The influence of birth site on short-term outcomes of encephalopathic newborn infants treated with therapeutic hypothermia at Groote Schuur Hospital, Cape Town, South Africa.

by

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Declaration

I, Victoria Nakibuuka hereby declare that the work presented in this dissertation is original and has not been presented for any other degree in any University

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This dissertation has been submitted for examination with approval of the following supervisors;

1. A/Prof Alan Horn

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Abstract

Background: International consensus guidelines recommend that term or near-term newborns with moderate or severe hypoxic ischaemic encephalopathy (HIE) should be treated with induced hypothermia within 6 hours of birth, but many of the affected babies are born outside treatment centers. There are conflicting data describing the influence of birth site on outcome after HIE – and no published data from South Africa.

Objective: To compare the frequency of abnormal outcome (mortality or abnormal aEEG) before discharge between inborn and outborn infants treated with hypothermia

Methods: This was a retrospective analysis of data extracted from a prospectively collated registry of babies with moderate or severe HIE, treated with hypothermia in a tertiary hospital in South Africa, between 1 January 2011 and 31 December 2012.

Results: A total of 57 babies were treated with hypothermia of which 23 (40%) were inborn and 34 (60%) outborn. Cooling was initiated earlier among the inborn babies (age 2.3 hours vs. 4.3 hours, p=0.002). Pregnancy complications and abnormal intrapartum fetal heart rates occurred more frequently in inborn infants (65.2 % vs. 24.2%, p=0.0001 and 47.8% vs. 20.6%, p=0.03 respectively). More outborn babies died or had an abnormal aEEG at 48 hours (32% vs. 22%, p=0.556) and fewer outborn babies achieved normal feeding at discharge (22% vs. 38%, p= 0.189), but these differences were not statistically significant.

Conclusion: The majority of infants treated with induced hypothermia in an urban/peri-urban setting in South Africa were not born in a cooling centre. There were significant delays in initiating cooling among the outborn babies. Short-term morbidity and mortality were not significantly different in outborn babies but interpretation is limited by the small sample size.

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List of Figures and Tables

Abbreviations

aEEG	Amplitude-integrated Electroencephalography
CFM	Cerebral Function Monitor
CI	Confidence interval
EEG	Electro-Encephalogram
GSA	Geographic Service Area
GSH	Groote Schuur Hospital
HIE	Hypoxic Ischemic Encephalopathy
ICE	Infant Cooling Evaluation
ICU	Intensive Care Unit
KMC	Kangaroo Mother Care
NMR	Neonatal Mortality Rate
OR	Odds ratio
SD	Standard deviation
UCT	University of Cape Town
WHO	World Health Organization

CHAPTER 1 Introduction

1.1 Context

Hypoxic–ischemic encephalopathy (HIE) is the altered neurological state that can occur after fetal hypoxia during labour; it is a significant cause of death and neuro-developmental delay in children. Worldwide 10–60% of affected newborn infants die, and at least 25% of survivors have an adverse long-term neurodevelopmental outcome.(1) It is one of the top 20 leading causes of burden of disease in all age groups (in terms of disability life adjusted years) according to the World Health Organization (WHO).(2) Even at referral centers in developed countries, death or moderate to severe disability occurs in 53–61% of newborn infants diagnosed as having moderate-severe HIE.(3, 4) The incidence of moderate-severe HIE is 0.5–1 per 1,000 live births in developed countries and estimates in developing countries range from 2.3–26.5 per 1,000 live births (5); a study including data from 2008 and 2009 in the Southern Cape Peninsula (now known as the Metro West Geographical Service Area (GSA)), South Africa, found that the incidence of moderate-severe HIE varied from 2.3 to 4.3 per 1,000 live births, depending on which definition of HIE was used.(6)

Neuronal death associated with HIE occurs in two phases; primary neuronal death due to cellular hypoxia with exhaustion of the cell's high energy stores (primary energy failure); then after a variable latent period, usually of at least 6 hours, the secondary phase of delayed neuronal death begins (secondary energy failure).(7,8) In the secondary phase the severity of the encephalopathy typically increases; cytotoxic oedema, seizure activity and apoptosis are perpetuated by a combination of hyperaemia, mitochondrial failure, accumulation of cytotoxic excitatory toxins

and release of free radicals. The interval between primary and secondary energy failure represents a latent phase that corresponds to a potential therapeutic window. Therapeutic hypothermia instituted within this therapeutic window has been shown to be an effective treatment for some infants with HIE and it is now a recommended standard of care for infants with moderate-severe HIE in settings where intensive care is available.(9)

Meta-analysis of therapeutic hypothermia for the treatment of HIE, published by the Cochrane Library in 2008 and 2012 reported a 24% and 25% reduction of mortality respectively.(10, 11) In the same analyses, the reduction of neurological disability at 18 months among surviving term infants with moderate and severe HIE that were treated within 72 hours of moderate hypothermia was 32% and 23% respectively.(10, 11)

