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Review Article

The efficacy of therapeutic hypothermia in adult patients with traumatic brain injury: a systematic review and meta-analysis

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Abstract: Therapeutic hypothermia (TH) has been one amazing treatment option for patients with traumatic brain injury (TBI), but its effect is still controversial. This systematic review is to assess the effectiveness of the application of therapeutic hypothermia to reduce mortality, and poor neurological outcome of adult patients admitted to hospital following TBI. A systematic review of 21 randomized controlled trials was conducted to investigate the effects of therapeutic hypothermia on the mortality and poor neurological outcomes after TBI. Review Manager (RevMan, Cochrane Collaboration, version 5.3) and Comprehensive Meta-Analysis (CMA version 2.0, Biostat) were used to perform the meta-analysis. Pooled effects were estimated for each outcome using a random-effects meta-analysis model. Twenty-one randomized controlled trials are included in the review. Nineteen studies with 2, 245 patients reported mortality at final follow-up. Therapeutic hypothermia was associated with a significant reduction in mortality (relative risk (RR) = 0.78, 95% CI = 0.64-0.96, P = 0.02). However, the pooled data from five recent studies after 2010 showed that this treatment increased the mortality (RR = 0.67, 95% CI = 0.53-0.84, P = 0.0005). Twenty-one trials involving 2, 302 patients reported death, vegetative state, and long-term disability and therapeutic hypothermia was associated with a significant reduction in poor outcomes (RR = 0.71, 95% CI = 0.60-0.84, P<0.00001). Although the studies before 2010 showed that therapeutic hypothermia improved the neurological outcomes, the ones after 2010 did not get this conclusion (RR = 1.02, 95% CI = 0.82-1.27, P = 0.880). In conclusion, therapeutic hypothermia may be beneficial in the treatment of TBI. Further large-scale, multi-center studies with careful matching and enough follow-up periods needed for more persuasive analysis.

Keywords: Therapeutic hypothermia, traumatic brain injury, mortality, meta-analysis

Introduction

Traumatic brain injury (TBI), also known as intracranial injury, constitutes a major health and socioeconomic problem throughout the world [1]. Recent statistics show a 21% increase in the incidence of traumatic brain injury during the past 5 years, which was three times greater than the increase in population [2]. Depending on the severity of the injury, TBI can have a lasting impact on quality of life for survivors of all ages. Nevertheless, the management of traumatic brain injury has been under-represented in medical research as compared with other health problems [3].

Therapeutic hypothermia (TH) is one treatment option for TBI patients. Although hypothermia is routinely used to treat elevated intracranial pressure in patients with TBI in some intensive care units (ICUs), its effect on outcome in this context has a limited evaluation [4]. Some previous trials of induction of hypothermia have shown benefit for death and neuroprotection [5], but recent studies [6, 7] showed trends toward unfavorable outcomes.

We identified all randomized controlled trials (RCTs) that investigate the relationship between TBI and the application of therapeutic hypothermia in adults. This meta-analysis primarily aimed to assess the effects of the implementation of therapeutic hypothermia on the risk of death and poor neurological outcome. The secondary aims were to investigate the various effects of hypothermia according to different years.

