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Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review

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Editor's key points

- This review aims to address an important issue of primary therapeutic hypothermia in traumatic brain injury.
- Overall 18 randomized controlled trials, involving 1851 patients, were identified.
- Hypothermia was associated with cerebrovascular disturbances on rewarming, and possibly increased incidence of pneumonia.
- No benefit on mortality or neurological morbidity could be identified from high quality trials.

Summary. This systematic review delineates the effect of primary therapeutic hypothermia (PTH) (initiated on presentation of the patient) on both mortality and neurological outcome in patients with traumatic brain injury. The safety profile of the therapy is also assessed. A systematic search of the following databases was performed: MEDLINE, EMBASE, Zetoc database of conference proceedings, the Cochrane Database of Systematic Reviews, and the clinicaltrials.gov website, up to July 28, 2011. Relevant journals were hand-searched for further articles and reference lists were checked against the retrieved results for additional resources. The retrieved results were filtered for randomized controlled trials in English where systemic hypothermia was applied for $\geq$12 h in the treatment arm and outcome was assessed at a minimum of 3 months. Randomized controlled trials were assessed for quality of evidence using the GRADE system. Eighteen randomized controlled trials (1851 patients) were identified. The overall relative risk of mortality with PTH when compared with controls was 0.84 [95% confidence interval (CI)=0.72–0.98] and of poor neurological outcome was 0.81 (95% CI=0.73–0.89). However, when only high-quality trials were analysed, the relative risks were 1.28 (95% CI=0.89–1.83) and 1.07 (95% CI=0.92–1.24), respectively. Hypothermia was associated with cerebrovascular disturbances on rewarming and possibly with pneumonia in adult patients. Given the quality of the data currently available, no benefit of PTH on mortality or neurological morbidity could be identified. The therapy should therefore only be used within the confines of well-designed clinical trials.

Keywords: brain injuries; hypothermia, induced; morbidity, critical care; mortality

Traumatic brain injury (TBI) is a major cause of death and disability throughout the world. Each year in the European Union, TBI accounts for 1 000 000 hospital admissions, for the majority of the 50 000 road traffic deaths, and for more than 10 000 severely neurologically impaired survivors.[1] The mortality and long-term morbidity of the disease are therefore associated with a huge financial and societal burden. Strategies to improve outcome therefore have a pivotal role in the acute management of patients with TBI.

The concept that therapeutic hypothermia may prove to be one such strategy evolved after the discovery that the final neuronal injury pattern after an ischaemic insult to the brain could be manipulated by variations in brain temperature.[2] Subsequent animal models of TBI have elucidated multiple pathways involved in neuronal injury which can be manipulated through the use of therapeutic hypothermia to positive effect (Fig. S1 in Supplementary Material online). As such, there is much clinical interest in the therapy and several clinical trials have now been conducted, leading the Brain Trauma Foundation to issue a level III recommendation for the use of primary therapeutic hypothermia (PTH) in the management of TBI in 2007.[3] Given the inconclusive nature of the data, the studies omitted from that meta-analysis, and the advent of further high-quality studies, this systematic review was undertaken to review the evidence now available and to re-evaluate the risks and benefits of PTH when used in the management of TBI. It aims to answer the following specific questions:

(i) Does PTH improve survival in patients with TBI?
(ii) Does PTH improve subsequent neurological function in patients who survive TBI?
(iii) Is PTH safe when used in the context of TBI?

PTH may be defined as the deliberate lowering of core body temperature initiated on presentation of the patient, in order to achieve a beneficial outcome. This should be differentiated from therapeutic hypothermia initiated reactively in response to a change in the patient's clinical state, usually an increase in intracranial pressure (ICP).

Methods

A systematic search of the MEDLINE and EMBASE databases was conducted with medical librarian assistance from 1966 to July 28, 2011, using the search terms 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pressure'. Filters were applied for clinical trials and review articles. Additional searches were performed using the search term: 'hypothermia, induced [Mesh] and brain injuries [Mesh]' and 'induced hypothermia [Emtree] and traumatic brain injury [Emtree]'. A search of the Zetoc database of conference proceedings was performed using the search term 'hypothermia traumatic brain injury'. The Cochrane Database of Systematic Reviews was searched using the terms 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pressure'. A search of the clinicaltrials.gov website was performed using the search term 'traumatic brain injury hypothermia'. Executive researchers of relevant trials were contacted via e-mail for further information on their respective studies. Relevant journals were hand-searched for further references. The abstracts of the retrieved results were analysed for relevance and appropriate papers were obtained in full for further analysis. Reference lists from selected articles and from review articles were then checked against the retrieved results for additional resources.

The following *a priori* minimum inclusion criteria were then applied to the articles obtained:

(i) English language.
(ii) Randomized controlled trial in patients with TBI.
(iii) Use of induced systemic hypothermia for $\geq$12 h in the treatment arm.
(iv) Assessment of survival and neurological outcome at a minimum of 3 months after injury.