Therapeutic hypothermia should be initiated within 6 hours of birth (7) and yet the majority of babies with HIE are born outside the tertiary institutions that offer cooling services. Data from studies on the effect of birth location on outcomes after induced hypothermia are conflicting. Girijja et al. reported that outborn babies experienced significant delays in initiation of therapy, had lower baseline temperatures and had increased occurrence of severe HIE (43% vs. 29%), compared to inborn babies.(12) Eicher et al. reported that 92% of the deaths of babies with HIE occurred among outborn babies.(13) The Infant Cooling Evaluation (ICE) trial that evaluated the effects of whole body cooling in 220 infants reported no significant difference in adverse outcomes between inborn and outborn babies.(14) However, in the ICE trial, cooling was initiated during transportation to the tertiary institutions and the lack of significant effect of birth site on outcomes in this study, suggests that the early initiation of cooling played a role.

Although, cooling is recommended for babies with HIE in settings where intensive care facilities are available, the greatest burden of HIE occurs in low- and middle-income countries and particularly in Sub-Sahara Africa (SSA). Many of the countries in the SSA region do not have intensive care facilities and therapeutic hypothermia is not used as part of standard care.(2, 9) In Africa, appropriate newborn care is significantly compromised by secondary delays including poor transportation as a result of poor road infrastructure which is a significant limitation in the implementation of therapeutic hypothermia.(15) Chaudhary et al. have recently proposed cooling during transportation to treatment centers to mitigate such delays.(16) The study reported in chapter two of this thesis aims to compare short-term outcomes (mortality or abnormal aEEG) between inborn and outborn infants with HIE who were treated with induced hypothermia. The results may influence policy on such critical issues as the need for cooling during transportation, the age of initiation of cooling and the measures needed to promptly identify newborn infants in need of referral for possible cooling. Section 1.1.1 emphasises methodological aspects of study site and cooling methodology in more detail than was possible within the constraints of the publication-ready manuscript presented in chapter two.

1.1.1 Methods

Study site

The study was conducted at the neonatal unit at Groote Schuur Hospital (GSH) which is a tertiary hospital providing neonatal intensive care to the Metro-west GSA of the Western Cape, South Africa. In 2012, this region had approximately 40,000 deliveries.(17) The GSH neonatal unit has 75 beds, including 20 intensive care beds. The resources in this setting are more limited than in high-income countries with a nurse to baby ratio in the intensive care unit varying from 1:2 to 1:4. The unit bed occupancy is above 100% throughout the year. However, there are

facilities for neonatal ventilation, blood gas analysis, invasive blood pressure monitoring, and administration of inotropic agents. A total of 2,202 babies were admitted to the unit in 2011 and 2,423 were admitted in 2012.(17) Therapeutic hypothermia is provided using the servo-controlled gel-pack method (18), or using the Tecotherm Neo [TEC COM GmbH, Halle, Germany], depending on availability.

Details of the cooling methods used

i) Tecotherm Neo

The baby was placed on a coolant-filled mattress which was wrapped around the trunk and legs. A rectal probe was inserted 4–5 cm to measure core body temperature. The automated mode was used; the mattress cooled the infant down to a rectal temperature of 33.5°C as fast as possible, usually within 30 minutes. Once 33.5°C was reached this temperature was held constant for 72 hours via a servo-control mechanism. After 72 hours the mattress automatically re-warmed the infant, aiming to increase the core temperature to 37.0°C in increments of no more than 0.5°C per hour.

ii) Servo-controlled gel-pack method

Cool gel packs (at 7-10°C) were applied to the head and upper body and replaced hourly. The core temperature was servo-controlled by an overhead radiant warmer [Servocrib, Servocare Medical Industries cc, Cape Town], capable of controlling to a low target temperature of 33.5°C. A heat shield was placed over the head to prevent local head heating. After 72 hours the cold gel packs were removed and the temperature of the radiant warmer was increased every hour by 0.2°C, until a core temperature of 36.5–37°C was achieved.

1.2 Ethical considerations

Approval to conduct the study was obtained from the University of Cape Town (UCT) Health Sciences Faculty Human Research Ethics Committee and approval number was 612/2013. Permission was obtained from the superintendent of Groote Schuur Maternity Block to proceed with the study. Rules and procedures for responsible conduct of research were adhered to, ensuring confidentiality throughout the study and thereafter. All records identifying the subject were kept confidential. All computer entry of data was password protected and the final data set for analysis had identifying data removed.

Informed consent was not required since the study is retrospective, the data was de-identified before analysis and the data was extracted from an existing HIE registry that has previously been approved by the UCT Health Sciences Faculty Human Research Ethics Committee.

There weren't any physical or psychological risks to the patients or parents, nor any direct benefit, since this was a retrospective review of stored data. However, the study was expected to be of potential benefit to the community from the knowledge gained by analysis of the data. The results of this study may be used to influence policy on the need for cooling during transportation, the need to research later cooling initiation periods and the need for appropriate resources to allow initiation of cooling at referral hospitals.