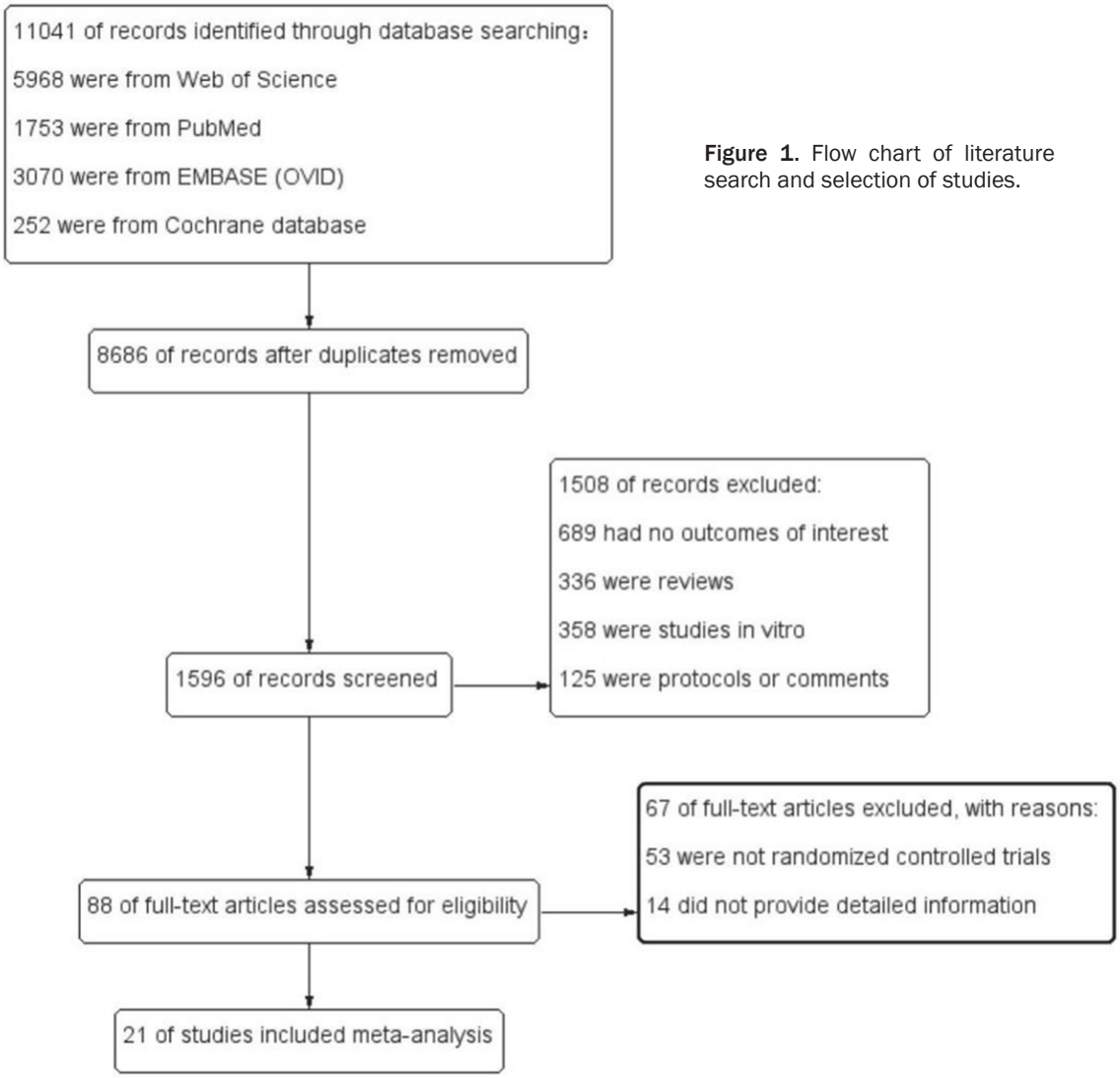

Figure 1. Flow chart of literature search and selection of studies.

Methods

Search strategy and data sources

We performed a computerized search to identify relevant published original studies (up to June 2016). Web of Science, PubMed, Cochrane Library, and EMBASE (OVID) databases was searched using medical subject headings (MeSH) or keywords. These words were "moderate hypothermia, mild hypothermia, hypothermia, sub-hypothermia, therapeutic hypothermia, head cooling, low temperature therapy, cryotherapy, temperature modulation, temperature management, targeted temperature management" and "traumatic brain injury, brain trauma, cerebral trauma, brain injury, head injury, craniocerebral trauma, cranio-cerebral injury". This search was not limited to English language or publication type.

Selection criteria

An initial eligibility screen of all retrieved titles and abstracts was conducted, and only studies reporting therapeutic hypothermia after traumatic brain injury were selected for further review. The following included criteria were used for final selection: (1) randomized controlled trials reporting the therapeutic hypothermia after traumatic brain injury, (2) studies providing detailed information about the mortality and/or poor neurological outcome during follow-up periods. We restricted our search to clinical studies performed in adult populations. Studies without detailed information or experimental studies were excluded.

