

Review

In neonates with hypoxic ischemic encephalopathy, is therapeutic hypothermia outside of current criteria safe? A literature review

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ABSTRACT

Introduction: Hypoxic Ischemic Encephalopathy (HIE) can lead to catastrophic consequences. Published trials mean that Therapeutic Hypothermia has revolutionised available treatment but infants often must meet strict criteria.

Objectives: To review relevant research that explores using Therapeutic Hypothermia in infants with HIE, who are usually excluded from Therapeutic Hypothermia.

Design: A literature review was undertaken of research that considered Therapeutic Hypothermia use outside of the standard criteria.

Data sources: Multiple databases formed part of a purposive search, alongside the open grey network, clinical trials network, Cochrane reviews, NICE guidance and National Institute for Health Research and local guidance.

Findings: Five papers were reviewed, discussing Therapeutic Hypothermia after 6 h of age, infants with a syndromic diagnosis, late preterm infants (34–35weeks), post-natal collapse, surgical and cardiac infants and infants with major cranial haemorrhage. Overall the findings of the review are encouraging except for cohorts with cranial haemorrhage or syndromic diagnoses.

1. Introduction

Hypoxic Ischemic Encephalopathy (HIE), is a condition which appears to mainly affect term infants and occurs following a perinatal hypoxic event; the exact timing of which is often unknown (Zanelli, 2016). It is suggested that HIE occurs in 3–5 per 1000 births, with moderate or severe HIE occurring in 0.5–1.0 per 1000 births (Jacobs et al., 2013; Rao et al., 2017) with the incidence increasing further in the developing world. However, there appears to be no consensus as to the affect HIE has on the term infant, with mortality figures quoted from 10 to 60% and morbidity quoted as high as 42%–100% in severe HIE (Shankaran, 2014). Nonetheless, there is no doubt that it has a significant disease burden for the patient, family and society.

HIE occurs when there is insufficient delivery of energy to brain tissue, leading to a disruption in homeostasis and neuronal cell death (Bennet et al., 2009). Several phases exist; the primary phase (initial hypoxic event), the latent phase (partial recovery of some neuronal cells), and the secondary phase (secondary energy failure resulting in apoptotic cell death), which may occur up to 6–15 h after the initial injury (Azzopardi et al., 1989). Davidson et al. (2015) also mention a

third stage, where ‘rewiring’ of the brain and adaptation occurs, allowing clinicians and parents to discover the true affect that HIE has had on development, if the infant survives (see Fig. 1.).

Therapeutic Hypothermia (TH) can limit further damage occurring following an insult and its impact. As a result of extensive trials between 2005 and 2011 which were powered sufficiently (AAP, 2014), TH has been quickly and widely accepted by the medical profession as the treatment for infants with HIE. These trials included the National Institute of Child Health and Human Development (NICHD) Neonatal Network Research Whole Body Cooling Trial (Shankaran et al., 2005) and the TOBY Trial (Azzopardi et al., 2009). According to Jacobs et al. (2013), two trials looked at selective head cooling instead of whole body cooling; however due to loss of follow up long term risks and benefits could not be ascertained. Whole body cooling was shown to offer a 25% reduction in death or severe neuro-disability by 18 months of age. Whole body cooling is now used as a routine treatment, but it is almost always used alongside strict Criteria (Table 1), supported by the National Institute for Health and Clinical Excellence (NICE, 2010), the American Academy of Paediatrics (AAP, 2014) and Jacobs et al. (2013). Classification of HIE is important; infants who meet other criteria

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Abbreviations

TH	Therapeutic Hypothermia
HIE	Hypoxic Ischemic Encephalopathy
IF	Impact Factor
NICHHD	National Institute of Child Health and Human Development
NICE	National Institute for Clinical Excellence;
ANNP	Advanced Neonatal Nurse Practitioner

infants can be problematic and that the pathology of HIE appears different, there is limited evidence available for its use in infants < 36 weeks.