1.3 Author guidelines for Journal of Tropical Pediatrics

The Journal of Tropical Pediatrics was chosen as a target journal for the manuscript as it is well known internationally and is tracked by Thomson Reuters. Moreover, it typically reports pediatric research relevant to resource-limited situations similar to those that occur in South

Africa. The author guidelines are included as Appendix 1 – the journal restricts the word count to 2000 words excluding references, tables and figures.

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CHAPTER 2 Publication–ready manuscript

2.1 Title Page

Title: The influence of birth site on short-term outcomes of encephalopathic newborn infants treated with therapeutic hypothermia at Groote Schuur Hospital, Cape Town, South Africa.

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Author contributions

VNK: Drafted the proposal, collected and analysed the data, and wrote the manuscript

NRR: Assisted with drafting the proposal and critically reviewed the manuscript

ARH: Assisted with drafting the proposal, data analysis and critically reviewed the manuscript

2.2 Summary

Background: International consensus guidelines recommend that term or near-term newborns with moderate or severe hypoxic ischaemic encephalopathy (HIE) should be treated with induced hypothermia within 6 hours of birth, but many of the affected babies are born outside treatment centers. There are conflicting data describing the influence of birth site on outcome after HIE – and no published data from South Africa.

Objective: To compare the frequency of abnormal outcome (mortality or abnormal aEEG) before discharge between inborn and outborn infants treated with hypothermia

Methods: This was a retrospective analysis of data extracted from a prospectively collated registry of babies with moderate or severe HIE, treated with hypothermia in a tertiary hospital in South Africa, between 1 January 2011 and 31 December 2012.

Results: A total of 57 babies were treated with hypothermia of which 23 (40%) were inborn and 34 (60%) outborn. Cooling was initiated earlier among the inborn babies (age 2.3 hours vs. 4.3 hours, p=0.002). Pregnancy complications and abnormal intrapartum fetal heart rates occurred more frequently in inborn infants (65.2 % vs. 24.2%, p=0.0001 and 47.8% vs. 20.6%, p= 0.03 respectively). More outborn babies died or had an abnormal aEEG at 48 hours (32% vs. 22%, p=0.556) and fewer outborn babies achieved normal feeding at discharge (22% vs. 38%, p= 0.189), but these differences were not statistically significant.

Conclusion: The majority of infants treated with induced hypothermia in an urban/peri-urban setting in South Africa were not born in a cooling centre. There were significant delays in initiating cooling among the outborn babies. Short-term morbidity and mortality were not significantly different in outborn babies but interpretation is limited by the small sample size.

2.3 Text

2.3.1 Background

Hypoxic–ischemic encephalopathy (HIE) can be defined as the altered neurological state that occurs after fetal hypoxia during labour; it is a significant cause of death and neuro-developmental delay in children.(1) Worldwide 10–60% of affected newborn infants die, and the majority of survivors of severe HIE have an adverse long-term neurodevelopmental outcome.(1) The incidence of moderate-severe HIE in the developing world is estimated to be 10–20 times more common than in the developed world.(2)

Neuronal death due to HIE occurs in two phases, and the interval between primary and secondary energy failure represents a latent phase that corresponds to a potential therapeutic window.(3,4) The most recent systemic review has shown that newborns with moderate or severe HIE who are treated with hypothermia have significantly improved neurological outcomes.(5,6) International consensus guidelines recommend that hypothermia should be provided as standard care in settings where intensive care is available; and it should be initiated within 6 hours of birth.(7)

Timeous initiation of cooling can be challenging as many infants are born outside treatment centres.(8,9) A study in the United States of America reported that outborn infants with HIE who were treated with induced hypothermia, were ten times more likely to die than inborn infants.(9) Other studies comparing outcomes of HIE management between inborn and outborn infants did not report any significant differences.(8,10) In middle-income countries such as South Africa, where therapeutic hypothermia is limited to very few centres (11), the extent to which being born outside a treatment centre compromises outcome may be substantial, but there are no published data. Long-term follow up is often difficult in resource-limited settings, but a severely

suppressed amplitude-integrated electroencephalography (aEEG) background at age 48 hours in cooled babies is strongly associated with poor long-term outcome.(12)

The Primary objective of this study was to compare the frequency of abnormal outcome (mortality or severely abnormal aEEG at 48 hours) before discharge, between inborn and outborn infants treated with hypothermia in a tertiary hospital in South Africa during a two-year period. The secondary objectives were: i) to describe the demographic and perinatal characteristics; and ii) to compare the age and temperature at initiation of cooling, and the proportions of co–morbidities between inborn and outborn infants.

