

The Role of Hypothermia in the Management of Severe Brain Injury

A Meta-analysis

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Context: Hypothermia is utilized in the management of severe traumatic brain injury despite the lack of unequivocal evidence supporting its use. Because of its widespread use, the effects of hypothermia are a concern.

Objective: To determine the effectiveness of hypothermia in the management of severe brain injury.

Data Sources: Two investigators working independently abstracted data in a blinded fashion from studies identified using multiple literature databases, including MEDLINE, Ovid, PubMed, the Cochrane Database of Systematic Reviews, EMBASE, and the abstract center for the American Association of Neurological Surgery and the Congress of Neurological Surgery, as well as the bibliographies of these articles. Additionally, experts in the field of hypothermia and neurotrauma provided additional references.

Study Selection: Seven studies met predetermined inclusion criteria: (1) the study was a randomized clinical trial comparing the efficacy of hypothermia vs normothermia in patients with posttraumatic head injury, (2) only subjects aged 10 years or older were included in the study, and (3) relative risks (odds ratios [ORs], cumulative incidence, or incidence density measures) and 95% confidence intervals (CIs) or weighted mean differences and 95% CIs could be calculated from the data presented in the article. These criteria were applied in a blinded fashion by 2 independent investigators.

Data Extraction: No single outcome variable was evaluated in all studies. The following outcome variables were assessed: intracranial pressure, Glasgow Outcome Scale score, pneumonia, cardiac arrhythmia, prothrombin time, and partial thromboplastin time. Either ORs or weighted mean differences (when the data provided did not permit calculation of an OR) comparing the effects of hypothermia vs normothermia were calculated from the data provided.

Data Synthesis: The weighted mean difference (hypothermia – normothermia) for intracranial pressure was -2.98 mm Hg (95% CI, -7.58 to 1.61 ; $P = .2$). The OR (hypothermia vs normothermia) for Glasgow Outcome Scale score was 0.61 (95% CI, 0.26 – 1.46 ; $P = .3$). The OR for pneumonia was 2.05 (95% CI, 0.79 – 5.32 ; $P = .14$). The OR for cardiac arrhythmia was 1.27 (95% CI, 0.38 – 4.25 ; $P = .7$). The weighted mean difference for prothrombin time was 0.02 seconds (95% CI, -0.07 to 0.10 ; $P = .7$). The weighted mean difference for partial thromboplastin time was 2.22 seconds (95% CI, 1.73 – 2.71 ; $P < .001$).

Conclusions: This meta-analysis of randomized controlled trials suggests that hypothermia is not beneficial in the management of severe head injury. However, because hypothermia continues to be used to treat these injuries, additional studies are justified and urgently needed.

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TRAUMA AFFECTS an estimated 1.9 million persons annually in the United States and accounts for approximately 1% of all injuries and annual visits to emergency departments.¹ In addition, traumatic brain injury accounts for 40% of all deaths from acute injuries. Of those surviving, 200 000 patients require hospitalization each year and often are permanently disabled. An additional 1.74 million persons suffer mild traumatic brain injury.¹ The direct costs of traumatic brain injury in the United States are

estimated at \$4 billion annually, with indirect costs estimated at 10 times that amount.² Although prevention has been the main focus of efforts to address the incidence of primary traumatic brain injury, efforts to address secondary injury have been quite varied. One of the oldest such modalities used is hypothermia.

Defined simply as body temperature significantly below 37°C, hypothermia has long been used for cerebral protection in the management of traumatic brain injury.³ Although the beneficial effects of hypothermia in head injury were reportedly

METHODS

The medical literature published since 1966 was searched in all languages using electronic databases. The initial search included the MEDLINE, Ovid, and PubMed databases. The commands used in these searches were "hypothermia and head injury," "hypothermia and brain injury," "hypothermia and trauma," and "hypothermia and neurosurgery." The Cochrane Database of Systematic Reviews, EMBASE, and the abstract center for the American Association of Neurological Surgery and the Congress of Neurological Surgeons were searched using the same keywords. Additional references from any year of publication were retrieved from the bibliographies of the relevant articles reviewed and from experts in the field of hypothermia and/or neurotrauma: Gary K. Steinberg, MD, PhD; Donald Marison, MD; Alois Zauner, MD; and one of us (P.G.M.).

