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Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome - A systematic review

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ABSTRACT

Aims: Hypoxic ischaemic encephalopathy (HIE) remains a significant cause of long term neurodisability despite therapeutic hypothermia (TH). Infants with mild HIE, representing 50% of those with HIE, are perceived as low risk and are currently not eligible for TH [1]. This review examines the available evidence of outcome in term infants with mild HIE.

Methods: Medline, Embase and Cochrane Clinical Trials databases were searched in March 2017.

Studies with well-defined HIE grading at birth and standardised neurodevelopmental assessment at ≥18 months were included. Abnormal outcome was defined as death, cerebral palsy or standardised neurodevelopmental test score more than 1 standard deviation below the mean.

Result: Twenty studies were included. Abnormal outcome was reported in 86/341 (25%) of infants. There was insufficient evidence to examine the effect of TH on outcome.

Conclusion: A significant proportion of infants with mild HIE have abnormal outcome at follow up.

1. Background

Neonatal hypoxic ischaemic encephalopathy (HIE) remains one of the leading causes of neonatal mortality and long term disability worldwide occurring in 3–5 per 1000 live births [1]. Outcome depends on the severity of the initial insult, traditionally graded using the clinical Sarnat Grading system, where infants with a mild Sarnat grade are felt to have an excellent prognosis without long term disability [2]. For this reason, many studies do not examine mild HIE beyond the newborn period, and randomised controlled trials of therapeutic hypothermia (TH) have not been designed to include infants with mild HIE.

In the few HIE cohorts where mild grade infants are assessed at school age and beyond, it is increasingly clear that they may experience significant disability [3,4]. Potential disabilities in this group include learning and neuropsychological difficulties, autism, epilepsy, visual and sensory loss. Recent studies have also shown a high percentage of abnormal MRI findings, similar to those found in infants with moderate HIE [5].

The aim of this systematic review was to identify the current available literature on reported outcome in infants with mild HIE.

2. Methods

Cochrane Systematic Review methods were used [6], adopting search strategies described by the Neonatal Cochrane Review Group [7]. However, since much of the literature on mild HIE outcome is inadvertently reported in studies with a broader focus, several scoping literature searches were made to identify key known reference papers prior to finalising the search strategy used for this review. An initial narrow search for HIE and outcome excluded many of the EEG, MRI and drug trials that did capture outcome in the mild HIE group. For this reason, the search strategy was expanded to include all papers reporting outcome in infants with mild HIE.

The RCT studies were analysed using Review Manager 5.3 [8] and odds ratios using a fixed effect model with 95% confidence intervals are reported.

2.1. Search strategy

A search strategy adapted from the Cochrane Neonatal Review Group [7] via OVID of Medline (1946–2017), Embase (1980–2017), Cochrane Trials Database (1996–2017), previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert

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informants and journal hand searching as per Cochrane Neonatal Review Group [7] was conducted on the 24th of March 2017. Databases to search were not restricted by language. Electronic search strategy used for Medline via OVID is presented below.

1. newborn hypoxia/
2. brain disease.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
3. hypoxic ischemic encephalopathy/
4. HIE.mp.
5. intrapartum hypoxia.mp.
6. fetus hypoxia/
7. fetal hypoxia.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. motor outcome.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
10. neurodevelopment*.mp.
11. neurodevelopmental outcome.mp.
12. 8 and (9 or 10 or 11)
13. limit 12 to (human and (infant or child or preschool child < 1 to 6 years > or school child < 7 to 12 years >))

After hand searching for key outcome papers a broader search was conducted using the search terms presented below.

1. ((outcome and hypoxic ischemic encephalopathy) or hypoxic ischaemic encephalopathy or HIE or perinatal asphyxia or neonatal encephalopathy).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. limit 1 to (humans and "all child (0 to 18 years)")

The two searches were indexed in Endnote® version 7.0 reference manager and combined excluding duplicates. An initial screen was done to exclude irrelevant papers by title and abstract. A second screen of full text articles was conducted to include/exclude papers based on inclusion/exclusion criteria listed below. The remaining papers were reviewed by DM and BW for final decision on quality and inclusion.

