

Short Term Outcome of Therapeutic Hypothermia in Term Infants with Moderate to Severe Hypoxic Ischaemic Encephalopathy; The Sungai Buloh Experience

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SUMMARY

This analysis is a case-series to document the outcome of term newborns with hypoxic ischaemic encephalopathy (HIE), enrolled into total body hypothermia therapy, in a tertiary neonatal unit in Malaysia. The method used to achieve total body hypothermia is a novel method using just environmental temperature, without the need of expensive equipment. A total of 17 babies were eligible to be included in this study, from the 1st of January 2010 to the 31st of December 2010. 14 out of 15 babies who had Stage 2 HIE had no neurological deficit at follow-up. All Stage 3 HIE babies passed away. Allowing for the small sample size, we can conclude that total body hypothermia therapy is feasible and is a safe treatment modality for HIE Stage 2 babies in a Malaysian setting, by manipulating environmental temperature to achieve therapeutic hypothermia. Further work is needed to determine the long-term outcome of passive cooling total body hypothermia in Stage 2 HIE babies in Malaysia.

KEY WORDS:

Hypoxic-Ischaemic Encephalopathy, Birth Asphyxia, Newborn, Therapeutic Hypothermia, Magnetic Resonance Imaging, Ct-Scan

INTRODUCTION

Therapeutic hypothermia is now widely used worldwide in the management of neonatal hypoxic ischaemic encephalopathy. The use of total body hypothermia in neonates have taken huge steps after well-designed randomised controlled-trials in North America and Europe. Such trials have shown promising outcomes especially in terms of reducing neurological deficits at follow-up appointments^{1,2,3,4}.

The usual method used in neonatal total body hypothermia is to cool term babies for 72 hours, aiming for a rectal temperature between 33.5 to 34.0 degrees Celcius. The cooling has to start within 6 hours of life. As to date, no studies have been published to look at different cooling temperatures, different duration of hypothermia or whether the current regimen is suitable for use in pre-term babies.

Many developed countries use cooling mattresses to achieve total body hypothermia, examples of which are Tecotherm and CritiCool. 5 The use of such treatment modality however, is yet to be proven cost-effective or suitable in with middle or low income countries⁶.

Only few detailed reports on therapeutic hypothermia in low-income countries are available in the literature. This first study was performed in Kampala, Uganda. Based on the data available for this study, the team can only conclude that such treatment modality is feasible and inexpensive in a low-resource setting. The team added to their conclusion that rigorous randomised trials are needed to determine the safety and efficacy of therapeutic hypothermia in such settings⁶.

Another similar study was conducted in Vellore, India. The authors concluded that it is feasible to achieve total body hypothermia without the use of expensive equipment. However, the study did not look at the long term outcome of babies who underwent total body hypothermia at their institution⁷.

The third paper on inducing therapeutic hypothermia without the need for expensive equipment was reported by a group in South Africa. Again, the study only reported the feasibility of achieving therapeutic hypothermia without expensive equipment but did not report on the long-term outcome of such babies⁸.

We aim to evaluate the outcome of total body hypothermia, in a Malaysian tertiary neonatal unit, where cooling circuits are not available. The method to achieve hypothermia is just by passive cooling.

The outcomes would be death and neurological deficit at follow-up (during any of the follow-up appointments).

MATERIALS AND METHODS

This case-series data collection was conducted in a tertiary neonatal unit in Malaysia, with an average admission of 3600 babies per year. We adopted passive total body hypothermia as the standard treatment for all babies with HIE Stage 2 and 3.

For the purpose of this report, we analysed the data regarding babies who underwent passive total body hypothermia from 01 January 2010 until 31 December 2010. The data were extracted from the patients' electronic summaries.

Total body hypothermia was achieved passively. The babies were nursed in an open-hood cot system, where the average temperature of the neonatal unit is kept between 18 to 19 degrees Celcius.

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Babies are included if they are more than 35 weeks gestation at birth, have completed 72 hours of total body hypothermia (within 6 hours of life), had magnetic resonance imaging (MRI) scan or computed tomography (CT) scan of their brain and also attended at least one out-patient follow-up.

Babies were excluded if they are either less than 35 weeks gestation at birth, had congenital malformations, did not complete 72 hours of hypothermic therapy or lost to follow-up.

The identification of babies to undergo total body hypothermia is based on Sarnat and Sarnat staging⁹. All Stage 2 and Stage 3 HIE babies are recruited for total body hypothermia.

