidence suggesting that HT could potentially have a negative effect on both mortality rates and functional outcomes.[11–13]

This observation indicates that the use of hypothermia as a therapeutic technique in patients with TBI continues to be a topic of debate and disagreement within the academic community. Systematic reviews may also present divergent findings. The findings of a comprehensive meta-analysis suggest potential advantages of HT; nonetheless, it is important to consider the potential influence of a substantial quantity of studies with low methodological quality on these results. Nevertheless, a recent meta-analysis indicates that HT may be associated with increased mortality rates and unfavorable outcomes in trials of high methodological quality.[12,13]

The current study unveiled the presence role of therapeutic hypothermia in improving outcome after traumatic brain injury.

METHODS

The person in charge of this study took steps to make sure that the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were followed to the letter. The goal of using this approach is to make sure that the investigation's findings are accurate. The main goal of this study was to show therapeutic hypothermia in improving outcome after traumatic brain injury. The main goal of this study is to show how important the things stated above and talked about in the book are. In order to qualify for inclusion in the study, researchers were required to satisfy specific criteria.

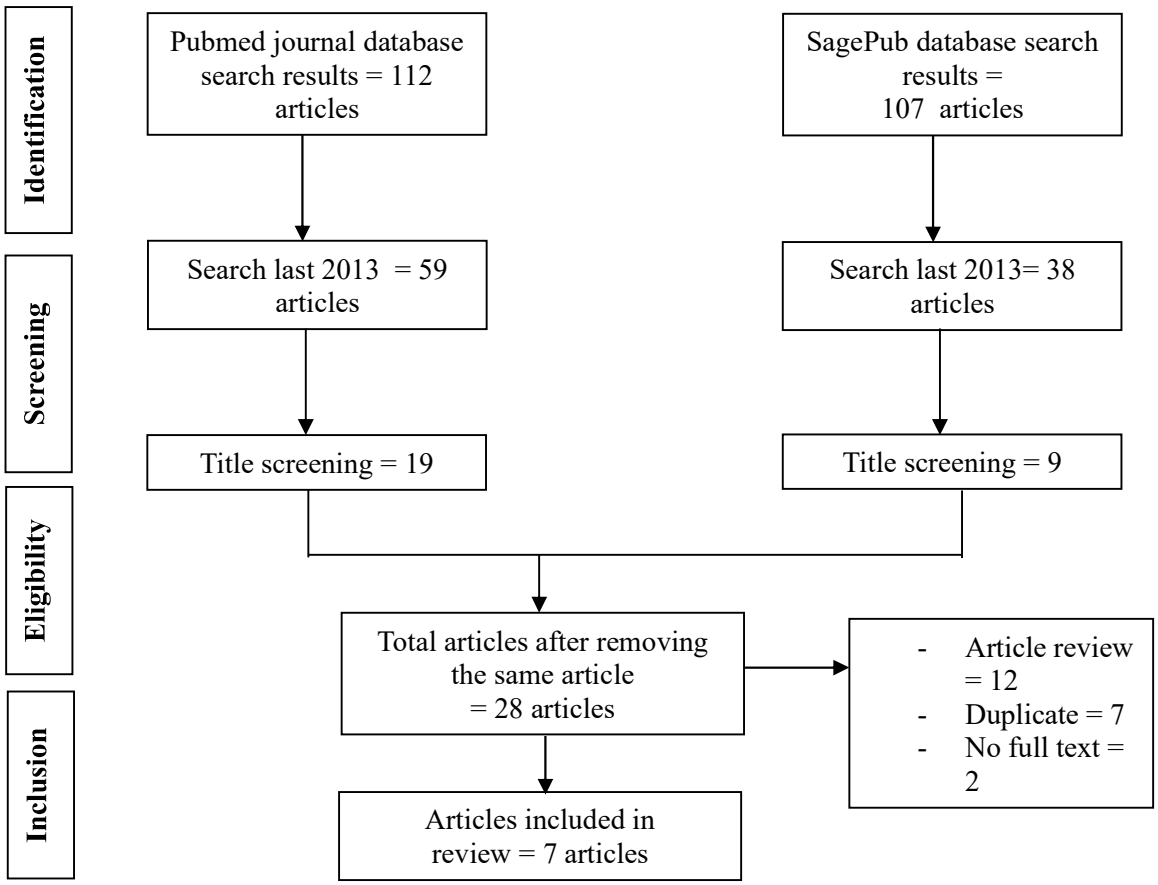

Figure 1. Article search flowchart

One of these conditions was that the paper had to be written in English and that it had to focus on therapeutic hypothermia in improving outcome after traumatic brain injury. For the paper to be released, it must meet both of these requirements. A number of the publications being evaluated were published within the period of 2013 and the predetermined timeframe considered relevant for the objectives of this systematic review. Prohibited in the academic context are editorials, submissions without a Digital Object Identifier (DOI), review articles that have been previously published, and submissions that effectively duplicate previously published journal papers.