Studies with titles or abstracts discussing hypothermia or the management of head injuries or trauma were retrieved. Any original randomized controlled trial investigating hypothermia as an exposure was submitted for further review with all references to author names, journal titles, and funding sources removed. All pertinent articles were reviewed, and the resulting studies were analyzed independently by 2 of us (O.A.H. and M.C.G.). The following inclusion criteria were applied: (1) the study was a randomized clinical trial comparing the efficacy of hypothermia vs normothermia in patients with posttraumatic head injury; (2) only subjects 10 years or older were included (established to exclude very young pediatric patients in whom the pathophysiologic effects of trauma are believed to be different²); and (3) relative risks (odds ratios [ORs], cumulative incidence, or incidence density measures) and 95% confidence intervals (CIs) or weighted mean differences and 95% CIs could be calculated from the data presented in the article. When multiple publications reported information from the same study subjects, only the publication with the most recent analysis of data was included.

The following data were abstracted from the eligible studies in a blinded fashion, using a standard data form (with the abstractors blinded to journal and author names): classification of head injury (Glasgow Coma Scale score), category of hypothermia (mild or moderate), ages of subjects, initiation and duration of hypothermia, extent of blinding, and the various outcomes studied. Several

variables were assessed in the studies included in the meta-analysis. Because no single variable was available for evaluation in every study, the decision was made to evaluate the more frequently used and clinically relevant variables²⁵: Glasgow Outcome Scale score, intracranial pressure, pneumonia, cardiac arrhythmia, prothrombin time, and partial thromboplastin time.

Relative risk estimates were not provided in any of the included studies. Thus, all estimates were calculated from the data provided. In the majority of the studies, 2×2 tables were reconstructed, and the appropriate estimates were calculated. When the means and SDs of outcome variables were given, this information was used directly to calculate weighted mean differences. Whenever possible, an OR was calculated and used in the summary calculations.

Summary relative risk estimates were then calculated as a weighted average of individual study results. Weightings and the summary estimate for each outcome were determined based on the random effects model (DerSimonian and Laird²⁶). This model explicitly incorporates any heterogeneity of treatment effects across studies and provides a conservative compensation for heterogeneity by inflating the estimated variance (thus enlarging the estimated CIs). Summary estimates were compared using a z statistic. All summary measures of effect and associated CIs were calculated using the software package RevMan,²⁷ developed by the Cochrane Collaboration for meta-analysis and systematic reviews. Heterogeneity was evaluated using the Mantel-Haenszel method, and the results were considered heterogeneous (ie, differences unlikely to be due to chance alone) if the P value was less than .2.²⁸

Study quality was assessed and scored using 3 criteria highlighted by the scale by Jadad et al.²⁹ The following items were used to measure the internal validity of each clinical trial: (1) concealment of treatment allocation, (2) randomization, (3) blinding of outcome assessment, and (4) handling of withdrawals and dropouts. All 7 trials scored points for randomization. None of the studies addressed blinding or gave a description of withdrawals and dropouts. However, given the critical nature of injury in both treatment and control groups, the loss of time introduced by blinding would have been clinically inappropriate. Furthermore, it may be inferred that no patient withdrew because of the clinical severity of injury. The likelihood of publication bias was addressed using funnel plots to compare relative outcome measure and sample size.

observed by Hippocrates,⁴ the first reported clinical application of hypothermia was performed by Fay in 1938.^{3,5} The procedure was limited to the terminally ill, who were subjected to temperatures of approximately 80°F (27°C). His results are noteworthy for tumor shrinkage and their palliative effect, specifically pain relief associated with metastatic cancer.^{3,6} His work led to widespread application of the procedure in neurosurgery and cardiothoracic surgery, where deep hypothermia (15°C-22°C) demonstrated an effective method of neuroprotection.⁷

Deep hypothermia, however, led to significant secondary complications, including cardiac arrhythmia; inhibition of coagulation cascade enzymes, predisposing patients to hemorrhage; and systemic complications, such as infection.⁷⁻¹⁴ In addition, it demanded significant use of hospital resources.^{7,9,15-17} Milder degrees of hypothermia

were later studied in an attempt to address the complications posed by cooling to deeper temperatures. At 30°C to 35°C, hypothermia was found to "offer significant neuroprotection in both global and focal models."^{7(p36),15,18-24} In addition, the milder temperatures were safer and less expensive to induce and maintain.^{7,8,22,24} These results led to the implementation of mild to moderate hypothermia in various clinical settings. The principal purpose of this meta-analysis is to investigate the hypothesis that induced hypothermia improves outcomes in patients with severe brain injuries when compared with normothermia.