The articles selected were assessed for quality of evidence by each author independently using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system of assessment.[4 5]

Relevant data were extracted from each paper by hand and entered into a spreadsheet (Excel, Microsoft Corporation, Redmond, WA, USA). These data included: details of trial design facilitating assessment of quality, number of patients, injury details (injury severity score, Glasgow coma score, ICP, and the nature of the brain injury, differences in baseline covariates), cooling details (site of temperature measurement, target temperature in study and control groups, time to achieving target temperature, method of cooling, whether active warming was used in the control group, trigger for rewarming, rate of rewarming, presence of pyrexia in the control arm), use of barbiturates, complications (cardiovascular, neurological, infectious, haematological), and outcomes (neurological morbidity and mortality). The power of each study and the relative risk of mortality and neurological outcome with respective confidence intervals were calculated if they were not presented in the paper. The assessment of neurological outcome was based on the dichotomized Glasgow outcome score (GOS) in adults and on the dichotomized paediatric cerebral performance category (PCPC) in children (Tables S2 and S3, Supplementary Material online); this was calculated from raw data where necessary. A GOS of 1–3 or a PCPC of 3–6 was used to indicate a poor neurological outcome. Forest and funnel plots were performed to facilitate data consolidation (RevMan 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The outcome from both fixed and random effects models were obtained in the meta-analysis; the model used did not influence the ultimate outcome and so the fixed effect model is presented in the Results section on the assumption that the same treatment effect was being assessed. The impact of duration of cooling and duration of follow-up on neurological morbidity and mortality was examined, along with the effect of confounding variables such as the effect of cooling on ICP.

Results

The results of the literature search are illustrated in Figure 1. Eighteen randomized controlled trials were selected and are summarized in Table 1. The authors independently reached consensus as to the quality of each trial. The overall quality of the evidence was graded as low. Fifteen trials were conducted in adults and three in children; three trials were graded as high quality, two as moderate, six as low, and seven as very low.

Does therapeutic hypothermia reduce mortality post-TBI?

A forest plot examining the pooled effect of PTH on mortality is shown in Figure 2. The relative risk of mortality after PTH compared with normothermia in TBI is 0.84 [95% confidence interval (CI)=0.72–0.98]. A funnel plot suggests that publication bias among this data set is unlikely (Fig. 3).

Only the trials by Clifton and colleagues,[6] Hutchison and colleagues,[7] and Clifton and colleagues[8] were deemed to be of high quality and important variables of these trials are further summarized in Table 2. The two former trials were performed in adults; the latter in children. Neither found benefit of PTH in reducing mortality after TBI; indeed, there was increased mortality in the PTH group in the trial by Hutchison and colleagues. A forest plot of only high-quality trials yields a pooled relative risk of mortality of PTH compared with normothermia of 1.28 (95% CI=0.89–1.83) as shown in Figure 4.

Does therapeutic hypothermia improve neurological outcome post-TBI?

A forest plot examining the pooled effect of PTH on poor neurological outcome is shown in Figure 5. The overall relative risk of a poor neurological outcome with PTH compared with normothermia in TBI is 0.81 (95% CI=0.73–0.89). Significant heterogeneity is noted in the data. A funnel plot suggests that publication bias among this data set is unlikely (Fig. 6).