We used “therapeutic hypothermia”; “outcome”; and “traumatic brain injury” as keywords.The search for studies to be included in the systematic review was carried out from September, 7th 2023 using the PubMed and SagePub databases by inputting the words: *((("hypothermia, induced"[MeSH Terms] OR ("hypothermia"[All Fields] AND "induced"[All Fields]) OR "induced hypothermia"[All Fields] OR ("therapeutic"[All Fields] AND "hypothermia"[All Fields]) OR "therapeutic hypothermia"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields]) AND ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR ("traumatic"[All Fields] AND “brain” AND "injury"[All Fields]) OR "traumatic brain injury"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))* used in searching the literature.

The researchers evaluated the inclusion of each paper's abstract and title. The essay's authors then selected pertinent research from the available literature. This result was the result of a comprehensive review of several investigations with a consistent pattern. All submissions must be in English and previously unpublished. Only publications that met all inclusion criteria were considered for the systematic review. This restricts search results to those that are relevant to the user's inquiry. Studies that do not meet our criteria are disregarded.

The research findings will be analyzed in depth. This research's investigation uncovered the following: names, authors, publication dates, location, study activities, and parameters. Before deciding which publications to investigate further, each author conducted an independent analysis of the research contained in the titles and abstracts of each publication. The following phase is to examine all of the articles that meet the review's criteria and determine which ones to include. Then, based on our findings, we'll select the stories for the review. This criterion is used to select papers that require closer examination. To make it as simple as feasible to select works for evaluation. This section discusses the preceding studies conducted and why they were included in the review.

RESULT

In the PubMed database, the results of our search brought up 112 articles, whereas the results of our search on SagePub brought up 107 articles. The results of the search conducted for the last year of 2013 yielded a total 59 articles for PubMed

and 38 articles for SagePub. In the end, we compiled a total of 28 papers, 19 of which came from PubMed and nine of which came from SagePub. We included seven study that met the criteria.

Fujita, et al (2023)[14] showed average ΔTjb-pa values in patients with favorable and unfavorable outcomes were 0.24 ± 0.23 and 0.06 ± 0.36°C, respectively (P < 0.001). ΔTjb-pa trended significantly higher in the favorable outcome patients than in the unfavorable outcome patients throughout the 120 h after onset of severe TBI (P < 0.001). The variation in ΔTjb-pa from 0 to 72 h was significantly lower in the favorable outcome patients than in the unfavorable outcome patients (0.8 ± 0.8 vs 1.8 ± 2.5°C, respectively, P = 0.013). From 72 to 120 h, there was no significant difference in the variation in ΔTjb-pa. Significant differences between patients with favorable and unfavorable outcomes in ΔTjb-pa and the variation in ΔTjb-pa were similar in the TH subgroup, but not evident in the FC subgroup.

Andrews, et al (2018)[15] enrolled 387 patients. On an intention-to-treat basis, 195 participants were randomised to hypothermia treatment and 192 to standard care. Regarding participant outcome, there was a higher mortality rate and poorer functional recovery at 6 months in the hypothermia group. The adjusted common odds ratio (OR) for the primary statistical analysis of the GOSE was 1.54 (95% confidence interval [CI] 1.03-2.31]; when the GOSE was dichotomised the OR was 1.74 (95% CI = 1.09-2.77). Both results favoured standard care alone. In this pragmatic study, we did not collect data on adverse events.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Intervention	Result
Fujita, 2023[14]	Japan	Randomised controlled trial	76 patients with TBI	Mild therapeutic hypothermia (TH = 32.0-34.0°C) or fever control (FC = 35.5-37.0°C) for the patients with severe TBI	A reduction in Tab-pa and greater variation in tub-pa were associated with an unfavourable outcome in patients with severe TBI, especially those treated with TH. When treating severe TBI patients, it is important to understand that there will be differences in temperature reflecting the brain environment and the systemic temperature, depending on the severity and outcome of TBI during TH.
Andrews, 2018[15]	United Kingdom	Randomised controlled trial	387 patients from 47 centres in 18 countries	Core temperature was initially reduced to 35 °C and decreased incrementally to a lower limit of 32 °C if necessary to maintain ICP at < 20 mmHg. Rewarming began after 48 hours if ICP remained controlled. Participants in the standard-care group received usual care at that centre, but without hypothermia.	In individuals who have experienced traumatic brain injury (TBI) and show intracranial pressure (ICP) levels over 20 mmHg, the implementation of titrated therapeutic hypothermia has been shown to effectively decrease ICP. However, it is important to note that this intervention is associated with increased mortality rates and poorer functional outcomes.
Cooper, 2018[16]	Europe – Australia	Randomised controlled trial	511 patients both out-of-hospital and in emergency departments after severe traumatic brain injury	Prophylactic hypothermia targeted the early induction of hypothermia (33°C-35°C) for at least 72 hours and up to 7 days if intracranial pressures were elevated, followed by gradual rewarming. Normothermia targeted 37°C, using surface-cooling wraps when required. Temperature was managed in both groups for 7 days. All other care was at the discretion of the treating physician.	In the cohort of individuals afflicted with severe traumatic brain damage, the implementation of early prophylactic hypothermia as opposed to maintaining normothermia did not yield any discernible enhancement in neurologic outcomes after a span of 6 months. The results of this study do not provide evidence in favour of implementing early preventive hypothermia as a treatment strategy for individuals with severe traumatic brain damage.
Rosario, 2018[17]	United States, Australia, and New Zealand	Randomised controlled trial	77 were examined for association with mortality and outcome	Therapeutic hypothermia versus normothermia following severe traumatic brain injury in children	Severe traumatic brain injury is a clinically heterogeneous condition that can manifest with a spectrum of neurologic impairment and a variety of injury patterns. This secondary analysis of prospectively acquired data identifies several variables associated with the outcome of children with severe traumatic brain injury.

