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THE USE OF THERAPEUTIC HYPOTHERMIA IN NEONATES WITH PERINATAL ASPHYXIA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL:

A Retrospective Review

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DECLARATION

I hereby declare that this research paper has been submitted for the degree of Master of Medicine in Paediatrics to the University of Witwatersrand, Johannesburg. It has not been submitted by me or anyone else for a degree at this, or any other university. This is my own work, and materials consulted have been properly acknowledged.

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Dr KN Sebetseba

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Contents

Abstract 5
Abbreviations 6
Introduction 7
Methods 9
Data Collection 10
Statistical Analysis 10
Ethics Approval 10
Results 11
Discussion 15
Study limitations 17
Conclusion 17
References 18
Appendix 1: Research Protocol 19
Appendix 2: Data Sheet 34
Appendix 3: Ethics Clearance Certificate 35
Appendix 4: Acceptance letter for publication 36
Appendix 5: Plagiarism (TURNITIN Report) 37

Abstract

Background: Therapeutic hypothermia (TH) has become the standard of care to reduce neurological damage following perinatal asphyxia. Current recommendations call for implementation of a standard, evidence-based protocol for the provision of TH. This is particularly challenging in resource-limited settings.

Objective: To determine whether neonates at Charlotte Maxeke Johannesburg Academic Hospital are receiving TH according to the unit protocol in place.

Methods: This was a retrospective, descriptive study. The study included all neonates with a birth weight greater than 1800g admitted to the CMJAH neonatal unit from 1 January 2013 to 30 June 2017 before 24 hours of life. Neonates were assessed as to whether they met the criteria for TH according to the protocol and reasons for not providing TH to those who qualified were investigated.

Results: The total number of neonates enrolled for the study was 485. Three hundred patients met the criteria for TH. 185/300 appropriately received TH. 43 were not cooled despite meeting TH criteria. The primary reason for this was a lack of equipment (27/43). Of the remaining 257 that did not meet TH criteria, 21 patients inappropriately received TH. A total of 206 neonates received TH.

Conclusion: Therapeutic hypothermia at CMJAH is largely being practiced as per protocol. Still, more resources are needed, not only to optimize the number of patients that have access to this treatment modality, but also in terms of imaging and support strategies.

Keywords: Perinatal asphyxia, Therapeutic hypothermia, resource limited settings

Abbreviations

aEEG: amplitude-integrated electroencephalogram

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

HIE: Hypoxic Ischaemic Encephalopathy

LMICs: Low to Middle Income Countries

MRI: Magnetic Resonance Imaging

PA: Perinatal Asphyxia

TH: Therapeutic Hypothermia

VON: Vermont Oxford Network

Introduction

Perinatal asphyxia (PA) is a significant and common cause of death and severe neurological impairment in developing countries. A study done at Chris Hani Baragwanath Academic Hospital by Bruckmann et al suggested an incidence of 8.7-15.2 /1000 live births, with an overall mortality rate of 14 %.[1] This incidence is much higher than that of 5-10/1000 live births, previously reported in developed countries.[2] Complications of perinatal asphyxia account for 23% of all early neonatal deaths worldwide. Without intervention, asphyxia is often followed by encephalopathy, with devastating consequences like death or severe disability.[3]

Several post-natal features are used to determine the severity of the asphyxia. The six major trials of therapeutic hypothermia: the CoolCap, TOBY, NIHCD, Eicher, NeonEuro, and ICE, used similar criteria to establish the diagnosis of perinatal asphyxia, see Table 1 below. With the exception of the Eicher and ICE trials, who used a gestational age of 35 weeks, neonates had to meet a gestational age of 36 weeks to be eligible for inclusion. The essential metabolic parameters included a blood gas sample performed less than one hour after birth showing an acidaemia (pH less than seven). Generally, a base deficit of 16 or more was used. However, the NIHCD, ICE and Eicher trials included slightly lower base deficits, of 12 and 13 respectively, signifying a move towards the inclusion of moderate asphyxia. Persistence of an Apgar score below five at ten minutes warranted inclusion in all studies except the Eicher trial, where a five minute Apgar less than five was deemed appropriate. Evidence of encephalopathy, varying from hypertonia and seizures, to coma; as well as evidence of multi-organ dysfunction in the immediate neonatal period. The use of more sensitive criteria, such as amplitude-integrated electroencephalogram (aEEG) patterns was used as an entry criterion in only three of the studies, and is restricted in resource-limited settings.[2]

Therapeutic hypothermia (TH) has become the standard of care to reduce neurological damage following perinatal asphyxia.[4] This treatment works by reducing cerebral perfusion and metabolism, mitigating reperfusion injury, depressing the immune response and various potentially harmful pro-inflammatory reactions, and supressing epileptic activity[4]. While previous studies suggested negligible benefit in Low and Middle Income Countries (LMICs), there is now enough data to encourage its proper, protocol-guided use with appropriate equipment.[5] Further, Rossouw et al showed, in a systematic review and meta-analysis comprising three studies and 461 patients, that even low technology TH methods, such as gel packs, reduced morbidity and mortality, with no significant differences in adverse events, provided there was adequate monitoring and support in a high care or ICU setting.[6]

Table 1: *Entry Criteria used in the major trials of TH* [2]

Study	CoolCap**(n=235)** TOBY**(n=325)** **>36weeks** **≤5.5 – 6hrs**	NIHCD**(n=208)** **≥36weeks** **≤6 hrs**	Eicher**(n=67)** **≥35weeks** **≤6 hrs**	NeonEuro**(n-129)** **≥36weeks** **≤6hrs**	ICE**(n=204)** **≥35weeks** **≤6hrs**
Metabolic	• 1 of 4 below • Apgar(10min) ≤5 • pH<7.00 • BE≤-16 • Ventilated/ rescus by 10 min	• 1 of 4 below • Apgar(10min) ≤5 • pH<7.00 • BE≤-12 • Ventilated /rescus by 10 min	• 1 of 6 below • Apgar(5min) ≤5 • pH<7.00/7.1 • BE≤-13 • Ventilated/ rescus by 10 min • Bradycardia ≤80bpm • Postnatal HI event	• 1 of 4 below • Apgar(10min) ≤5 • pH<7.00 • BE≤-16 • Ventilated /rescus by 10 min	• 1 of 4 below • Apgar(10min) ≤5 • pH<7.00 • BE≤-12 • Ventilated /rescus by 10 min
Neurology	• Cosciousness, lethargy, stupor or coma • **And** 1 of 3 below • Hypotonia • Abnormal reflexes • Abnormal suck • **OR** clinical seizures	• 3 of 6 • Abnormal consciousness • Tone • Autonomic reflexes • Primitive reflexes • Activity • Posture • **OR** seizures	• 3 of 6 • Abnormal consciousness • Tone • Autonomic reflexes • Primitive reflexes • Activity • Posture • Seizures	• Moderate or severe encephalopa- thy	• Moderate or severe encephalopa-thy (Sarnat modified)
aEEG	Abnormal	No aEEG	No aEEG	Abnormal	No Aeeg

