Review Article

Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review

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ABSTRACT

Introduction: During the past 7 years, considerable new evidence has accumulated supporting the use of prophylactic hypothermia for traumatic brain injury (TBI). Studies can be divided into 2 broad categories: studies with protocols for cooling for a short, predetermined period (e.g., 24–48 h), and those that cool for longer periods and/or terminate based on the normalization of intracranial pressure (ICP). There have been no systematic reviews of hypothermia for TBI that include this recent new evidence.

Methods: This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement. We developed a comprehensive search strategy to identify all randomized controlled trials (RCTs) comparing therapeutic hypothermia with standard management in TBI patients. We searched Embase, MEDLINE, Web of Science, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, ProceedingsFirst and PapersFirst. Additional relevant articles were identified by hand-searching conference proceedings and bibliographies. All stages of study identification and selection, quality assessment and analysis were conducted according to prospectively defined criteria. Study quality was determined by assessment of each study for the use of allocation concealment and outcome assessment blinding. Studies were divided into 2 a priori–defined subgroups for analysis based on cooling strategy: short term (≤ 48 h), and long term or goal-directed (> 48 h and/or continued until normalization of ICP). Outcomes included mortality and good neurologic outcome (defined as Glasgow Outcome Scale score of 4 or 5). Pooling of primary outcomes was completed using relative risk (RR) and reported with 95% confidence intervals (CIs).

Results: Of 1709 articles, 12 studies with 1327 participants were selected for quantitative analysis. Eight of these studies cooled according to a long-term or goal-directed strategy, and 4 used a short-term strategy. Summary results demonstrated lower mortality (RR 0.73, 95% CI 0.62–0.85) and more common good neurologic outcome (RR 1.52, 95% CI 1.28–1.80). When only short-term cooling studies were analyzed, neither mortality (RR 0.98, 95% CI 0.75–1.30) nor neurologic outcome (RR 1.31, 95% CI 0.94–1.83) were improved. In 8 studies of long-term or goal-directed cooling, mortality was reduced (RR 0.62, 95% CI 0.51–0.76) and good neurologic outcome was more common (RR 1.68, 95% CI 1.44–1.96).

Conclusion: The best available evidence to date supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (Glasgow Coma Scale score ≤ 8) to decrease mortality and improve rates of good neurologic recovery. This treatment should be commenced as soon as possible after injury (e.g., in the emergency department after computed tomography) regardless of initial ICP, or before ICP is measured. Most studies report using a temperature of 32°–34°C. The maximal benefit occurred with a long-term or goal-directed cooling protocol, in which cooling was continued for at least 72 hours and/or until stable normalization of intracranial pressure for at least 24 hours was achieved. There is large potential for further research on this therapy in prehospital and emergency department settings.

Keywords: brain injuries; hypothermia, induced; review; traumatic brain injury; prophylactic hypothermia; systematic review

RÉSUMÉ

Introduction : Au cours des 7 dernières années, il s'est accumulé un nombre considérable de preuves appuyant l'utilisation de l'hypothermie thérapeutique après un traumatisme crânien. On peut diviser les études en 2 grandes catégories : études sur l'utilisation d'un protocole d'hypothermie sur une courte période de temps prédéterminée (par exemple, de 24 à 48 heures), et celles sur l'application d'une hypothermie sur de plus longues périodes et/ou la cessation du traitement hypothermique sur normalisation de la pression intracrânienne (PIC). Aucune analyse systématique de l'application de l'hypothermie en cas de traumatisme crânien ne porte sur ces nouvelles preuves.

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Méthodes : Cette analyse a suivi les recommandations du *Cochrane Handbook for Systematic Reviews of Interventions* et la déclaration QUOROM (Qualité des rapports de méta-analyse). Nous avons élaboré une stratégie de recherche globale pour repérer tous les essais contrôlés randomisés (ECR) comparant l'hypothermie thérapeutique à la prise en charge habituelle des patients traumatisés crâniens. Nous avons interrogé les bases de données Embase, MEDLINE, Web of Science, le Registre central Cochrane des essais contrôlés, la base de données Cochrane des revues systématiques, ProceedingsFirst et PapersFirst. D'autres articles pertinents ont été retenus grâce à la recherche manuelle d'actes de conférences et de bibliographies. Toutes les étapes de repérage et de sélection des essais, de l'évaluation de la qualité et de l'analyse ont été réalisées selon des critères définis prospectivement. Nous avons évalué la qualité des essais selon l'utilisation de l'occultation des répartitions et de l'évaluation des résultats en insu. Les études ont été divisées en 2 sous-groupes définis a priori aux fins d'analyse selon la stratégie de refroidissement : à court terme (environ 48 h) et à long terme ou orientée vers un but (> 48 h et/ou traitement poursuivi jusqu'à la normalisation de la PIC). Les mesures de résultats incluaient la mortalité et un bon résultat à l'examen neurologique (score à l'échelle de Glasgow de 4 ou 5). Le regroupement des principaux critères d'évaluation a été réalisé en utilisant le risque relatif (RR) avec des intervalles de confiance (IC) à 95 %.

