NICC	nicc_12242	B	Dispatch: March 15, 2016	Journal: NICC	CE: Vaishnavi. M
Journal Name	Manuscript No.		Author Received:	No of pages: 11	TS: David

LITERATURE REVIEW

doi: 10.1111/nicc.12242

Therapeutic hypothermia in patients following traumatic brain injury: a systematic review

Steven Dunkley and Anne McLeod

ABSTRACT

Background: The efficacy of therapeutic hypothermia in adult patients with traumatic brain injury is not fully understood. The historical use of therapeutic hypothermia at extreme temperatures was associated with severe complications and led to it being discredited. Positive results from animal studies using milder temperatures led to renewed interest. However, recent studies have not convincingly demonstrated the beneficial effects of therapeutic hypothermia in practice.

Aim: This review aims to answer the question: in adults with a severe traumatic brain injury (TBI), does the use of therapeutic hypothermia compared with normothermia affect neurological outcome?

Design: Systematic review.

Method: Four major electronic databases were searched, and a hand search was undertaken using selected key search terms. Inclusion and exclusion criteria were applied. The studies were appraised using a systematic approach, and four themes addressing the research question were identified and critically evaluated.

Results: A total of eight peer-reviewed studies were found, and the results show there is some evidence that therapeutic hypothermia may be effective in improving neurological outcome in adult patients with traumatic brain injury. However, the majority of the trials report conflicting results. Therapeutic hypothermia is reported to be effective at lowering intracranial pressure; however, its efficacy in improving neurological outcome is not fully demonstrated. This review suggests that therapeutic hypothermia had increased benefits in patients with haematoma-type injuries as opposed to those with diffuse injury and contusions. It also suggests that cooling should recommence if rebound intracranial hypertension is observed.

Conclusion: Although the data indicates a trend towards better neurological outcome and reduced mortality rates, higher quality multi-centred randomized controlled trials are required before therapeutic hypothermia is implemented as a standard adjuvant therapy for treating traumatic brain injury.

Relevance to clinical practice: Therapeutic hypothermia can have a positive impact on patient outcome, but more research is required.

Key words: intracranial pressure • neurological outcome • systematic review • therapeutic hypothermia • traumatic brain injury

BACKGROUND

Traumatic brain injury (TBI) is a leading cause of death and disability, with around 7·7 million people living with TBI-related disabilities in the European Union (Stocchetti *et al.*, 2015). Severity is diagnosed using radiological criteria (Bersten *et al.*, 2014) along with the Glasgow coma scale (GCS), with a GCS of 3–8 signifying severe injury (Maas *et al.*, 2008). In severe TBI, the primary injury (diffuse damage and contusions) can lead to the development of a secondary injury (cerebral oedema and/or haematomas) (Bersten *et al.*, 2014). TBI management primarily focuses on maintaining adequate cerebral blood flow (CBF), controlling intracranial pressure (ICP) <20 mmHg and reduction of neuronal metabolic requirements through the use of, for example, sedation (Brain Trauma Foundation, American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), AANS/CNS Joint Section on Neurotrauma and Critical Care, 2007).

Therapeutic hypothermia (TH) is the induced cooling of patients to 32–35°C and is proposed to ameliorate the mechanisms of secondary brain injury, improving neurological outcome by decreasing free radical production, preserving the blood–brain barrier (BBB), attenuating ionic disruption and inhibiting excitatory amino-acid release. This inhibits the formation of cerebral oedema and lowers ICP (Busto *et al.*, 1989; Smith and Hall, 1996). Three studies in the early 1990s documented that TH lowered ICP and improved neurological outcome compared to normothermic patients (Clifton *et al.*, 1993; Marion *et al.*, 1993; Shiozaki *et al.*, 1993). However, a subsequent study by Clifton *et al.* (2001) found that TH did not lead to improved neurological outcome. Further studies reported limited success and have failed to provide statistically significant evidence advocating its use (Chen *et al.*, 2001; Shiozaki *et al.*, 2001, 2003). Refractory intracranial hypertension (IH) during re-warming of patients has been noted, suggesting that TH delays the pathological processes of brain injury rather than preventing injury. However, the trend towards improved neurological outcomes means TH remains an area of research, with guidelines suggesting that TH for more than 48 h may reduce mortality (Brain Trauma Foundation, American Association of Neurological

Authors: S Dunkley, BSc (Hons), RN, Staff Nurse, Adult Critical Care Unit, Royal London Hospital, Barts Health NHS Trust, London, UK; A McLeod, MSc, PGDip Teaching Learning, BSc (Hons), RGN, Senior Lecturer in Critical Care, School of Health Sciences, City University, London, UK

Address for correspondence: A McLeod, PGDip Teaching and Learning, Senior Lecturer in Critical Care, School of Health Sciences, City University, Northampton Square, London EC1V 0HB, UK.

E-mail: a.c.mcleod@city.ac.uk

Surgeons (AANS), Congress of Neurological Surgeons (CNS), AANS/CNS Joint Section on Neurotrauma and Critical Care, 2007).

AIM AND OBJECTIVES

The aim of this review is to appraise recent research examining the effects of TH in patients with TBI to answer the question in adults with a severe TBI, does the use of TH compared with normothermia affect neurological outcome?

Secondary objectives are:

1. Investigate the relationship between TH and ICP.
2. Identify relationships between brain pathology and effectiveness of TH.
3. Identify any complications associated with TH.
4. Consider future implications for practice.

METHODOLOGY

Search strategy

A comprehensive search of the PubMed, MEDLINE, CINAHL and Cochrane Library databases was undertaken to identify peer-reviewed primary research investigating the effects of TH in adult patients with TBI. The following search terms, which incorporated MeSH terms, were used: 'cool*' OR 'hypotherm*' OR 'temperature management' AND 'traumatic brain injury' OR 'TBI' OR 'head injury' OR 'IH' OR 'ICP'. The reference lists of selected studies were also manually searched as were the contents of relevant journals.

Selection criteria

During the selection process, the following inclusion criterion was applied: articles published in English, primary research, involve adult patients, investigate the effectiveness of induced hypothermia for traumatic brain injury and published since 2004. Articles were excluded if they considered TH following stroke, spontaneous intracerebral bleeds, hepatic encephalopathy or cardiac arrest. In addition, studies investigating different methods of inducing hypothermia, measuring ICP, cerebral perfusion or blood flow were excluded.