The Cochrane review (Jacobs et al., 2013) included infants > 35 weeks gestation, however, only two of the eleven trials reviewed included infants > 35 week gestation infants or greater than 2 kg in weight. The mean gestation for both the ICE trial (2011) and trial published by Eicher et al. (2005) was 38.8–39.2 weeks gestation, meaning that specific data relating to late preterm infants may be skewed by their term counterparts. In the latter study the participants

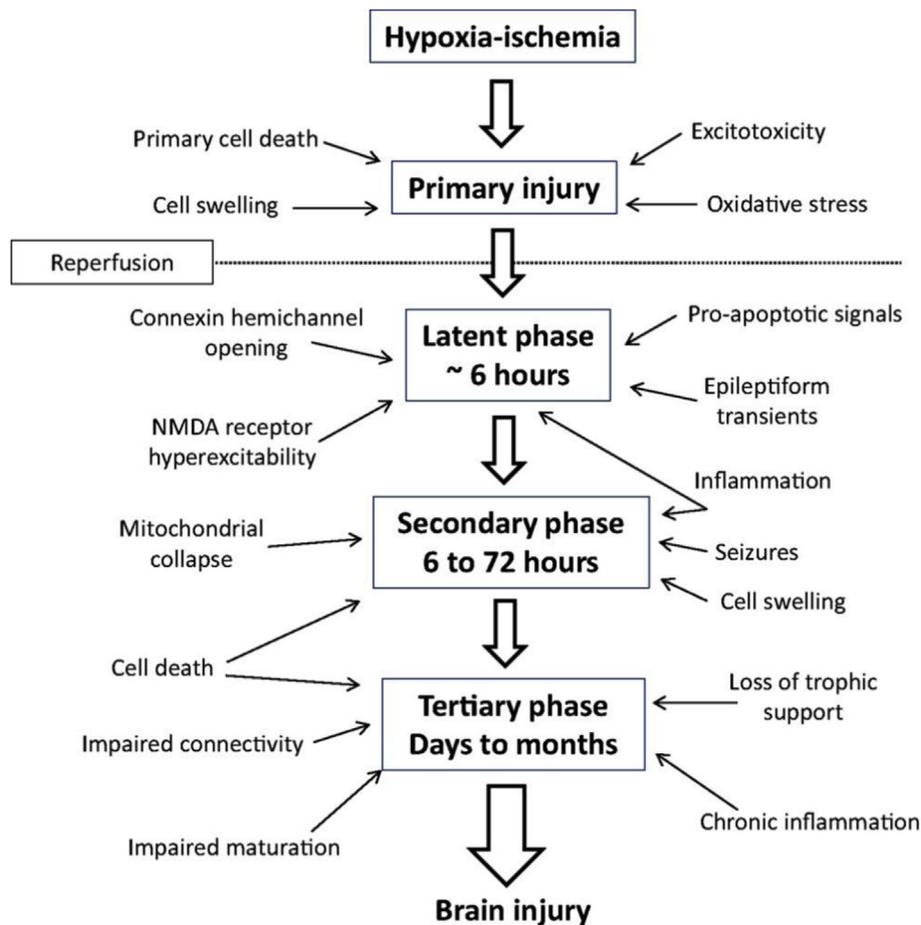


Fig. 1. HIE cascade (Davidson et al., 2015).

currently need to have moderate to severe HIE to be considered for TH due to a high mortality rate within this cohort, with survivors often suffering substantial neurological sequelae (Jacobs et al., 2013).

Thoresen and Whitelaw (2000) discussed that adverse effects related to the treatment (increased oxygen requirement, hypotension and bradycardia) were transient and reversed once rewarming had been commenced. Balancing the short term risks and long term benefits, the National Institute for Health and Clinical Excellence (2010) issued guidance on its use in treatment for HIE, with the majority of available literature including infants ≥ 36 weeks gestation (NICE, 2010).

This leaves clinicians with an ethical dilemma when the infant is not within the inclusion criteria (Table 1). Leventhal et al. (2012) discusses the use of TH “off label” and considers the ethical balance required, more importantly providing a framework for clinicians to use when faced with such decisions. With evidence strongly supporting TH for an improvement in outcome in ≥ 36 week infants, some clinicians choose to use TH outside of criteria. Knowing that the preterm cohort is particularly vulnerable to cold stress, that the diagnoses of HIE in preterm

were only cooled for 48 h to 32.5–33.5 °C, whereas NICE recommends 33–35 °C for 72 h. Despite this Jacobs et al. (2013) feels there is enough evidence to suggest TH in term and late preterm infants (> 35 weeks) reduced both mortality and morbidity.