2.3.2 Method

The study was conducted at Groote Schuur Hospital (GSH) a tertiary hospital providing neonatal intensive care to the Metro West Geographic Service Area of the Western Cape, South Africa. Therapeutic hypothermia was the standard of care for infants with moderate-severe HIE and was provided using the servo-controlled gel-pack method (13), or the Tecotherm Neo [TEC COM GmbH, Halle, Germany].

This was a retrospective analysis of data extracted from a prospectively collated registry of babies with moderate or severe HIE, who were admitted to the neonatal intensive care unit (NICU) and treated with hypothermia at GSH between 1 January 2011 and 31 December 2012. The study was approved by the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee.

2.3.3 Inclusion and exclusion criteria

All the following criteria (A+B+C) were required for both provision of therapeutic hypothermia and inclusion in the study:

A. Infants ≥ 36 weeks gestation and birth weight ≥ 1800 grams with moderate to severe HIE at age < 6 hours

B. Potential intrapartum hypoxia, suggested by at least one of:

- a 10-minute Apgar score of < 7, *and/or*
- ongoing respiratory support at 10 minutes, *and/or*
- a cord pH ≤ 7 or a base deficit of ≥ 12 within 60 minutes of birth

C. Signs of encephalopathy during the first 6 hours of life indicated by at least one of:

- three clinical signs of moderate-severe HIE, using the modified Sarnat classification as defined by Shalak et al. (14) *and/or*
- a depressed level of consciousness plus abnormal tone, *and/or*
- clinical seizure(s), *and/or*
- Abnormal amplitude-integrated Electro-encephalopagram(aEEG) defined by at least one of: moderately abnormal background, suppressed background, discontinuous normal voltage, burst suppression, low voltage, flat trace or seizures.

Infants with any of the following conditions were excluded: a severe congenital anomaly; congenital infection; persistent pulmonary hypertension, systemic hypotension or bleeding that was not responding to treatment; moribund and unlikely to benefit from cooling.

2.3.4 Data collection and analysis

The following infant/maternal data were extracted from the registry data forms: demographic characteristics at birth; temperature and age at cooling commencement at GSH; mortality; background aEEG pattern at 6, 24 and 48 hours; the presence of seizures and systemic co-morbidities; and the severity of the encephalopathy. Published data shows wide variations in the outcomes of inborn vs. outborn infants and data were-not adequate to guide sample size.(8-9,17) Our research is therefore exploratory using a convenience sample including all infants with moderate or severe HIE during a two-year period. The Chi square or Fischer's exact tests were used to compare categorical variables and the Student t-test or the Wilcoxon Mann-Whitney U test (depending on the distribution of the data) were used to compare continuous variables. Stata version 12 (Stata Corporation; College station, USA) was used for statistical analyses, all tests were two-sided and statistical significance was assigned at $P < 0.05$.

2.3.5 Results

During the study period, a total of 57 infants with moderate or severe HIE were treated with induced hypothermia, of which 23 (40%) were inborn and 34 (60%) were outborn. The characteristics of the infants and their mothers at initiation of cooling are shown in Table 1. The median age of initiaton of cooling in the outborn infants was double that of the inborn infants. Biochemical and clinical indicators of intrapartum hypoxia and encephalopathy were similar between the groups, but pre-exisiting maternal complications, pregnancy complications and abnormal fetal heart rate were more frequent among the inborn group (52.2% vs. 26.5%, p=0.048; 65.2% vs. 24.2%, p=0.001; and 47.8% vs. 20.6%, p=0.03; respectively). The individual pregnancy complications are shown in Figure 1 and the frequencies of clinically

important morbidities are shown in Table 2; there were no significant differences between the two groups.

The mortality and neurological outcomes at discharge are shown in Figure 2. A greater proportion of outborn infants died or had a severely abnormal aEEG at 48 hours (the primary outcome) compared to inborn infants (32% vs. 22%) but the difference was not statistically significant (Odds ratio (OR) 1.72, 95%Confidence Interval (CI) 0.45–7.45, p=0.382). A tendency towards poorer outcomes in outborn infants was also shown for the other individual short-term neurological outcomes but the differences did not reach statistical significance.

2.3.6 Discussion

This retrospective study describing the influence of birth site on short-term outcomes of infants with HIE who were treated with therapeutic hypothermia found that; a large proportion of the babies were outborn; the inborn infants had a higher rate of reported antenatal and intrapartum complications; the time to initiation of cooling in the outborn infants was twice that of the inborn infants; and abnormal outcome at discharge was more common in outborn infants, though the difference was not statistically significant.