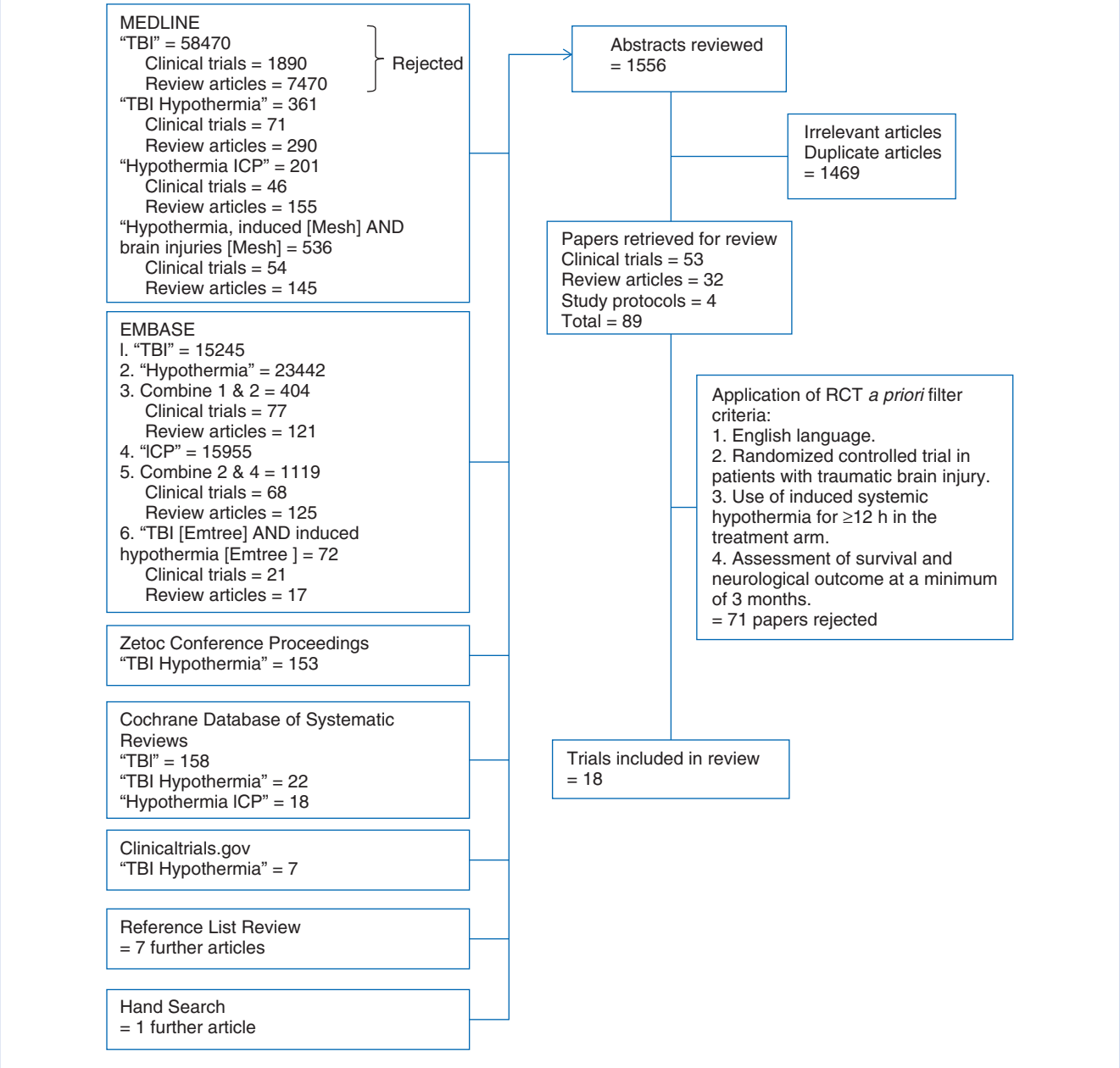

Fig 1 Flow diagram of literature search and retrieved results.

None of the high-quality trials[6–8] found benefit of PTH in reducing neurological morbidity after TBI. Neurological outcomes were worse in the PTH group in the trial by Hutchison and colleagues[7] and in the subgroup aged >45 yr of age in the trial by Clifton and colleagues,[8] although the trials are not internally comparable (paediatric patients cooled for 24 h *vs* adult patients cooled for 48 h). A forest plot of only high-quality trials yields a pooled relative risk of poor neurological outcome with PTH compared with normothermia of 1.07 (95% CI=0.92–1.24) as shown in Figure 7.

Three trials which followed patients up for ≥12 months found benefit of PTH on neurological outcome.[9–11] Of these, caution is advised in the interpretation of one study, where the CIs were not presented in the paper, so were calculated and found to cross 1.0[9] (Table 1). Of the remaining trials, the second began cooling immediately after craniotomy[10] and the time from injury to attainment of target temperature was not specified; the third began cooling at widely variable time intervals after injury.[11] Omission of data examining confounding variables makes interpretation with regard to prolonged follow-up extremely difficult. In contrast, one moderate-quality trial[12] followed up patients for 12 months and found no benefit of PTH on neurological outcome. Conclusions regarding neurological morbidity after PTH and

Table 1 Summary of trials included for review. Data for relative risk of poor neurological outcome are derived from comparison of GOS 1–3 *vs* 4–5 for all trials with the exception of Hutchison and colleagues[7] where it is for PCPC 4–6 *vs* 1–3. *The confidence intervals (relative risk) presented in the paper are different from those calculated manually. However, the direction and magnitude of the effect are unchanged. †Relative risk and confidence intervals not presented in the paper so calculated from data provided. ‡Caution is advised over the conclusions made in this paper; the calculation of relative risk and confidence intervals were not presented in the original paper and when performed were found to cross 1.0. ↑, increased incidence; ↓, decreased incidence; AP, arterial pressure; HR, heart rate; plts, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; K^+, serum potassium; Na^+, serum sodium; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; Hb, haemoglobin; Hct, haematocrit; WCC, white cell count; Cr, creatinine; DI, diabetes insipidus; MOF, multi-organ failure

Study	Quality of trial (GRADE)	Setting	Evidence of adequate allocation concealment/outcome assessor blinding	Number of patients	Target temperature in the PTH group (°C)/ duration of PTH (h)	Did PTH lower mortality? Relative risk of mortality (95% CI)	Did PTH improve neurological outcome? Relative risk of poor outcome (95% CI)	Complications in the PTH group
Clifton and colleagues[6]	High	Multi-centre	Yes/yes	97	33/48	No 1.30 (0.58–2.89)	No 1.08 (0.76–1.53)	↑ ICP ↓ APTT, K^+ More +ve fluid balance
Hutchison and colleagues[7]	High	Multi-centre	Yes/yes	225	32.5/24	No 1.40 (0.90–2.27)*	No 1.41 (0.89–2.22)	↓ AP, HR, and plts. ↑Glucose, PT, lactate vasoactive drugs
Qiu and colleagues[10]	Low	Single-centre	Yes/yes	80	33–35/96	No 0.69 (0.44–1.09)*	Yes 0.57 (0.33–1.00)*	↑ Pneumonia ↓ plts
Adelson and colleagues[15] HYPO I and HYPO II	Very low	I=Multi-centre II=Single-centre	Yes/yes	48 (I) and 26 (II)	32–33/48	No I: 0.58 (0.12–2.90)* II: 0.94 (0.22–4.00)*	No (actual data not presented) $P \leq 0.05$ at 3 and 6 months	Nil
Qiu and colleagues[11]	Very low	Single-centre	Yes/yes	86	33–35/103	Yes 0.50 (0.28–0.90)†	Yes 0.56 (0.35–0.89)†	↑ Pneumonia ↓ plts
Smrcka and colleagues[22]	Very low	Single-centre	Unclear/yes	72	34/72	No 0.48 (0.19–1.24)†	Yes 0.28(0.12–0.66)†	Nil
Zhi and colleagues[23]	Low	Single-centre	Unclear/unclear	396	32–35/62.4	Yes 0.71 (0.52–0.96)†	Yes 0.62 (0.50–0.76)†	↓ K^+
Hashiguchi and colleagues[17]	Very low	Single-centre	Unclear/unclear	17	33.5–34.5/48	No 2.70 (0.13–58.24)†	No 2.67(0.34–20.78)†	↑Pneumonia and meningitis
Biswas and colleagues[12]	Moderate	Single-centre	Unclear/yes	21	32–34/48	No 7.64 (0.44–131.75)†	No 9.82 (0.59–162.24)†	Nil
Clifton and colleagues[8]	High	Multi-centre	Yes/Yes	392	33/48	No 1.0 (0.74–1.44)	No 1.0 (0.83–1.18)	↑ Alkalosis, Hb, Hct, PT, APTT, and Cr ↓ HR and MAP. ↓ MAP and CPP on rewarming. More +ve fluid balance