Experienced clinicians are now using TH for a range of infants. A recent survey in the USA reported up to a third of all respondents ($n = 447$) would cool an infant > 6 h old, up to 58% were willing to cool preterm infants > 34 weeks and 45% of respondents would cool infants following a postnatal collapse (Burnsed and Zanelli, 2017). This survey had a very low response rate and up to 90% worked in large neonatal units; this implies they are more likely to be confident with TH and how to manage infants safely, possibly having had first-hand experience. In contrast those less experienced and therefore less comfortable with TH and its adverse effects were more likely to stick to the published guidance. Locally, two infants of approximately 34 weeks, with HIE, have been transferred to the tertiary centre for TH but none in other categories such as postnatal collapse or > 6 h of age. There is a multi-centred, randomised control trial underway in USA recruiting

infants 33–35 weeks gestation and ≥ 1500 g (Preemie trial - Clinical trials identifier NCT 01793129); given Hall's et al. (2010) pilot study suggested it was feasible and safe to cool infants of 26–30 weeks with necrotising enterocolitis, one can be hopeful that the preemie trial could see TH being offered to these infants consistently rather than on a rescue therapy basis, results dependent.

With a growing body of evidence looking at the safety and efficacy of this treatment in infants who would have otherwise been excluded, it highlights a need to review the literature looking specifically at the use of TH in these cohorts.

With the ultimate aim being to balance non-maleficence and beneficence as an Advanced Neonatal Nurse Practitioner (ANNP), if TH is safe and efficacious in different cohorts it is our duty consider it a viable treatment option, as stated in the NMC code of conduct (NMC, 2015). When working in an advanced role, such as the ANNP, it is even more important, that as clinical leaders decisions about patient care are based on the best available evidence. This is further supported by The Department of health (Department of Health, 2010) suggesting strongly that evidenced based therapeutic interventions should be used to underpin patient management plans in partnership with the patient or parent in this instance.

2. Methodology

Throughout this literature review, the EBK process was followed. A systematic literature search was completed between January 2017 and January 2018. This purposive sampling used synonyms, natural language, free text searching, truncation, index terms and MeSH terms, combined with Boolean operators to guarantee a rigorous and reliable search (Grove et al., 2013). In order to confirm triangulation, alternative spellings and keywords of relevant articles have been included, and the search has been conducted via multiple databases (McGovern et al., 2001; Aveyard and Sharp, 2013). Many online sources and databases were searched, including grey literature in order to limit publication bias. Rothstein et al. (2005) argue that publication bias threatens the validity of even the most thorough of reviews, if the only articles reviewed are, themselves, biased.

A successful literature review requires the application of inclusion and exclusion criteria, as per by Gerrish and Lacey (2010). Table 2 provides the inclusion/exclusion criteria and the rationale for them.

Once the inclusion/exclusion criteria were applied, the abstracts of remaining literature were analysed to ensure the evidence was relevant to the question. The CASP tools (CASP, 2017a; CASP, 2017b), STROBE statements (STROBE, 2009) and the Centre for Evidence Based Management case study tool (CEBM, 2017) were used to highlight the strengths and weaknesses of the evidence in order to confirm or refute

Table 1

Criteria for therapeutic hypothermia (Azzopardi et al., 2009).

<p>A. Infants ≥ 36 completed weeks gestation admitted to the neonatal unit with at least one of the following:</p> <ul style="list-style-type: none"> ● Apgar score of ≤ 5 at 10 min after birth ● Continued need for resuscitation, including endotracheal or mask ventilation, at 10 min after birth ● Acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial or capillary pH < 7.00) ● Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 min of birth <p>Infants that meet criteria A should be assessed for whether they meet the neurological abnormality entry criteria (B)</p> <p>B. Seizures or moderate to severe encephalopathy, consisting of:</p> <ul style="list-style-type: none"> ● Altered state of consciousness (reduced response to stimulation or absent response to stimulation) and ● Abnormal tone (focal or general hypotonia, or flaccid) and ● Abnormal primitive reflexes (weak or absent suck or Moro response). <p>Exclusion:</p> <p>Major congenital abnormalities, syndromic disorders where outcome or neurological function is unsure. If it will be > 6 h of age to target temperature</p>

its validity and reliability.