Résultats : Parmi les 1709 articles analysés, 12 essais portant sur 1327 participants ont été sélectionnés aux fins d'analyse quantitative. Huit de ces essais portaient sur l'hypothermie thérapeutique à long terme ou orientée vers un but, et 4 portaient sur une hypothermie thérapeutique à court terme. Les résultats sommaires ont révélé une mortalité plus faible (RR = 0,73, IC à 95 %, de 0,62 à 0,85) et une incidence plus élevée de bons résultats neurologiques (RR = 1,52, IC à 95 %, de 1,28 à 1,80). Lorsque seules les études sur l'hypothermie thérapeutique à court terme ont été analysées, ni la mortalité (RR = 0,98, IC à 95 %, de 0,75 à 1,30), ni les résultats neurologiques (RR = 1,31, IC à 95 %, de 0,94 à 1,83) ne se sont améliorés. Dans 8 études sur l'hypothermie thérapeutique à long terme ou orientée vers un but, le taux de mortalité a diminué (RR = 0,62, IC à 95 %, de 0,51 à 0,76) et les bons résultats neurologiques étaient plus fréquents (RR = 1,68, IC à 95 %, de 1,44 à 1,96).

Conclusion : Les meilleures preuves disponibles à ce jour appuient l'utilisation de l'hypothermie thérapeutique légère à modérée chez les patients présentant un traumatisme crânien sévère (score à l'échelle de Glasgow ≤ 8) pour réduite le taux de mortalité et améliorer les taux de récupération neurologique. Ce traitement doit être entrepris le plus tôt possible après la blessure (p. ex., à l'urgence après la tomodensitométrie), peu importe la PIC initiale, voire même avant qu'elle ait été mesurée. La plupart des essais rapportent avoir utilisé une température de 32 à 34 °C. On a noté les meilleurs résultats avec l'utilisation d'un protocole d'hypothermie à long terme ou orienté vers un but, où l'hypothermie a été maintenue pendant au moins 72 heures et/ou jusqu'à ce que la PIC soit stable pendant au moins 24 heures. Les possibilités de recherches additionnelles sur ce traitement en pré-hospitalier et dans les urgences sont immenses.

OVERVIEW

Traumatic brain injury (TBI) is a major cause of death and long-term morbidity. Induced hypothermia is now an accepted measure to improve outcome following anoxic brain injury associated with cardiac arrest,[1–3] but its benefits in TBI are uncertain. Several older meta-analyses concluded that hypothermia is not effective for TBI.[4–6] Since those reviews were first published, a number of trials evaluating various hypothermia regimens for TBI have shown a trend of significant benefit from hypothermia. One more recent meta-analysis[7] did not include the largest study ever conducted on this topic (396 patients).[8] We were unable to identify a comprehensive, up-to-date systematic review that prospectively evaluated the role of short- and long-term hypothermia in TBI. Therefore, we attempted to address this shortfall in the literature.

Death and disability from blunt TBI is due to a combination of the primary brain injury (shearing and damage to neurons or glial cells at the time of impact) and secondary brain injury (ischemia and reperfusion injury). Brain ischemia in this setting results from impaired autoregulation, elevated intracranial pressure (ICP), local and global hypoperfusion, and increased cerebral metabolic demands.[9,10] Reperfusion injury is due to a complex cellular cascade leading to apoptosis.[11] Hypothermia may be beneficial for the injured brain not only by reducing ICP and cerebral metabolic demands,[12] but also by decreasing disruption of the blood–brain barrier[13] and inhibiting the inflammatory cascade that leads to reperfusion injury.[14,15]

Although therapeutic hypothermia for TBI was first studied in 1943,[16] little progress was made until the publication of 2 trials of mild-to-moderate hypothermia in 1993.[17,18] These trials found a statistically significant benefit in survival and neurologic outcome in patients with severe TBI who were cooled to 32°–34°C, and demonstrated that cooling to no lower than 32°C was safe. In 2001, a much-anticipated randomized controlled trial (RCT) of 392 patients was published by Clifton and colleagues[19] in the *New England Journal of Medicine*. This study found no benefit from 48 hours of therapeutic hypothermia for patients with severe TBI. Subgroup analysis suggested a trend toward benefit for young patients (< 45 yr) and for those already hypothermic on

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admission, and a trend toward harm in older patients. Since the publication of the Clifton study, however, numerous trials investigating different hypothermia regimens in TBI have been published and reported varying benefits. These studies fall into 2 broad categories: those that cool TBI patients for a relatively short, predetermined period (24–48 h) and those that cool for a longer period or do not terminate cooling until specific physiologic criteria (i.e., normalization of ICP) have been met. The benefit from longer cooling may be because of its effect on cerebral edema and reperfusion injury, which peaks at 3–5 days after the TBI[20] and may last for several days beyond that. Adverse effects from longer-term cooling have not been shown to be significantly different from short-term cooling, with the exception of certain laboratory parameters such as a slowly decreasing platelet count.[21] Although there is a Cochrane Review and other meta-analyses on this subject,[4–7] the most recent article included in any of these reviews is Clifton and colleagues' paper from 2001.