The body temperature of the babies undergoing total body hypothermia was measured rectally. This was done continuously via a rectal probe (10 FR re-usable rectal temperature probe, Philips Healthcare, The Netherlands) by the nursing staff. The probe was inserted into the rectum and left there for the total duration of hypothermia. The rectal temperature is then displayed continuously on the patient's monitor display (Philips IntelliVue MP70 patient monitor, Philips Healthcare, The Netherlands) along with the baby's heart rate, respiratory rate, oxygen saturation and blood pressure. The target rectal temperature was between 33.5 degrees Celcius to 34.0 degrees Celcius. Any diversions from the above range will trigger an alarm on the patient's monitor.

All babies underwent the same passive cooling method. This is achieved by nursing the babies in an open-hood cot system. The neonatal unit's temperature was maintained between 18 to 19 degrees Celcius.

If the rectal temperature drops below 33.5 degrees Celcius, a radiant warmer is placed above the baby. The radiant warmer is subsequently switched off if the rectal temperature rises above 33.5 degrees Celcius.

Re-warming after 72 hours is achieved by placing a radiant warmer above the baby. The temperature rise was aimed to be at 1 degree Celcius every 4 hours. If the rate of rise exceeds this, the radiant warmer is switched off.

No routine use of analgesia or sedation was practised during the duration of hypothermia. In the event of babies having seizures, our unit uses Phenobarbitone as the first line treatment. Phenytoin or Midazolam is used in cases where Phenobarbitone fails to control the seizures. We do not have an amplitude EEG machine.

In our setting, it is relatively difficult to obtain an MRI scan of the brain during the first few days of life. Therefore, for the purpose of this study, any Stage 2 or Stage 3 HIE babies who had MRI or CT scans of their brain at any particular stage are included for analysis.

In addition to the brain MRI or CT scan, only babies who attend at least one follow-up appointment (at any time) as an out-patient will be included in the study.

RESULTS

There were a total of 30 term newborns who underwent total body hypothermia during the period of study (01 January 2010 until 31 December 2010). However, only 17 patients completed 72 hours of therapy, had an MRI or CT scan of the brain and attended at least one out-patient follow-up. Thus, for the purpose of this report, only 17 patients were included as illustrated in Figure 1.

Table I illustrates the demographic details of babies included in this report.

Out of the 17 babies, 15 had Stage 2 HIE and 2 had Stage 3 HIE. All successfully completed 72 hours of total body hypothermia using the passive method of cooling.

All Stage 3 HIE babies passed away. All Stage 3 HIE babies had MRI or CT scan changes as illustrated in Table II.

Details of Stage 2 HIE babies are as illustrated in Table III. Only one child had marked head lag and hyper-reflexia at out-patient review (Baby 3, Table III).

Attempts were made to contact the parents of babies who were lost to follow-up but no successful contact were made.

DISCUSSION

To the authors' knowledge, there are limited published papers on neonatal total body hypothermia in low-resource settings. The published studies did not look at the long term outcomes of babies who underwent total body hypothermia at their respective institutions.

To establish a neonatal therapeutic hypothermia programme is not without difficulties. As quoted by the neonatal team at the University of Michigan, one will need to look into many aspects of care such as safety, efficacy, cost-effectiveness and long-term outcomes before implementing therapeutic hypothermia¹⁰.

Our study sheds more light on the feasibility of achieving total body hypothermia without the need of expensive equipment.

The method used is simple, but dependent on the ambient temperature of the neonatal unit.

Tight temperature control of the baby is also required. This involves continuous monitoring of rectal temperature via a rectal probe, and places a significant amount of work on the nurses. The nurses will also need to be very vigilant towards any fluctuations in rectal temperature during the 72 hours of hypothermia therapy.

The process of re-warming should also be undertaken with care. In our study, we chose to raise the temperature by 1 degree Celcius every 4 hours. This rate of rise is similar to the other conducted studies.

Unfortunately, the two Stage 3 HIE babies included in this study passed away. One baby had an MRI-scan of her brain and one baby had a CT-scan of her brain. Both scans showed

Table I: Patients demographic details

Minimum gestation	Maximum gestation	Minimum birthweight	Maximum birthweight	Minimum cord pH	Maximum cord pH
37+1	39+5	2.10 Kg	3.74 Kg	6.6	7.1

Table II: Details of Stage 3 HIE babies

Stage 3 HIE	Gender	Apgar score at 1,5,10 minutes	Cord pH	Gestation at birth	Mode of delivery	MRI/CT findings
Baby 1	Female	0,1,3	6.6	Term	Spontaneous vaginal delivery	Generalised ischemic changes with basal ganglia infarct
Baby 2	Female	0,3,4	7.0	Term	Emergency Caesarean section	Generalised ischemic changes with basal ganglia infarct