Quality assessment

Identified literature was screened for relevance using a three-stage process ensuring a systematic approach. Firstly, the title was reviewed, and following this, the abstract was reviewed to ensure the inclusion/exclusion criteria were adhered to. The third stage of screening involved reviewing the studies in full to ensure all fulfilled the search criteria. Both authors undertook the review process independently and then agreed on the eligibility of the studies for inclusion.

Data extraction and appraisal

The two authors extracted the data, such as methodology, sample sizes and statistics (mean scores, standard deviation, *p* values), from each included study using a standardized extraction form. Outcomes for neurological outcome at different time points were extracted as well as other data recorded during the study (such as ICP). The eligible studies were appraised using either the critical appraisal skills programme (CASP) randomized controlled trial (RCT) checklist or the CASP cohort study checklist depending on research methodology/design.

Findings

Search outcome

The initial electronic search yielded 122 results (excluding duplicates) once inclusion/exclusion criteria were applied (Figure 1). The hand search identified 2 further studies, resulting in a total of 124 studies. During the screening process, studies were removed as follows: firstly, 75 studies were excluded as within the title, they investigated different monitoring methods, hypothermia generally or involved liver failure/cardiac arrest situations. Secondly, following abstract review, a further 20 studies were excluded as they did not adhere to the inclusion/exclusion criteria. The remaining 29 studies were read in full, and 21 were excluded as they did not match the inclusion/exclusion criteria of primary research and involving TBI. Therefore, eight studies were identified via the search process.

The eight identified studies involved 689 patients and consisted of six RCTs, two of which were multi-centred, and two quasi-experimental studies involving retrospective comparisons against historical control data (Table 1). Six studies compared the effectiveness of TH against the use of normothermia; one compared the effectiveness of long-term (5 days) TH against short-term (2 days) TH; and a further study compared the effectiveness of TH maintained at 35°C as opposed to 33°C. Inclusion and exclusion criteria varied between the studies as well as the methods of inducing and managing TH. Following critical appraisal, four common themes emerged:

1. Influence on neurological outcome.
2. Influence on ICP.
3. Correlation between neurological outcome and brain pathology.
4. Complications.

Influence on neurological outcome

As with previous reviews, it was found that the influence on neurological outcome of TH is conflicting, with some studies showing a benefit and others not; this may be due to variations in study design and when outcomes were measured. All eight studies measured neurological outcome using the Glasgow outcome score (GOS) (Jennet and Bond, 1975), although at varying periods after initial injury (6 months to 2 years). All studies considered a score of ≥4 as a favourable outcome and a score ≤3 as an unfavourable outcome. Three studies concluded that TH improves neurological outcome with statistical significance (Smrčka *et al.*, 2005; Inamasu *et al.*, 2006; Lee *et al.*, 2010). Lee *et al.* (2010) reported a favourable outcome in 71·4% of patients managed with TH in conjunction with $P_{ti}O_2$ (brain tissue oxygenation)-guided management of cerebral perfusion pressure (CPP), 60% in the TH group without $P_{ti}O_2$-guided management and 50% in the normothermia group ($p = 0{\cdot}04$). However, the use of three treatment strategies makes it difficult to distinguish whether the improved outcomes were because of the guided CPP management or TH, and the sample size is limited. Inamasu *et al.* (2006) also reported a higher rate of favourable outcome in patients treated with TH compared to normothermia; 27·8% of patients treated with TH had a favourable outcome, with a survival rate of 33·3% compared to 6·7% of patients in the normothermia group ($p < 0{\cdot}05$). However, the study design and sample size offers questionable reliability. Smrčka *et al.* (2005) likewise reported a statistically significant increase in GOS score in the TH group compared to the normothermia group ($p = 0{\cdot}01$); however, there are gaps in the reporting of TH protocols, such as re-warming rates, and their defined physiological goals, such as ICP and CPP, which may differ from the other studies.