Given this encouraging data, one cannot dispute the importance of a clinical audit to review the use of TH in a resource-limited academic hospital setting. The Vermont Oxford Network (VON) Collaborative set out to achieve an evidence based approach to neonatal encephalopathy in order to improve consistency of care and improve neonatal outcomes.[7] This was performed using standard quality improvement methodology. Despite the existence of guidelines and protocols, a gap between recommended care and clinical practice often exists. The recommendations provided by the VON collaborative are an ideal that may unfortunately be difficult to achieve in centres with resource constraints such as lack of equipment and inadequate staff. The Neonatal protocol currently in use at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) stipulates the following inclusion criteria for TH:

- Gestational age greater than or equal to 34 weeks and birth weight greater than or equal to 2000 grams.

- Apgar score less than six at ten minutes, or continued need for resuscitation or intubation at ten minutes.
- Initial blood gas done within an hour of life must have shown a pH less than seven or base deficit greater than 16.
- Thompson score greater than seven
- Evidence of encephalopathy, defined as lethargy, stupor or coma and at least one of the following: hypotonia, abnormal reflexes, absent or weak suck, and/or clinical seizures
- Amplitude EEG monitoring, for at least 30 minutes, showing moderate or severely abnormal background, or normal background with seizure activity

Normothermic infants with no spontaneous respiration after 30 minutes post resuscitation, after excluding the effects of anaesthesia; or with a heart rate below 100 at fifteen minutes post-resuscitation, are not offered TH.

These criteria were formulated as an adaptation of the TOBY criteria, and serve to include a larger group of neonates, while taking into account the resource limitaions in our setting. A 2012 study by Joolay et al reviewing the practice of TH in South Africa showed that, although 76% of respondents agreed that TH was effective in reducing neurological injury following PA, only 42% were able to implement it, with a further 9% having access to referral centres that would provide TH . TH at CMJAH was first offered in 2013. At the onset, only two machines were available, which provided an obvious limitation to the number of infants who could receive TH at any given time. In 2015, the Neonatal unit acquired a third TH machine

This study reviews the practice of TH at CMJAH, looking at the burden of perinatal asphyxia, and the application of therapeutic hypothermia in this setting in order to establish whether neonates are receiving TH appropriately, and according to the unit protocol.

Methods

This is a retrospective, descriptive study of all neonates with a birth weight greater than 1800g admitted to the CMJAH neonatal unit from 1 January 2013 to 30 June 2017 before 24 hours of life. Neonates were included in the study group if they received TH (irrespective of other demographic, Apgar or weight criteria, or had a five minute Apgar score less than six. Five minute Apgar score was used, instead of ten minute score, in order to ensure the inclusion of all possibly asphyxiated neonates. Neonates with missing Apgar scores or TH information were excluded from the study, as were neonates with other causes for low Apgar such as major congenital abnormalities of the central nervous system. Owing to limitation of resources in our settings, including the paucity of early antenatal ultrasound, the decision to use 1800g as the weight cut off was to potentially include small for gestational age (SGA) infants, as is common given the demographics of our patient population. Also, time of admission, in hours, is not routinely documented, hence the decision to include all infants admitted on their date of birth.

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary academic hospital situated in Central Johannesburg. The neonatal unit has 35 low care, and 35 high care beds. There were approximately 1800 admissions to this unit annually. The Intensive Care Unit is a 14 bed, combined paediatric and neonatal unit which caters to surgical patients as well.

The decision to offer TH was at the discretion of the attending physician. The neonatal unit had three MTRE Criticool ® Whole Body Cooling servo-controlled machines. Therapeutic hypothermia was carried out in the high care area with half-hourly temperature monitoring. Patients were sedated with Morphine at an infusion of 10-40mcg/kg if normotensive and ventilated, or orally at 0.05-0.1mg/kg/dose four to six hourly if not ventilated. If required, given an anticonvulsant at the start of TH. Vital signs were checked hourly, and adverse events were managed as they arose. Ventilation was not routinely provided to neonates undergoing TH. Use of aEEG was limited, and Magnetic Resonance Imaging (MRI) was not available in the unit at the time of the study as the hospital had no functioning MRI machine.

Data Collection

The CMJAH neonatal database was used to obtain information including maternal, obstetric and neonatal parameters and interventions.[8] Clinical data was collected on an ongoing basis at the time of patient discharge and recorded by Medical Officers, Registrars and Consultants in the department. Data was verified against patient records at different points. Various aspects of the patient's demographics, admission information, clinical presentation, vital data and biochemical parameters of birth, treatment received and outcome were documented, filtered and arranged as required.

Eligibility criteria for TH were noted and reviewed against the unit protocol. Data was managed using Research Electronic Data Capture (REDCap) hosted by the University of the Witwatersrand. [9]

Statistical Analysis

Data collected was entered into a Microsoft excel spreadsheet and basic statistical analysis was performed using IBM SPSS Version 24 (IBM, USA). Appropriate descriptive statistical analysis using valid percentages and means or medians was used. Neonates in the TH, and non-TH groups were compared. Continuous variables were compared using the Mann Whitney U or unpaired T- tests and categorical data using chi- square analysis. All expected cell frequencies were greater than five and all statistical assessments were considered significant for a p-value below 0.05. Neonates were then classified according to whether they met criteria for TH or not, and Kappa statistics were applied.