Table 1. Characteristics of included randomized controlled trials

Author, Year	Study location	Sample size	No. of patients		Age (years)		Method of intervention	Target cooling (°C)	Duration of intervention (hours)	Outcome measures	Follow-up (Months)
			Control	Hypothermia	Control	Hypothermia					
Andrews, et al. 2015 [2]	United Kingdom	387	192	195	36.7±14.9	37.4±15.4	Hypothermia was induced by a bolus of intravenous, refrigerated 0.9% sodium chloride (20 to 30 ml per kilogram of body weight) and thereafter maintained with the usual cooling technique of each site	32-35	≥48	Day 28, Hospital Discharge, or Death MOHS grade, length of stay in ICU and hospital 6-Month Follow-up GOS-E score	6
Maekava, et al. 2015 [6]	Japan	148	50	98	39±18	39±19	Cooling blankets, rapid cold fluid infusion and/or cold gastric lavage	32-34	≥72	GOS	6
Clifton, et al. 2011 [9]	USA	97	45	52	31±11	26±9	Intravenous cold crystalloid, wet sheets, gel packs, surface cooling and gastric lavage	33	48	GOS, neurological complications	6
Zhao, et al. 2011 [10]	China	81	41	40	37.5±15.2	36.9±14.8	Cooling blankets	33	72	GOS	3
Lee, et al. 2010 [11]	China	31	16	15	43.5±16.4	44.0±15.1	Water circulating cooling blankets and ice pillows placed on the head and neck	33-35	NR	The ICP values, favorable neurologic outcome, mortality, complications	During hospitalization
Qiu, et al. 2007 [12]	China	80	40	40	40.2	41.3	Water cooling blankets and refrigerated ice bags	33-35	96	GOS, complications	1 year
Liu, et al. 2006 [13]	China	66	23	43	42.3	39.9	Cooling cap and neck band, cooling blankets and refrigerated ice bags	33-35	3 days	GOS, complications	2 years
Qiu, et al. 2005 [14]	China	86	43	43	42.3	40.0	Cooling blankets, cooling cap and ice bags	33-35	72-96	GOS, complications	2 years
Smrcka, et al. 2005 [15]	Czech Republic	72	17	21	NR	NR	Cooling blankets	34	72	ICP, CPP, SvjO2, GOS	6 months
Guo, et al. 2004 [16]	China	100	32	68	35.0±11.5	36.0±12.0	Cooling blankets in a low temperature room	32-34	≥24	GOS	6 months
Hashiguchi, et al. 2003 [17]	Japan	17	8	9	NR	NR	Water blankets	34	48	GOS, infectious complications	2 years
Zhi, et al. 2003 [18]	China	396	198	198	42±19	43±17	Cooling blankets	32-35	24 hours to 7 days	GOS	6
Gal, et al. 2002 [19]	Czech Republic	30	15	15	39±14	35±13	Air cooling and circulating water matrass	34	72	GOS	6
Clifton, et al. 2001 [20]	USA	368	193	199	32±13	31±12	Application of ice, gastric lavage with iced fluids, room-temperature air in the ventilator circuit, and temperature control pads	33.2±1.0	47.2±3.0	GOS, mortality	6
Jiang, et al. 2000 [21]	China	87	44	43	40.6	42.2	Cooling blankets	33-35	72	GOS	1 year
Shiozaki, et al. 1999 [22]	Japan	16	8	8	NR	NR	Cooling blankets	33.5-34.5	48	GOS, pneumonia	1 year

Marison, et al. 1997 [23]	USA	82	42	40	35±15	31±12	Cooling blankets and gastric lavage with iced saline	32-33	24	GOS	1 year
Hirayama, et al. 1994 [24]	Japan	22	10	12	NR	NR	Cooling blankets	33	48	GOS	3
Cliffton, et al. 1993 [25]	USA	46	22	24	NR	NR	Cooling blankets set at 5°C	33	48	GOS	3
Marion, et al. 1993 [26]	USA	40	20	20	32.1	31.9	Cold saline gastric lavage and cooling blankets	32-33	24	GOS, DRS	6
Shiozaki, et al. 1993 [27]	Japan	33	17	16	35.4±12.6	35.3±15.3	Water cooling blankets	33.5-34.5	48	GOS	6

Abbreviations: ICU = Intensive care unit; MOHS = Modified Oxford Handicap Scale; GOS-E = Extended Glasgow Outcome Scale; GOS = Glasgow Outcome Scale; ICP = Intracranial pressure; DRS = Disability Rating Scale.