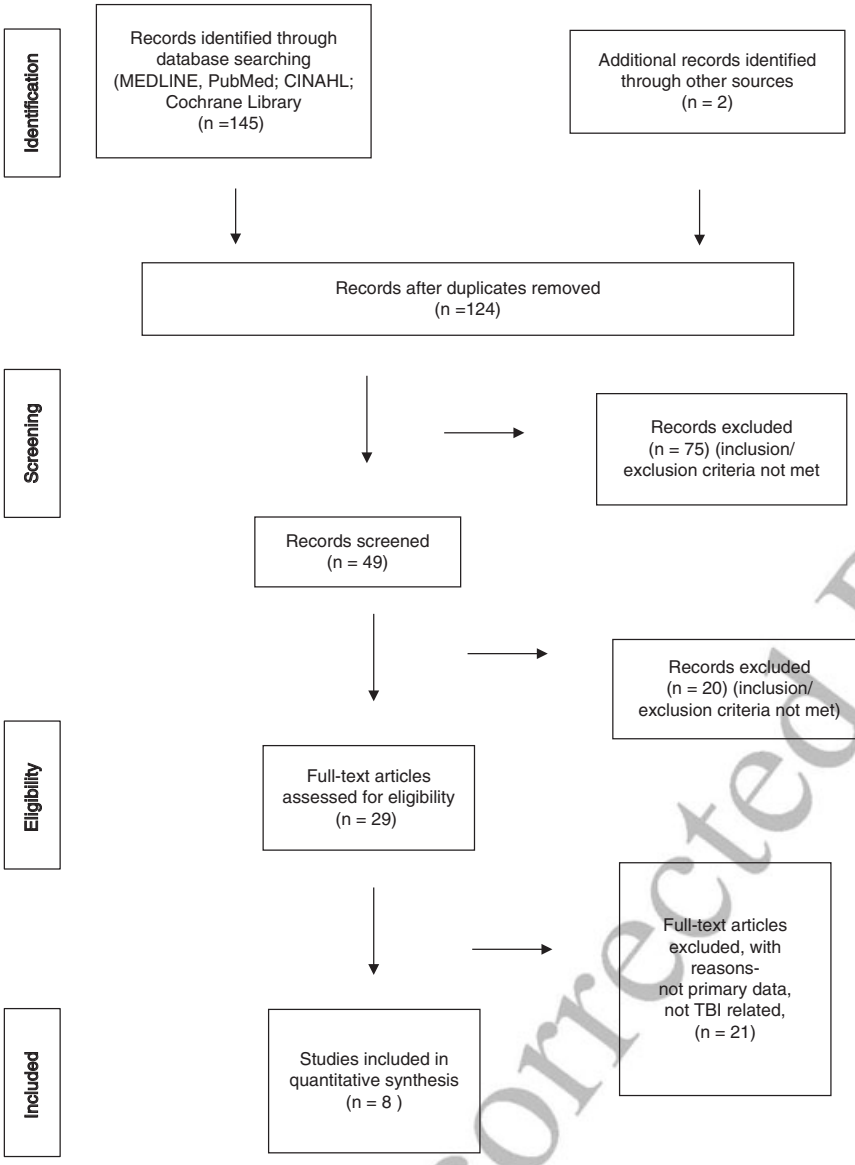

Figure 1 Study selection process.

In contrast, three studies concluded that there is no statistically significant evidence that TH improves overall neurological outcome in patients with TBI (Qui *et al.*, 2005; Qiu *et al.*, 2007; Clifton *et al.*, 2011); however, a higher rate of favourable outcome in the TH groups was found. Clifton *et al.* (2011) reported no statistical difference in the rate of poor outcome between the TH group and normothermia group (60 and 56%, respectively, $p = 0{\cdot}67$), and no difference was observed in mortality rates between the two groups (23 and 18%, respectively, $p = 0{\cdot}52$). However inconsistency in the treatment between both groups in regards to evacuation of haematomas may have influenced the findings and creates a bias in this RCT. Clifton *et al.* (2011) reported that 33% of the patients in the TH group had craniotomies compared to 46% in the normothermia group, which may have influenced the incidence of rebound IH and affected the neurological outcome between the two groups. Qui *et al.* (2005) reported that 53·5% had a favourable outcome in the TH group compared to 27·9% in the normothermia group ($p < 0{\cdot}05$), indicating that TH was effective at improving neurological outcome; however, there are some inconsistencies in the study design and a small sample size. Qiu *et al.* (2007) reported similar figures. However, despite the statistical significance, neurological outcome was assessed at different times (ranging 6 months to 2 years in all studies); therefore, patients had a substantially longer time to recover compared to others, which would influence results.

Jiang *et al.* (2006) and Tokutomi *et al.* (2009) evaluated the influence duration and temperature of TH has on neurological outcome respectively. Jiang *et al.* (2006) reported that long-term (5 days) TH improved the rate of favourable neurological outcome compared to short-term (2 days) TH (43·5% versus 29%, $p < 0{\cdot}05$), suggesting that longer periods of cooling are more efficacious. This was a multi-centred RCT with a reasonable sample size, so these results have a greater reliability than other studies. Tokutomi *et al.* (2009) reported weak evidence that the mortality rate was lower in the 35°C group ($p = 0{\cdot}08$), suggesting that the milder temperature caused lower risk to the patients. However, this study used historical data as the control, which leads to questionable reliability of these findings.

Influence on ICP

All the studies reviewed monitored ICP, with five reporting that TH significantly lowered ICP during TH compared to treatment with normothermia (Qui *et al.*, 2005; Smrčka *et al.*, 2005; Inamasu *et al.*, 2006; Qiu *et al.*, 2007; Lee *et al.*, 2010). However, only Lee *et al.* (2010) demonstrated a sustained decrease in ICP levels following re-warming; this was the only study to titrate re-warming in relation to rebound IH and opted to re-induce hypothermia when ICP values increased. Jiang *et al.* (2006) found that ICP significantly rebounded after re-warming in the short-term TH group and was significantly higher thereafter compared to the long-term TH group ($p < 0{\cdot}05$). Tokutomi *et al.* (2009) found that TH maintained at 35°C and 33°C both controlled ICP under 20 mmHg, with no significant differences in the incidence of IH; however, ICP did rebound above 20 mmHg in both groups 8 days after injury. Clifton *et al.* (2011) reported the only adverse effect on ICP, with a significantly higher incidence of IH compared to the normothermia group (71% versus 60%, $p = 0{\cdot}003$).

These findings suggest that TH does help to reduce ICP, but this does not consistently have a lasting effect. If rebound IH occurs

Table 1 Primary research on effectiveness of therapeutic hypothermia in patients with traumatic brain injury from 2004 onwards

Author and year	Setting	Study design	Sample	Methods	Findings	Implications for practice
Qui *et al.* (2005)	Hangzhou Second Hospital, China	Single-centre RCT	86 patients aged 19–65 with severe TBI confirmed by CT within 24 h of injury and a GCS of ≤8	Patients were randomized into two groups: treatment with hypothermia ($n = 43$) and treatment with normothermia ($n = 43$). Hypothermia was maintained between 33°C and 35°C for 3–5 days and passively re-warmed. Influence of hypothermia on vital signs, extradural pressure (EDP), serum superoxide dismutase (SOD), complications and GOS score 2 years after injury was analysed	There was a significantly higher rate of favourable outcome and lower mortality rate in the hypothermia group compared to the normothermia group. EDP values were significantly lower at 24, 48 and 72 h post-injury in the hypothermia group, whilst the highest EDP was observed at 48 h post-injury in both groups. Serum SOD levels were significantly higher at days 3 and 7 compared to the normothermia group. Patients who underwent surgical decompression had a lower mortality rate in the hypothermia group compared to the normothermia group. There was no evidence indicating there is a significantly higher incidence of severe complications in patients treated with therapeutic hypothermia; however, there was a higher incidence of pulmonary infection and thrombocytopenia in the therapeutic hypothermia group	There is evidence that therapeutic mild hypothermia reduces ICP, increased serum SOD levels and improves neurological outcome without severe complications
Smrčka *et al.* (2005)	University Hospital Brno, Czech Republic	Single-centre RCT	72 patients aged <60 years with severe TBI and a GCS of ≤8	Patients were randomized into two groups: treatment with hypothermia ($n = 35$) and treatment with normothermia ($n = 37$). Hypothermia was maintained at 34°C for 3 days. Influence of hypothermia on ICP, CPP and GOS score 6 months after injury was analysed	The use of hypothermia significantly decreased ICP, $S_{vj}O_2$ and increased CPP. There were significantly more favourable outcomes in the hypothermia group compared to the normothermia group. Hypothermia was more beneficial in patients with extra-cerebral haematomas compared to patients with primary brain lesions	Therapeutic hypothermia significantly improves the outcome in patients with extra-cerebral haematomas. Therapeutic hypothermia in patients with primary brain lesions should be used in cases with otherwise intractable intracranial hypertension