QUESTION

The purpose of this review was to answer the following question: In adults with acute, severe blunt TBI (Glasgow Coma Scale [GCS] score ≤ 8) without major contraindications (e.g., hypotension, ongoing hemorrhage), does early prophylactic (e.g., in the emergency department after computed tomography), regardless of ICP or before ICP is measured, mild-to-moderate (32°–35°C) hypothermia, in addition to standard of care, improve mortality and/or chance of good neurologic outcome (Glasgow Outcome Scale [GOS] score of ≥ 4 out of 5) at a specified time after rehabilitation, compared with standard of care alone? The GOS is a widely used 5-point scale measuring neurologic outcome where 1 indicates death, 2–3 indicates vegetative state or dependent living, and 4–5 indicates independent living or return to work/school.

METHODS

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[22] and the QUOROM (quality of reporting of meta-analyses) statement[23] in this meta-analysis. We developed a comprehensive search strategy and, using database-appropriate keywords, searched MEDLINE, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PapersFirst and ProceedingsFirst. A sample search strategy is provided (Appendix 1, available at www.cjem-online.ca). In addition, we hand-searched conference proceedings, abstracts and the bibliographies of other literature reviews and of all short-listed studies. Articles were then eliminated in stepwise fashion (Fig. 1, Appendix 2, available at www.cjem-online.ca). First duplicates were eliminated, then we eliminated clearly irrelevant papers that did not meet our inclusion criteria based on the title or abstract. The remaining papers were retrieved for full-text review by 1 reviewer and short-listed for final review if the reviewer could not eliminate the possibility that the paper was a clinical trial of hypothermia for TBI. All short-listed papers that had not been eliminated by this stage were reviewed in their entirety by 2 independent reviewers according to an a priori protocol (Appendix 3, available at www.cjem-online.ca). We assessed agreement on inclusion and exclusion between the 2 reviewers as a simple ratio of studies agreed on to total studies assessed. Data in the form of mortality and dichotomized GOS were extracted in duplicate by 2 independent reviewers.

All included studies had to be prospective RCTs of early prophylactic mild-to-moderate hypothermia for patients with acute, severe TBI that reported mortality as an outcome measure (most also assessed GOS). Complete blinding was not achieved in any of the studies because of the difficulty in blinding patients and caregivers to the nature of the study intervention; however, outcome assessment blinding and allocation concealment were rated as adequate, unclear or inadequate.

Previous meta-analyses have used GOS (dichotomized into good [GOS score 4–5] or poor [GOS score 1–3]) as a simplified measure of neurologic outcome after TBI.[4–7] We also sought to determine whether there is a difference in the efficacy of short-term cooling compared with a long-term or goal-directed strategy. Two previous meta-analyses that subdivided studies into those cooling for up to 48 hours and those cooling for longer than 48 hours reported a statistically significant benefit for long-term but not for short-term cooling.[6,7] In addition, one RCT (n = 215) directly comparing a 48-hour cooling protocol with a 5-day protocol reported a significantly higher rate of good neurologic outcome in the long-term group.[24] Therefore, we defined a priori subgroups of short-term (≤ 48 h) and long-term (> 48 h) hypothermia for our subgroup analysis. Most studies in the long-term subgroup cooled for at least 72 hours and many did not initiate rewarming until ICP had normalized (Table 1[8,17,19,25–33]).

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One study by Zhi and coworkers[8] applied a purely goal-directed cooling protocol, with intent to maintain hypothermia for as long as was necessary to achieve normal ICP for at least 24 hours, resulting in a range of cooling durations from 1–7 days (mean 62.4 h), and was included in our long-term subgroup. When reported, we compared adverse effects associated with hypothermia with control.

Data from each study was entered in Review Manager (RevMan) software version 4.2 for Windows (The Nordic Cochrane Centre, The Cochrane Collaboration). As there was significant clinical heterogeneity among the studies, we chose to perform a random effects meta-analysis using RevMan to calculate relative risk (RR) and absolute risk with 95% confidence intervals (CIs) for mortality and, when reported, for functional independence (GOS of 4–5 out of 5). As planned a priori, these analyses were performed for all studies