Shiozaki and colleagues[18]	Very low	Multi-centre	Unclear/unclear	91	34/48	No	1.29 (0.83–2.00)†	↑ Pneumonia, meningitis, amylase, and Na^+
						1.36 (0.51–3.62)†	Yes‡	↓ WCC, plts, K^+
Jiang and colleagues[9]	Low	Single-centre	Unclear/yes	87	33–35/72–336	Yes‡	Yes‡	Nil
						0.56 (0.31–1.03)†	0.74 (0.53–1.03)†	
Aibiki and colleagues[21]	Low	Single-centre	Unclear/yes	26	32–33/72–96	No	Yes	↓ plts
						0.24(0.03–2.05)†	0.31 (0.10–0.95)†	
Shiozaki and colleagues[19]	Low	Single-centre	Unclear/unclear	16	33.5–34.5/48	No deaths	No	↑ DI and Na^+
							2 (0.22–17.89)†	
Marion and colleagues[14]	Low	Single-centre	Yes/yes	82	32–33/24	No	No	↓ HR and CPP on rewarming
						0.97 (0.44–2.13)	0.5 (0.2–1.2)	
Clifton and colleagues[16]	Moderate	Single-centre	Yes/Yes	46	32–33/48	No	No	↓ MAP and CPP on rewarming
						0.92 (0.42–2.02)†	0.72 (0.42–1.23)†	↑ PT, APTT, K^+, and glucose
Shiozaki and colleagues[20]	Very low	Single-centre	Unclear/unclear	33	33.5–34.5/48	No[c]	Yes	↑ Pneumonia, CNS infection, MOF, and arrhythmias
						0.61 (0.35–1.04)†	0.66 (0.45–0.99)†	↓ MAP on rewarming
Clifton and colleagues[13]	Very low	Single-centre	Yes/unclear	10	30–32/24	No	No	↓ K^+↑ arrythmias
						1.0 (0.08–11.93)†	0.5 (0.06–3.91)†	

duration of follow-up cannot therefore be made from the data currently available.

After reaching target temperature, three trials cooled patients for 24 h[7 13 14] and nine trials for 48 h.[6 8 12 15–20] Only in the latter group did one very low-quality trial find a reduction in poor neurological outcome with PTH.[20] Given that 12 out of 17 patients in the control group of this study died from intractable elevations in ICP, firm conclusions outside of the ICP-lowering effects of PTH cannot be made. Six trials cooled patients for ≥62 h after reaching target temperature.[9–11 21–23] All trials found a reduction in poor neurological outcomes with PTH (although caution is advised in interpretation of one these trials as outlined above).[9] Four of these trials[9–11 22 23] also showed reductions in ICP (in the fifth, ICP was not described),[21] confounding the findings significantly.

Analysis of confounding influences

Of the 18 trials selected for review, 11 found a reduction in ICP associated with PTH.[7–11 14 15 18 20 22 23] Of these, two found an improvement in mortality[11 23] and six found an improvement in neurological morbidity.[10 11 14 20 22 23] Differentiating the effect on mortality and morbidity of a lower ICP from the application of hypothermia as a treatment modality in its own right is therefore complex. However, no reduction in neurological morbidity was seen in high-quality trials where PTH was associated with a decrease in ICP,[7 8] or in trials where ICP was controlled to <25, 22, or 20 mm Hg.[16 18 19] This suggests that the two effects can be differentiated and clear evidence of a beneficial association is not observed. There was evidence of pyrexia (temperature >37.5°C) in the control group in 11 trials[6 8 9 11–17 20] which may have adversely biased outcome in the PTH group. Despite this, a beneficial effect on mortality and morbidity in the PTH groups was only reported in two trials.[11 20] In the trial by Qiu and colleagues,[11] a target temperature of 38°C was sought in the control group. In the trial by Shiozaki and colleagus,[20] the target temperature was not specified, but control patients were found to be 37.9 (±0.8)°C at randomization and only benefits in neurological morbidity (not mortality) were identified.

Is therapeutic hypothermia a safe intervention post-TBI?

The cardiovascular effects of cooling and rewarming were noted in all but three trials.[11 17 21] The most common complication reported was a reduction in mean arterial pressure on rewarming, with or without an increase in ICP. The net result was a reduction in cerebral perfusion pressure (CPP) on rewarming from hypothermia in five trials,[7 8 14 16 20] and an increase in the dose of vasopressor used.[7 8] Overall fluid balance was significantly more positive in the group exposed to PTH[6 8] and this was associated with higher ICPs in one trial[6] (although a causal link cannot be established). Of the five trials which identify a reduction in CPP on rewarming, one found an increase in morbidity in the PTH group;[7] none