Table 1 Continued

Author and year	Setting	Study design	Sample	Methods	Findings	Implications for practice
Inamasu *et al.* (2006)	National Tokyo Medical Centre, Japan	Quasi-experimental (using historical control group)	33 severely head-injured patients with ASDH and a GCS score of ≤6 on admission and treated with haematoma evacuation	Patients who met the inclusion and exclusion criteria were treated with therapeutic hypothermia ($n = 18$). Hypothermia was maintained between 34°C and 35°C for 3 days. The effect of hypothermia was evaluated retrospectively by comparing the outcome with a historical control with similar injury and treatment ($n = 15$) that were treated with normothermia. The outcome of all patients was evaluated using the GOS score at 6 months. Effect on ICP was also considered	Patients treated with therapeutic hypothermia had significantly lower ICP, higher survival rate and more favourable outcome compared to the historical control group. Therapeutic hypothermia was more effective at improving outcome of patients with haematomas compared to patients with contusion. Patients with a GCS score of 5 or 6 and treated with therapeutic hypothermia had a higher survival rate compared to patients with a GCS of 3 or 4	Therapeutic hypothermia is potentially efficacious post operatively in patients with ASDH who have undergone haematoma evacuation and without concomitant cerebral contusion.
Jiang *et al.* (2006)	Three medical centres in China	Multi-centred RCT	215 patients aged 18–45 years old with non-penetrating severe TBI with cerebral contusion and intracranial hypertension and a GCS of ≤ 8 within 4 h of admission.	Patients were randomized into two groups: long-term hypothermia (5 days, $n = 108$) and short-term hypothermia (2 days, $n = 107$). Hypothermia was maintained at 33°C–35°C in both groups and both were re-warmed no faster than 1°C per h. The neurological outcome of all patients was assessed using the GOS score 6 months after injury. Effect on ICP and incidence of complications were also evaluated	Patients treated with long-term therapeutic hypothermia had a higher rate of favourable outcomes compared to the short-term group. The ICP of patients in the short-term group rebounded after re-warming and was significantly higher compared to the long-term group. There was no significant difference in the incidence of complications between the two groups	Long-term therapeutic hypothermia is more effective at controlling refractory intracranial hypertension than short-term therapeutic hypothermia

Table 1 Continued

Author and year	Setting	Study design	Sample	Methods	Findings	Implications for practice
Qiu *et al.* (2007)	Hangzhou Second Hospital, China	Single-centre RCT	80 patients aged 19–65 with severe non-penetrating TBI confirmed by CTwithin 6 h of injury, a GCS of ≤8 having undergone craniotomy	Patients were randomized into two groups: treatment with hypothermia ($n = 40$) and treatment with normothermia ($n = 40$). Hypothermia was maintained between 33°C and 35°C for 4 days and passively re-warmed. Influence of hypothermia on vital signs, ICP, SOD, complications and GOS score 1 year after injury was analysed	There was a significantly higher rate of favourable outcome in the hypothermia group compared to the normothermia group. ICP values measured in the hypothermia group were significantly lower compared to the normothermia group at 24, 48 and 72 h post-injury. The highest ICP was measured at 48 h post-injury. Serum levels of SOD were significantly higher in the hypothermia group compared to the normothermia group. There was no evidence indicating that there is a significantly higher incidence of severe complications in patients treated with therapeutic hypothermia; however, there was a higher incidence of pulmonary infection and thrombocytopenia in the therapeutic hypothermia group	Therapeutic hypothermia reduces ICP, increases serum SOD levels and improves neurological outcome in patients with severe TBI; however, there is an indication of increased risk of pulmonary infection and thrombocytopenia. Large randomized studies are required to further investigate the efficacy of therapeutic hypothermia after craniotomy
Tokutomi *et al.* (2009)	Japan	Quasi-experimental study (using historical control)	61 patients aged 15–70 years with severe TBI and a GCS of ≤5	Patients who met the inclusion/exclusion criteria were treated with hypothermia maintained at 35°C for 48–72 h if ICP was controlled under 20 mmHg ($n = 30$). The effect of hypothermia at 35°C was evaluated retrospectively by comparing the outcome with a historical control of were treated with hypothermia maintained at 33°C ($n = 31$). Influence of hypothermia on ICP, CPP, biochemical markers, and GOS score 6 months after injury	Mean ICP values did not differ statistically between the two groups. The incidence of intracranial hypertension and low CPP did not differ between the two groups although CPP was controlled at a slightly higher level in the 35°C group. Patients in the 33°C hypothermia group had significantly lower serum potassium levels on days 3 and 5 compared to the 35°C group. The mean CRP values on days 14 and 21 were also significantly lower in the 35°C group, whilst there high CRP levels were more prolonged in the 33°C group. There were no significant differences in neurological outcome between the two groups; however, there was a tendency of increased incidence of complications and higher mortality rate in the 33° group	Therapeutic hypothermia maintained at 35°C is sufficient at controlling ICP and is safer and as effective as hypothermia at 33°C