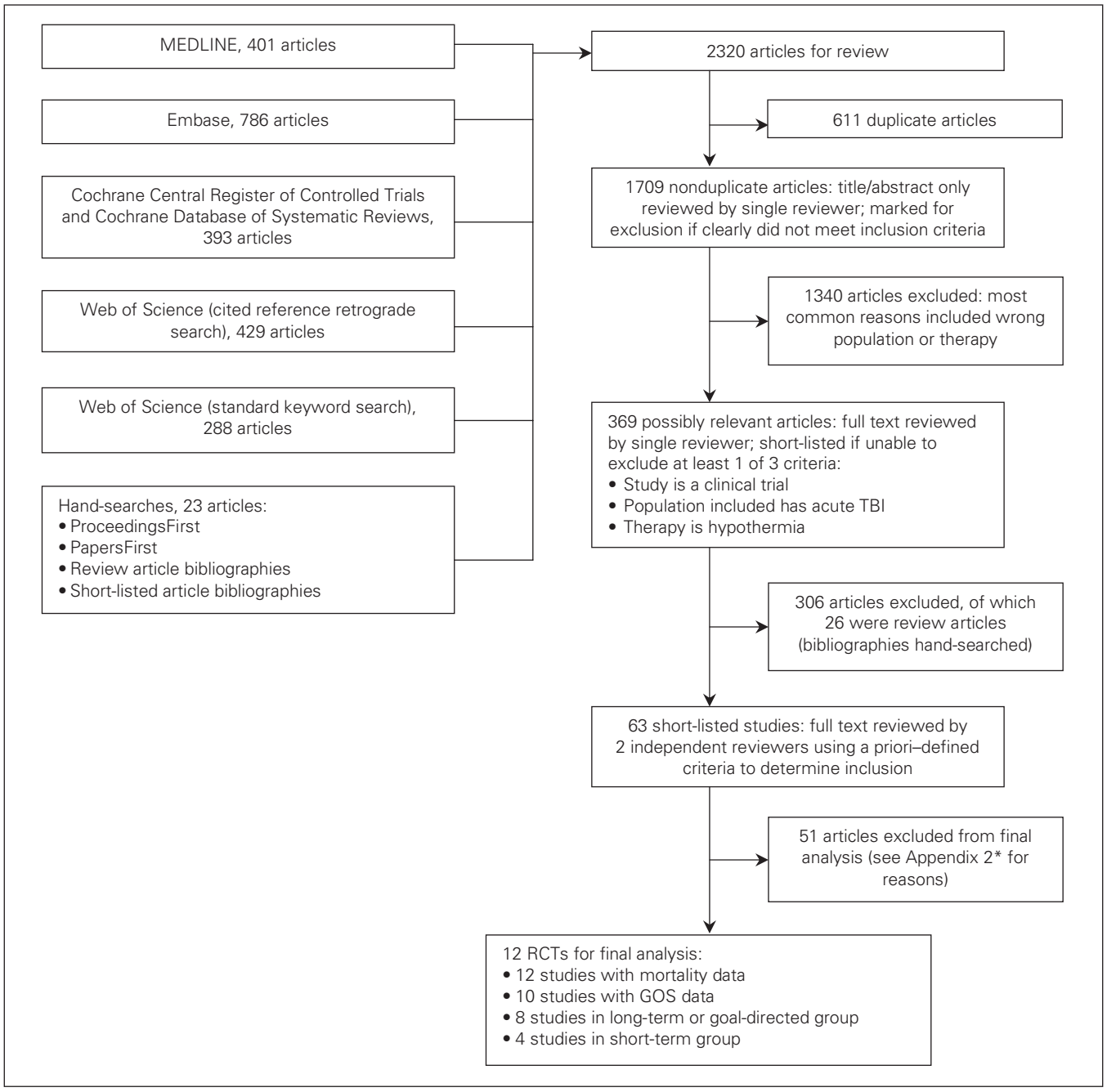

Fig. 1. Flow chart showing the elimination of articles. GOS = Glasgow Outcome Scale; RCT = randomized controlled trial; TBI = traumatic brain injury. *Available at www.cjem-online.ca.

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combined as well as for short-term, and long-term or goal-directed subgroups. We tested for the presence of statistical heterogeneity using the χ^2 test and I^2 value, using a priori–defined cutoffs of $p < 0.10$ or $I^2 > 50\%$. In case these cutoffs were surpassed, we planned sensitivity analyses with low-quality studies removed. We also constructed a funnel plot to assess the likelihood of publication bias.

RESULTS

Our search strategy yielded 1709 articles for review. Using the protocol described (Fig. 1 and Appendix 3, available at www.cjem-online.ca), 63 studies were short-listed for the final stage of review. Of these, 5 were in Chinese and were reviewed by the single Chinese-speaking author (all 5 were excluded), and 58 studies were reviewed by 2 authors. Agreement on inclusion and exclusion was high, at 56/58 (96.6%). The 2 papers for which there was disagreement were considered for exclusion because some of the patients were pediatric.[27,34] As these studies reported individual patient data, we were able to exclude the pediatric data and we included only the adult data in our final analysis. During a later stage of analysis it was discovered that both of these studies were reporting the same set of patient results; therefore, only the most recent one was included.[34] We identified 12 studies with 1327 participants that met our criteria for inclusion in this analysis (Table 1). All 12 studies included mortality data and 10 also had data on functional outcome (dichotomized GOS). Four studies evaluated a short-term (24–48 h) cooling strategy, and the remaining 8 evaluated a long-term (cooled for ≥ 72 h) and/or goal-directed (cooled for ≥ 24 h after normalization of ICP) strategy. Five studies were low quality, which we defined as studies for which both allocation concealment and outcome assessment blinding were either absent or unclear.