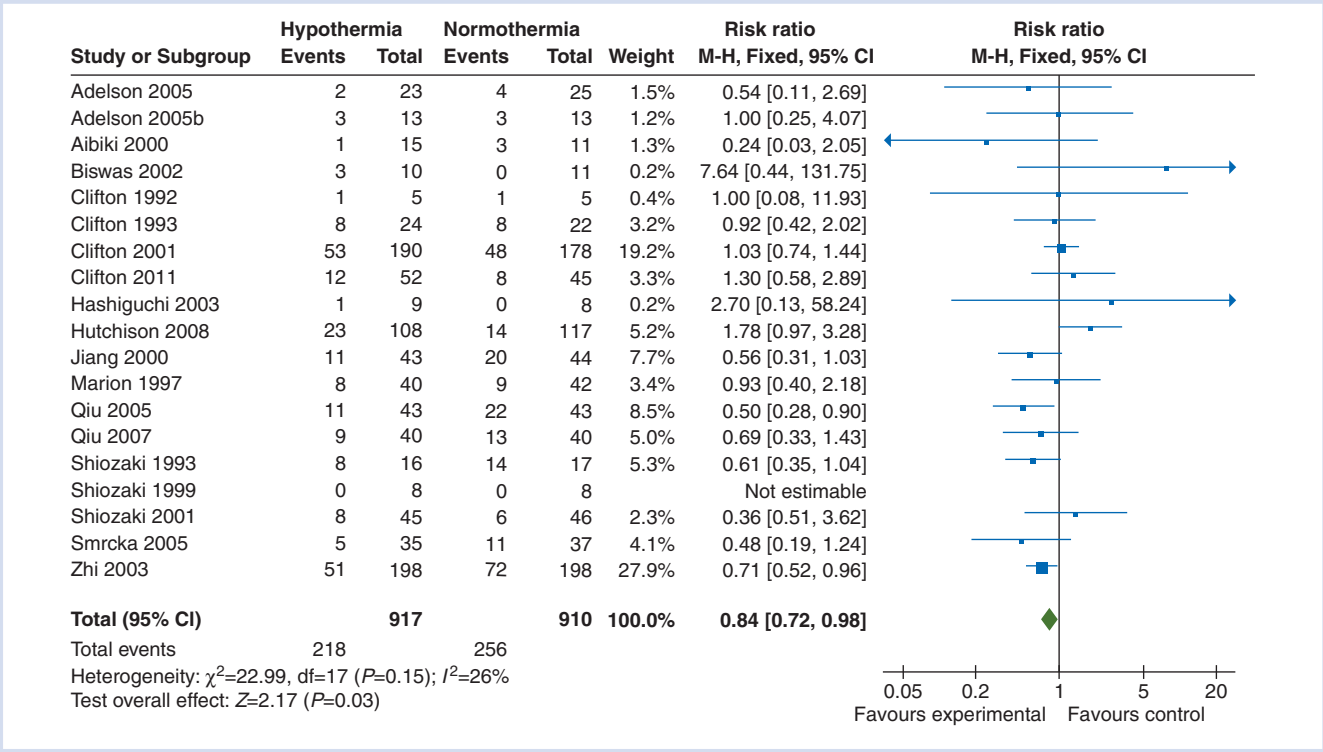

Fig 2 Forest plot of all included trials examining the effect of prophylactic therapeutic hypothermia *vs* normothermia on mortality in TBI. The estimate of heterogeneity places a numerical value on the variation in the results of individual studies, thereby suggesting the confidence that one can have in the combined estimate. The results from these studies are relatively heterogeneous.

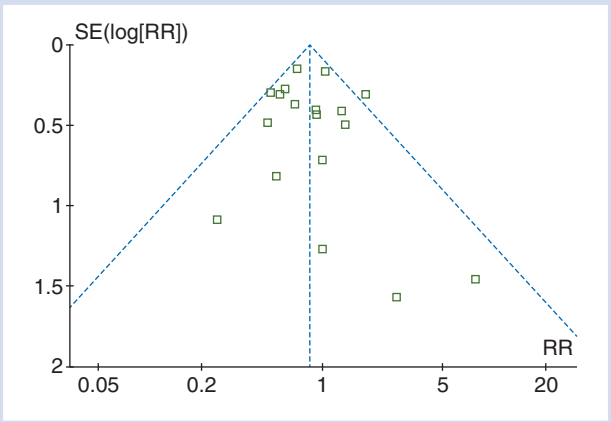

Fig 3 Funnel plot of all included trials examining the effect of publication bias in trials reporting mortality outcomes of prophylactic therapeutic hypothermia *vs* normothermia in TBI. The *y*-axis represents a measure of the precision of the estimated treatment effect. Thus, smaller trials with wider confidence intervals will appear lower on the *y*-axis and increase the chance of the inverted funnel being non-symmetrical. Publication bias is a common explanation for a funnel plot being non-symmetrical. The symmetry of this plot suggests publication bias is unlikely.

found a reduction in mortality and only one found a reduction in neurological morbidity.[19] The possibility that the reduction in CPP masks any benefit of PTH cannot be overlooked.

Pneumonia was actively sought in all but three trials,[8 13 23] although only three trials provided a definition for pneumonia.[17 19 21] Six trials, all of which were of low or very low quality, reported an increased incidence of pneumonia in the group receiving PTH.[10 11 17–20] Overall, there was inadequate control of confounding influences such as serum glucose outside of high-quality trials, to make firm conclusions about the development of pneumonia in those exposed to PTH. Barbiturates were used in four of the six trials which report an increased incidence of pneumonia in the group allocated to PTH,[17–20] although the doses used vary considerably; their use was not specified in the remaining two trials.[10 11] Barbiturate use was, however, not associated with pneumonia in children.[7 12 15]

Discussion

This comprehensive systematic review has failed to identify high-quality data in support of the use of PTH to reduce mortality or neurological morbidity after TBI. The pooled relative risk for both outcomes suggests clear benefit of PTH; however, the positive effect is only seen in low or very low quality trials where the presence of confounding influences and the consequences of poorly controlled studies manifest. There is no evidence from high- or even moderate-quality trials to suggest that PTH reduces mortality or neurological morbidity after TBI either before or after 1 yr of follow-up. Furthermore, some concerns regarding the effects on CPP