3. Results

Due to the paucity of research advocating that TH is safe outside of current criteria and the ethics, resources, time and cost (both monetary and to the patient themselves) involved in executing a randomised control trial, only one RCT was found. Therefore evidence was included that ranks low on the traditional hierarchy of evidence when looking at trial design, ranging from a prospective cohort study to a simple case study. Several editorials and narratives were found between 2011 and 2015 and discounted due to lack of analytical data (see Audit trail Fig. 2). In the case of editorials/narratives that used the same data as an original piece of research, the original was chosen as this review aims to build on the current body of evidence with an in-depth critique of papers chosen. The final number of papers reviewed totalled five and considered cohorts that included initiating TH after 6 h of age, TH and a syndromic diagnosis, late preterm infants (34–35weeks), post-natal collapse, surgical and cardiac infants and major cranial haemorrhage.

4. Discussions and findings

Five articles were reviewed and were published in a variety of journals. The impact factor (IF) ranged from 44.4 (JAMA) down to 1.385 (Journal of Child Neurology). The perception is the higher the IF the better the quality of the journal, but the validity of this as a tool has yet to be proven (Saha et al., 2003). Therefore, it is important to critique each article on its own merit, rather than just that of the journal it is published in. Clearly from the articles found, whilst there is a paucity of evidence, the topic of TH outside of criteria has been debated for at least six years with no consensus published. Study designs of the five articles ranged from the early, single centred, case study by Laura et al. (2012) through to the paper by Laptook et al. (2017) which is a multicentre RCT carried out by well-known experts in this field, further adding credibility. One could argue that the quality of the case study by Laura et al. (2012) is poor and therefore should not be published. This in itself could be perceived as publication bias (Joober et al., 2012) and without case studies there would be little evidence to base the need for further, more rigorous research in this area. Four articles reviewed were single centred, meaning a cheaper set up, more flexibility and requiring smaller sample sizes when compared to a multicentre trial. In comparison however, one is much more likely to get type 2 errors (accepting the null hypothesis when it is false) (Greenhalgh, 2014) with a smaller sample size. With this in mind, treatments that may have shown a significant effect in a larger, powered study might not be recommended due to the lack of significance shown by a smaller under-powered study.

Generally throughout the five papers, the sample sizes were small and for the single centred studies ranged from 1 (case study) through to 36, but recruitment took between 6 and 8 years. In contrast the multicentre RCT recruit 168 participants over a 6 year period, which is one of the advantages of a multicentre trial. A power calculation was utilised in this study, further reducing the risk of type 2 errors and increasing validity and generalisability (Gerrish and Lacey, 2010). In a population where the numbers of infants diagnosed with HIE is extremely small and those diagnosed with HIE outside of the main criteria is even smaller the ability to study large numbers of infants outside of a multicentre trial is unlikely.

The study design for the RCT was clear and transparent, with inclusion and exclusion criteria and could be replicated if required. The three observational studies included one prospective study and two retrospective studies. Prospective studies allow accurate data collection, the ability to assess multiple exposures and outcomes, and the ability to control multiple variables, but can be expensive and time consuming. In contrast, retrospective studies are less expensive, timely and can assess multiple exposures (McGovern et al., 2001; Thiese,

Table 2
Inclusion/exclusion criteria.