AQ4

Table 1 Continued

Author and year	Setting	Study design	Sample	Methods	Findings	Implications for practice
Lee *et al.* (2010)	China Medical University Hospital, Taiwan	Single-centre RCT	45 patients aged 12–70 with severe TBI confirmed by CT within 4 h of admission and a GCS of 4 to 8.	Patients were randomized into three groups: normothermia with (group A, $n = 16$), therapeutic hypothermia (group B, $n = 15$) and therapeutic hypothermia with $P_{ti}O_2$ guided management (group C, $n = 14$). Hypothermia was maintained between 33°C and 35°C for 5 days. GOS score, ICP, $P_{ti}O_2$, length of hospital stay and complications were analysed	Groups B and C had more favourable outcomes and lower mortality rates compared to the normothermia group. ICP values in the groups B and C increased less in the first 3 days post-injury and were significantly lower than those in the group A. ICP peaked at 72 h in group A group compared to 24–48 h in the groups B and C. It was found that $P_{ti}O_2$ values increased as ICP values decreased. The mean ICU stay was shorter in group A; however, the total hospital stay was shortest in group C	Therapeutic hypothermia in conjunction with $P_{ti}O_2$ guided CPP and ICP management is beneficial in treating TBI, warranting further research using a multi-centre RCT
Clifton *et al.* (2011)	Six medical centres in the United States and Canada	Multi-centred RCT	97 patients aged 16–45 years with non-penetrating severe TBI with a GCS of ≤8 on admission	Patients were randomized into two groups: early induction of hypothermia ($n = 52$) and patients maintained at normothermia ($n = 31$). The hypothermia group were cooled to 33°C for 48 h and re-warmed at a rate of 0·5°C every 2 h regardless of ICP. The primary outcome measured was neurological outcome measured with the Glasgow outcome score at 6 months. The therapeutic intervention score quantifying the intensity of interventions, effect on ICP, incidence of complications and various laboratory data were also compared	There was no significant difference in outcome between the two groups. The hypothermia group had a significantly higher incidence of increased ICP compared to the normothermia group. Patients in the hypothermia group required more interventions for ICP control in the first 96 h and more interventions in total. Patients treated with surgical removal of haematoma and treated with hypothermia had significantly fewer poor outcomes compared to the normothermia group. Patients with diffuse brain injury and treated with hypothermia had a higher rate of poor outcomes compared to the normothermia group. There was a significant difference in the incidence of complications in the two groups	There is no further need for investigation of early therapeutic hypothermia as a neuroprotectant. The use of therapeutic hypothermia used in conjunction with evacuation of haematomas requires further investigation

CT, computed tomography; CPP, cerebral perfusion pressure; GCS, Glasgow coma scale; RCT, randomized controlled trial; TBI, traumatic brain injury; ICP, intracranial pressure.

during re-warming, re-inducing the TH may be helpful. Titration of re-warming against response to changes in ICP may again be helpful, but the evidence supporting this is limited.

Correlation between neurological outcome and brain pathology

Three studies investigated the correlation between brain pathology and neurological outcome, finding that patients with a haematoma and treated with TH had better neurological outcomes than patients with primary brain injury only (Smrčka *et al.*, 2005; Inamasu *et al.*, 2006; Clifton *et al.*, 2011). Clifton *et al.* (2011) reported a higher rate of favourable outcome in patients treated with TH and surgical removal of intracranial haematomas compared to patients with diffuse brain injury ($p = 0{\cdot}01$). Further analysis identified that patients treated with surgical removal of haematomas had better outcomes when treated with TH instead of normothermia ($p = 0{\cdot}02$), and patients with diffuse injury had poorer outcomes in the TH group compared to the normothermia group ($p = 0{\cdot}09$) and a higher mortality rate ($p = 0{\cdot}08$) (Clifton *et al.*, 2011). Furthermore, IH was more common in patients with diffuse brain injury and treated with TH compared to normothermia ($p = 0{\cdot}003$), suggesting that TH is not as effective with diffuse brain injury. Both Inamasu *et al.* (2006)and Smrčka *et al.* (2005) found that patients with haematoma-type injuries had better outcomes and survival rates compared to patients with contusions when treated with TH compared to normothermia ($p < 0{\cdot}05$). Their findings suggest that patients with contusions do not benefit from treatment with TH.

These studies, although limited, suggest that TH is more effective with haematomas; when considering other reviews, this suggestion is not explicit.

Complications

There are potential complications of TH; however, five of the studies concluded that TH was not associated with severe complications (Qui *et al.*, 2005; Smrčka *et al.*, 2005; Qiu *et al.*, 2007; Lee *et al.*, 2010; Clifton *et al.*, 2011). Pulmonary infection was the complication with the highest incidence in the studies, with the exception of Clifton *et al.* (2011) who reported a significantly higher rate of overall complications, such as IH and infection in the TH group (408 episodes versus 208, $p = 0{\cdot}01$); however, this was influenced by the high incidence of IH in the TH group, whilst infectious, cardiovascular and bleeding complications showed no significant difference. Qui *et al.* (2005) observed a higher incidence of pulmonary infection in the TH groups compared to the normothermia groups (60·5% versus 39·5%, $p < 0{\cdot}05$), with similar findings by Qiu *et al.* (2007) (57·5% versus 32·5%, $p = 0{\cdot}025$). Additionally, Tokutomi *et al.* (2009) found evidence that patients cooled at a lower temperature (33°C compared to 35°C) were more susceptible to pneumonia ($p = 0{\cdot}09$); however, this was not statistically significant.

Three studies noted an increase in coagulopathies in patients treated with TH. Qui *et al.* (2005) and Qiu *et al.* (2007) observed thrombocytopenia in 62·8% and 57·5%, respectively, of patients treated with TH. Clifton *et al.* (2011) noted decreases in partial thromboplastin times (PTT) ($p = 0{\cdot}004$), although these were slight, and there was no significant difference in bleeding complications between the TH and normothermia groups.

Serum potassium level abnormalities in the TH groups were noted in two studies. Clifton *et al.* (2011) reported minor but significant decreases in mean serum potassium levels in the TH group (3·6 versus 3·8 mmol/L, $p = 0{\cdot}0005$). Tokutomi *et al.* (2009) also reported decreases in serum potassium levels in patients cooled to 33°C compared to 35°C, most significantly on day 5 post-injury (3·7 versus 4·0 mmol/L respectively, $p = 0{\cdot}005$). Interestingly, both studies cooled their patients to 33°C, whilst others used milder temperatures, therefore highlighting a possible interaction between TH depth and serum potassium abnormality. This has clear clinical implications with regards to the depth of TH.