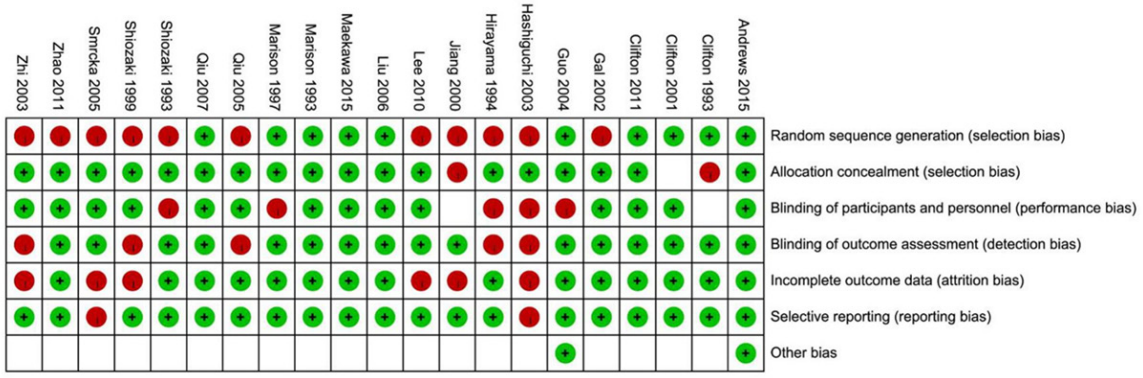

Figure 2. Screening of bias and methodological quality based on the Cochrane Collaboration's tool for assessing the risk of bias.