Table 2 Summary of papers of high and moderate quality (GRADE criteria). PTH, primary hypothermia; NORMO, normothermia; ↑, increased incidence; ↓, decreased incidence; NS, not specified; ISS, injury severity score; PTS, paediatric trauma score; RTS, revised trauma score

Study (GRADE)	Inclusion criteria	Injury scores (score type)		Admission GCS		Difference in baseline covariates	Temperature targets		Did cooling lower ICP?	Use of barbiturates	Follow-up (months). Did PTH reduce mortality/ morbidity?
		PTH	NORMO	PTH	NORMO		Time from injury to commencement of cooling/to target temp. (h)	Rate of rewarming (°C h^{-1})			
Clifton and colleagues[6] (high)	Age 16–45 Non-penetrating Not responsive to instructions	30 (ISS)	30 (ISS)	5–8 (63%) 3–4 (37%)	5–8 (49%) 3–4 (51%)	↑ Pre-hospital hypoxia in PTH	2.5/4.4	0.25	No	NS	6 No/no
Hutchison and colleagues[7] (high)	Age 1–17; GCS ≤8; CT-acute brain injury; need mechanical ventilation	3 (PTS)	3 (PTS)	5 (4–6) Median (IQR)	5 (3–6) Median (IQR)	↑ Hypotension and hypoxia on admission, midline shift, oedema, and epidural bleeds in PTH	6.3/3.9	0.25	Yes Rebound increase on rewarming	Yes No difference between the groups	6 No/no
Clifton and colleagues[8] (high)	Age 16–65; non-penetrating; GCS 3–8 after resuscitation	28 (ISS)	28 (ISS)	5–8 (74%) 3–4 (26%)	5–8 (79%) 3–4 (21%)	Non- significant ↑ in pre-hospital hypoxia in NORMO	4.3/8.4	0.25–1.0	Yes	NS	6 No/no
Biswas and colleagues[12] (moderate)	Age <18; GCS ≤8; within 6 h of injury; ICP monitor placed	4.7 (RTS)	5.7 (RTS)	5–8 (50%) 3–4 (50%)	5–8 (73%) 3–4 (27%)	↑ GCS 3 in HYPO	4.1/<10	0.04	No	'Considered' difference between groups NS	3, 6, and 12 No/no
Clifton and colleagues[16] (moderate)	Age 16–60 GCS 4–7 post-resuscitation Non-penetrating	NS (exclude major systemic injuries requiring laparotomy, pulmonary failure, and sustained hypotension)		4–5 (50%) 6–7 (50%)	4–5 (41%) 6–7 (59%)	Nil Other injuries not specified	<6/<13.8	0.25	No (But all ICPs <22 mm Hg)	No	3 No/no

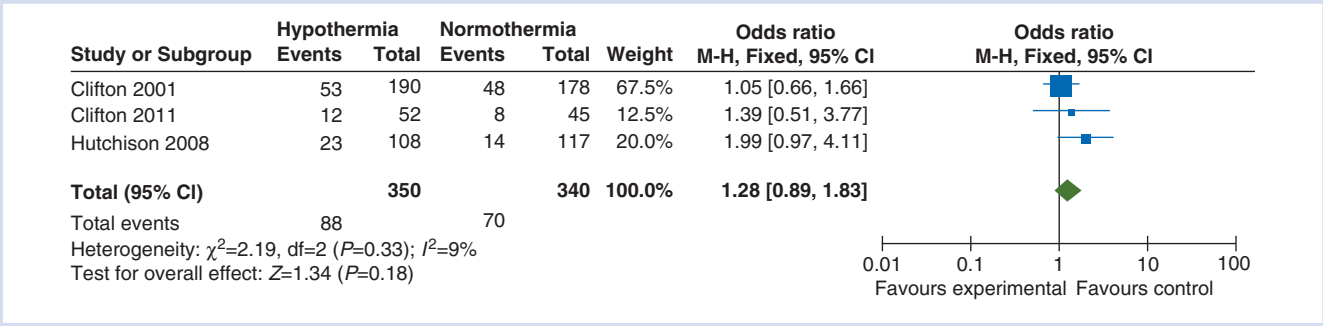

Fig 4 Forest plot of only high-quality trials, examining the effect of prophylactic therapeutic hypothermia *vs* normothermia on mortality in TBI. The analysis of heterogeneity suggests that these studies are very homogeneous.