Inclusion Criteria	Exclusion Criteria	Rationale
Full text English Language 2008–2017	Abstract only Non – English Language Before 2008	To allow a thorough critique of entire paper To avoid translation costs To include research which included the register utilised by the Toby trial (Azzopardi et al., 2009).
Cooling of infants outside of the TOBY trial criteria	Cooling within criteria defined by TOBY trial	To ensure up to date evidence is available for review. To ensure the question was answered
Research studies – retrospective and prospective	Opinions	Due to the paucity of evidence all study designs needed to be considered but ideally the best available evidence

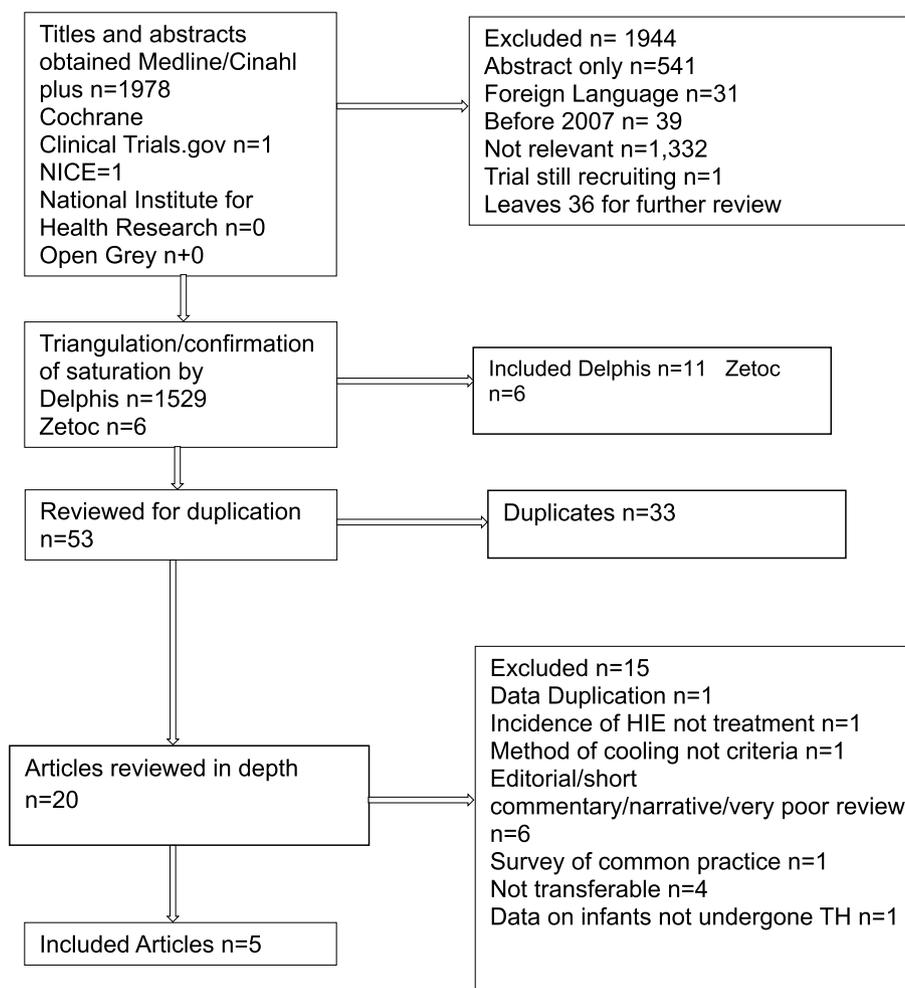


Fig. 2. Audit trail.

2014). Limitations of this approach involve bias, particularly selection and information bias, which can affect the internal validity and reliability of the study (Vandenbrouke et al., 2007). The time taken to recruit/record data for the studies ranged from three to eight years; obviously the case study was just the one patient and therefore time frame is not applicable in this study. All papers clearly defined the inclusion criteria which utilised the TOBY cooling criteria except for the characteristic being investigated, meaning the diagnosis of HIE was the same throughout the cohorts. Notable differences include Laptook et al. (2017) required infants to weigh > 1800g, which is justifiable as they reviewed a term cohort, and Mrelashvili et al. (2015) used a BE as –12 rather –16 to help diagnose HIE suggesting that their infants may have been less metabolically compromised. The procedure of cooling infants was standard throughout four of the five papers with only Laura et al.