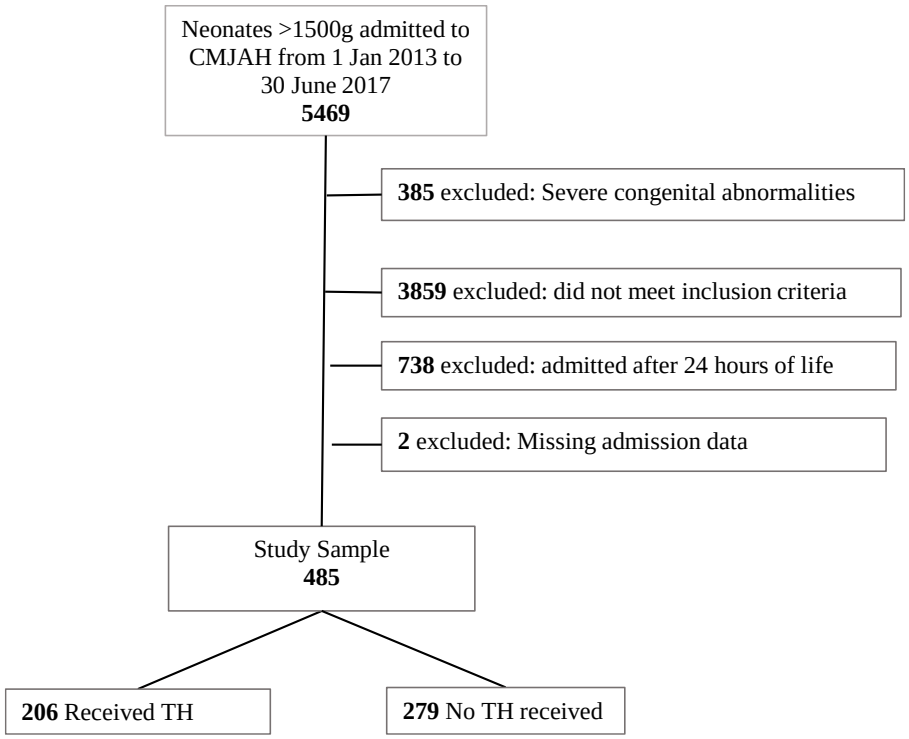
Ethics Approval

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand Clearance Certificate no. M170549.

Results

Over the four year period, a total of 485 neonates were included in the study (Figure 1).

Figure 1: *Derivation of study sample*



Of the 485 patients, a large majority (80.5%) were born at CMJAH, at a median gestational age of 38.5 (IQR 28-43) weeks. Other main demographic and clinical characteristics are shown in Table 1. Three hundred and sixty five of these neonates required prolonged resuscitation at birth, defined as the requirement of anything more than face mask ventilation (i.e. endotracheal intubation, Nasal CPAP or cardiac compressions, with or without Adrenaline) with a Mean Apgar score of 2.76 ± 1.9 at one minute. It was noted that 438 patients had no documented Thompson score, as these were not routinely captured onto the database until two years into the study period. Not all neonates were allocated an HIE grade (Sarnat score), at the time of admission. Mean body temperature on admission was 34.4°C ± 7.7. The reasons for these fairly low temperatures are unclear from the data. Body temperature was greater than 38°C in 2 cases, whereas hypothermia (<35°C) was reported in 21% of the patients. Gestational age ($p < 0.01$), birth weight ($p<0.01$) and five minute Apgar were significant predictors of whether neonates received TH or not. Smaller neonates of lower gestational ages and lower Apgar scores did not receive TH, in keeping with the protocol. Neonates with lower pH ($p<0.05$) and higher Thompson scores ($p<0.002$) were also less likely to receive TH.

Table 2: *Comparison of clinical and demographic characteristics of TH and non-TH groups*

	Variable	Total Group	TH (n=206)	No TH (n=279)	p-value
NEONATAL PARAMETERS	Mean Birth weight (grams)	2880 ± 660	3088 ± 568	2784 ± 707	<0.001
	Mean Gestational Age (weeks)	37.7 ±2.9	38.3 ± 2.3	37.3 ± 3.3	<0.001
	Mean duration of hospital stay (days)	7.3 ± 7.9	8.1 ± 7.8	6.7± 8	0.53
PERINATAL PARAMETERS	Median Apgar at 5 min (range)	4.5 (0-8)	4.8 (0-8)	4.1 (0-8)	<0.001
	Median Apgar at 10 min (range)				
	Mean Temp on admission (°C)	34.4 ± 7.7	34.4 ± 6.9	34.2 ± 8.3	0.733
	Respiratory Support: NCPAP	68	17	51	
	Respiratory Support: IPPV/ HFOV	44	37	7	
	Prolonged Resuscitation	75.2% (365/485)	74.7% (154/206)	75.6% (211/279)	0.756
HIE PARAMETERS	Mean pH	7.08 ± 0.22	7.1 ± 0.2	7.03 ± 0.2	0.05
	Mean base deficit	18.2 ± 6.6	17.5 ± 6.3	19.2 ± 6.8	0.134
	Mean Thompson's Score	9.2 ± 4	7.6 ± 3.9	11.8 ± 3.8	0.002

Most of the patients in the study needed little or no respiratory support. Of the 112 patients requiring ventilator support, 68 (60%) required NCPAP. The remaining 40% (44 /112) required invasive ventilation. Very little imaging was done on this cohort of patients. Eighty-six patients had cranial ultrasonography, 51% (n=44) of which were normal. Amplitude EEG monitoring was only performed in 18 patients. 15 showed abnormalities by way of seizures, continuous low voltage, and burst suppression.

Of the 482 patients with confirmed short-term outcomes, 408 survived to discharge, with a mean hospital stay of 7.3 ± 7.9 days.

The grade of HIE was a statistically significant determinant of TH, see **Table 2** below. Neonates born by emergency Caesarean Section were less likely to receive TH.