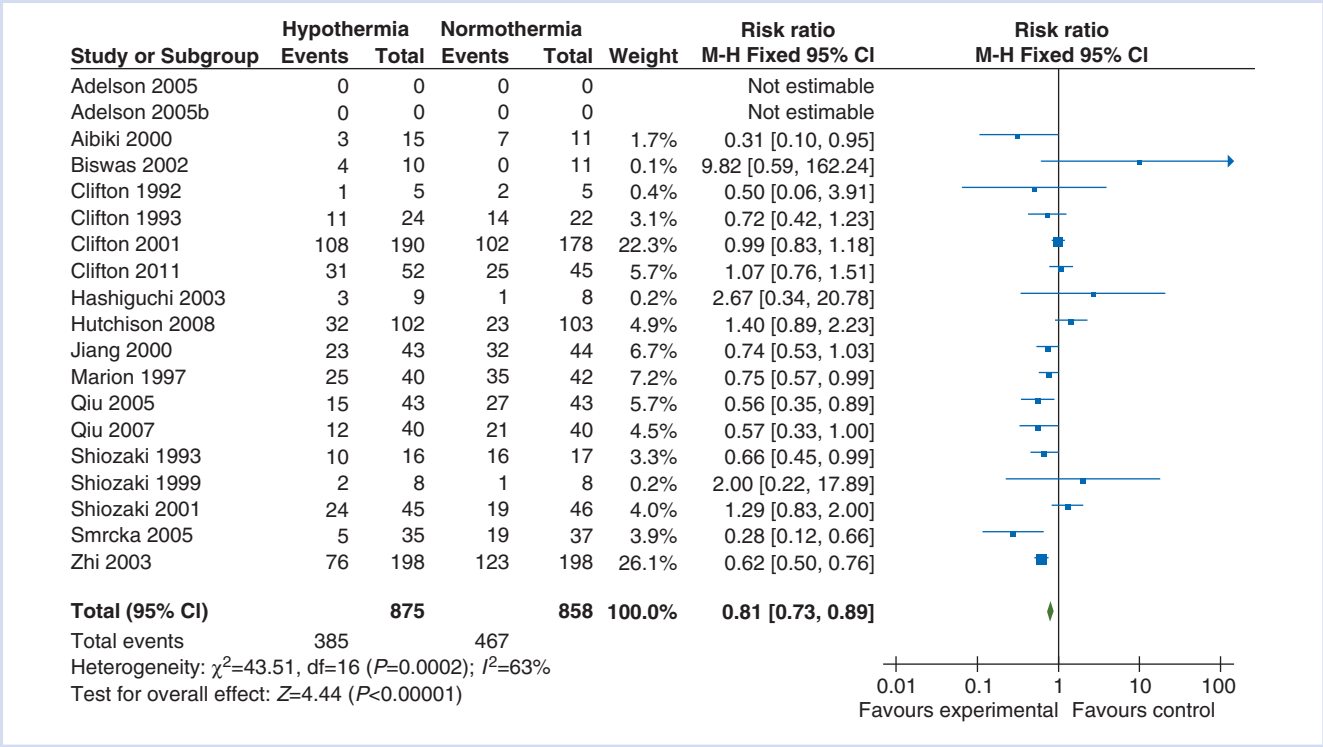

Fig 5 Forest plot of all included trials examining the effect of prophylactic therapeutic hypothermia *vs* normothermia on poor neurological outcome after TBI. The analysis of heterogeneity suggests that these studies are very heterogeneous.

on rewarming are identified, together with a possible association with pneumonia, although the implications of these findings for patient outcome are unknown.

This review addresses clinically relevant questions regarding the effects of PTH on mortality, neurological morbidity, and the safety of the therapy in the setting of TBI. Of the 18 trials identified, 13 were graded as low or very low quality using the GRADE system. Common methodological flaws necessitating downgrading of the trial evidence were:

(i) Only nine trials showed evidence of adequate allocation concealment.[6–8 10 11 13–16]

(ii) Only 12 trials showed evidence of adequate outcome assessor blinding.[6–12 14–16 21]

(iii) Trials frequently involved small numbers of patients.

(iv) Frequently, no correction was made for baseline variables in the condition of the patients.

(v) Detailed important treatment variables were only presented in the studies of high and moderate quality. Such details include ICP, overall fluid balance, and glucose control.

Of note, only three trials[6 13 16] described the method of arterial blood gas analysis during the period of hypothermia

(α-stat or pH stat), increasing the complexity of trial comparison.

Attempts at collating these data have culminated in the publication of eight meta-analyses on the use of PTH in TBI[3 24–30] (Table S4, Supplementary Material online). The findings are illustrated graphically (Fig. S5, Supplementary Material online). The most comprehensive analysis is by the Cochrane group.[30] As in this analysis, an overall benefit from PTH in terms of mortality and neurological morbidity was found, but this was lost when only high-quality trials were analysed. Despite the similarity in conclusion, two important differences are noteworthy between the methodology used in this review and in those used by the Cochrane group. First, this review uses the GRADE system of trial quality assessment, whereas the Cochrane group uses a system based on the risk of bias in a trial.[31] Secondly, this analysis includes four trials not included in the Cochrane analysis,[6 7 11 23] two of which were of high quality.[6 7] This inclusion represents two-thirds of the high-quality data available according to the GRADE criteria. It excludes seven trials[32–38] found in the Cochrane study, six on the basis of having laboratory but not clinical outcome measures[32–37] and one on the basis of non-English publication.[38] It is hoped therefore that this review offers a high-quality review of our current understanding of this topic and gives a more pragmatic summary of data relevant for the practising clinician. Of the other meta-analyses published, four report a significant increase in the risk of pneumonia with PTH,[24 27 29 30] as alluded to in this analysis. Inadequate control of confounding influences in poorly conducted trials give us reason to temper the strength of this finding, although the association appears to be increased when barbiturates are used in adult patients, a finding supported by Peterson and colleagues.[29]

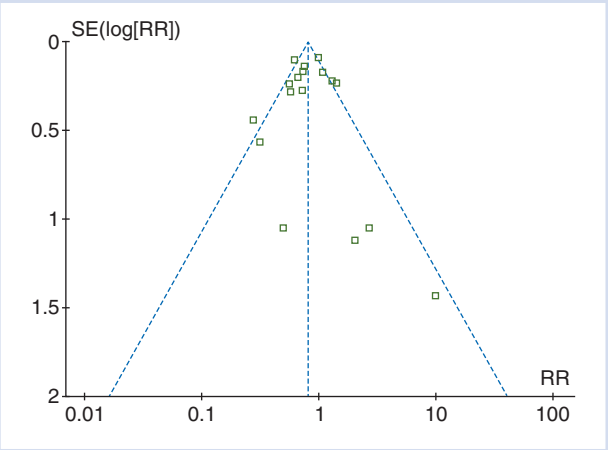

Fig 6 Funnel plot of all included trials examining the effect of publication bias in trials reporting neurological outcomes of prophylactic therapeutic hypothermia *vs* normothermia in TBI. The symmetry of this plot suggests that publication bias is unlikely.