In the field of traumatic brain injury, several clinical studies have sought to establish hypothermia as a treatment modality. The results of early studies suggesting the benefits of hypothermia were met with significant scrutiny because of their lack of randomization and the het-

Study Characteristics

Source	Year of Publication	Type of Study	Type of Injury	No. of Patients	Exposure (Hypothermia)	Induction/Duration of Hypothermia	Variables Assessed
Shiozaki et al ¹¹	1993	Prospective randomized trial	Severe traumatic brain injury	33	Mild (34-35°C)	NA/48 hours	ICP, CBF, GOS, MOF, death, pneumonia, arrhythmia, CMRO ₂ , CNS infection
Shiozaki et al ³¹	1999	Prospective randomized trial	Severe traumatic brain injury	16	Mild (34°C)	Within 6 h postinjury/48 h	GOS, pneumonia, arrhythmia, DI, CNS infection, EAA, hypernatremia, platelet count
Marion et al ³²	1997	Prospective randomized trial	Severe traumatic brain injury	82	Moderate (32-33°C)	Within 6 h postinjury/24 h	ICP, CPP, GOS, death, PT, PTT, platelet count, HR
Clifton et al ³³	2001	Prospective randomized trial	Severe traumatic brain injury	368	Moderate (32.5-34°C)	Within 6 h postinjury/48 h	ICP, MAP, CPP, GOS
Jiang et al ³⁴	2000	Prospective randomized trial	Severe traumatic brain injury	87	Mild (33-35°C)	Mean of 15 h postinjury/3-14 d	Pneumonia, arrhythmia, infection, ICP, glucose, seizures
Clifton et al ³⁵	1993	Prospective randomized trial	Severe traumatic brain injury	46	Moderate (32-33°C)	Within 6 h postinjury/48 h	ICP, CPP, MAP, HR, PT, PTT, platelet count, glucose, potassium
Resnick et al ³⁶	1994	Prospective randomized trial	Severe traumatic brain injury	36	Moderate (32-33°C)	Within 6 h postinjury/24 h	PT, PTT, platelet count, DTICH

*ICP indicates intracranial pressure; CBF, cerebral blood flow; GOS, Glasgow Outcome Scale score; MOF, multiple organ failure; CPP, cerebral perfusion pressure; CMRO₂, cerebral metabolic rate of oxygen consumption; CNS, central nervous system; DI, diabetes insipidus; EAA, excitatory amino acids; MAP, mean arterial pressure; PT, prothrombin time; PTT, partial thromboplastin time; HR, heart rate; DTICH, delayed traumatic intracerebral hemorrhage; and NA, not available.

erogeneous subject populations. The generalizability of the data was thus limited, and the efficacy of the procedure remained in question. More recent studies have responded to these criticisms. These studies include several single-center trials and 1 multicenter trial, with various outcomes of interest. As a result, it has been difficult to fully assess the efficacy of induced hypothermia and, thus, endorse the procedure as beneficial in the management of traumatic brain injuries.

RESULTS

A total of 528 references (445 when duplicates were deleted) were retrieved from PubMed (n=327), Ovid (n=83), pre-MEDLINE (n=4) and MEDLINE (n=79), the abstract center for the American Association of Neurological Surgery and the Congress of Neurological Surgeons (n=1), contacting experts (n=5), and bibliographic review (n=29). Fifty-four publications were submitted for blinded review. The blinded review excluded all but 9 studies because the studies did not contain original data or because they lacked information regarding hypothermia specific to the management of severe head injury. Another study was excluded because of redundancy in data reporting⁸ and another because it was a nonrandomized trial in which there was no control group.³⁰ The final 7 studies are summarized in the **Table**. Each study focused on several variables as outcomes of interest. Because no single variable was evaluated in every study, the more frequently reported and clinically relevant variables were chosen as the focus of this analysis.

GLASGOW OUTCOME SCALE SCORE

Four of the 7 studies included in the meta-analysis assessed Glasgow Outcome Scale score as a variable of interest.^{11,31-33} The summary estimate (OR, 0.61; 95% CI,

0.26-1.46; $P=.3$) demonstrated no statistically significant effect for hypothermia (**Figure A**). There was evidence of heterogeneity among these studies ($P=.08$).