Table 2*: Univariate analysis for determinants of TH*

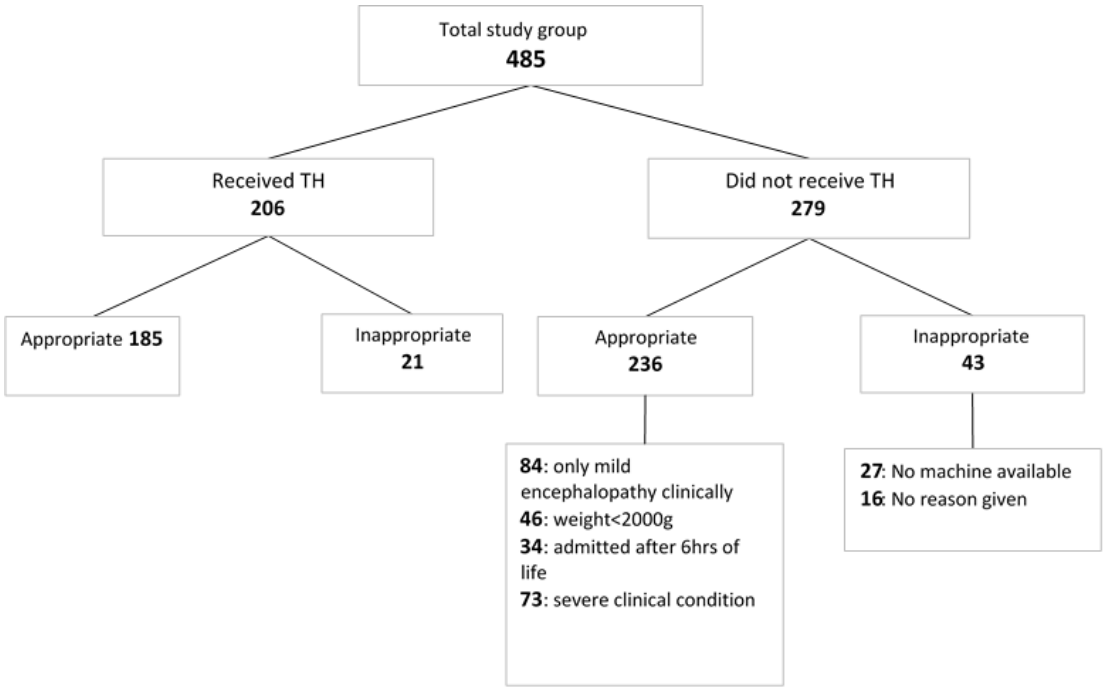
	Variable	Total Group	TH (n=206)	No TH (n=279)	Chi square	p-value
	Male Gender	62.8% (305/485)	26.2% (127/206)	36.7% (178/279)	196[a]	0.658
Place of Birth	Inborn	82.1% (391/476)	34.2% (163/476)	47.9% (228/476)	2.128[a]	0.345
	Born at MOU/ Another hospital	17.6% (84/476)	8.6% (41/476)	9% (43/476)		
	Born before arrival	0.002% (1/476)	0	0.002% (1/476)		
Mode of delivery	NVD (Includes vaginal breech and assisted delivery)	50.4% (244/483)	24.4% (118/483)	26% (126/483)	8.701[a]	0.034
	Elective C/S	5.8% (28/483)	2.1% (10/483)	3.7% (18/483)		
	Emergency C/S	43.5% (210/483)	15.7% (76/483)	27.7% (134/483)		
	Prolonged Resuscitation	75.3% (365/485)	31.8% (154/485)	43.5% (211/485)	0.96[a]	0.756
HIE Grade (Sarnat Score)	HIE I	21.1% (64/303)	10.9% (33/303)	10.2% (31/303)	10.793[a]	0.005
	HIE II	54.8% (166/303)	37.3% (113/303)	17.5% (53/303)		
	HIE III	24.1% (73/303)	11.6% (35/303)	12.5% (38/303)		

a. 0 cells have expected count less than 5. The minimum expected count is 76.67

Therapeutic hypothermia

A total of 228 neonates met criteria for TH, see Figure 2. Two hundred and six neonates received TH. 185 of these (89.8%) met protocol criteria. Two hundred and seventy nine patients assessed as having perinatal asphyxia did not receive TH. Fifteen percent of these, (43/279) met the criteria set in the CMJAH neonatal protocol. Reasons for these neonates not receiving TH included a lack of equipment in 23% of the patients (27 / 115). No reason for not receiving TH was given for 16 of these neonates. Thirty four patients were transferred in from other hospitals and MOUs didn't meet eligibility criteria for TH as they arrived at the hospital after the six hour timeframe.

Figure 2: *Breakdown of study group*



Cohen's kappa (K) was run to determine agreement between meeting protocol criteria for TH and actually receiving the treatment, see Table 3 below. The result was statistically significant, and showed moderate agreement between the two. K=0.734 (CI 0.662 to 0.806) p <0.001

Table 3: *Cross-tabulation using Kappa test*

	MET PROTOCOL CRITERIA	
RECEIVED TH	YES	NO
YES	185 of 206 (89.8%)	21 of 206 (10.2%)
NO	43 of 279 (15.4%)	236 of 279 (84.6%)

Discussion

This study reviewed the application of TH at CMJAH. It is encouraging that the majority of neonates receiving TH (89.8%) met the TH protocol criteria and were cooled appropriately. Fifteen percent of neonates who met the protocol criteria for TH did not receive it. The reason for this was primarily a lack of equipment.

In our study, the five minute Apgar score was used as a marker of potential asphyxia. This is highly controversial and potentially problematic. A paper published by the American Academy of paediatrics in 2014, defined a 5 minute Apgar score of four to six as moderately abnormal. An Apgar score of zero to three was interpreted as low, and a possible non-specific marker of illness or encephalopathy. However, the committee on Obstetric practice have highlighted that Apgar score is on its own, in the absence of biochemical or clinical evidence, not a predictor of intrapartum compromise, and that its inappropriate use in this regard has led to an erroneous definition of asphyxia.[10] In our setting however, it was evident that the Apgar score is the one constant assessment that almost all neonates receive. As was shown in this study, many neonates, even those with suspected of definite asphyxia, are not allocated an HIE or Thompson score; and many more do not have a blood gas sample taken within one hour of birth.