Table III: Details of Stage 2 HIE babies

Stage 2 HIE	Gender	Apgar score at 1,5,10 minutes	Cord pH	Gestation at birth	Mode of delivery	MRI findings
Baby 1	Male	4,8,9	7.1	Term	Emergency Caesarean section	Old changes of hypoxic ischaemic encephalopathy
Baby 2	Female	5,7,9	7.0	Term	Vacuum assisted delivery	Normal
Baby 3	Male	4,not recorded	6.9	Term	Vacuum assisted delivery	Normal
Baby 4	Female	6,7,9	6.9	Term	Vacuum assisted delivery	Normal
Baby 5	Female	3,7,8	7.0	Term	Spontaneous vaginal delivery	Hypogenesis of corpus callosum.
Baby 6	Male	6,7,8	7.1	Term	Spontaneous vaginal delivery	Normal
Baby 7	Female	5,7,8	7.0	Term	Spontaneous vaginal delivery	Right subaponeurotic bleed but no evidence of cerebral ischaemia/infarct
Baby 8	Male	6,9,9	7.1	Term	Spontaneous vaginal delivery	Normal
Baby 9	Male	unknown	6.8	Term	Spontaneous vaginal delivery	Normal
Baby 10	Male	7,9,9	7.1	Term	Spontaneous vaginal delivery	Periventricular hypointense lesion in the left caudate.
Baby 11	Male	5,6,7	6.7	Term	Spontaneous vaginal delivery	Normal
Baby 12	Female	2,5,10	6.9	Term	Spontaneous vaginal delivery	Normal
Baby 13	Female	0,3,5	7.0	Term	Spontaneous vaginal delivery	Normal
Baby 14	Male	3,7,8	6.9	Term	Spontaneous vaginal delivery	Normal
Baby 15	Female	3,5,8	6.8	Term	Vacuum assisted delivery	Normal

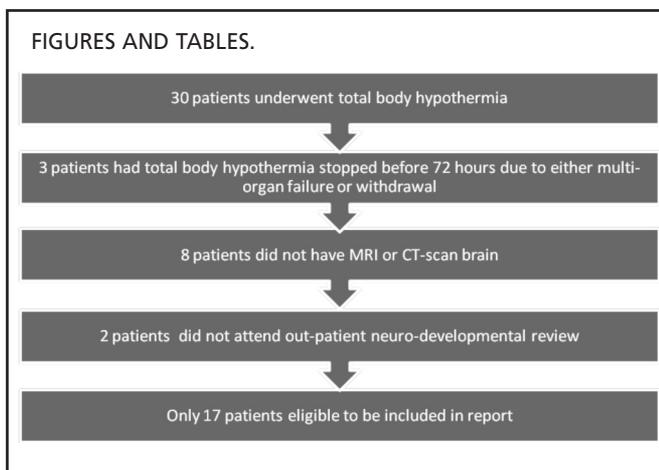


Fig. 1: Flow-chart illustrating sample size.

global ischaemic changes. Due to the small number of babies included in this category, it is difficult to determine the exact outcome of instituting total body hypothermia in this cohort of babies. Further work with better sample size is needed in this group.

With regards to the Stage 2 HIE babies, the outlook based on this study is far more promising. No babies passed away in this cohort of babies and encouragingly, only 1 patient had neurological deficits at 2 months of age.

In addition, the good clinical outcome is also supported by good radiological outcome. Only one Stage 2 HIE baby had confirmed ischaemic changes by MRI scan.

Furthermore, no adverse events were recorded due to the passive cooling method itself.

The authors acknowledge that the sample size is small.

The authors attempted to have a historical control group. However, prior to establishing the current hypothermia protocol, babies in the past either did not have scans of their brain or were lost to follow-up.

Further work is needed to establish whether total body hypothermia by means of passive cooling is suitable and safe in middle or low income countries, especially in the Stage 3 HIE cohort. A larger multi-centre data collection or a randomised controlled-trial will be invaluable.

CONCLUSION

Within the limitations of this case series, the data suggest encouraging outcome both radiologically and clinically, in babies with Stage 2 HIE in our NICU who underwent passive total body hypothermia.

In addition, the method to achieve total body hypothermia is innovative and cheap, without the need for expensive cooling equipment.

However, further work is needed to establish whether total body hypothermia by means of passive cooling is suitable and safe in middle or low income countries, especially in the Stage 3 HIE cohort. A larger multi-centre data collection or a randomised controlled-trial will be invaluable.

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