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Hypothermia for perinatal asphyxial encephalopathy

A Swiss survey of opinion, practice and cerebral investigations

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Summary

BACKGROUND: Perinatal asphyxial encephalopathy occurs in 1– per 1000 live births and is associated with high mortality and morbidity. Therapeutic hypothermia increases intact survival and improves neurodevelopmental outcome in survivors.

AIMS: To evaluate (i) the opinion and practice of therapeutic hypothermia as a therapy for moderate to severe perinatal asphyxial encephalopathy amongst Swiss neonatologists and paediatric intensive care specialists, (ii) the current clinical management of infants with perinatal asphyxial encephalopathy and (iii) the need for a national perinatal asphyxia and therapeutic hypothermia registry.

METHODS: Two web-based questionnaires were sent to 18 senior staff physicians within the Swiss Neonatal Network.

RESULTS: Therapeutic hypothermia was considered effective by all responders, however only 11 of 18 units provided therapeutic hypothermia. Cooling was initiated during transfer and performed passively in 82% of centres with a target rectal temperature of 33–34 °C. Most units ventilated infants with perinatal asphyxial encephalopathy if clinically indicated and 73% of responders gave analgesia routinely to cooled infants. Neuromonitoring included continuous amplitude integrated EEG (aEEG) and EEG. Neuroimaging included cranial ultrasound (cUS), magnetic resonance imaging (MRI) and computed tomography (CT). Sixty-seven percent of units treating infants with perinatal asphyxial encephalopathy performed MRI routinely. All heads of departments questioned indicated that a "Swiss National Asphyxia and Cooling Registry" is needed.

CONCLUSIONS: In Switzerland, access to therapeutic hypothermia is widespread and Swiss neonatologists believe that therapeutic hypothermia for perinatal asphyxia is effective. National cooling protocols are needed for the management of infants with perinatal asphyxial encephalopathy in order to ensure safe cooling, appropriate monitoring, imaging and follow-up assessment. A national registry is needed to collect data on diagnosis, treatment, adverse events and outcome.

Key words: *neonatal encephalopathy; hypothermia; national registry*

Abbreviations

aEEG	Amplitude integrated Electroencephalogram
CI	Confidence Interval
CT	Computed Tomography
cUS	Cranial Ultrasound
EEG	Electroencephalogram
FU	Follow-up
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy

Introduction

Perinatal asphyxial encephalopathy is a clinically defined syndrome of disturbed neurologic function in the earliest days after birth in infancy, manifested by difficulty with initiating and maintaining respiration, depression of muscle tone and reflexes, subnormal level of consciousness and often seizures [1]. Perinatal asphyxial encephalopathy is a major cause of death and disability worldwide occurring

in 1–2 per 1000 births in the developed world [2, 3]; in low resource settings, the incidence is much higher [4, 5]. Moderate to severe encephalopathy is associated with high mortality and morbidity rates; sequelae of early brain injury require significant resources.

Experimental studies have shown that neural damage after hypoxia-ischaemia is delayed for several hours and that prolonged, moderate hypothermia reduces cerebral injury and improves neurological outcome [6–8]. Clinical studies have shown a reduction in mortality and long-term neurodevelopmental disability at 12 to 24 months of age with the most benefit seen in moderately encephalopathic infants [9–14]. Meta-analyses of the trials of therapeutic hypothermia [11, 15, 16] consistently show that therapeutic hypothermia increases survival with normal neurological function (pooled risk ratio of 1.53) with a number needed to treat of 8 (95% confidence interval (CI) 5–17), and in survivors it reduces the rates of severe disability and cerebral palsy [17, 18]. The most recent randomised controlled hypothermia trial (Neo.nEURO.network RCT) reported a number needed to treat of 4 [95% CI: 3–9]). Furthermore, therapeutic hypothermia also had a statistically significant protective effect in the group with severe encephalopathy (n = 77; p = .005; odds ratio: 0.17 [95% CI: 0.05–0.57]) [19].

Following the completion of the recruitment phase of the Whole Body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy (TOBY) trial in December 2006, therapeutic hypothermia continued to be offered as a therapy outside of any clinical trial in some UK units. A UK national registry was set up to provide surveillance of the use of therapeutic hypothermia in clinical practice and to identify possible complications of this therapy outside a clinical trial [13]. Even before the publication of the UK TOBY trial [20], access to hypothermia was widespread in the UK with more than half of the responders of a UK survey considering therapeutic hypothermia effective [20]. In the US in 2006, the American Academy of Paediatrics Committee on Fetus and Newborn stated that now that clinical trials had stopped recruiting, registries of infants with perinatal asphyxial encephalopathy should be established to facilitate data collection regarding diagnoses, treatments and outcomes [12]. Following the publication of the TOBY trial, the National Institute for Health and Clinical Excellence (NICE) endorsed Therapeutic Hypothermia with Intracorporeal Temperature Monitoring for Hypoxic Perinatal Brain Injury in 2010. NICE guidelines specify that therapeutic hypothermia should be performed "in carefully selected infants", "in units experienced in the care of severely asphyxiated infants" who "enter details of infants undergoing cooling into the UK TOBY cooling registry" (see website: http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf).