Although not explicitly stated in the neonatal protocol, 73 of the 279 patients (26.1%) did not receive TH as they were assessed as being too severely asphyxiated. In LMICs, it is fairly common practice to exclude these neonates from TH, as the benefits of TH have previously not been shown to outweigh the risks.[5] Original trials suggested that the largest benefit of TH was seen in neonates with moderate encephalopathy[11]. More recent data has shown that around one-quarter of neonates with asystole ten minutes after birth, who receive TH, have normal outcomes.[12] In the current study, HIE grade emerged a significant predictor of whether patients received TH or not. For multiple reasons, scoring systems such as the Thompson's and Sarnat scores, have shown to be variable, unreliable predictors of neurological outcomes.[13] Amplitude EEG has shown more promise as a predictive tool, with a positive predictive value of more than 80%.[13] However, due to equipment shortages, only 18 patients in this cohort had amplitude EEG tracing. In view of the above, the TH protocol at CMJAH should be reviewed. A more pragmatic approach would be to provide TH to all neonates with moderate to severe encephalopathy in an ICU setting, provided a bed is available. The neonate's response to TH and clinical condition can then be reviewed after 48 to 72 hours. Management can then be individualized. Withdrawal of care may be appropriate in severely affected neonates with a poor response to therapy. Studies on more definitive prognostication tools are warranted.[12]

Seven percent of neonates in the study group did not receive TH as they arrived at the hospital after the six hour timeframe; considered to the optimal time period for neuroprotection.[7] Numerous studies have shown some benefit to initiating TH after six hours. The TOBY Trial reported limited neuroprotection when TH was started as late as 12 hours after the insult.[11] However, the time of initiating TH is one of the questions still under evaluation at present.[12] In a retrospective review of neonates referred to a regional tertiary centre in Canada, 44% of the patients had TH initiated after six hours of age, with preceding passive TH.[14] Due to resource constraints, CMJAH does not routinely offer TH to Neonates who present more than six hours after birth. Fairchild et al showed in a review done in Canada, that initiating

hypothermia prior to referral resulted in significant time saving, and thus improved outcomes [11]. However, excessive hypothermia (rectal temperature below 32°C) was demonstrated in about one third of these patients. [15,16].For this reason, it may be feasible to educate and train referring units on when and how to initiate therapeutic hypothermia. This could be executed both passively and actively; by switching off radiant warmers during the initial resuscitation and assessment, and then by the application of icepacks with rigorous temperature monitoring for the duration of transport[17]. More studies need to be carried out in this regard, as clinical protocols and devices for TH in transport would need to be developed to ensure safety and efficacy .The implementation of this process would also only be effective if transport systems were optimized, which may be difficult in an already overloaded healthcare system.

Forty six patients in the present study were preterm neonates, weighing less than 2000g and thus did not receive TH. The VON encephalopathy registry recently reported that 2.4% of neonates undergoing hypothermia had a gestational age <36 weeks.[18] The potential benefit of TH as a neuroprotective strategy in preterm neonates has been hypothesized in several trials. Concerns regarding thermoregulatory dysfunction and its deleterious effects warrant further studies with meticulous monitoring and evaluation of long term outcomes.[18]

For multiple reasons, safety data on therapeutic hypothermia from developed countries cannot be readily extrapolated to the neonatal units in resource limited settings like the study unit. The benefits of TH may only be apparent with proper equipment, close monitoring and supportive management, including ventilatory support. Twenty six of the patients in the cohort had no TH machine available to them, as the neonatal unit only had three TH machines. Rossouw et al showed that therapeutic hypothermia can be achieved by low technology methods such as gel packs, ice and water bottles provided patients were managed in an ICU setting with mechanical ventilation available to them.[6] Low technology, manual TH methods tend to have a higher temperature variability and lower effective TH time and need to be monitored and changed stringently. Thus, it would be difficult to employ the effective use of these methods in settings like CMJAH, where resource constraints dictate a nurse to patient ratio of 1:8 or more. Current practice at CMJAH is that TH is administered in High Care. This is an inadequate setting for the ill, asphyxiated neonate undergoing therapeutic hypothermia, especially because albeit fairly benign, TH is known to have adverse effects such as sinus bradycardia, thrombocytopaenia and subcutaneous fat necrosis.[16] Failure to provide mechanical ventilation to neonates undergoing TH may contribute to worse outcomes.

The present study suggests that many neonates are receiving TH appropriately, and in accordance with the unit protocol in place. There are still many asphyxiated neonates who qualify, but don't receive TH, primarily due to resource limitations. It is inappropriate that 21 patients received TH without meeting criteria, but difficult to assess this further in the absence of more information. Future protocol amendments may be necessary in order to maximise the number of neonates who may benefit from this treatment.

Study limitations

As this was a retrospective study, all information was accessed from the existing neonatal database, which is updated by clinical staff at the hospital. There were instances were data was incompletely or inaccurately captured. Apgar scores and HIE Classifications are often assigned both retrospectively and subjectively by midwives and admitting doctors. The age of infants at admission is captured in days, and not hours, which makes it difficult to ascertain if they were admitted within the 6 hour timeframe. This may result in further inaccuracies, and may bias results obtained. This study also does not focus on the complications reported as a result of TH, and the outcomes thereof. This needs to be evaluated in subsequent trials.

Conclusion

The introduction of therapeutic hypothermia, as well as a protocol governing its use has revolutionized both the care and outcomes of patients with perinatal asphyxia at CMJAH. The majority of babies who are receiving TH at CMJAH are meeting the eligibility criteria set out by the unit protocol. However, the fact that a significant number of neonates who qualify are not receiving this treatment shows that more resources are needed, not only to optimize the number of patients that can benefit from this treatment modality, but also in terms of imaging and support strategies.

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Appendix 1: Research Protocol

THE USE OF THERAPEUTIC HYPOTHERMIA IN NEONATES WITH PERINATAL ASPHYXIA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL:

A retrospective review

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Abbreviations

HIE: Hypoxic Ischaemic Encephalopathy

PA: Perinatal Asphyxia

TH: Therapeutic Hypothermia

VON: Vermont Oxford Network

PBPs: Potentially Better Practices

IH: Induced Hypothermia

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

LMICS: Low and Middle Income Countries

Background

Epidemiology

Perinatal asphyxia (PA) is a significant and common cause of death and severe neurological impairment in developing countries. Hospital based studies suggest an incidence of 5-10/1000 live births, with a 10-60% mortality, and 25% of survivors developing long-term neurological sequelae.[1,7] A recent study done at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) showed an incidence of 5-6 cases of PA with a live birth rate of approximately 1300 per month. Although the in-hospital mortality was relatively low at 13%, the bulk of the burden is anticipated to be in those survivors with significant handicap.[5] Perinatal Asphyxia is a condition of suffocation and impaired gaseous exchange in the, post, or perinatal periods, and results in primary energy failure, free radical accumulation, and

subsequent neuronal cell death.[7, 9] There are numerous causes for PA occurring in-utero, during labour and delivery, or in the immediate neonatal period. These include foetal distress, cephalopelvic disproportionality, meconium aspiration, malpresentation, and birth trauma. [5]