The high proportion of outborn infants (60%) in our study is similar to the data reported by Eischer et al. where 75% of infants were outborn.(9) This trial was conducted in the USA and it studied the feasibility of initiating hypothermia in outlying hospitals. The high incidence of outborn infants in both studies is to be expected following the recommendation from the World Health Organization (WHO), that cooling should *only* be conducted in facilities with intensive care, necessitating referral of babies born in centres without these facilities.(15) The WHO recommendation can be expected to increase the burden of disease of HIE in the tertiary

institutions and it is also likely to result in the referral of a large number of infants with borderline signs of HIE who do not meet all the criteria for cooling. In the absence of aEEG, an early clinical indicator that predicts abnormal neurological outcome might be useful to identify infants who need referral for further assessment, as well as those who don't. An early Thompson HIE score of ≥ 5 at age 1–3 hours identified all infants who had an abnormal aEEG at age

3 or 6 hours (16) – the application of this score in settings where aEEG is not available may decrease the burden of disease of infants referred with mild HIE in tertiary centres.

In our study maternal complications including pre-eclampsia, diabetes and seizures, were reported more frequently among the inborn babies (65.2%). This distribution is expected, because these complications are indications for referral to a tertiary centre. Abnormal fetal heart rate was also reported more often among the inborn infants – this difference is difficult to explain because all inborn and outborn infants had HIE and similar proportions would be expected to have an abnormal fetal heart rate during labor. Additionally, caesarean sections, breech deliveries and instrumental deliveries occurred more often among the inborn infants. This is expected as some infants would have been referred for that reason and facilities for caesarean section are not available at all primary care centers. The data may also suggest that infants are not being timeously referred in-utero.

The initiation of cooling of the outborn babies was significantly delayed. This finding was similarly reported in two studies in North America.(17, 18) Natarajan et al. reported initiation of cooling at a mean (SD) time of 5.5 (1.1) hours compared to 4.4 (1.2) hours for inborn babies (17); and Khurshid et al. reported a median (IQR) age at initiation of cooling of 6 (7.6–9.6) hours for outborn babies.(18) The delay is likely to be most affected by transport from referring centres

in the absence of cooling in transit, but difficulty with the recognition of moderate to severe HIE at the referring hospital or tertiary institution would be expected to compound the delay further.

Despite the increased frequency of complicated deliveries and abnormal fetal heart rates among the inborn infants, adverse outcomes including mortality, abnormal CFM at 48 hours and delayed nutritive suck at discharge occurred more often in the outborn infants. Although the difference between the groups was not statistically significant, our findings were similar to those reported by Eischer et al, where 70% of the mortality was among the outborns (9), however in Eischer's study 77% of the babies in the outborn group had severe HIE. In contrast, Jacobs et al. found no differences in outcomes of inborn vs. outborn infants, but passive cooling and rectal temperature monitoring was initiated at the referral hospital and continued during transportation.(8) Experimental data in animal models suggest that cerebral hypothermia that is initiated as early as possible in the latent phase of injury is associated with neuroprotection,(19). However, in the Cool Cap trial there was no greater improvement in those treated earliest after birth compared to those treated later (2.6–6hours).(20)

The strengths of this study are that the source database was prospectively collated and the study contributes novel data in the geographical setting. However, the study is limited by the small sample size and the lack of long-term follow up data due to the poor follow-up attendance in our setting.

2.3.7 Conclusion

In conclusion, this study demonstrates that the majority of babies who were treated with induced hypothermia in an urban/periurban setting in South Africa were not born in a tertiary hospital. The significant delays in initiating of cooling and the apparent lower occurrence of fetal heart

rate abnormalities in the outborn babies are highlighted. Although short-term morbidity and mortality were not significantly different in outborn babies, the data could be used to inform a larger study. Moreover, our data indicates the need to implement techniques of rapid screening and/or diagnosis of HIE at referral hospitals to allow prompt and appropriate initiation of therapeutic hypothermia.

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2.5 Acknowledgements

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2.7 Legends to figures

Figure 1: Pregnancy complications in mothers of inborn vs. outborn cooled infants

Figure 2: Short term outcomes of inborn vs. outborn cooled infants

2.8 Tables

Table 1: Maternal and infant characteristics at initiation of cooling

Variable	In-born N=23 N (%)	Out-born N =34 N (%)	P value
Male	11(47.8)	13(38.2)	0.472
Cord or infant blood gas done within the first hour of birth	22(95.6)	31(91.2)	0.641*
Base Deficit (mmol/l): Mean (SD)	16.7 (8.4)	16.7 (5.9)	0.999
Lactate (mmol/l): Mean (SD)	10.4 (3.9)	9.4 (3.3)	0.312
Chest compressions at birth	4(17.4)	8(23.5)	0.744*
Adrenaline at birth	3(13.0)	5(14.7)	1.000*
Preexisting maternal conditions[a]	12(52.2)	9(26.5)	0.048
Pregnancy complications[b]	15(65.2)	8 (24.2)	0.001
Non-reassuring CTG or fetal bradycardia	11(47.8)	7(20.6)	0.030
Delivery complications[c]	14 (60.9)	19 (55.9)	0.708
Mode of delivery:			
Pre-labour CS	5 (21.7)	3 (8.8)	0.001*
In-labour CS	10 (43.5)	5 (14.7)	0.02
SVD cephalic	4 (17.4)	21 (61.8)	0.009
SVD (Breech)	4(17.4)	1(3)	0.05
Instrumental	0	4(11.8)	0.08
Maternal HIV status:			
Positive	3(13)	7(21.2)	0.789*
Unknown	0	1 (3)	0.456*
On treatment	2 (8.7)	2 (6)	0.495*
Abnormal CFM Pattern at 6 hours	9/21 (42.9)	17 (50)	0.606
Severely abnormal CFM at 6 hours	7/21 (33.3)	15 (44)	0.428
Cooled with gel pack method	20 (87)	25 (74)	0.325*
Age at initiation of cooling in hours. Median (IQR)	2 (1–4)	4 (4–5)	0.0001‡