The aim of this Swiss study was to undertake a survey among neonatologists and paediatric intensive care specialists within Switzerland to (i) evaluate opinion regarding the use of therapeutic hypothermia, (ii) assess current clinical management of infants with perinatal asphyxial encephalopathy and (iii) assess opinion of the need for a national registry.

Methods

The Swiss Neonatal Network & Follow-Up Group is a non-profit voluntary collaboration of health care professionals dedicated to improving the quality and safety of medical care for high-risk newborn infants and their families. The Network consists of all neonatal Intensive Care Units (NICUs), Special Baby Care Units (SBCU) and most Neuropaediatric Centres in Switzerland under the auspices of the Swiss Society of Neonatology. A list of heads of departments of neonatal and paediatric intensive care units was obtained from the Swiss Neonatal Network and in May 2009, a 32 item web-based questionnaire with focus on clinical management of infants with perinatal asphyxial encephalopathy was sent out to the heads of departments of 18 neonatal units in Switzerland (see appendix 1). An additional 25 item questionnaire with detailed questions on follow-up procedures was sent in March 2010 to the same neonatal units (see appendix 2). Reminders were sent four weeks later.

In Switzerland, neonatal units are divided into two main categories. Those which initially stabilise the infants and then transfer the infants to regional centres for further care, and those which provide neonatal intensive care beyond the initial stabilisation period.

Results

The response rates of the first and second questionnaires were 67% (12/18) and 94% (17/18), respectively. Of the responding neonatal units, 11/17 provided mechanical ventilation beyond the stabilisation period. Of the non-responders, all were units not providing mechanical ventilation beyond the stabilisation period. The hospitals' delivery rate was 1000–3000/year in 15/17 (88%) of the responding units, 3000–5000/year in 1/17 (6%) units and one unit has no inborn infants. Almost half of the responding units (8/17) had a birth rate of 5000–10000/year within their catchment area, 4/17 (24%) had a birth rate of 3000–5000/year within their catchment area and 3/17 (18%) units of 1000–3000/year, and two units did not answer this question.

A total of 88% (15/17) of the responding units treat infants with perinatal asphyxial encephalopathy. The remaining two units transfer any infant with perinatal asphyxial en-

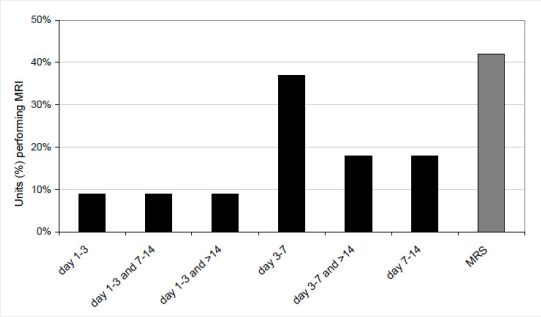

Figure 1

Timing of MRI in the units (n = 10) that routinely perform MRI in all infants with perinatal encephalopathy. MRS: Magnetic Resonance Spectroscopy.

cephalopathy to their regional centre for further care. Of those units treating such infants, 73% (11/15) provided therapeutic hypothermia on their unit and 27% (4/15) of the units refered severely sick infants to their regional centre for further care and/or cooling. Units that do not offer therapeutic hypothermia are those which do not provide mechanical ventilation beyond the initial stabilisation.

In the first questionnaire, the majority of responders felt that therapeutic hypothermia is effective; only one centre felt more evidence is necessary to offer therapeutic hypothermia. The second questionnaire showed that during the interim period, 5/17 (30%) of heads of department were influenced by the UK TOBY trial results, published in 2009, and all of the responder considered therapeutic hypothermia as an effective therapy. None of the neonatal units have taken part in trials for therapeutic hypothermia. All responders felt it important and necessary to build up a national registry of infants with perinatal asphyxial encephalopathy to facilitate data collection with focus on clinical management, adverse events and follow-up data.

Cooling on transfer

If transport is needed, 77% (13/17) initiated cooling during transport and cooling was always done passively during transport.

Hypothermia

Eleven of the 17 (65%) responding units provided therapeutic hypothermia. All units providing therapeutic hypothermia performed whole body cooling. A total of 82% (8/11) of units that offer therapeutic hypothermia aimed to cool passively. If the target temperature cannot be achieved or maintained by passive cooling, then a cooling mattress device was used in 54% (6/11) of the units to reach target temperature. The duration of cooling was 72 hours in all centres. Cooling details and clinical management during the cooling period are found in table 1.