INTRACRANIAL PRESSURE

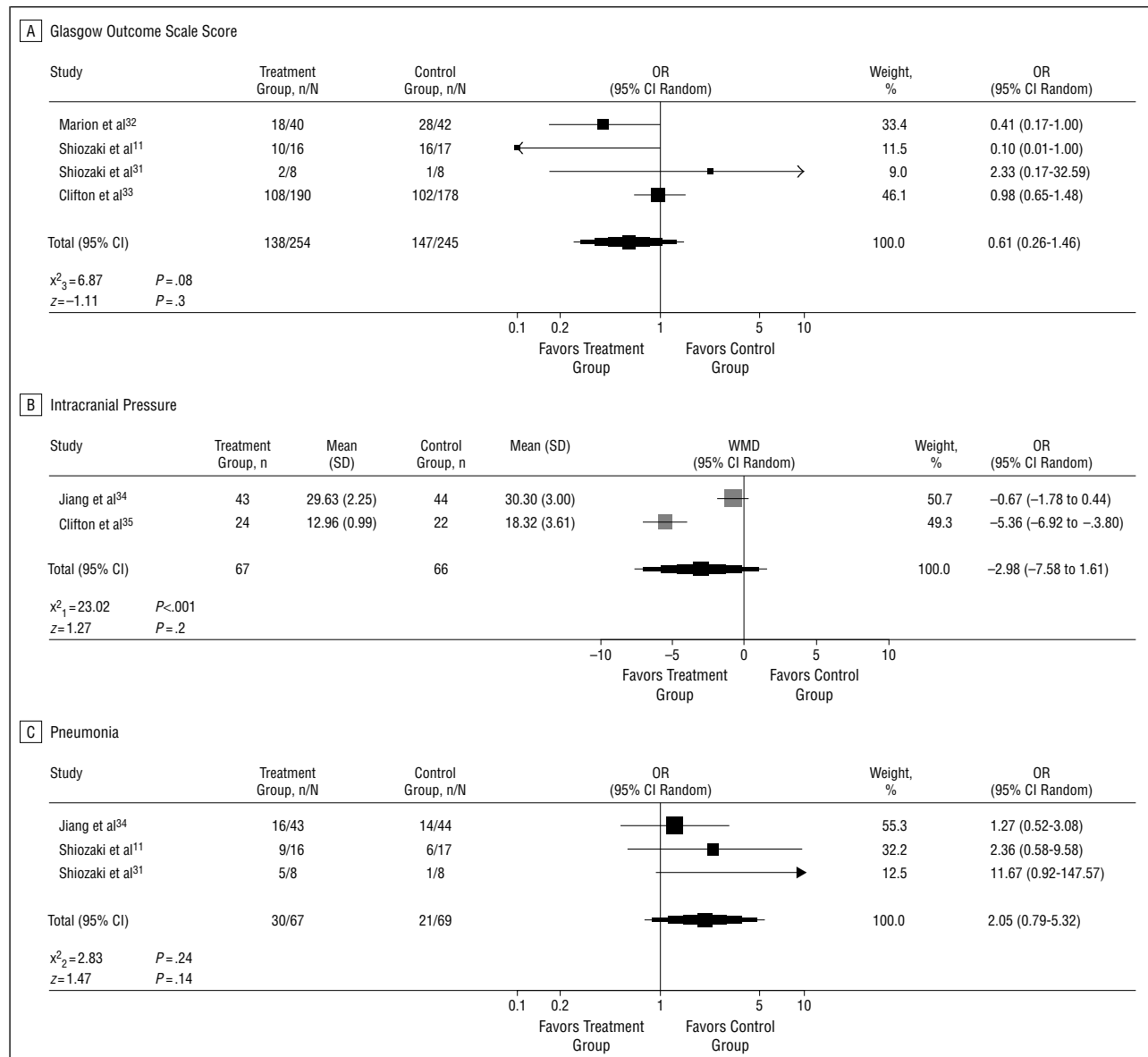
Five studies assessed intracranial pressure as an outcome variable.^{11,32-35} However, only 2 studies provided sufficient data to allow statistical analysis of this outcome. Using the random effects model, the weighted mean difference was -2.98 (95% CI, -7.58 to 1.61; $P=.2$; **Figure B**), suggesting that hypothermia had no benefit. There was evidence of heterogeneity among these studies ($P<.001$).