Table 1. Summary of included studies

Study	Population*	Therapy	Short- or long-term subgroup	Allocation concealment	Outcome assessment blinding
Clifton et al.[17]	*n* = 46 (24 hypothermia, 22 control)	Cooled to 32°–33°C for 48 h	Short term	Adequate†	Yes
Hirayama et al.[25]	*n* = 22 (12 hypothermia, 10 control)	Cooled to 32°–34°C for 48 h	Short term	Unclear	Unclear
Marion et al.[26]	*n* = 81 (39 hypothermia, 42 control)	Cooled to 32°–33°C for 24 h	Short term	Adequate	Yes
Aibiki et al.[27]	*n* = 22 (12 hypothermia, 10 control)	Cooled to 32°–33°C for 3–4 d; rewarmed when ICP normalized	Long term	Inadequate†	Yes
Jiang et al.[28]	*n* = 87 (43 hypothermia, 44 control)	Cooled to 33°–35°C for 3–14 d; rewarmed when ICP normalized	Long term	Unclear	Yes
Chen et al.[29]	*n* = 60 (30 hypothermia, 30 control)	Cooled for 4–10 d; rewarmed when ICP normalized	Long term	Unclear	No; dichotomized GOS score NA, only mortality data used
Clifton et al.[19]	*n* = 392 (190 hypothermia, 178 control)	Cooled to 33°C for 48 h	Short term	Adequate†	Yes
Yan and Tang[30]	*n* = 44 (24 hypothermia, 20 control)	Cooled to 32°–34°C for 3–5 d; rewarmed when ICP normalized	Long term	Unclear	No; dichotomized GOS score NA, only mortality data used
Zhi et al.[8]	*n* = 396 (198 hypothermia, 198 control)	Cooled to 32°–35°C for 1–7 d; rewarmed when ICP normalized for at least 24 h	Long term	Unclear	Unclear
Qiu et al.[31]	*n* = 86 (43 hypothermia, 43 control)	Cooled to 33°–35°C for 3–5 d; rewarmed when "conditions allowed"	Long term	Adequate†	Yes†
Smrcka et al.[32]	*n* = 72 (35 hypothermia, 37 control)	Cooled to 34°C for 3 d	Long term	Inadequate†	Yes†
Liu et al.[33]	*n* = 44 (21 hypothermia, 23 control)	Cooled to 33°–35°C for 3 d	Long term	Unclear	Unclear

GOS = Glasgow Outcome Scale; NA = not available.
*All patients had acute, severe traumatic brain injury, Glasgow Coma Scale score ≤ 8.
†Adjusted based on personal correspondence with author.

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There was significant heterogeneity among studies in the following areas: study quality (adequate allocation concealment described in 4/12 studies), outcome assessment blinding described in 7/12 studies, various depth/duration of hypothermia and criteria for rewarming in hypothermia protocols (Table 1), and variations in the control group mortality (24% to 80%). None of the pooled estimates met the a priori criteria for statistical heterogeneity (Fig. 2 and 3). In the mortality subgroup pooled estimates, heterogeneity was limited in the long-term or goal-directed subgroup, and moderate in the short-term subgroup (Appendix 4, available at www.cjem-online.ca). To evaluate this heterogeneity further, sensitivity analyses for all mortality and GOS comparisons were performed with low-quality studies removed, and results remained unchanged (Appendices 5 and 6, available at www.cjem-online.ca). Our funnel plot indicated a probable publication bias where small, negative studies were less likely to be published (Appendix 7, available at www.cjem-online.ca).

When data from all 12 included studies were pooled, mortality was reduced for patients receiving hypothermia (RR 0.73, 95% CI 0.62–0.85) and good neurologic outcome (GOS score of 4 or 5) was more common (RR 1.52, 95% CI 1.28–1.80) (Fig. 2). The absolute risk reduction in mortality was 11% (95% CI 5.0%–17.0%), corresponding to a number needed to treat (NNT) of 10 (95% CI 5.9–20.0) (Appendix 8, available at www.cjem-online.ca). The absolute risk increase in good neurologic outcome was 22% (95% CI 12%–31%), corresponding to an NNT of 4.5 (95% CI 3.2–8.3) (Appendix 4, available at www.cjem-online.ca).

When the 4 studies in the short-term hypothermia subgroup were pooled, mortality was not reduced for patients in the hypothermia group (RR 0.98, 95% CI 0.75–1.30) (Fig. 2) and GOS score was not improved (RR 1.31, 95% CI 0.94–1.83) (Fig. 3).