Tang, 2017[18]	China	Randomised controlled trial	60 adults with intracranial pressure (ICP) of more than 20 mm Hg after decompressive craniectomy	Standard care (control group) or hypothermia (32°C-35°C) plus standard care	The implementation of mild induced hypothermia has been observed to have a beneficial effect in mitigating cerebral pressure subsequent to decompressive craniectomy, hence resulting in a reduction in patient mortality. The inclusion of hypothermia as a primary therapeutic approach for managing intracranial hypertension after decompressive craniectomy in individuals suffering from traumatic brain injury warrants consideration.
Andrews, 2015[19]	United Kingdom	Randomised controlled trial	387 patients	Standard care (control group) or hypothermia (32 to 35°C) plus standard care	The addition of therapeutic hypothermia to standard care for patients with a post-traumatic brain injury and intracranial pressure over 20 mm Hg did not yield superior outcomes compared to standard care alone.
Flynn, 2015[20]	United Kingdom	Randomised controlled trial	17 patients	Standard care or standard care and TH (intervention group) titrated between 32°C and 35°C to reduce ICP	This study provides more evidence to corroborate previous findings that indicate a correlation between temperature and intracranial pressure (ICP) lowering. Such a correlation may potentially lead to a decrease in the necessity for hyperosmolar medicines or other stage II therapies. The observed reduction in PbtO2 does not fall below the recommended treatment threshold of 20 mmHg; nonetheless, it may potentially signify a decline in cerebral blood flow (CBF).

Cooper, et al (2018)[16] conducted a study. Hypothermia was initiated rapidly after injury (median = 1.8 hours [IQR = 1.0-2.7 hours]) and rewarming occurred slowly (median = 22.5 hours [IQR = 16-27 hours]). Favorable outcomes (Glasgow Outcome Scale-Extended score = 5-8) at 6 months occurred in 117 patients (48.8%) in the hypothermia group and 111 (49.1%) in the normothermia group (risk difference [RD] = 0.4% [95% CI = -9.4% to 8.7%]; relative risk with hypothermia, 0.99 [95% CI = 0.82-1.19]; P = 0.94). The hypothermia and normothermia groups had 55.0% and 51.3% pneumonia and 18.1% and 15.4% cerebral hemorrhage, respectively.

Rosario, et al (2018)[17] showed two fixed pupils (14.17 [3.38-59.37]), abdominal Abbreviated Injury Severity score (2.03 [1.19-3.49]), and subarachnoid hemorrhage (3.36 [1.19-8.36]) were bivariately associated with a worse Glasgow Outcome Scale-Extended Pediatric Revision. Forward stepwise regression revealed a significant association between Abbreviated Injury Severity spine (3.48 [1.14-10.58]) and midline shift on CT (8.35 [1.05-66.59]) and mortality. Forward stepwise regression revealed that the number of fixed pupils (one fixed pupil 3.47 [0.79-15.30]; two fixed pupils 13.61 [2.89-64.07]), hypoxia (5.22 [1.02-26.67]), and subarachnoid hemorrhage (3.01 [1.01-9.01]) were independently related to a worse Glasgow Outcome Scale-Extended Pediatric Revision.