PNEUMONIA AND CARDIAC ARRHYTHMIA

Three studies included pneumonia and cardiac arrhythmia as outcome variables.^{11,31,34} The summary estimate for the effect of hypothermia on pneumonia was OR, 2.05 (95% CI, 0.79-5.32; $P=.14$), suggesting that hypothermia had no benefit (**Figure C**). There was no evidence of heterogeneity among these studies ($\chi^2=2.83$; $P=.24$). The summary estimate data for the effect of hypothermia on cardiac arrhythmia (OR, 1.27; 95% CI, 0.38-4.25; $P=.7$) suggested that hypothermia had no benefit (**Figure D**). There was no evidence of heterogeneity among these studies ($P=.23$).

PROTHROMBIN TIME AND PARTIAL THROMBOPLASTIN TIME

Three studies assessed prothrombin time and partial thromboplastin time.^{32,35,36} Only 2 of these studies provided sufficient data to allow statistical analysis. Using the random effects model, the weighted mean differ-



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ence for prothrombin time was 0.02 (95% CI, -0.07 to 0.10; $P = .7$; Figure E). There was no evidence of heterogeneity among these studies ($\chi^2 = 1.0$; $P = .32$). For partial thromboplastin time, the weighted mean difference was 2.22 (95% CI, 1.73-2.71) with an overall effect ($P < .001$; Figure F). These results favored normothermia over hypothermia. There was no evidence of heterogeneity among these studies ($\chi^2 = 0.62$; $P = .43$).