Neuromonitoring

Neurological examinations to assess the severity of the perinatal asphyxial encephalopathy was done in 94% (16/17) of all responding units using the Sarnat Score [21] and in one unit (6%) using both Thompson [22] and Sarnat Score.

All units providing therapeutic hypothermia therapy (11/17) used amplitude integrated EEG (aEEG) to monitor brain function. Seven units (64%) monitored brain function with aEEG during the cooling and re-warming period, one unit (9%) was intermittently monitoring with aEEG, two units (18%) monitored during cooling period only and one (9%) monitored depending on aEEG availability. Eight seven percent of the units were using BrainZ monitor and 13% the Olympic 6000 monitor to record aEEG. All responding units had access to neonatal EEG, however 31% of the units only operated during office hours. A total of 75% of the units which treat infants with perinatal asphyxial encephalopathy requested EEG between day 1–3 and 25% of the units between day 3 and 7.

Fifty-eight percent of the units treating infants with perinatal asphyxial encephalopathy obtained neuroimaging within the first six hours after birth: all units would use cranial ultrasound (cUS). If additional imaging was used within the first six hours after birth, then MRI was done in 29% of the units and CT in 14% of the units.

A total of 67% (10/15) of the units treating such infants performed brain MRI routinely in all infants at any time

Table 1: Clinical management during therapeutic hypothermia in eleven cooling centers.

	n (%)
Cooling devices	
• Passive cooling	8 (82)
• Cooling mattress	6 (54)
Target temperature	
• 32–33 °C	2 (18)
• 33–34 °C	9 (82)
Temperature monitoring	
• Rectal temperature	6 (58)
• Oesophageal temperature	3 (25)
• Surface temperature	2 (17)
Mechanical ventilation	
• Routinely	3 (25)
• As clinically indicated	8 (75)
Analgesia	
• Routinely	8 (73)
• If required	3 (27)
• 1st line medication morphine	11 (100)
Sedation	
• Routinely	1 (9)
• If required	8 (73)
• No	2 (18)
• 1st line medication Midazolam	8 (73)
• 1st line medication Chloralhydrate	1 (9)
• Unknown	2 (18)
Seizures	
• 1st line medication Phenobarbital	10 (92)
• 1st line medication Midazolam	1 (8)
Relaxation	
• Routinely	None
• If required	11 (100)

during hospitalisation. Timing of MRI is shown in figure 1. Ninety two percent of all responders used phenobarbital as first line treatment for seizures and phenytoin as 2nd line therapy in all units.

Neurodevelopmental assessment

Thirteen of the 17 responding units answered the question about neurodevelopmental follow-up (FU) assessment. These centres had different FU programmes for infants with perinatal asphyxial encephalopathy. The details of FU assessment are shown in table 2.

Discussion

The birth rate in Switzerland is 10 per 1000 population; the estimated number of infants with perinatal asphyxial encephalopathy in Switzerland is thus ~76 infants per year. A recent meta-analysis of the three large hypothermia trials, showed that moderate hypothermia increased survival with normal neurological function with a number needed to treat of eight (95% CI 5 to 17) and in survivors it reduced the rates of severe disability, cerebral palsy and the mental and psychomotor developmental index to less than 70 [18].

All neonatologists taking part in this survey believed that therapeutic hypothermia is effective and offer hypothermia to infants with perinatal asphyxial encephalopathy even when transport to a regional centre is necessary. However, it became evident in these surveys that infants with perinatal asphyxial encephalopathy in Switzerland are managed differently depending on where they are treated. This information emphasises the need for the establishment of national guidelines for the clinical management of infants with perinatal asphyxial encephalopathy and of a hypothermia protocol to ensure best clinical practice, treatment and FU for such infants. Furthermore, a national registry is mandatory to identify adverse events, to enable systematic follow-up of survivors and to facilitate further clinical trials of neuroprotection following asphyxia.

Two methods of cooling have been evaluated: whole body cooling and selective head cooling with mild systemic hypothermia. Whole body cooling relies on the core and deep brain temperature being similar, while selective head cooling leads to temperature gradients within the brain. Techniques to provide whole body cooling are water mattress devices (servo controlled or manual and semi-automated), servo-controlled fans [23], water bottles [24], refrigerated gel packs with passive cooling at ambient temperature with cessation of active warming and the radiant warmer turned off [25], and phase-changing material mattresses [26]. Selective head cooling techniques include the Cool-Cap system [19] and ice-water-filled rubber gloves or ice packs applied to the head.