2.2. Inclusion criteria

Studies were included if they reported human studies of term infants ≥36 weeks GA. All randomised controlled trials, quasi-randomised trials and cohort studies that described neurodevelopmental outcome assessed using a standardised assessment test in infants with mild HIE were included. HIE needed to be clearly defined as mild, moderate or severe according to Sarnat and/or EEG grading [2,9]. Studies were only included if standardised outcome assessment was reported at a minimal follow-up age of 18 months and included a standardised cognitive outcome measure. In the meta-analysis infants with alternate diagnoses, including congenital malformations, were excluded.

Abnormal outcome was defined as death, or major neurodevelopmental disability (cerebral palsy (CP), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification), or developmental delay or intellectual impairment. This was defined as formal cognitive assessment more than one SD below the mean or intellectual impairment (IQ more than one SD below mean).

Papers were extracted using the online version of EndNote™ (www.myendnoteweb.com) [10] as reference manager. Duplicates were deleted. Extracted papers were then filed into phase 1 accept or reject folders by title and abstract. Due to the large number of papers extracted this first step was conducted to reject papers which were not relevant to our research question (Fig. 1 PRISMA flow chart). A second phase of screening was subsequently undertaken to screen papers for inclusion/exclusion criteria followed by expert review of all papers meeting inclusion criteria.

Papers reporting the same cohorts were grouped by country/centre and cohort recruitment year. Within these groups the paper reporting the longest complete outcome was chosen for analysis. These grouped papers are reported as one cohort to avoid duplication. See Supplementary S1 table for excluded repeat cohort papers n = 28. Systematic reviews were also removed however kept for cross referencing. See Supplementary S2 table for excluded systematic review papers (n = 19). Once this process was complete and the experts reached a consensus 20 papers remained for analysis.

Studies were critically appraised using the ten question Quality Appraisal Checklist (Supplementary S3 table) adapted from the Consolidated Standards of Reporting Trails (CONSORT) [12]. Each of the 10 appraisal questions were allocated one for yes, and zero for no. Articles with a total score > 75% were deemed high quality; 50–74% medium quality and < 50%, low quality. All studies were assessed by two independent researchers, and disagreements were resolved by consensus.

2.3. Data analysis

Included studies are presented in Tables 1a and 1b characteristics of included studies. RCT trials were analysed using Review Manager 5.3 [6,8]. Heterogeneity was assessed for appropriateness for meta-analysis. Meta-analysis of neurodevelopmental outcomes was performed in review manager reporting odds ratios with a fixed effects model and 95% confidence intervals. Abnormal outcome was defined as death, cerebral palsy or a cognitive score more than 1 standard deviation below the mean.

3. Results

Twenty studies were included in this review. Quality assessment is presented in Supplementary S3 Table. 14 articles were rated high, 6 were rated medium quality with none yielding a low score.

Following this quality assessment, no articles were excluded leaving a total of 20 articles for systematic review. Two of the RCT's were multicentre international trials and encompassed global recruitment. Eight studies were conducted in Europe, 7 in Asia, 2 in Australasia and 1 in North America. The twenty studies included reported on a total of 341 infants with mild HIE. Most trials included were prospective cohort studies that studied mild HIE and reported long term outcomes with the exception of four RCT's [13–16] who reported mild HIE and outcome as part of therapeutic hypothermia trials. These trials were included in a meta-analysis for effect of therapeutic hypothermia treatment. In addition three authors (Diviney et al. [17], Jacobs et al. [14], Murray et al. [3]) were contacted for raw neurodevelopmental test scores and of these 1 supplied raw outcome scores, Murray et al.

Across the 16 non-RCT studies outcome was reported in 250 mild HIE infants. Of this group, 56 (22%) had an abnormal outcome (see Table 1b) at 18 months of age or older. If we focus on those studies reported since 1990, 194 mild HIE infants were reported and of this group, 50 (26%) had an abnormal outcome. Studies reported > 25 years previously may bias the results as clinically there have been significant changes to obstetric and neonatal care over this time. However, the Robertson paper from 1989 was a large cohort and a seminal paper and so was included in our overall analysis.

Within the RCT studies (see Table 1a), 91 infants with mild HIE were included for analysis; 45 cooled and 46 uncooled. Abnormal outcome in the cooled versus uncooled groups was 29% versus 37% with an odds ratio of 0.67 (95% CI: 0.28 to 1.61, p = 0.59). By combining both RCT and non-RCT studies, outcome was reported in a total of 341 mild HIE infants, with 86 (25%) having an abnormal outcome.