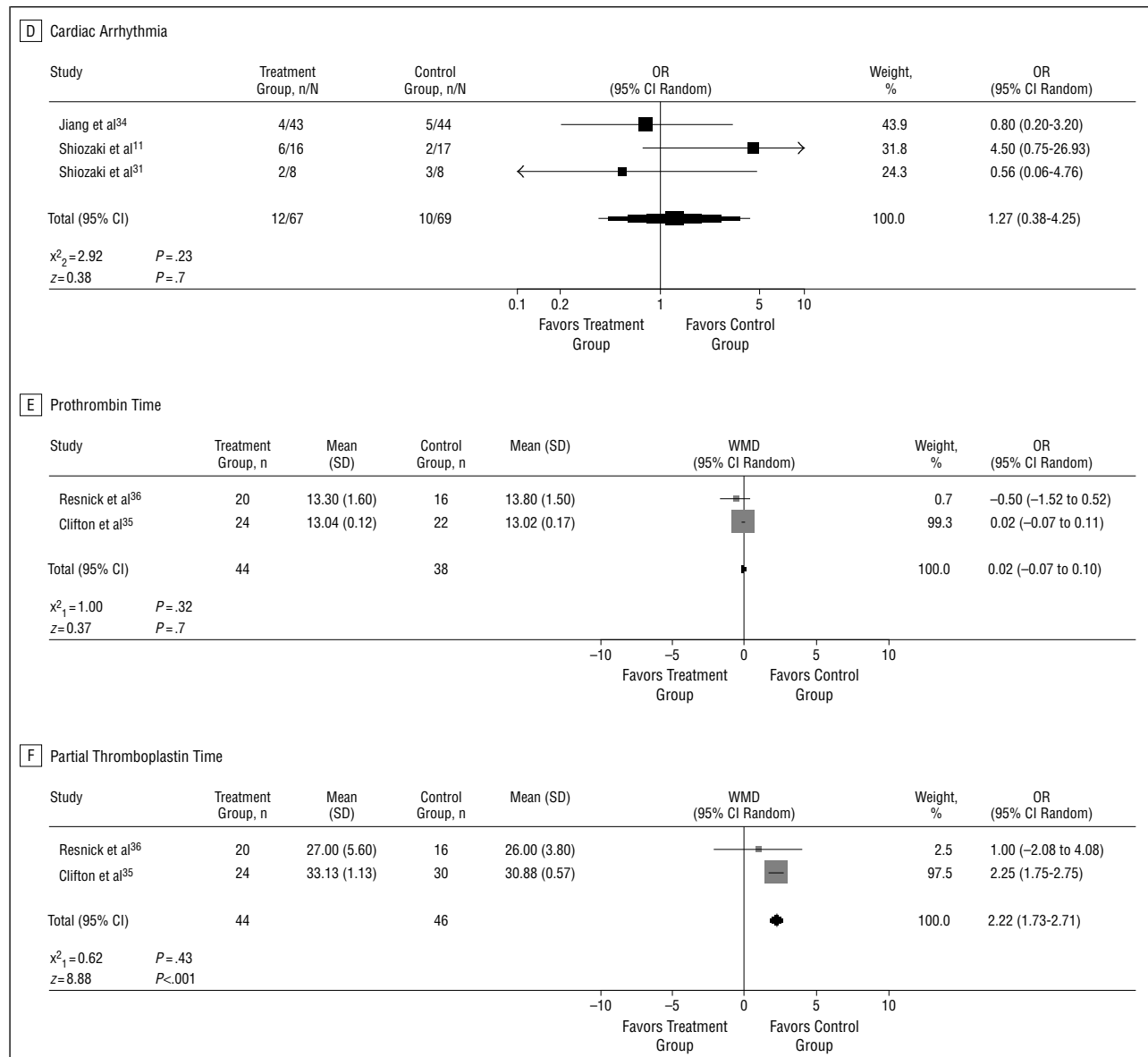
PUBLICATION BIAS

The possibility of publication bias in the literature on hypothermia was assessed using a funnel plot.²⁸ The studies that evaluated Glasgow Outcome Scale score and cardiac arrhythmia were chosen as representative because they included the largest subcategory of studies. Each of the funnel plots examines effect size vs sample size. These plots do not support the existence of publication bias in these studies.

COMMENT

Meta-analyses are relatively uncommon in the field of neurosurgery; fewer than 20 studies have been published in the last 10 years. Because this method of analysis is useful in the synthesis and evaluation of available data, we believe increased use will add greatly to the field. This meta-analysis is the first study evaluating the use of hypothermia in the management of severe brain injury.

We examined 5 clinically relevant outcome variables in the evaluation of the value of hypothermia in the management of patients with severe head injury: Glasgow Outcome Scale score, intracranial pressure, cardiac arrhythmia, pneumonia, prothrombin time, and partial thromboplastin time.²⁵ Glasgow Outcome Scale score is widely recognized as a functional rating scale in neurosurgical trauma.³⁷ The meta-analysis of Glasgow Outcome Scale score indicated a statistically significant risk



The odds ratios (ORs) or the weighted mean differences (WMDs) and 95% confidence intervals (CIs) comparing the effects of hypothermia vs normothermia with the outcome variables Glasgow Outcome Scale score (A), intracranial pressure (B), pneumonia (C), cardiac arrhythmia (D), prothrombin time (E), and partial thromboplastin time (F). With regard to sample size, n indicates the number of subjects who were positive for the outcome; N, the total number of subjects in the group.

associated with hypothermia (Figure B). Intracranial pressure was included in this meta-analysis because it is an integrated marker of cerebral edema, secondary injury, and deteriorating neurologic status.³⁸ The meta-analysis of the effects of hypothermia on intracranial pressure did not suggest that hypothermia was beneficial for patients with severe head injury (Figure A).

The added morbidity of the systemic effects observed during the use of hypothermia is one criticism of its early use. We chose to examine cardiac arrhythmia and pneumonia as representatives of systemic effect because several studies included them as outcome variables. Neither of these meta-analyses suggested that hypothermia had any benefit (Figure D and C).

Early studies involving deep hypothermia were plagued by concerns regarding coagulopathy and the resulting hemorrhage.³⁹⁻⁴² Subsequent research demon-

strated a disruption in the extrinsic and intrinsic clotting pathways, fibrinolytic cascade, and platelet number and function.^{5,43,44} The results of current studies were reported to be without any clinically deleterious effect. We chose to look more closely at this issue and selected prothrombin time and partial thromboplastin time as markers for coagulation. There was no evidence that hypothermia affected prothrombin time, although our meta-analyses suggested that hypothermia is associated with a statistically significant risk of elevated partial thromboplastin time (Figure F).

There are several limitations inherent to the design of the individual studies included in the meta-analysis. Potential confounding factors, such as sex, age, mechanism of injury, time to initiation of hypothermia, duration of treatment, rate of rewarming, and ideal target temperature range, could introduce bias into the results.