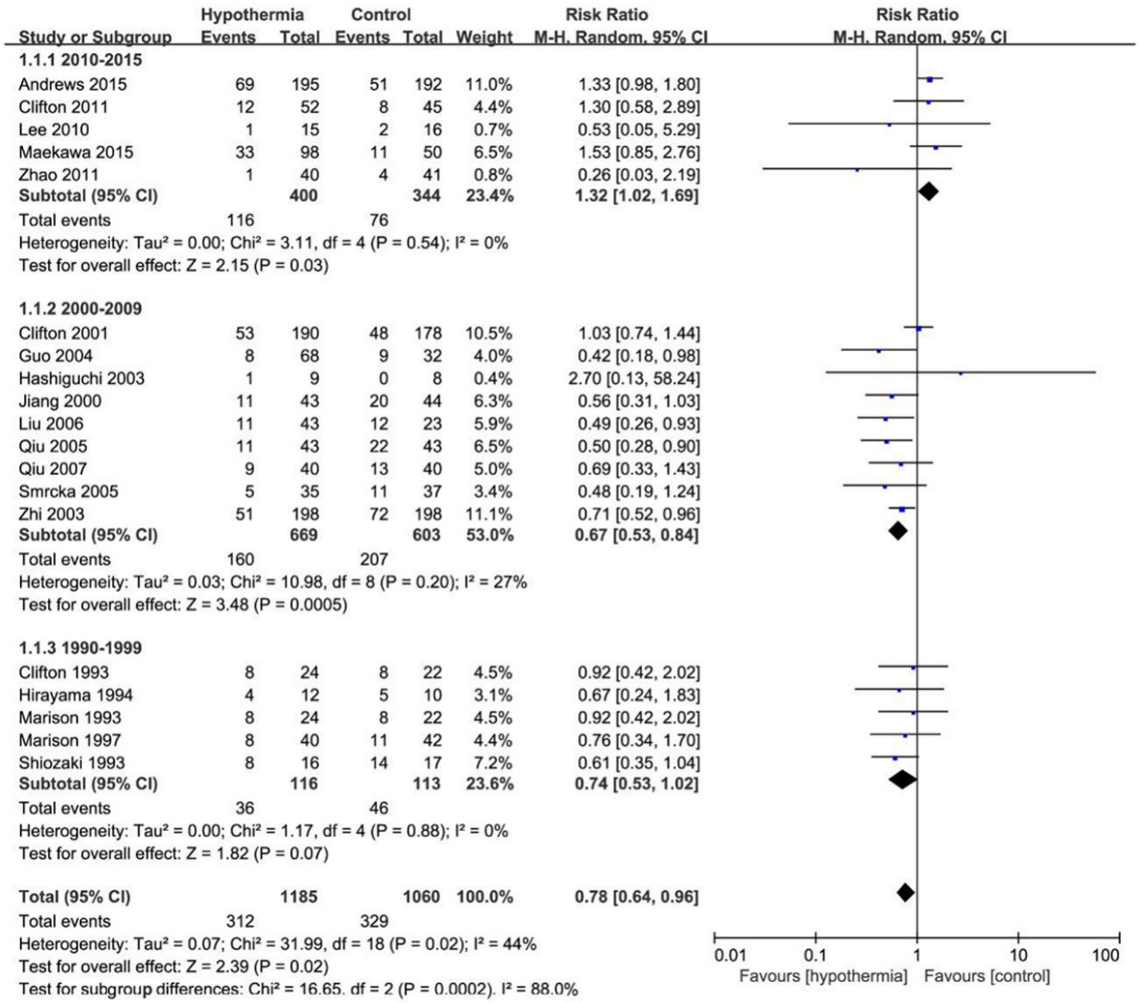

Figure 3. The Forest plot of therapeutic hypothermia on mortality at final follow-up.

Data extraction and quality assessment

Data extraction included country of origin, year of publication, sample size, patient characteristics (age and sex), and protocols of therapeutic hypothermia. The primary outcome was mortality at final follow-up, while the secondary outcome was the poor neurological outcome. The-