Important confounding influences identified in this review were the anticipated benefit which a decrease in ICP (induced by PTH) may bring and the implication of pyrexia in the control group. Multivariate analysis was not performed due to the heterogeneity in study design and so an in-depth analysis of the data presented was performed manually. This failed to identify a positive role of PTH when these confounding influences were excluded, although insufficient high-quality data meant that conclusive statements could not be made. Tighter control of temperature in the control arm alone is unlikely to produce positive results for PTH, given that current data fail to show benefit when pyrexia was a frequent occurrence in the control group. Data from the cardiac arrest literature suggest that some of the benefit of PTH may be in the avoidance of pyrexia,[39] but no evidence of that phenomenon was seen in the trials of TBI to date. Differentiating the effect on mortality and morbidity of a lower ICP from the application of hypothermia as a treatment modality in its own right is complex. Limited high-quality data from this analysis suggest no additional benefit of PTH outside of its ICP-lowering properties, but more definitive data are likely to be forthcoming from the Eurotherm3235 trial which is currently recruiting.[40]

Why then does the clinical data available fail to support the efficacy of PTH seen in over 37animal trials published to date?[41] Although the animal trials lack both internal and

Study or Subgroup	Hypothermia Events	Total	Normothermia Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Clifton 2001	108	190	102	178	67.9%	0.99 [0.83, 1.18]
Clifton 2011	31	52	25	45	17.3%	1.07 [0.76, 1.51]
Hutchison 2008	32	102	23	103	14.8%	1.40 [0.89, 2.23]
Total (95% CI)		**344**		**326**	**100.0%**	**1.07 (0.92, 1.24]**
Total events	171		150			

Heterogeneity: χ^2=2.02, df=2 (P=0.36); I^2=1%
Test for overall effect: Z=0.84 (P=0.40)

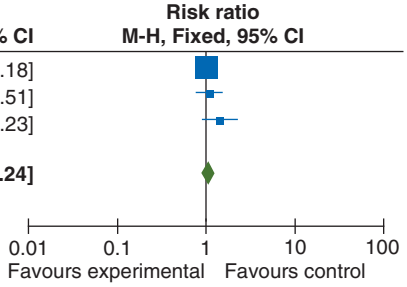

Fig 7 Forest plot of only high-quality trials, examining the effect of prophylactic therapeutic hypothermia *vs* normothermia on poor neurological outcome after TBI. The analysis of heterogeneity suggests these studies are very homogeneous.

external validity,[41] the human trials have lacked the methodological robustness required to detect a benefit of PTH, should one exist:

(i) The disease 'TBI' is heterogeneous in nature and although attempts have been made to discriminate the relative effects of PTH in different types of brain injuries,[6 11 22] no study has been adequately powered to do so.

(ii) All but three trials[9 21 23] began rewarming patients after a pre-determined length of time, regardless of the ICP. This time was 24–48 h in 12 trials[6–8 12–20] and ≥72 h in three trials.[10 11 22] Given the peak ICP after TBI usually occurs >48 h after injury, it is likely that several trials rewarmed patients at the peak of fluctuation in cerebral pathophysiology, possibly negating many of the theoretical benefits of PTH. Indeed, three trials note a rebound increase in ICP on rewarming.[7 15 20] In clinical practice, a significant increase in ICP on rewarming may prompt re-cooling until the ICP is controlled, but this practice was not reflected in 15 of the trials assessed. Of the three trials that rewarmed patients in response to ICP criteria, one found significant benefits on mortality and neurological outcome[23] and one solely on neurological outcome.[21]

(iii) Peak neuronal death occurs days after cardiac arrest but hours after TBI. Only three trials achieved the target PTH temperature within 8.4 h of the injury;[6–8] even this would be regarded by many as too long. Animal data suggest a therapeutic window for hypothermia where induction of PTH beyond 90–120 min post-injury confers no neurological benefit.[2] In the trial by Clifton and colleagues,[8] patients who were hypothermic on admission to hospital and randomized to PTH had better neurological outcome than those who were hypothermic on admission and randomized to the control arm. This finding reached significance in the subgroup of patients ≤45 yr of age.

(iv) The GOS and the PCPC are somewhat crude assessment tools, feasibly allowing for subtle differences in outcome to be missed. For example, assessment of 'return to work' (GOS 4 or 5) may be biased by the type of work or financial dependency; 'return to school' (PCPC 1–3) may be biased by parental attempt, access to private tuition, or legal mandates. A more detailed assessment may involve the use of the GOS Extended (GOSE).[42]

Future studies may therefore consider the initiation of hypothermia in the pre-hospital setting, its maintenance for >48 h with rewarming according to physiological rather than time-based criteria, and follow-up using the GOSE, in conjunction with current best neurocritical care practice. Many of these methodological adaptations are incorporated into the design of ongoing trials, such as POLAR[43] and a Japanese trial in adults,[44] HiTBIC[45] and CoolKids[46] trials in children (the latter of which has recently been stopped for reasons of futility; J. Beca, CoolKids lead Western Australia, personal communication, 2012). Their results will therefore be eagerly awaited.

In conclusion, the pooled benefit of PTH on mortality and neurological outcome in TBI is lost when only high-quality data are analysed and recommendations for its use cannot be made outside of the realm of controlled clinical trials, particularly when the safety of the therapy is yet to be fully elucidated. The paucity of high-quality data in this area means that the possibility of these conclusions changing with the advent of high-quality data from trials currently ongoing cannot be excluded.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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