Unlike the large randomised controlled trials of cooling, in Switzerland 82% (8/11) of the cooling centres aimed to cool passively. Passive cooling is done by removing external heating devices such as incubators and radiant heat sources allowing the baby to naturally cool down. Fifty-four percent of the cooling centres used additional cooling devices to induce and maintain hypothermia during 72 hours if passive cooling does not succeed. To shorten the time between birth and the start of cooling, most transport teams of the responding centres initiated cooling already during transfer.

Cerebral function monitoring using the aEEG has provided an efficient tool for identifying infants with moderate or severe encephalopathy or seizures [27, 28] and helps to predict outcome [28]. A total of 66% of the responding centres treating infants with perinatal asphyxial encephalopathy and all centres providing therapeutic hypothermia used aEEG to monitor cerebral function, although not consistently during the cooling period and re-warming phase. It is important to continuously monitor brain function during the cooling and re-warming period as seizures may not be clinically apparent. However, if such monitoring is used to select which infants should be treated with therapeutic hypothermia, knowledge of artefacts which alter the aEEG trace is important [29].

Fifty-eight percent of the units treating infants with perinatal asphyxial encephalopathy acquired early imaging, always using cranial ultrasound; if additional early imaging was done then it was mainly done by MRI (29%) or by CT (14%). cUS is important to document any established injury and to exclude brain malformation on admission [30, 31]. Furthermore, it helps to show the evolution of injury over time and in combination with Doppler sonography helps to predict outcome [30, 32, 33]. Severely abnormal cUS findings were highly predictive of an adverse outcome at two years of age in infants with perinatal asphyxial encephalopathy; however, normal to mildly abnormal findings were not a strong predictor for favourable outcomes [30]. MRI is the best imaging modality to detect perinatally acquired cerebral lesions, and the pattern and severity of lesion are predictive of outcome [34–37]. The timing of scanning is important as the evolution of injury seen on MRI progresses over several days and the severity of injury might be underestimated during the first few days after birth [38]. Rutherford et al published the imaging findings of the infants of the UK TOBY trial showing that MRI at a median of 8 days accurately predicted outcome at 18 months in cooled and non-cooled infants [39]. Cooling was associated with a significant reduction in abnormalities in the basal ganglia, thalami and white matter, and the prognostic accuracy of MRI following perinatal asphyxial encephalopathy was not altered by therapeutic hypothermia [39]. A recent meta-analysis reported deep gray matter lact-

Table 2: Neurodevelopmental follow-up assessment at 2 years in thirteen follow-up centres of the Network.

Neurodevelopmental follow-up assessment	n (%)
Neurological examination	11 (85)
Neurodevelopmental assessment	13 (100)
Psychological assessment	4 (32)
MRI	2 (16)
EEG	3 (23)

ate/NAA acquired with MRS during the neonatal period to be the most accurate quantitative MR biomarker for prediction of neurodevelopmental outcome in infants with perinatal asphyxial encephalopathy [40]. In this survey, 10 responders (59%) requested brain MRI in all infants with perinatal asphyxial encephalopathy and about half of those (42%) performed MR spectroscopy. It is important to obtain brain MRI in all infants treated with therapeutic hypothermia and if possible the MR sequences should be standardised.

As infants with perinatal asphyxial encephalopathy are a high risk population for motor and cognitive impairment [41–45] and since, even in the absence of motor disability, long term cognitive deficits such as language and memory deficits can occur, close and long term neurodevelopmental assessment should be performed [42, 46]. A total of 87% (13/15) units treating infants with perinatal asphyxial encephalopathy in Switzerland have established follow-up programmes for such infants.

In a systematic review of 13 published clinical cooling trials, an increased risk of arrhythmia with a number to treat to harm of 25 (95% CI 16 to 100) and thrombocytopenia with a number to treat to harm of 10 (95% CI 5 to 33) in the hypothermia group was reported [17]. However, these conditions could be corrected with appropriate clinical care [17]. Azzopardi et al reported how cooling is managed outside of clinical trials in the UK. Reported clinical complications such as coagulopathy and pulmonary haemorrhage were thought to be due to asphyxia or other conditions than hypothermia [13]. National registries give the opportunity to record and monitor adverse events and to help ensure that therapeutic hypothermia is applied effectively and safely in clinical practice.

Conclusion

In Switzerland, access to hypothermia is widespread and Swiss neonatologists believe that therapeutic hypothermia is effective. National cooling and follow-up protocols are needed to standardise management of infants with perinatal asphyxial encephalopathy to provide safe cooling, appropriate monitoring, imaging and follow-up assessment. A national register is needed to collect data on diagnosis, treatment, adverse events and neurodevelopmental outcome.

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Appendix

First and second questionnaire are provided in the appendix.