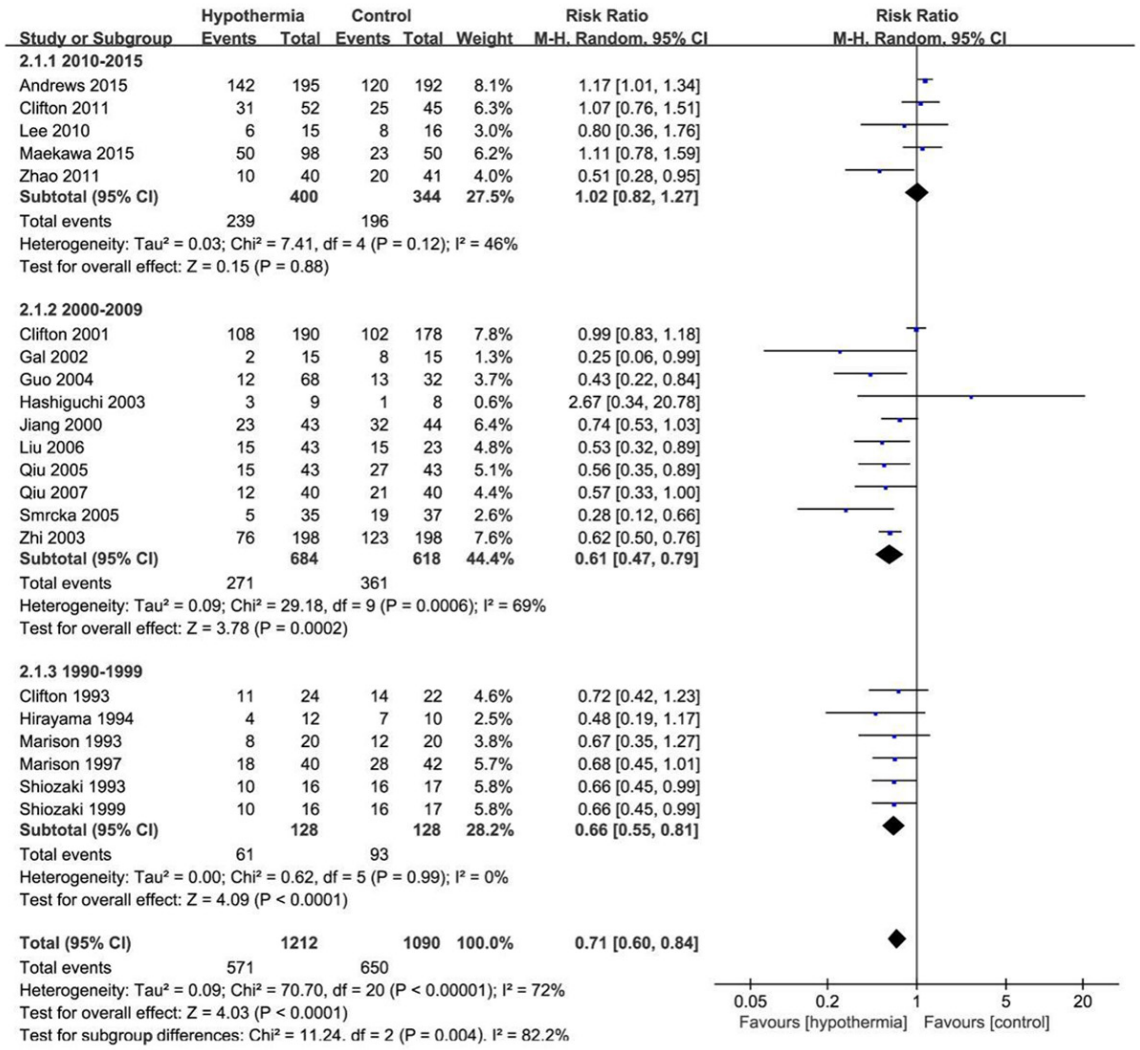

Figure 4. The Forest plot of therapeutic hypothermia on poor neurological outcome at final follow-up.

rapeutic hypothermia was defined as any intervention carried out with the intention of reducing core body temperature to below the physiological norm (36.0°C). Poor neurological outcome at the end of the follow-up period included death, persistent vegetative state or severe disability as defined by the Glasgow outcome scale (GOS) or equivalent scoring scale (Ranchos Los Amigos scale) [5]. The study selection, data extraction, and reporting of results were all based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist [7]. The quality of the studies was assessed independently by pairs of two authors. The methodology described for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective reporting were assessed in our data extraction process using the Cochrane Collaboration's tool for evaluating the risk of bias [8].

Data synthesis and statistical analysis

Review Manager (RevMan, Cochrane Collaboration, version 5.3) and Comprehensive Meta-Analysis (CMA version 2.0, Biostat) were used to perform the meta-analysis. The relative risk and corresponding 95% CI for mortality and poor neurological outcome were extracted where they were available or were calculated where this was not stated in the original trial report. Pooled effects were estimated for each outcome using a random-effects meta-analysis model. Statistical evidence for heterogeneity between trials was assessed using the *Q*-test, and the I^2 index was used as an esti-

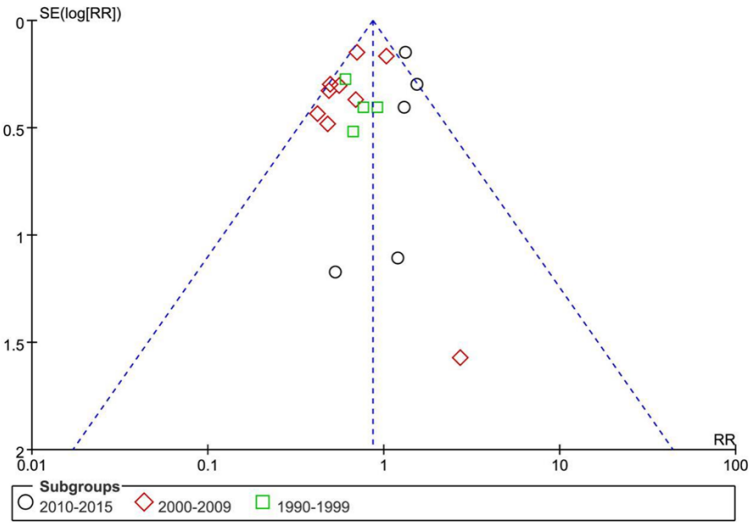

Figure 5. Funnel plot of therapeutic hypothermia on mortality at final follow-up.

mate of the extent of between-trial variability. *P*-value statistical significance was measured at 0.05. Publication bias was assessed by constructing a funnel plot and Egger's regression test using CMA.

Results

Study selection

The article selection process is outlined in **Figure 1**. 1, 1041 of records were identified through database searching. After removal of duplicates and preliminary screening, 88 articles were selected for full-text review for their relevance to this study. After screening, 21 RCTs were included in this systematic review [2, 6, 9-27]. Agreement between investigators at the full-text review stage was excellent as indicated by a κ of 0.8.