There is a consensus that initiation of hypothermia in the treatment of traumatic brain injury should be done as soon as possible. Although the majority of the clinical trials (5 of 7) included in this meta-analysis initiated treatment in patients randomized to hypothermia within 6 hours postinjury (Table), there was no uniform protocol established to determine the ideal interval for humans. Further complicating the issue was the time to target temperature level, which varied considerably among trials. Of those reporting this parameter, the range was 8 to 15 hours postinjury. This differs significantly from the animal studies in which delay in treatment initiation demonstrated a decrease in potential benefit.^{42,43}

The duration of hypothermia and the ideal rate of rewarming are controversial. The duration of treatment employed by the clinical trials included in the meta-analysis ranged from 24 hours to 14 days. Two of the 7 studies maintained hypothermia for 24 hours, 4 for 48 hours, and 1 for 3 to 14 days (Table). The rewarming schedule used in recent trials varied as well, ranging from 12 hours to 5 days. From these studies, the optimal length of therapy and rate of reversal remain uncertain.

The definition of the specific target temperature for hypothermia is another important potential source of bias. Although hypothermia is defined as temperature significantly below 37°C, there are many subcategories of hypothermia to be considered, and each is associated with its own benefits and complications.³ There are several classification schemes for hypothermia, ranging from mild to ultra-profound.^{3,44} Regardless of the classification scheme, among studies included in the meta-analysis, little distinction exists between mild (34°C-35°C) and moderate (32°C-33°C) hypothermia. Recent studies have been too few to determine whether any benefit exists between the subcategories of mild and moderate hypothermia.

Temperature determination was another source of potential bias. Available methods for assessing temperature included ventricular, bladder, rectal, and intravascular sites. Although there is evidence to suggest that the route of measurement was irrelevant,^{15,45} it must be noted that several methods were used to assess temperature in the studies included in the meta-analysis. The majority used a thermistor placed in the ventricle.

Patient age is an important factor in traumatic brain injury. Two of the studies included the specific age range of the patients, approximately 15 to 75 years. Two additional studies excluded only the very young, with an age inclusion criterion of 10 years or older. One study did not report specific ages but provided a mean age of 42.2 years for the hypothermia group and 40.6 years for the normothermia group. Average age provided little useful information because it did not exclude the possibility of either the very young or very old, 2 groups with different posttraumatic pathophysiological characteristics, being included. With regard to sex and mechanisms of injury, in all studies, the majority of patients were men, and the primary mechanism of injury was motor vehicle accident. This is consistent with previous studies outlining the demographics of trauma.^{1,2}

The severity of neurologic impairment may act as a confounder and as such would be important to control.

Thus, subcategorizing severe traumatic brain injury beyond a Glasgow Coma Scale score of 3 to 8 would be important because lower scores indicate a greater degree of neurologic impairment. Of the studies included in this meta-analysis, only 3 took this into account by using a block randomization scheme to balance the injury severity between hypothermia and normothermia groups. There was insufficient data to explore this issue further, specifically to determine if there was an excess of patients with lower Glasgow Coma Scale scores in either the hypothermia or normothermia groups, which could have influenced the summary estimates of effect.

There are several limitations inherent in all meta-analyses.^{28,45} Any biases present in the individual studies are not removed when a quantitative synthesis is performed. Thus, any summary estimate generated from a synthesis of studies represents an estimate of the association of interest (hypothermia and outcome variable) available from the literature. Both the availability of the literature and the studies presented may be biased. Many potential confounding variables of interest (time to target temperature, choice of specific target temperature, and duration of hypothermia) could not be thoroughly explored because of inconsistencies in reporting or lack of relevant information for subgroup analyses. Although every attempt was made to secure all published and unpublished studies in all languages, publication bias may never be totally excluded.

CONCLUSIONS

The meta-analysis of the existing literature does not support the use of hypothermia in the management of post-traumatic brain injury. We do not believe that the results of this meta-analysis should define the clinical use of hypothermia because of the limitations imposed by the low number of studies and the lack of consistent outcome measurement. However, because hypothermia is widely used and the results of this meta-analysis suggest that there may be no benefit to this treatment, a definitive and rigorously conducted randomized controlled trial is urgently needed.

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