Diagnosis

Several post-natal features are used to determine the severity of the asphyxia. The essential parameters include an umbilical cord sample done less than 1 hour after birth showing a metabolic or mixed acidaemia (pH less than 7), with a base deficit of 16 or more; persistence of an Apgar score less than 5 at 10 minutes; evidence of encephalopathy, varying from hypertonia and seizures, to coma; as well as evidence of multi-organ dysfunction in the immediate neonatal period. The use of more sensitive criteria, such as amplitude-integrated encephalogram patterns, is restricted by resource limitations in our setting.[2, 5]

Pathophysiology

Under normal circumstances, the delivery process is a uniquely stressful time for the neonate. Some element of asphyxia is expected after delivery, as reflected in the early blood gas analysis; but a prolonged or complicated delivery can worsen this asphyxia. Multiple pathophysiological responses occur as a result of the asphyxial insult; as illustrated in figure 1, below. Primary energy failure occurs secondary to severe hypoxia and hypercapnia [15]. Circulatory and non-circulatory adaptive mechanisms exist that allow the neonatal brain to preserve vital function. With prolonged insult, these mechanisms fail, resulting in hypoxic ischaemic injury, and subsequent cell death as a result of necrosis and apoptosis.[18]

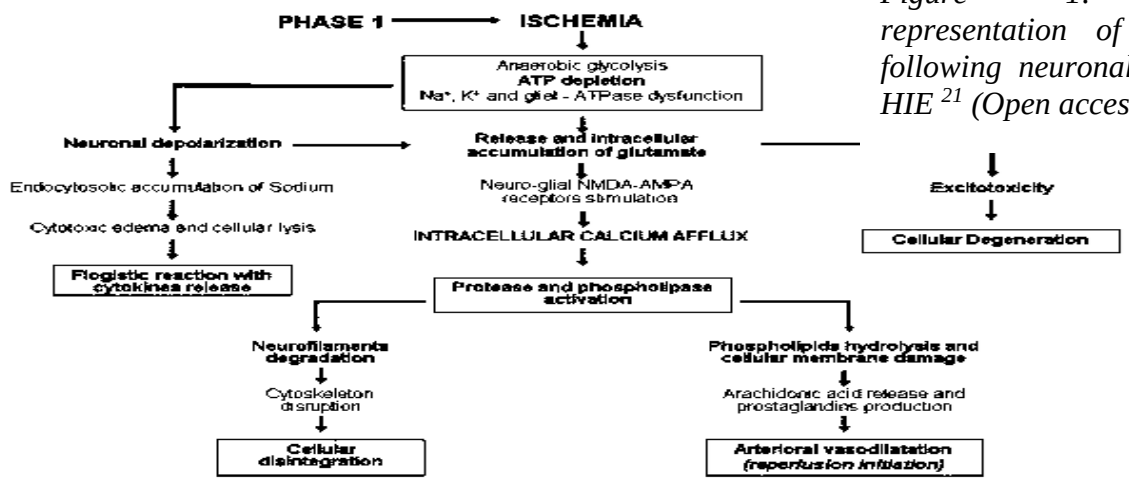


Figure 1: Schematic representation of the cascade following neuronal ischaemia in HIE [21] (Open access)

Prognosis

Perinatal asphyxia is an important cause of later neurodevelopmental impairment. The prognosis varies according to the severity of the asphyxia event and long term sequelae are monitored to better document outcomes. Traditionally, research and follow up have focused on early neurodevelopmental consequences. In addition, the effects of PA have often been treated as an “all or nothing” phenomenon with little or no mention of those cases that show only mild symptoms in later life. The classification of Sarnat and Sarnat (figure 2) has been used to grade neonatal encephalopathy. This classification combines both clinical signs such as irritability, lethargy of hypertonia, with Amplitude EEG findings, and the scores are used to predict neurodevelopmental outcomes. In general, very few children with mild encephalopathy (Sarnat 1) show neurological deficit, or have developed severe cognitive

problems at preschool age. In contrast, children classified as severe encephalopathy (Sarnat 3) nearly always die, or develop severe impairments such as Cerebral Palsy, Mental Retardation, Epilepsy, Sensorineural Hearing loss or cortical visual impairment.[16] The Thomson score (figure 3) is another scoring system that is commonly used to predict neurodevelopmental outcome using clinical characteristics such as tone, level of consciousness and respiratory effort and its improvement or deterioration over a set period of time.

Sarnat staging of hypoxic-ischemic encephalopathy.

	Grade 1 (mild)	Grade2 (moderate)	Grade 3 (severe)
Level of consciousness	Irritable/hyperalert	Lethargy	Coma
Muscle tone	Normal or hypertonia	Hypotonia	Flaccid
Tendon reflexes	Increased	Increased	Depressed or absent
Seizures	Absent	Frequent	Frequent
Complex reflexes	Normal	weak	Absent
Prognosis	Good (100%) Normal	Variable (80%) Normal	High mortality and neurological disability (50% Death 50% major sequelae)

12/23/2013 81

Figure 2: Sarnat & Sarnat staging [22] (OPEN ACCESS [25])

Thompson Score

Sign	0	1	2	3
Tone	normal	hyper	hypo	flaccid
LOC	normal	hyperalert, stare	lethargic	comatouse
Fits	none	< 3 per day	> 2 per day	
Posture	normal	fisting, cylcing	strong distal flexion	decerebrate
Moro	normal	partial	absent	
Grasp	normal	poor	absent	
Suck	normal	poor	absent ± bites	
Respir	normal	hyperventilation	brief apnea	IPPV (apnea)
Fontanell	normal	full, not tense	tense	

Figure 3. The Thomson score[23] (OPEN ACCESS [24])

Cerebral palsy

The most common type of CP seen in our setting is Spastic Quadriplegia, followed by spastic Diplegia, and dyskinetic and Mixed CP. This trend is similar to that seen in most developing countries [17]. Spastic Quadriplegia is more commonly seen following severe and total insult, where MRI abnormalities are present in the deep grey nuclei and perirolandic cortex [15]. A study done in Tygerberg showed perinatal asphyxia as the cause of Cerebral Palsy in 45% of cases [17]. A higher occurrence of spastic diplegia was found in developed countries. This may be attributed to the higher rates of survival of extremely premature infants.