Study description and quality assessment

A detailed description of the included studies is provided in **Table 1**. The included studies were published between 1993 and 2015. The total number of patients included in the primary meta-analysis was 2,302 with a median (interquartile range) of 80 (17-396) patients per study. Detailed information on age and gender and protocols of hypothermia were also listed in **Table 1**.

All studies were screened for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias (**Figure 2**). Ten of the included studies were high-quality studies.

Effects of therapeutic hypothermia on mortality at final follow-up

Nineteen studies [2, 6, 9-18, 20, 21, 23-27] with 2, 245 patients reported mortality at final follow-up. When the results of the 19 RCTs were statistically aggregated, therapeutic hypothermia was associated with a significant reduction in mortality (relative risk (RR) = 0.78, 95% CI = 0.64-0.96, *P* = 0.02). However, this pooled effects varied according to different publishing years in subgroup analysis. Studies before 1999 could not come to a definitive conclusion (RR = 0.74, 95% CI = 0.53-1.02, *P* = 0.07), while most of the trials during 2000 to 2009 showed that therapeutic hypothermia reduced the mortality (RR = 0.67, 95% CI = 0.53-0.84, *P* = 0.0005). Conversely, the pooled data from five recent studies after 2010 showed that this treatment increased the mortality (RR = 0.67, 95% CI = 0.53-0.84, *P* = 0.0005) (**Figure 3**).

Effects of therapeutic hypothermia on poor neurological outcome

In an analysis of trials that reported poor neurological outcome at final follow-up, 21 trials involving 2,302 patients reported death, vegetative state, and long-term disability. The results of 21 RCTs showed that therapeutic hypothermia was associated with a significant reduction in poor neurological outcomes (RR = 0.71, 95% CI = 0.60-0.84, *P*<0.00001). Furtherly, the studies before 2010 showed that therapeutic hypothermia improved the neurological outcomes, but the ones after 2010 did not get this conclusion (RR = 1.02, 95% CI = 0.82-1.27, *P* = 0.880) (**Figure 4**).

Publication bias

The funnel plots for **Figure 5** showed no evidence of publication bias. Egger's test for a regression intercept gave a *P*-value of 0.056

for mortality at final follow-up, indicating no publication bias.

Discussion

This systematic review shows there is evidence that therapeutic hypothermia may be beneficial in the treatment of TBI. In the 21 trials included in this systematic review, treatment with therapeutic hypothermia resulted in significantly reduced mortality and poor neurological outcome. However, there was an increase in the RR for mortality and no effects on RR for poor neurological outcome according to trials after 2010. The results indicate that it is an insufficiency of statistical evidence to show that treatment with hypothermia has a decreased risk of death and poor neurological outcome.

Over the past two decades, there has been considerable interest in the use of hypothermia in the management of severe traumatic brain injury. Polderman summarized recent single-center studies and reviewed them [28]. Many studies performed to investigate the favorable outcomes by therapeutic hypothermia (TH) in a single center. Although results from earlier clinical studies have demonstrated its benefit [5], recent multiple centers studies [2, 6] have shown a tendency to worse outcomes in those patients randomized to therapeutic hypothermia. It is clear that TH had a good effect and side effect in experimental studies. We need the protocol which had minimal side effect and maximal therapeutic effect. In the protocol, the optimal cooling time and temperature should be contained, as well as rewarming phase. Moreover, cooling devices and pharmacologic agents should be evaluated for the best therapeutic result. More studies will supplement the sum mentioned earlier, the patients in TBI will be treated with the TH actively.

The present study may have limitations. Firstly, significant difference across studies may lead to high heterogeneity. Secondly, many of the studies included in this analysis were a moderate risk of bias, and so the conclusions drawn in this analysis are limited. Finally, for large limited studies, we could not remove many small studies. Further multiple centers and well-designed RCTs were needed.

In conclusion, results of our systematic review suggest that therapeutic hypothermia may be beneficial in the treatment of TBI. Further large-scale, multi-center studies with careful matching and enough follow-up periods needed for more persuasive analysis.

Disclosure of conflict of interest

None.

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