DISCUSSION

Influence on neurological outcome

This review suggests that TH may improve neurological outcome in patients with TBI; however, the results from the studies are varied with contradictions regarding its efficacy. The studies are of variable quality, with little explanation of randomization methods and allocation concealment affecting the reliability and validity of results, whilst the small samples sizes means that findings cannot be confidently generalized to the wider population (Parahoo, 2014). Perhaps the highest quality study in this review, Clifton *et al.* (2011), concluded that TH is not effective at improving neurological outcome and has no basis for further research. Nevertheless, there are still undeniable trends that demonstrate that TH increases GOS scores and reduces mortality rates. With regards to neurological outcome, the findings of this review are consistent with current systematic reviews and meta-analyses (McIntyre *et al.*, 2003; Alderson *et al.*, 2004; Peterson *et al.*, 2008; Pengcheng and Chaohua, 2014), which all identify a trend towards a positive influence on neurological outcome and acknowledge that there is a lack of uniformity with regards to TH protocols among the studies.

Within the studies, there are variations relating to methods of inducing TH, target temperature, duration of cooling and rate of re-warming, all of which are key factors known to influence neurological outcome (Finkelstein and Alam, 2010). It is accepted that TH must be induced as early as possible in order to be of benefit (Clifton *et al.*, 2001, 2011; Bersten *et al.*, 2014). Neuronal death is known to occur within hours following primary brain injury compared to several days for secondary brain injury as a result of ischaemic damage (Berger *et al.*, 2006). It is therefore interesting that Clifton *et al.* (2011), a study which reported the most rigorous protocols for early induction, did not find a positive relationship between TH and neurological outcome. The efficacy of early-induced TH can be considered in relation to the pathogenesis of TBI. Bersten *et al.* (2014) outline three phases of TBI and changes in CBF and ICP spanning 2 weeks post-injury. TH would influence the first two phases:

1. The first 72 h (hypoperfusion phase) after initial injury marks a decrease in CBF and resultant global/regional ischaemia because of impaired autoregulation, which requires an adequate systemic blood pressure in order to maintain CPP.
2. This is followed by the hyperaemic phase during which autoregulation mechanisms may start to recover in some patients, resulting in improved CBF. However, any hyperaemia combined with intracranial inflammation and compromised BBB permeability can result in vasogenic cerebral oedema, and therefore, therapies that aim to maintain CBF may potentiate the occurrence of IH (Bersten *et al.*, 2014).

In this context, TH may be more effective 72 h post-injury when CBF is more controlled, especially as TH is associated with hypotension and may further compromise CBF during the initial hypoperfusion stage (Polderman, 2008). This correlation has not previously been considered in other reviews.

Duration of cooling is also considered to influence neurological outcome (McIntyre *et al.*, 2003). Jiang *et al.* (2006) observed that patients who were cooled for 5 days had significantly better neurological outcomes compared to patients cooled for 2 days. Two meta-analyses found that only TH maintained for longer than 48 h was associated with a lower mortality rate and improved neurological outcome (McIntyre *et al.*, 2003; Bratton *et al.*, 2008). The optimal duration of TH is unknown; however, this review suggests that TH is more effective when instituted for longer than 48 h. The ability to cope with an increased ICP differs from person to person (McLeod, 2004), therefore requiring individualized management and reassessment of re-warming rates depending on initial responses of ICP, which has nursing implications. It is therefore unsurprising that Lee *et al.* (2010) was successful in improving neurological outcome by re-warming patients only when the ICP returned to acceptable levels and cooling for a further 48 h if there was indication that ICP was rebounding; this is, however, a small study involving one centre. A previous study adopted a similar protocol with positive results by slowing or stopping re-warming when ICP began to increase, noting an average duration of 4·8 days and even up to 21 days in some patients (Polderman *et al.*, 2002). However, this recommendation is not within current clinical guidelines and should be considered by clinicians.

Influence on ICP

All studies, with the exception of Clifton *et al.* (2011), found that TH was effective at reducing ICP. Clifton *et al.*'s (2011) findings were unique in that the TH group had a higher incidence of IH compared to the normothermia group; however, lower doses of morphine and higher doses of vasopressors were used to reduce TH-induced hypotension as observed in their previous study (Clifton *et al.*, 2001). Most studies used surgical decompression and external ventricular drainage when ICP could not be controlled. It is therefore difficult to ascertain whether TH or other interventions influenced decreases in ICP.

This review has, however, identified a link between the duration of cooling and the occurrence of rebound IH. Jiang *et al.* (2006) found that ICP was more likely to rebound during re-warming when TH was maintained for 48 h. This may be because of exacerbation of the hyperaemia phase by early re-warming causing a subsequent increase in CBF, which may then cause ICP to rebound (Bersten *et al.*, 2014). It is also acknowledged that reduced ICP does not necessarily correlate to improved neurological outcome (Stocchetti *et al.*, 2015) as TH is also considered to improve outcome through prevention of neuronal death and attenuation of various chemical cascades (Polderman, 2004).

Correlation between neurological outcome and brain pathology

There is a trend of improved neurological outcome in patients with haematoma-type lesions compared to patients with diffuse brain injury and contusions. This is supported by previous studies, which also reported that the effectiveness of TH in patients with extra-cerebral haematomas correlated to the degree of midline shift, whereas patients with focal cerebral lesions were found to benefit the most from TH (Shiozaki *et al.*, 1998, 2003).

Complications

Fewer complications and an improved mortality rate were associated with TH at 35°C compared to cooling at 33°C (Tokutomi *et al.*, 2009), which has implications with regards to the recommended depth of TH. It is known that lower temperatures increase the likelihood of severe complications such as severe ventricular arrhythmias and hypokalaemia (Clifton *et al.*, 1992, 1993; Wright, 2005). Hypokalaemia was documented in studies cooling patients to 33°C, suggesting a link to lower temperature management (Tokutomi *et al.*, 2009; Clifton *et al.*, 2011). Additionally, two studies noted higher incidence of thrombocytopenia in the TH groups (Qui *et al.*, 2005; Qiu *et al.*, 2007), whilst Clifton *et al.* (2011) reported a slight but significant increase in PTT, indicating an increased risk of bleeding. Coagulopathies are known complications of TH; however, the incidence is variable (Finkelstein and Alam, 2010). Interestingly, none of the studies addressed the effects of TH on glycaemic control, despite its importance in head-injured patients (Bersten *et al.*, 2014). TH is known to cause insulin resistance and decreased production causing, hyperglycaemia (Polderman, 2004). Glucose control is an area requiring further research in the context of TH and TBI.