When the 8 studies in the long-term or goal-directed cooling subgroup were pooled, mortality was reduced for patients receiving hypothermia (RR 0.62, 95% CI 0.51–0.76,) (Fig. 2) and good neurologic outcome was more common (RR 1.68, 95% CI 1.44–1.96) (Fig. 3). The absolute risk reduction in mortality was 16% (95% CI 10%–22%), corresponding to an NNT of 7 (95% CI 4.5–10.0) (Appendix 8, available at www.cjem-online.ca). The absolute risk increase in good neurologic outcome was 26% (95% CI 19%–33%), with an NNT of 4 (95% CI 3.0–5.3) (Appendix 4, available at www.cjem-online.ca).

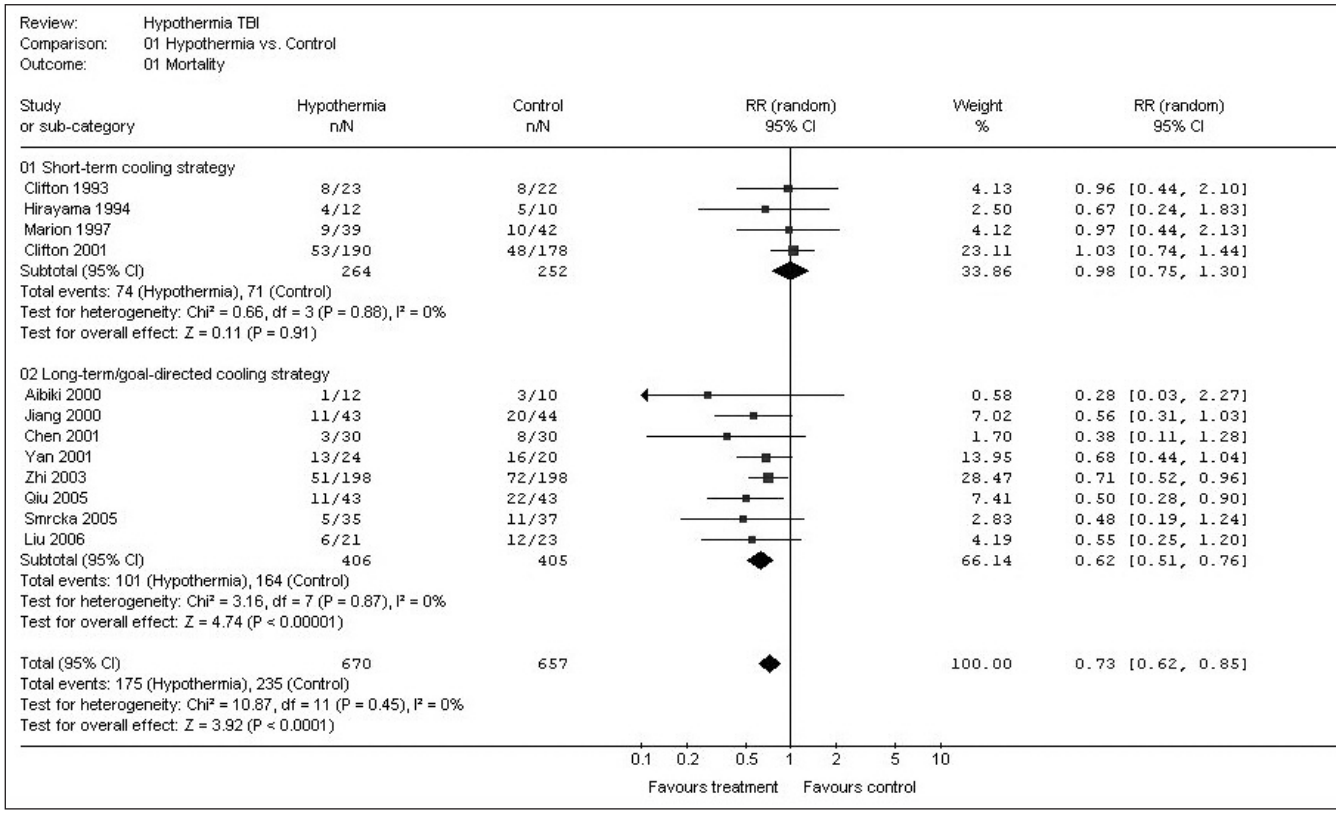

Fig. 2. Forest plot showing relative risk of mortality in trials of short- and long-term cooling compared with standard therapy. CI = confidence interval; TBI = traumatic brain injury.