Tang, et al (2017)[18] showed disparity in ICP and cerebral perfusion pressure (CPP) between two cohorts. Favorable results were observed in 12 (40.0%) and 7 (36.5%) patients in the hypothermia and control groups, respectively, with no statistically significant difference between the two groups (P = 0.267). The Kaplan-Meier curves demonstrated a significant disparity in survival rates between the hypothermia and control cohorts (P = 0.032). The study observed notable disparities in lung infection and electrolyte abnormalities between the hypothermia and control groups, with statistical significance observed at P-values of 0.038 and 0.033, respectively.

Andrews, et al (2015)[19] enrolled 387 patients. Stage 3 treatments were required to control intracranial pressure in 54% of the patients in the control group and in 44% of the patients in the hypothermia group. The adjusted common odds ratio for the GOS-E score was 1.53 (95% CI = 1.02-2.30; P=0.04), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 26% of the patients in the hypothermia group and in 37% of the patients in the control group (P = 0.03).

Flynn, et al (2015)[20] showed mean decrease in ICP of 4.3 ± 1.6 mmHg ($p < 0.04$) from 15.7 to 11.4 mmHg, from precooling to the first epoch of hypothermia in the intervention group (n=9) that was not seen in the control group (n = 8). A decrease in ICP was maintained throughout all time periods. There was a mean decrease in PbtO2 of 7.8 ± 3.1 mmHg ($p < 0.05$) from 30.2 to 22.4 mmHg, from precooling to stable hypothermia, which was not seen in the control group. This study

supports others showing that heating lowers ICP, which could reduce the use of hyperosmolar medicines or other stage II therapies. Although PbtO2 is not below the treatment threshold of 20 mmHg, it may indicate a drop in CBF.

DISCUSSION

Various mechanisms can cause head trauma, the most common of which are motor vehicle accidents (for example: collisions between vehicles, pedestrians hit by motor vehicles, or bicycle accidents), falls, sports-related injuries, and penetrating trauma. Head trauma that occurs in developing countries is generally caused by motorized accidents, while in industrialized countries it is caused by work-related accidents.[4] Primary injury is an injury resulting from mechanical trauma in the form of a physical impact to the head which results in compression and injury to adjacent tissues either with or without loss of consciousness.[3,13,17,19]

The surrounding brain cells will be functionally impaired, but not dead and if conditions are favorable the cells will recover within minutes, hours or days. The subsequent stage is referred to as the secondary pathogenic process. The occurrence of biochemical processes and the presence of damaged mass structures can lead to significant cellular damage in both injured and undamaged cells.[3] Secondary injury is a complex process occurring within hours and days after the primary injury that includes cranial and systemic complications.[9,21]

HT management for TBI patients is contentious. Hypothermia does not benefit TBI patients like cardiac arrest, according to extensive study. In high-quality trials, HT may cause more deaths, according to this meta-analysis. HT started within 24 hours reduces TBI mortality. Researchers showed HT treatment, not prophylactic, helped TBI patients. Post-craniectomy TBI patients may benefit more from HT than patients who have not received a craniectomy. In terms of functional outcomes, this meta-analysis is consistent with previous meta-results. Patients with TBI may demonstrate improved neurologic outcomes with HT within 72 hours of injury.[9,19,21]

Hypothermia can lower ICP, slow the brain's metabolism, lower blood flow in the brain, change the release of chemicals, and keep the blood-brain barrier working. It has been shown in many studies that HT can help protect neurons in many ways.[19] Not only that, but HT may lower the inflammatory reaction and biochemical cascades that start early on after a TBI, which would stop secondary brain injury from happening.[15] Study demonstrated that HT can improve the functional prognosis of GOS (4–5) by reducing ICP. Studies find that hypothermia can improve patient functional outcomes.[17,22]

Several investigations have demonstrated that hypothermia can have negative consequences. Multiple large multicenter RCTs have demonstrated that HT not only fails to reduce patient mortality within six months, but may also be detrimental to patients with less impairment.[22] Long-term hypothermia is a form of immunosuppression that increases the incidence of pneumonia and sepsis. In addition, it has been reported that hypothermia can cause propofol infusion syndrome due to propofol's ability to reduce hepatic metabolism; this may be a significant cause of fatal symptoms at low temperatures.[23]

Temperature can have an effect on the metabolic processes of certain drugs, notably muscle relaxants like atracurium. As a result, this could have an effect on the mortality rate over a period of six months. The CRASH study also found that those who were exposed to hypothermia had a lower chance of surviving for six months, while patients who were treated with methylprednisolone had an increased risk of passing away within two weeks of receiving the medication. The administration of antipyretic steroids is another potential factor that has a substantial role in determining death rates.[23,24]

CONCLUSION

HT has not reduced, but may have increased, mortality in TBI patients in some high-quality studies. However, TBI patients with elevated ICP may benefit from hypothermia as therapy rather than as prophylaxis when initiated within 24 hours.

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