Limitations

The main limitation of this review is the distinct variation in protocols between the eight studies, making comparison difficult and findings less generalizable. There are gaps in data reporting, predominately relating to the time taken to induce TH and re-warming rates, leading to insufficient data to fully analyse the effects of TH. Aside from the differences in TH management, variations exist in the use of co-interventions such as surgical decompression and ventricular drainage as well as inclusion/exclusion criteria between the studies, making it difficult to conclude whether any positive effects are because of TH, co-interventions or differences in sample demographics or disease severity. Six of the eight studies were conducted in Asia, so consideration of transferability of results to other health care systems is required.

IMPLICATIONS AND RECOMMENDATIONS FOR PRACTICE

Clinically, it is difficult to confidently recommend the use of TH because of the variable quality of studies and differences between management protocols and patient characteristics. However, the need for individualized TH management has been highlighted. The ability to cope with increased ICP differs between patients and is influenced by the protocols of TH induction, duration and time of re-warming. Of particular note is the role of autoregulation and the influence temperature management has on cerebral haemodynamics. In short, the key messages from this review are that patients need to be cooled soon enough, long enough and re-warmed slowly depending on ICP responses in order to effectively improve neurological outcome and reduce the risk of complications. Current clinical guidelines do not make these recommendations explicit.

Further prospective multi-centred RCTs are needed to fully investigate the beneficial effects of TH. This review has

highlighted areas for further research: titrating target temperatures in line with cerebral haemodynamic changes known to occur with TBI and further investigation of the efficacy of TH depending on the type of brain injury. Additionally, multi-centred RCTs would reduce inter-centre variance of TH management and ensure that the research protocols are consistent, therefore enabling accurate analysis of results.

Conclusion

Despite the lack of high-quality research, this review shows that TH may improve neurological outcome in patients with TBI, with low risk of severe complications. This review suggests that patients with contusions demonstrate little or no benefit from receiving TH in place of normothermia treatment. It also suggests that a longer duration of cooling may be beneficial, and continuation of cooling should be considered by the clinical teams if rebound IH occurs.

WHAT IS KNOWN ABOUT THIS TOPIC

- Research has shown variable effectiveness of TH following traumatic head injury in improving patient outcome.
- TH does not necessarily have a sustained effect on controlling ICP.

WHAT THIS PAPER ADDS

- There needs to be an individualized approach to TH, especially if rebound intracerebral hypertension is observed during re-warming.
- Therapeutic hypothermic should not be limited to 48 h, and if rebound intracerebral hypertension is observed, there is some evidence to suggest that recommencing TH may be of help.
- With regards to the timing and extent of TH, underlying alterations in cerebral haemodynamics should be taken into consideration.
- TH may be more effective in improving patient outcome when haematomas have developed as opposed to patients with cerebral contusions and/or diffuse injuries.

REFERENCES

Alderson P, Gadkary C, Signorini DF. (2004). Therapeutic hypothermia for head injury. *Cochrane Database Systematic Review*: http://onlinelibrary.wiley.com/store/10.1002/14651858.CD001048.pub2/asset/CD001048.pdf;jsessionid=E5C9FADF1FC73A2F9AA8E994AFDEBC67.f04t03?v=1&t=ia5fxb8f&s=a287f553d98470cf79282339df83cd6e58ec8349 (accessed 26/05/15).

Berger RP, Adelson PD, Richichi R, Kochanek PM. (2006). Serum biomarkers after traumatic and hypoxemic brain injuries: insight into biochemical response of the pediatric brain to inflicted brain injury. *Developmental Neuroscience*; **28**: 327–335.

Bersten AD, Soni N, Oh TE. (2014). *Oh's intensive care manual*. 7th edn. Edinburgh: Butterworth-Heinemann.

Brain Trauma Foundation, American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), AANS/CNS Joint Section on Neurotrauma and Critical Care. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma*; **24**: 1–106.

Bratton SL, Chesnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. (2008). Guidelines for the management of severe traumatic brain injury. III. Prophylactic hypothermia. *Journal of Neurotrauma*; **24**: 21–25.

Busto R, Dietrich WD, Globus MY, Valdes I, Schneinberg P, Ginsberg MD. (1987). Small differences in intra-ischemic brain temperature critically determine the extent of ischemic neuronal injury. *Journal of Cerebral Blood Flow and Metabolism*; **7**: 729–738.

Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. (1989). Effect of mild hypothermia on ischemia-induced release of neuro-transmitters and free fatty acids in rat brain. *Stroke*; **20**: 904–910.

Chen L, Piao Y, Zeng F, Lu M, Kuang Y, Xun L. (2001). Moderate hypothermia therapy for patients with severe head injury. *Chinese Journal of Traumatology*; **4**: 164–167.

Clifton GL, Taft WC, Blair RE, Choi S, Delorenzo RJ. (1989). Conditions for pharmacologic evaluation in the gerbil model of forebrain ischemia. *Stroke*; **20**: 1545–1552.

Clifton GL, Allen S, Berry J, Koch SM. (1992). Systemic hypothermia in treatment of brain injury. *Journal of Neurotrauma*; **9**: 487–495.

Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes R, Choi S. (1993). A phase II study of moderate hypothermia in severe brain injury. *Journal of Neurotrauma*; **10**: 263–271.

Clifton GL, Miller ER, Choi S, Levin H, McCauley S, Smith K, Muizelaar P, Wagner F, Marion D, Luerssen T, Chesnut RM, Schwartz M. (2001). Lack of effect of induction of hypothermia after acute brain injury. *The New England Journal of Medicine*; **344**: 556–563.

Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, Janis LS, Wilde E, Taylor P, Harshman K, Conley A, Puccio A, Levin HS, McCauley SR, Bucholz RD, Smith KR, Schmidt JH, Scott JN, Yonas H, Okonkwo DO. (2011). Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *The Lancet. Neurology*; **10**: 131–139.

Finkelstein RA, Alam HB. (2010). Induced hypothermia for trauma: current research and practice. *Journal of Intensive Care Medicine*; **25**: 205–226.