CS – caesarean section; CFM – cerebral function monitor; CTG – Cardiotocograph; IQR – interquartile range

a: Preexisting maternal conditions - Diabetes Mellitus, Hypothyroidism, Hypertension

b: Pregnancy Complications - Diabetes, Illicit Drug use/ Alcohol use, Maternal seizure, Placaenta Preavia, Pre-eclampsia, Thyroid disease, bleeding, infection, anaemia, smoker, Chorioamnionitis:

c: Delivery Complications - Head entrapment, Placental Abruptio, Cord Prolapse, Ruptured Uterus, Shoulder dystocia

‡: Wilcoxon-Mann-Whitney test

*: Fisher's exact test

Table 2: Neonatal morbidity

Variable	In born	Out born	OR (95% CI)	P value
Hypoglycemia	6(26.1)	3(8.8)	0.27 (0.04 – 1.51)	0.137*
Hypomagnesaemia	3(13.0)	11(32.4)	3.19 (0.69 – 19.91)	0.097
Hypotension	3(13.0)	6(17.7)	1.43 (0.26 – 9.82)	0.726*
Serum Creatinine >115 μmol/l	1(4.4)	2(5.9)	1.38 (0.07 – 84.75)	1.000*
Pulmonary hypertension	2(8.7)	3(8.8)	1.02 (0.11 – 13.14)	1.000*
Meconium aspiration	3(13.0)	4(11.8)	0.89 (0.13 – 6.74)	1.000*
Mechanical ventilation	7(30.4)	13(38.2)	1.41 (0.40 – 5.20)	0.545
Late onset sepsis	1(4.3)	1(2.9)	0.67 (0.01 – 54.68)	1.000*
Necrotising enterocolitis	0	1 (2.9)		0.407
Bradycardia < 80 bpm	3(13.0)	3(8.8)	0.64 (0.08 – 5.35)	0.677*

CI – confidence interval; OR – odds ratio

*: Fisher's exact test

2.9 Figures

Figure 1

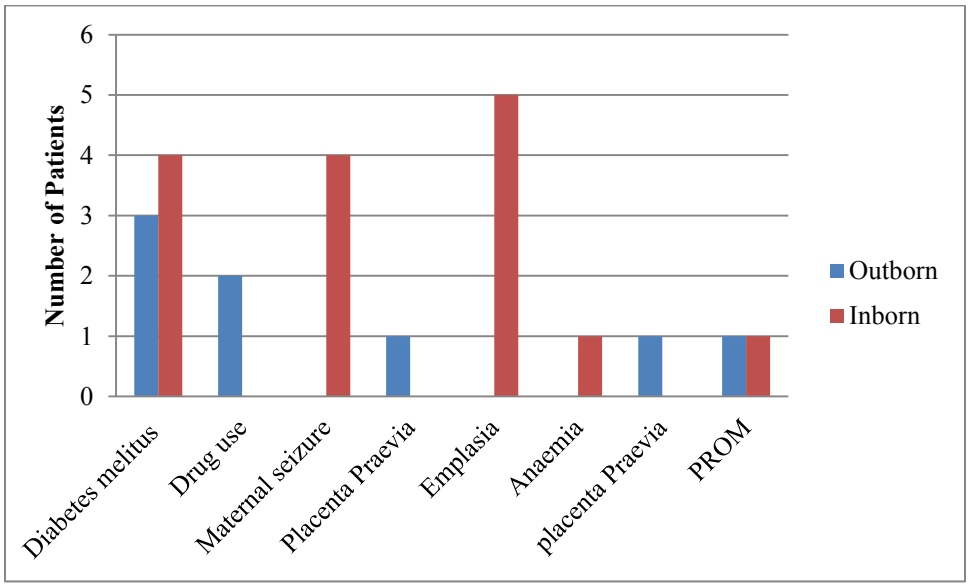
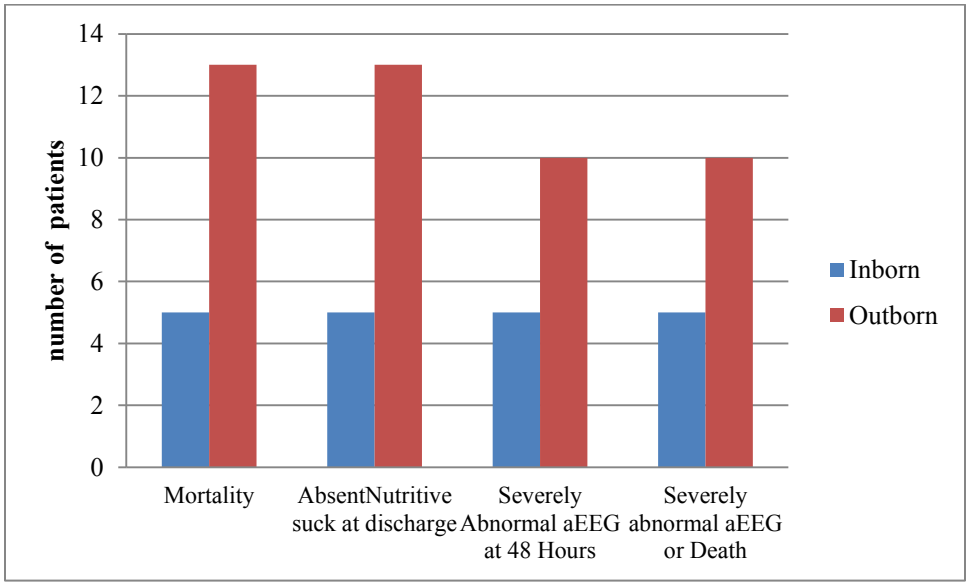