(2012) deviating from normal protocol. The infant only reached a target temperature of 34.9 °C for less than the recommended 72 h. This was due to concerns over prolonged QT and sinus bradycardias (also seen in term infants Thoresen and Whitelaw (2000)) and decreased platelets/cutaneous bleeding however, it is worth noting this was the earliest report reviewed and therefore experience and confidence in TH may have been less than the authors who published more recently. Follow up and poor outcomes were clearly defined in four studies with the case study being the weakest in this area. The same studies utilised a validated developmental tool (Bayley Scale) as assessment of outcome allowing for easy comparison.

Due to the different characteristics of the populations studied it is impossible to generalise the results across all papers. For this reason the results of the papers in the categories will be reviewed.

5. Infants cooled > than 6 h of age

Two of the five papers considered infants who would be > 6 h of age at the time TH was initiated. This included the RCT and prospective observational study (Laptook et al., 2017; Smit et al., 2015). Notably they are both written by well-known authors in this field which adds credibility. Laptook et al. (2017) involved the larger, power calculated, sample size, which as previously mentioned adds validity to the study whereas Smit et al. (2015) prospectively collected data for only 11 infants. Laptook et al. (2017) also attempted to minimise selection bias by using a randomisation method for allocating individuals into the treatment arm or the control group (Aveyard and Sharp, 2013). Similarly, Smit et al. (2015) limit recall bias by recording data prospectively to ensure accuracy and completeness. In contrast the use of unmasked observers recording the adverse events in Laptook et al. (2017) may have the potential for increased bias.

The control groups in both studies were different. In light of this, results need careful interpretation. Laptook et al. (2017) compared the treatment arm with infants > 6 h of age who did not receive TH, conversely the Smit et al. (2015) study compared infants > 6 h who received TH with infants who were treated within the 6 h time frame. Characteristics between these two treatment arms however, were very similar allowing for the effects of confounders to be minimalised. With the differing sample sizes in mind, both studies used different statistical calculations appropriate to the cohort being studied. Laptook's et al. (2017) sample size was large enough to produce confidence intervals (CI) and p values. In contrast due to the smaller sample Smit et al. (2015) were limited in the analysis and CI were notably missing, despite this however, both provide results that are interesting. Laptook et al. (2017) concluded that there was a 76% possibility of reduction in death or disability using Bayesian analysis with a neutral prior with a posterior adjusted risk ratio of 0.86 (95% CI 0.58–1.29). The authors of the RCT suggest that there was an absolute risk reduction or 1–2% depending on the prior used. Importantly this was compared to other medical treatments, such as Magnesium sulphate and preterm infants which a risk reduction of 1.6% for cerebral palsy but is common practice. With all things considered, even with some uncertainty, this may be clinically significant due to the catastrophic outcomes for infants with HIE who are not offered TH. Laptook et al. (2017) results are interesting, as it compares offering treatment or not offering it, to the similar cohort of patients. They also stratified by postnatal age > 6 h but ≤ 12 h and > 12 h of age however the results showed no difference between these groups. Smit et al. (2015) concluded that there was a 31% total outcome of death or poor outcome vs a 45% total outcome of death or disability in the control group, suggesting cooling after 6 h of age certainly confirmed no worse an outcome for those infants. These results both suggest that by instigating TH > 6 h of age, where there is no chance to instigate it sooner, may improve the outcome of these patients but that, arguably, until further research is completed delay in TH should be avoidable at all costs. Due to the severe impact of the neurological sequelae the decision to use TH or not must be done case by case and in consideration of other treatments available, of which currently there is only palliation for severe HIE. With this in mind a reduction of death or disability of 76% is definitely worthy of consideration.

6. Postnatal collapse

Smit et al. (2015) looked at 10 infants that collapsed postnatally for varying reasons including three infants collapsing at the breast, three collapsed whilst being held, two had seizures and two were found unresponsive in the cot. Two out of the ten cases were found to have an underlying cause, hyperinsulinism and long chain acetyl-CoA dehydrogenase deficiency. The age at time of the collapse ranged from 15 min up to 32 h post birth, however they were all cooled within 6 h of the acute event and importantly they all met the other inclusion criteria

for TH, except Apgar score which is understandable for this cohort. The postnatal collapse group also had very similar characteristics to the control group. With minimal statistical information available for this cohort, likely due to the small sample size, the results must be interpreted with caution. From the 80% who were followed up, making the sample size even smaller, 38% of this cohort suffered mortality or morbidity compared to the 45% control group who met all criteria. With no P values or CI for this cohort, again likely due to sample size, it is difficult to say if this is significant but it at least suggests the morbidity and mortality is no worse. In light of this study, it further supports the use of TH in this cohort with caution and in full discussion with the parents, highlighting possible benefits may be limited but that if it helps it could improve the negative sequelae significantly.