Management over the ages

Until recently, treatment modalities for PA have been mainly supportive and the lack of a definitive therapeutic approach remains clinically frustrating. Despite the advancement of diagnostic and life-support techniques, the prognosis for infants who suffer a severe asphyxia insult is still poor. Because the primary aetiologies differ, therapeutic modalities used in adults and older children have not proven beneficial in neonates. Clinical interest in potential benefits of induced hypothermia first began in the 1950s, where it was noted that infants who had been abandoned and exposed to cold often remained viable for prolonged periods. Early clinical trials were, however, abandoned secondary to the side effects, uncertain benefit, and management problems associated with induced hypothermia [6]. With time, the pathogenesis of neuronal injury has become better understood and defined, allowing for the development of a specific technique for applying induced hypothermia.

Therapeutic hypothermia

Hypothermia is defined as a core body temperature, below 35°, where normal metabolic, muscular and cerebral functions are impaired. Studies have shown that neural damage following an asphyxial insult is delayed for several hours, and that treatment with prolonged moderate hypothermia reduces cerebral injury and improves neurological outcome.[2] Possible mechanisms of action of hypothermia include reduced neuronal metabolic demand, reduced cytotoxin accumulation and prevention of apoptosis during secondary energy failure, as discussed previously. Historically, its use was limited by the resultant global physiological disturbances, particularly to the cardiovascular, respiratory and metabolic systems. Cold injury syndrome, a potential complication of therapeutic hypothermia, can result in pulmonary haemorrhage, renal failure, Disseminated Intravascular Coagulopathy, hypovolaemia, glucose instability and pulmonary hypertension.[3] However, advents in modern medicine have improved the early identification, and therefore adequate management of these adverse effects.

The efficacy of induced hypothermia to treat Hypoxic Ischaemic Encephalopathy in term infants has been evaluated in multiple trials. A Cochrane review, comparing different outcomes of normothermia vs. induced hypothermia in 8 different randomised controlled trials, comprising 638 term infants, done in Australia, showed evidence of the benefit of cooling on survival and neurodevelopment.[8] Another review, comprising 25 studies, all done in Britain and the U.S., showed only 1 study, containing 208 infants, with good evidence that hypothermia significantly reduced mortality and neurodevelopmental disability in infants with perinatal asphyxia.[1]

The CoolCap trial was the first international multicentre trial, and demonstrated a significant neuroprotective effect of therapeutic head- cooling.[10] The TOBY Trial also showed benefit to whole body cooling, with a significant improvement in neurological outcomes.[11.] Given the number of clinical trials that have been done, it has become important to establish a standardized treatment protocol for inducing hypothermia.

Improving the quality of therapeutic hypothermia

The Vermont Oxford Network Collaborative originated as a pilot project in 1995, with the primary objective of providing consistency of medical care and optimizing outcomes in perinatal asphyxia, by developing Potentially Better Practices (PBPs). These include 1) Timely identification of neonates with neonatal encephalopathy, with the aim of a standardized neurological exam, preferably in the form a checklist, to be performed on all infants at risk for encephalopathy before 4 hours of age. 2) A coordinated referral system ensuring that those neonates who qualify for therapeutic hypothermia (TH), receive it within 6 hours of birth. This could be achieved by educating referring healthcare teams about sentinel peripartum events that may lead to encephalopathy, eligibility criteria for TH, as well as pre-referral management of these infants. 3) There must be implementation of a standard, evidence-based protocol for the provision of TH and a standard of monitoring care, with adequate education of staff. Training should be provided to staff, with training workshops and step-by-step instructions for setting up the equipment. Due to potential infrequent use, neonatologists, neurologist, radiologists, nurses and allied workers should together compile a simple and readily available protocol. They are to hold periodic meetings with the aim of reviewing and updating the protocol.

4.) Standard practice of MRI on encephalopathic patients without sedation in the first 10 days of life, as it is the most accurate imaging modality in the evaluation of severity and pattern of brain injury in encephalopathy. 5) Amplitude-integrated EEG evaluation as part of the TH protocol, for its well established role in assessing cerebral function, detecting seizures and predicting neurological outcome. The duration of EEG monitoring to vary from 1 hour to continuous monitoring, depending of the severity of encephalopathy. 6) A standardized system of neurodevelopmental follow-up and the enrolment of all treated infants in a national registry.[11]

Current recommendations are that TH should only be used as per protocol, i.e. Implemented within 6 hours of birth, cooled to between 32 and 34 degrees Celsius for 72 hours and then gradually rewarmed. In LMICS, neonates are most often resuscitated by junior staff; there are inadequate resources (cooling machines and ventilators) and insufficient nursing staff. It is therefore difficult to implement cooling strictly as per protocol. In addition, some suitable candidates may not be cooled due to lack of suitable equipment. Although Horn et al have shown that ice packs can successfully cool a neonate, this procedure was conducted in a NICU with a dedicated ICU nurse.[19] This would not be feasible in a high care ward with a nurse to patient ratio of 1:8 or more.

Obstacles in the developing world.

Theoretically, the strategies proposed by the VON collaborative will go a long way in optimizing outcomes and developing an improved management standard. However, there are many potential challenges in achieving this, particularly in LMICS.

Few clinical trials have been done in developing countries to demonstrate the efficacy of induced hypothermia in settings with resource restrictions. Pauliah et al have recently published a meta-analysis which has shown significant differences both in the pathophysiology and outcomes of neonatal encephalopathy in developing countries including Uganda, South Africa and India [20.] These include a longer time from brain injury to cooling, due to more incidents of obstructed labour and babies born before arrival at the hospital. Many babies with severe encephalopathy require ventilation, which is not always readily available. NICU capacity is limited in developing countries, and this almost certainly affects decision making, e.g. an otherwise well premature baby with respiratory compromise vs a patient with HIE III.

The paper thus hypothesized that mortality rates could actually be higher in patients that were cooled. This was however, based on outcomes found in centres with very limited resources, that relied on low technology devices such as frozen gel packs, servo controlled fans and water bottles to carry out the actual cooling.

Issues raised included an inconsistency in management protocols, resulting in patients with severe encephalopathy being given ‘the benefit of the doubt’, potentially resulting in higher mortality rates; not because of the induced hypothermia, but rather, because the clinical condition of the patient is severe from the onset. This highlights the need for the implementation of Potentially Better Practices, as discussed earlier. Albeit not without challenges, this may greatly improve both execution and outcomes.