Figure 2


14
12
10
8
6
4
2
0
number of patients
Mortality
AbsentNutritive suck at discharge
Severely Abnormal aEEG at 48 Hours
Severely abnormal aEEG or Death
Inborn
Outborn

APPENDICES

Appendix 1: Author guidelines for Journal of Tropical Pediatrics

PREPARATION OF MANUSCRIPTS

Original papers should not usually be more than 2000 words in length; brief reports should not be more than 1000 words in length, and letters not more than 500 words. Manuscripts should be legibly typed, using double spacing throughout, with 25 mm margins at each side. Regular full length papers should be divided into the following sequence of sections, and each section should begin on a new page:

- Title page
- Summary
- Text
- Acknowledgements
- References
- Legends to figures
- Tables.

Number each page at the top right corner consecutively, beginning with the title page. Please avoid footnotes; use instead, parentheses within brackets. Underline only words which should appear in italic. Clearly identify unusual or handwritten symbols and Greek letters. Differentiate between the letter O and zero, and the letters I and l and number 1. Mark the position of each figure and table in the margin. SI units should be used for scientific measurements.

References

Number references consecutively in the order in which they are cited in the text. Published articles and those in press (state the journal which has accepted them) may be included. References should include (in the following order) author's names, editors (books only) paper title in full, journal/book title, name and address of publisher (books only), year, volume number

and inclusive page numbers. Personal communication should be authorized by those involved, in writing, and unpublished data should be cited as (unpublished data). Papers in preparation or submitted for publication should not be in the reference list. They should be cited in the text as follows: H. G. Jones, unpublished results/submitted for publication/in preparation (as appropriate).

Style in the reference section should be as follows:

1. Kennedy T, Jones R. Effect of obesity on esophageal transit. Am J Surg 1985;149:177–81.
2. Long HC, Blatt MA, Higgins MC et al.. Medical Decision Making. Boston: Butterworth-Heinemann, 1997.
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5. Public Health Laboratory Service. Antimicrobial Resistance in 2000: England and Wales. http://www.hpa.org.uk./infections/topics_az/antimicrobial_resistance/amr.pdf (7 January 2004, date last accessed).

Tables

Tables should be typed on separate sheets, and numbered consecutively. Tables should be self-explanatory and include a brief descriptive title. Footnotes to tables indicated by lower case letters are acceptable, but they should not include extensive experimental detail. Cite each table in the text in consecutive order.

Illustrations

All illustrations must be cited in the text in consecutive order. The back of each figure should be labelled clearly with the title of the paper, the name of the first author, and the figure number. Also indicate clearly the top margin of the figure. Figures should be submitted in the desired

final size so that reduction can be avoided. The type area of a page is 206 (height) mm x 150 mm (width); a single column is 71 mm (width).

Photographs. Photographs should be of sufficiently high quality with respect to detail, contrast, and fineness of grain to withstand the inevitable loss of contrast and detail inherent in the printing process. Indicate the magnification by a rule on the photographs.

Line drawings. These should be clear, sharp prints, suitable for reproduction as submitted. Ensure that the size of lettering is in proportion with the overall dimensions of the figure.

Figure legends. These should be on a separate, numbered manuscript sheet. Define all symbols and abbreviations used in the figure.