Inamasu J, Saito R, Nakamura Y, Horiguchi T, Kuroshima Y, Ichikizaki K. (2006). Therapeutic hypothermia for severely head-injured patients with acute subdural haematoma. *Journal of Clinical Neuroscience*; **13**: 733–737.

Jennet B, Bond M. (1975). Assessment of outcome after severe brain injury. A practical scale. *Lancet*; **1**: 480–484.

Jiang J, Xu W, Li W, Gao G, Bao Y, Liang Y, Luo Q. (2006). Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *Journal of Cerebral Blood Flow & Metabolism*; **26**: 771–776.

Lee H, Chuang H, Cho D, Cheng K, Lin P, Chen C. (2010). Applying cerebral hypothermia and brain oxygen monitoring in treating severe traumatic brain injury. *World Neurosurgery*; **74**: 654–660.

Maas AI, Stocchetti N, Bullock R. (2008). Moderate and severe traumatic brain injury in adults. *The Lancet. Neurology*; **7**: 728–741.

Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. (1993). The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *Journal of Neurosurgery*; **73**: 354–362.

McIntyre LA, Fergusson DA, Hébert PC, Moher D, Hutchison JS. (2003). Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA*; **289**: 2992–2999.

McLeod A. (2004). Traumatic injuries to the head and spine 2: nursing considerations. *British Journal of Nursing*; **13**: 1041–1049.

Parahoo K. (2014). *Nursing Research: Principles, Process and Issues*. Basingstoke: Palgrave Macmillan.

Pengcheng L, Chaohua Y. (2014). Moderate hypothermia treatment in adult patients with severe traumatic brain injury: a meta-analysis. *Brain Injury*; **28**: 1036–1041.

Peterson K, Carson S, Cairney N. (2008). Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *Journal of Neurotrauma*; **25**: 62–71.

Polderman KH. (2004). Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality – part 2: practical

aspects and side effects. *Intensive Care Medicine*; **30**: 757–759.

Polderman KH. (2008). Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*; **371**: 1955–1969.

Polderman KH, Tjong Tjin Joe R, Peerdeman SM, Vandertop WP, Girbes AR. (2002). Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury. *Intensive Care Medicine*; **28**: 1563–1573.

Qiu W, Zhang Y, Zhang J, Sheng H, Wang W, Liu W, Chen K, Zhou J, Xu Z. (2007). Effects of therapeutic mild hypothermia on patients with severe traumatic brain injury after craniotomy. *Journal of Critical Care*; **22**: 229–235.

Qui W, Lui W, Shen H, Wang W, Zhang Z, Zhang Y, Jiang S, Yang X. (2005). Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chinese Journal of Traumatology*; **8**: 27–32.

Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. (1993). Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *Journal of Neurosurgery*; **79**: 363–368.

Shiozaki T, Sugimoto H, Taneda M, Oda J, Tanaka H, Hiraide A, Shimazu T. (1998). Selection of severely head injured patients for mild hypothermia therapy. *Journal of Neurosurgery*; **89**: 206–211.

Shiozaki T, Hayakata T, Taneda M, Yoshikazu N, Hashiguchi N, Fujimi S, Nakamori Y, Tanaka H, Shimazu T, Sugimoto H, Mild Hypothermia Study Group in Japan. (2001). A multicentre prospective randomised controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. *Journal of Neurosurgery*; **94**: 50–54.

Shiozaki T, Nakajima Y, Taneda M, Tasaki O, Inoue Y, Ikegawa H, Matsushima A, Tanaka H, Shimazu T, Sugimoto H. (2003). Efficacy of moderate hypothermia in patients with severe head injury and intracranial hypertension refractory to mild hypothermia. *Journal of Neurosurgery*; **99**: 47–51.

Smith SL, Hall ED. (1996). Mild pre and posttraumatic hypothermia attenuates blood–brain barrier damage following controlled cortical impact injury in the rat. *Journal of Neurotrauma*; **13**: 1–9.

Smrčka M, Vidlák M, Máca K, Smrčka V, Gál R. (2005). The influence of mild hypothermia on ICP, CPP and outcome in patients with primary and secondary brain injury. *Acta Neurochirurgica*; **95**: 273–275.

Stocchetti N, Taccone FS, Citerio G, Pepe PE, Le Roux PD, Oddo M, Polderman KH, Stevens RD, Barsan W, Maas AI, Meyfroidt G, Bell MJ, Silbergleit R, Vespa PM, Faden AI, Helbok R, Tisherman S, Zanier ER, Valenzuela T, Wendon J, Menon DK, Vincent J. (2015). Neuroprotection in acute brain injury: an up-to-date review. *Critical Care*; **19**: 186–197.

Tokutomi T, Miyagi T, Takeuchi Y, Karukaya T, Katsuki H, Shigemori M. (2009). Effect of 35 °C hypothermia on intracranial pressure and clinical outcome in patients with severe traumatic brain injury. *The Journal of Trauma*; **66**: 166–173.

Wright J. (2005). Therapeutic hypothermia in traumatic brain injury. *Critical Care Nurse Quarterly*; **28**: 150–161.

QUERIES TO BE ANSWERED BY AUTHOR

IMPORTANT NOTE: Please mark your corrections and answers to these queries directly onto the proof at the relevant place. DO NOT mark your corrections on this query sheet.

Queries from the Copyeditor:

AQ1. Please confirm that given names (red) and surnames/family names (green) have been identified correctly

AQ2. We have changed Bersten and Soni (2014), Qui et al. (2007), Smrkča et al. (2005), McIntyre, (2003), Mass et al. (2008) to Bersten et al. (2014), Qiu et al. (2007), Smrčka et al. (2005), McIntyre et al. (2003), Maas et al. (2008) to match with reference list, kindly check and confirm.

AQ3. Please provide expansion for ASDH.

AQ4. Please provide the center name for organization name for Japan for reference Tokutomi et al. (2009) in Table 1.

AQ5. Please provide Volume number, Page range for reference "Alderson et al. (2004)".

AQ6. Reference “Busto et al. (1987)” is not cited in the text. Please indicate where it should be cited; or delete from the reference list.

AQ7. Reference “Clifton et al. (1989)” is not cited in the text. Please indicate where it should be cited; or delete from the reference list.