7. Late preterm infants

Three out of the five papers looked at TH in preterm infants. Gestational age ranged from 34 to 35 + 4 weeks and a total of 38 preterm infants received TH with the paper by Rao et al. (2017) having the largest sample size of 31 infants. Two out of the three papers compared the preterm outcomes with their term counterparts with limited adjustments made for their gestational age. The third paper was the case study by Laura et al. (2012). The disadvantage when comparing the preterm groups to term infants is the multiple confounders to developmental outcomes that needed to be adjusted for but were not taken into account. In addition to this birthweight, gestation, use of steroids postnatally and length of hospital stay in these groups were found to be significantly different, but this is possibly just skewed by the gestational difference rather than TH. Conversely, the ethical issues involved in comparing preterm infants with HIE treated with TH and those not treated means that this type of comparison should not be conducted outside of a well-controlled clinical trial, like the preemie trial for instance (Clinical trials identifier NCT 01793129).

Rao et al. (2017) focused on short term outcomes and reported there was a significant increase in mortality (P value 0.04) in the preterm cohort (12.9% of all preterm infants) vs the term cohort. However, the authors suggested this was lower than the meta-analyses of trials of infants > 36 weeks gestation who had a 25% mortality rate. This is a valid argument, and should be considered when looking at this mortality figure. Often treatments used “off licence” such as TH are used as a rescue treatment in these situations, when the severity of the morbidity or chance of mortality is such that it is deemed appropriate to try all that one can to improve an otherwise bleak situation. It may be worthy to consider the likely mortality of this cohort with HIE without TH in order to see if the increase in mortality truly is significant. Rao et al. (2017) also reviewed MRI findings, rather than with Bayley scale like Smit et al. (2015). They found that there was a non-significant trend of increased injury noted on the MRI with more of the white matter and cerebellum injured in preterm infants vs term infants, however the sample is so small significance is hard to prove. This indicates Rao et al. (2017) was comparing only very short term outcomes making it hard to transfer these results without further follow up and analysis. TH is not only about the short term morbidity and mortality, although the treatment must be deemed to be safe, but aims to decrease the longer term neurological sequelae that can be so catastrophic that it severely affects the quality of life of the infants and families involved. The case study by Laura et al. (2012) commented that the 34 + 6 week infant's MRI was normal at 2 weeks of age however the infant was only cooled to 34.9 °C and was rewarmed before 72 h. In consequence the case study is not transferable in today's TH climate but may add a small amount of weight to needing to investigate this subject further. Dis-similarly Smit et al. (2015) used the Bayley scale as previously mentioned so it is difficult to compare the results however, with this in mind they suggest 25% of their six preterm infants had a poor outcome vs the 45% poor outcome for their term counterparts.