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There was much variability in adverse events reported by studies in this review. Many studies noted hemodynamic changes associated with hypothermia: bradycardia in 7 trials[8,17,19,25,26,28,32] and hypotension in 3 trials.[17,19,25] A rebound increase in ICP associated with rewarming was reported in 3 of the short-term cooling studies;[17,25,26] however, this adverse event was not reported in any of the long-term cooling studies. No difference in the development of pneumonia between control and hypothermia groups was reported in 5 trials,[26–28,32] and sepsis or pneumonia were more commonly reported in hypothermic patients in 2 trials.[17,31] No study reported an increase in hemorrhagic complications with hypothermia (either intracranial or systemic), though 4 reported thrombocytopenia[19,27,31,33] and 3 reported slight prolongations in the partial thromboplastin time or prothrombin time.[17,19,26] Although hypokalemia was the most common electrolyte abnormality, reported in 6 trials,[8,17,19,25,26,28] it was treated without serious sequelae in all studies.

DISCUSSION

We found that early prophylactic (regardless of initial ICP, or before ICP was measured) mild-to-moderate hypothermia (most studies cooled to 32°–34°C) had a clinically and statistically significant benefit on mortality and functional outcome of patients with severe TBI (GCS ≤ 8), particularly when a long-term or goal-directed cooling strategy was applied (patients were cooled for at least 72 h and/or not rewarmed until ICP had normalized for 24 h). Furthermore, the improvement is highly clinically significant, with very low NNTs to improve both mortality and chance of independent life after head injury. The principal reason this meta-analysis is positive where previous ones were negative is that we included numerous recent studies that were not included in previous reviews; many of the newer studies used a long-term or goal-directed strategy of cooling, which appears to be more effective.

The pathophysiology of TBI helps to explain why there is benefit to cooling beyond 48 hours. In a recent observational study of ICP after TBI, only one-third of patients achieved their highest ICP within the first 2 days after injury, and 20% did not achieve their peak ICP until after day 5.[20] A number of studies have reported a rebound increase in ICP associated with the

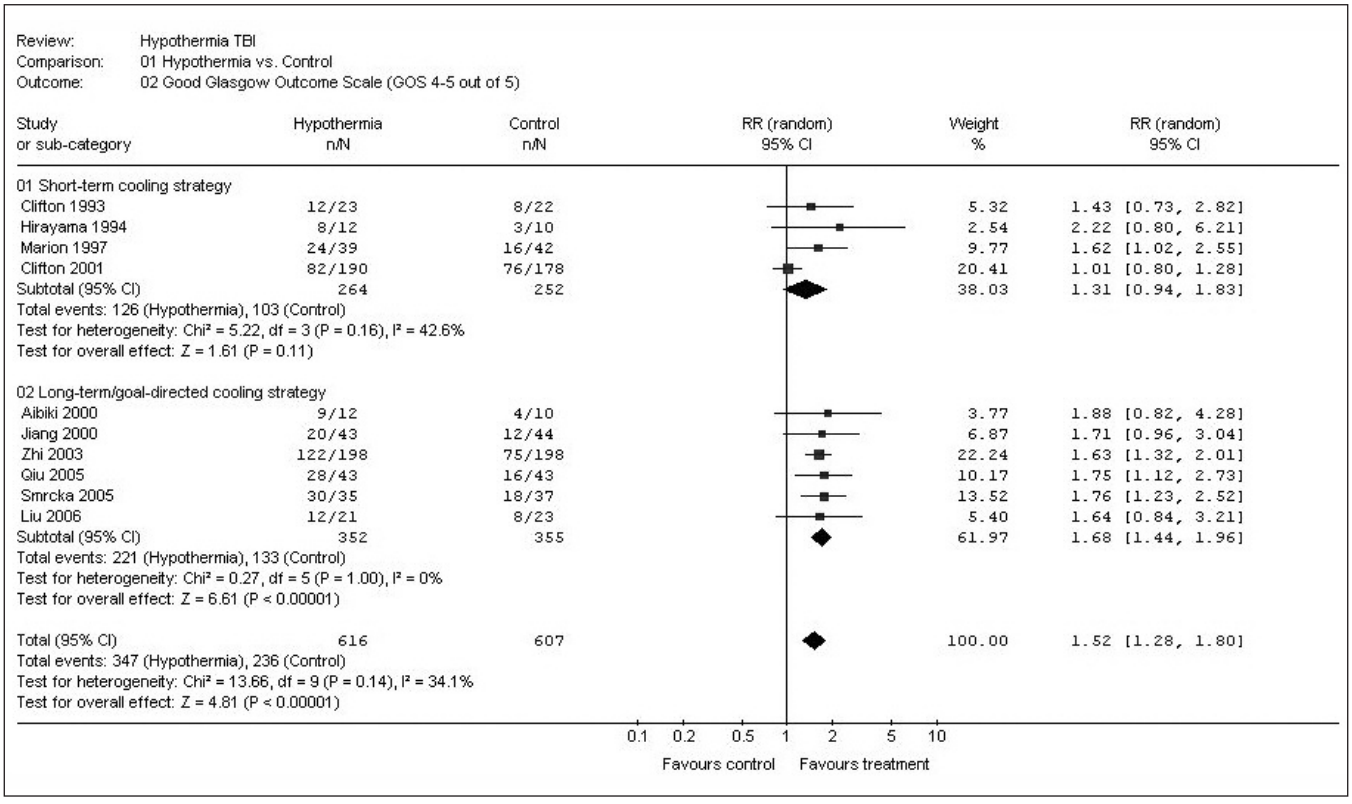

Fig. 3. Forest plot showing relative risk of good neurologic outcome in trials of short- and long-term cooling compared with standard therapy. CI = confidence interval; TBI = traumatic brain injury.