Funding

Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section
The following rules should be followed:

- The sentence should begin: 'This work was supported by …'
- The full official funding agency name should be given, i.e. 'National Institutes of Health', not 'NIH' (full RIN-approved list of UK funding agencies) Grant numbers should be given in brackets as follows: '[grant number xxxx]'
- Multiple grant numbers should be separated by a comma as follows: '[grant numbers xxxx, yyyy]'
- Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)
- Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'.

An example is given here: 'This work was supported by the National Institutes of Health [AA123456 to C.S., BB765432 to M.H.]; and the Alcohol & Education Research Council [hfygr667789].

Appendix 2: HIE Cooling registry data forms

Section 1:

Surname……..

Infant folder number …… DOB…….. Time OB……

Other Infant ID No…….. Mother folder no…….

Birth site: GSH/MNH/NSH/TGBG/George/MOU/Ambulance/Home/Other……..

Hospital providing cooling: GSH/MMH/TBGB/George, Other…….

Clinical details of Baby at Birth Gestation at Birth ……. Completed weeks Sex M/F

Birth weight …….gm COH ……..cm First gasp at ……. Min

Chest compressions Y/N Adrenaline Y/N

Early blood gas results (worst base excess within 60 minutes of birth including cord blood) available Y/N

Result: PH…… Base excess…… Lactate……

Section 2:

Clinical details at Age 3-6 hours

Visible seizures Y/N Thompson HIE score …….. HIE grade……..

Cooling Details

Cooling none/cap/mat/ fan/ gel

Age commenced ……. Hrs …….. Min ……. Target core temp……..°C

Temperature at the time of initiation of cooling ……°C

Maternal Details

Age …… Gravidity……. RVD pos/neg/UK / Pos+ ARV VDRL Pos/neg/UK/Post+ Fully treated

Pre-existing maternal Medical conditions or treatment Y/N

If yes give details……

Section 3:

Pregnancy complications Y/N If yes Diabetes Y/N Illicit Drug or alcohol abuse Y/N

Maternal seizure Y/N Placenta praevia Y/N Pre-eclampsia Y/N Thyroid disorder Y/N

Bleeding Y/N Infection Y/N Anaemia Y/N Pyrexia illness Y/N Smoker Y/N

PROM > 18 h Y/N Chorioamnionitis Y/N Other Y/N detail……

Mode Of delivery Pre labour CS / In – labour CS/ SVD cephalic / SVD breech/ instrumental

Delivery complications Y/N If yes: Head entrapment Y/N Placental abruption Y/N

Prolapse cord Y/N Ruptured Uterus Y/N Shoulder dystocia Y/N

Meconium Stain Liquor Y/N Non – reassuring CTG or Fetal Bradycardias Y/N/UK

Prolonged 2nd Stage Y/N/UK other Ante Partum Haemorrhage Y/N Maternal Hypoxia Y/N

Other sentinel Events Y/N detail ……

Congenital Abnormalities present at Birth Y/N detail …….

Was an AEGG (CFM) Performed in the first 6 hours of life? Y/N

CFM findings (1st 6 Hours)

Voltage (Normal) or moderately abnormal or severely abnormal seizures Y/N

Pattern FT/BS/CLV/DNV/CNV

Section 4:

During the time of admission were any of these present?

Clinical or EEG Seizures Y/N

Sepsis Y/N

Hypoglycaemia Y/N

CPAP or Nasal Canula Oxygen Y/N

Mechanical ventilation Y/N

Hypotension Y/N

Coagulopathy Y/N

Arrhythmia Y/N

Sinus Bradycardia Y/N

Serum Hyponatraemia Y/N

Hypomagnesaemia Y/N

Bleeding /SAH Y/N

Section 5:

Head scan structural abnormality Y/N

Diagnoses during admission None of the below Y / N

Major cerebral Anomaly Y/N Pneumonia Y/N

Major Cerebral Anomaly Y/N

Meconium Aspiration Y/N

Necrotising enterocolitis Y/N

Late Onset Sepsis (> 72 hrs) Y/N

Pulmonary air leak Y/N

Pulmonary Haemorrhage Y/N

Pulmonary Hypertension Y/N

Renal failure with Dialysis Y/N

Adverse effects due to cooling or re warming

……..

Cooling for less than 72 hours; Explain Why…… ……..

……..

Full sucking/ Cup Feeding established by discharge Y/N If yes, age established (d)……

…….

HIE Score at 6 hours……..

HIE Score at 24 hours …….

HIE Score at 48 hours……..

HIE Score at day 5……

Appendix 3: The Thompson HIE Score

SCORE	0	1	2	3
Limb tone	Normal	Generally Hypertonic	Generally Hypotonic	Flaccid
LOC	Normal	Hyper alert or staring	Lethargic or obtunded	Coma or stuporose
Visible Fits	None	Infrequent	Frequent	
Posture	Norm/Other	Fisting	Strong Distal Flexion	decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent/ Bites	
Respiration	Normal	Normal	Transient Apnoea	Apnoea requiring IPPV
Fontanel	Normal	Full	Tense	

Appendix 4: Ethics approval