8. TH and syndromic diagnoses/major cranial haemorrhage

Mrelashvili et al. (2015) reviewed infants who had either a known syndrome or syndromic features plus HIE whilst Smit et al. (2015) considered infants with major cranial haemorrhages. As previously discussed the sample sizes were extremely small ($n = 8$ and $n = 5$) and this was after three to six years' worth of data collection. The control group for these studies were similar in all other characteristics but were infants undergoing TH without syndromes/major cranial haemorrhages. This in itself is a major flaw in the study as the syndromes/haemorrhages often come with poor neurological outcomes regardless of the additional diagnosis of HIE. Conversely, in the case of Mrelashvili et al. (2015), it is unlikely that the authors would have had enough infants born with a similar syndrome without HIE to enter a control group due to the rarity of these syndromes. Consequently the only way this study was feasible is to compare them, unfairly, to a cohort who were expected to have normal neurological outcomes independent of the HIE diagnosis. It is also difficult to attribute the findings that led to a diagnosis of HIE to HIE alone or were they an indication of the syndrome already present. The results showed the overall outcome to be poor with a high mortality rate with only one infant out of the eight surviving with a good outcome. Two infants had dysmorphic features rather than a diagnosis. One was lost to follow up and the other had a normal outcome following TH. It is possible, that due to the lack of formal diagnosis, the neurological outcome for this particular child without HIE may have been good anyway; therefore the TH worked as it would do in the control group. Three out of the eight patients received palliative care (including one with an isolated brain malformation) and it is hard to distinguish whether this is as a result of the syndrome alone or compounded by the effects of the HIE. In a similar situation Smit et al. (2015) reviewed infants who had been cooled with major cranial haemorrhages ($n = 5$). Four infants suffered subgaleal haemorrhages, two with associated skull fractures. These infants are known to have a high mortality rate. As expected, this group had the worst outcome in terms of mortality and morbidity of all of the cohorts in Smit et al. (2015) review, with the only infant surviving with a good outcome having bilateral intracranial haemorrhages (grade unknown). There was a significant coagulopathy found in the haemorrhage group ($p = 0.0004$), perhaps indicative of why they haemorrhaged in the first place and only aggravated by TH. The decision to use TH in these circumstances should be based on an open discussion with parents and clinicians, depending on the long term impact of the comorbidities. Questions need to be asked around ethical impacts of using TH as a rescue therapy in an infant already known to have severe neurological outcome, especially considering TH is not without risks, even if only transient, such as the increase in pain endured.

9. Cardiac and surgical infants

Smit et al. (2015) considered infants who had a surgical or cardiac diagnoses. Again these are extremely small sample sizes – two candidates in each, making it very hard to draw conclusions from this data. The risk of mortality of morbidity in this small number was deemed 50% vs the 45% in the control group however, as above, one has to consider the initial diagnosis of the infant and whether the TH was used as rescue therapy or a clear decision to treat following in-depth discussions. Two infants in this group survived with a good outcome, one surgical patient had a poor developmental outcome (assessed by Bayley Scale) and one cardiac patient died following the redirection of care. It is hard to know if this outcome is due to HIE independent of the comorbidities, or if the comorbidities played some part in the outcome.

10. Ethics and limitations

All papers reviewed have the relevant ethics approval. In Laptook et al. (2017) RCT they also had a safety review after every 20 infants

received TH and they were the only paper to seek written consent from parents. The other four studies ensured parents were spoken to and took their opinions on board when deciding to treat with TH. The major limitations across the studies, as briefly discussed, were the extremely small sample size, except for Laptook et al. (2017) study which was powered appropriately. The small sample size makes it very hard to perform meaningful statistical analysis and also can affect the ability to transfer this data to another setting. The majority of the papers reviewed are also retrospective, which may have increased the potential for bias and relies upon excellent record keeping. Limitations of this review involve single researcher bias and selection bias, although by using strict inclusion/exclusion criteria and rigorous tools to critique the literature this has been limited as much as possible (McDonagh et al., 2013). Selection bias is also self-limiting in this case due to the paucity of evidence to review.

11. Conclusion

It is clear that for some infants who meet the exclusion criteria, TH can reduce morbidity and mortality but it is not without uncertainty at present. Reviewing the literature it is felt that there is enough evidence to suggest a case by case discussion about infants who present with HIE outside of the normal criteria should be had and that TH should be considered in most infants, except for those with conditions that suggest a high chance of severe morbidity or mortality is likely. This is particularly relevant to cranial haemorrhages and syndromic diagnoses cohorts. Due to the low incidence of HIE and even smaller incidence of HIE in infants who do not meet standard criteria there will always be an issue with sample size unless this topic is considered as part of a large, multicentre trial and the result of the Preemie trial will be eagerly awaited and reviewed (Clinical trials identifier NCT 01793129).

Ethics/Conflict of interest and funding

Ethical approval was not required for this literature review. Conflicts of interest: none. Funding: none.

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