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discontinuation of cooling,[17,25,26,35–37] perhaps negating any benefit accrued during the first 48 hours of cooling. In earlier studies, a 24–48 hour duration of cooling was chosen because of concerns that longer periods of hypothermia would be associated with increased risk of adverse events.[17,18] However, increased duration of hypothermia has not been shown to increase risk of delayed hemorrhage or pneumonia,[21,38] with cooling being successfully extended up to 19 days in one study.[39] It appears that the majority of adverse effects occur during the initial phase of cooling, when hypotension, diuresis, hypokalemia, sinus bradycardia and other mild arrhythmias do commonly occur.[19,21] In TBI, treatment of these side effects is crucial to prevent hypoperfusion and further ischemic insult. However, as the duration of cooling is extended there is only a mild worsening of side effects (e.g., gradual thrombocytopenia), while benefits (e.g., control of ICP, prevention of reperfusion injury) continue to accrue. These observations from clinical trials and bench research favour the theory that, although the balance of adverse effects occur early on with the initiation of cooling, the benefit is not fully realized until cooling is extended beyond the period of significant cerebral edema and elevated ICP.

There are several limitations of this review. Most importantly, the quality of data used to derive our conclusions were poor; among included studies, blinding, concealment of allocation and outcome assessment blinding were infrequently reported. Although 3 of the included studies were published in English, they were originally written in Chinese, and the methodology in these articles was sometimes unclear because of issues with translation.[29,30,31] To mitigate this, authors of all studies were contacted in an attempt to clarify any details that were unclear. It could also be argued that by separating the long-term from the short-term studies we have artificially removed the higher quality, negative studies from the long-term subgroup, which could have had the effect of inflating the apparent benefit in that group. However, mortality outcome data should not be affected by lack of outcome assessment blinding, and our sensitivity analysis did not detect a change in results in any comparison when low-quality studies were removed (Appendices 5 and 6, available at www.cjem-online.ca). It should also be noted that our division of studies into short- and long-term strategies has a scientific basis: in the only large direct comparison of the 2 strategies by Jiang and coauthors[24] in 2006, the long-term (5 [standard deviation 1.3] d) cooling group performed much better than the short-term (2 [standard deviation 0.6] d) group with rates of favourable outcome of 43.5% versus 29% ($p < 0.05$). Finally, the funnel plot was asymmetric, suggesting the possibility that small, negative studies have not been published (Appendix 7, available at www.cjem-online.ca).

Future research may help shed new light on this important field. There are currently 5 ongoing studies of hypothermia for TBI registered with the clinicaltrials.gov registry. One is a study of discrete hypothermia (cooling helmet) initiated within 48 hours of injury in patients with severe TBI requiring an ICP monitor.[40] Another study is using a 48-hour protocol similar to the Clifton 2001 trial,[19] but with very early (< 2.5 h post-injury) initiation of cooling and exclusion of older patients (> 45 yr),[41] 2 factors which could increase the likelihood that the trial will find a benefit. One trial is a pediatric study cooling early (< 6 h) to 32°–33°C for 48 hours.[42] One study will cool to 32°–34°C "for at least 72 hours,"[43] which may indicate an ICP-targeted strategy, and one pilot pediatric study is applying an early/prophylactic and long-term/goal-directed cooling strategy but is enrolling only 50 patients.[44] Another recently published study on hypothermia in pediatric brain injury, which cooled for only 24 hours and then rewarmed regardless of ICP, showed a negative effect of the intervention on functional outcomes.[45] Indeed, given what is known about rebound increases in ICP and timing of cerebral edema, it is not surprising that this protocol was found to be harmful. It would be of great value for Western researchers to attempt to reproduce the success of prophylactic long-term hypothermia achieved in Asia, where most of the long-term cooling studies were performed.

CONCLUSION

We found that the best available evidence to date supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (GOS score ≤ 8) to decrease mortality and improve neurologic recovery. This should be commenced as soon as possible after injury (e.g., in the emergency department after computed tomography) regardless of initial ICP, or before ICP is measured. Most studies report using a temperature of 32°–34°C. The greatest benefit occurred with a long-term or goal-directed cooling protocol, in which cooling was continued for at least 72 hours and/or until stable normalization of ICP for at least 24 hours was achieved.

Competing interests: None declared.

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