Due to resource limitations, there are strict limitations and criteria that need to be fulfilled, as documented in the neonatal protocol. Patients need to be of a gestational age greater than 34 weeks, or a weight greater than 1.8kg. There must be a documented Apgar score ≤5 at 10 min or continued need for resuscitation for more than 10 minutes. Arterial blood gas within 60 minutes of life must show a metabolic acidosis with a pH less than 7.00 or base deficit ≥16. There needs to be an initial Thomson score more than 7; as well as signs of encephalopathy. Preterm infants, and infants weighing less than 2kg are not considered for IH. The same rules apply to infants with no spontaneous respiratory effort after 30 minutes post- resuscitation or those who arrive at the hospital more than 6 hours after birth.

Infants with severe congenital malformations, especially those involving brain dysgenesis, or those which are deemed incompatible with life, are also not considered. At present, there is one Criticool, whole body cooling machine available and in use. The protocol that is currently in use at CMJAH closely resembles international standards. Amplitude EEG is, however, for the moment not done as electrode leads are not available. MRI is also not routinely done on all patients with suspected neonatal encephalopathy. Most patients do however, get at least one Cranial Ultrasound for the duration of their stay.

The aim of this study is to review the practice of therapeutic hypothermia at CMJAH in order to determine how properly the protocol is implemented. The study will investigate selection criteria that are actually adopted, and the limitations to ideal practice (PBPs) experienced in our setting. This will be done as a retrospective review, with the objective of identifying potential areas of improvement, and better understanding perinatal asphyxia in the developing world. The information obtained will be used to inform future protocols for therapeutic hypothermia at CMJAH, individualised to the unique clinical characteristic experienced in our setting.

Aims and objectives

1. To determine the characteristics of neonates cooled at CMJAH, including demographics and clinical characteristics, site and method of cooling, mechanical ventilation, use of aEEG and MRI, and survival to discharge
2. To determine whether the cooling protocol was correctly implemented with regard to timing, grade of HIE, Thomson Score and initial blood gas
3. To determine the number of suitable neonates not cooled and the reasons for this

Methods

Study design

This is a retrospective, descriptive study. The study population will be all neonates with a birth weight greater than 1500g admitted to the CMJAH neonatal unit from 1 January 2013 to 30 June 2017. The CMJAH Neonatal database (REDCap) will be used to obtain information including maternal, obstetric and neonatal parameters and interventions. REDCap is online based data bank where clinical data is collected and recorded by the department on an ongoing basis. This allows reliable and easy access to clinical information and statistics. REDCap allows for capturing of data of all patients admitted into the neonatal unit.

Various aspects of the patient's clinical stay, initial presentation, mode of delivery, vital data, biochemical parameters of birth, treatment received and outcome are documented.

This information will be accessed and arranged in such a way that it will clarify the current practice in the diagnosis and management of these patients, how many receive cooling and limiting factors to optimal management. In addition, patient records will be retrieved and reviewed to capture data not routinely included in the database.

Subjects

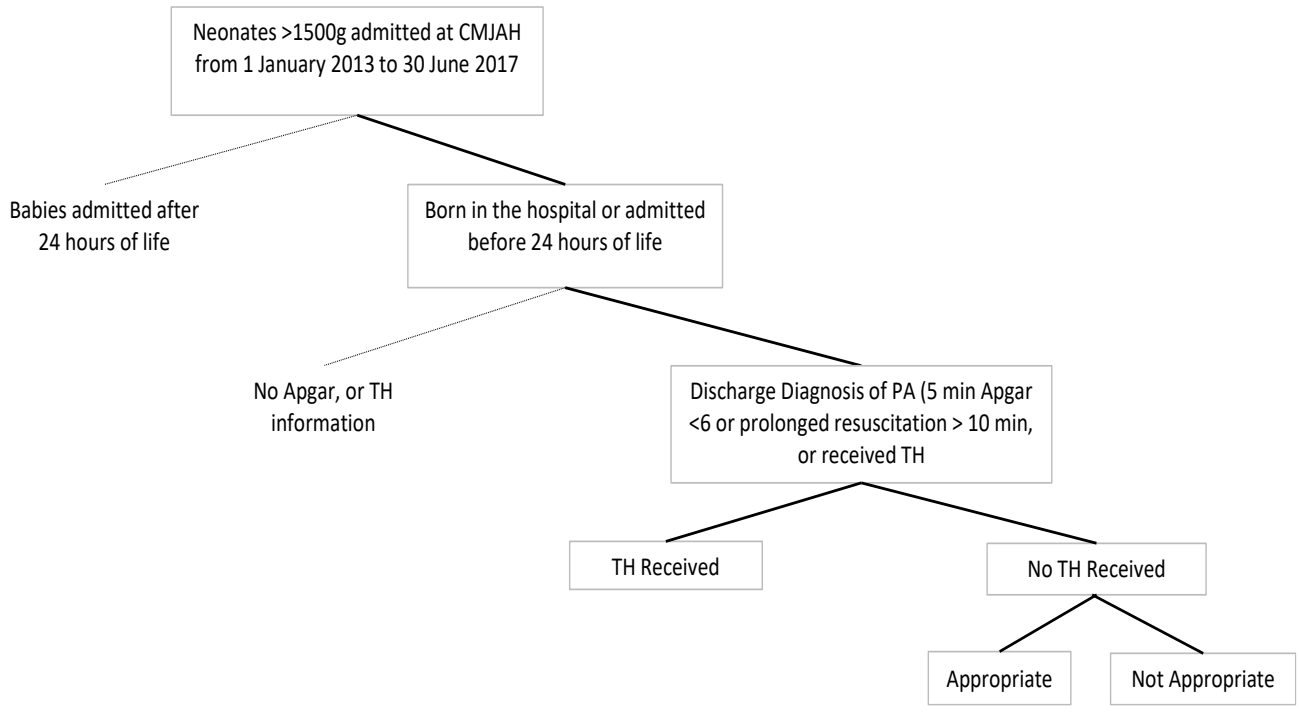
Inclusion criteria

- All neonates with a discharge diagnosis of PA ; neonates that received Therapeutic hypothermia, and neonates with a 5 minute Apgar less than 6, or need for resuscitation for longer than 10 minutes, admitted to the CMJAH neonatal unit within 24 hours of birth. This will include babies born outside the hospital and transferred in, and babies born before arrival at the hospital.

Exclusion criteria

- Those patients with inadequate or incomplete cooling information
- Neonates with major or severe congenital abnormalities

Figure 4. *Algorithmic representation of study population*



Data collection

All variables measured will be accessed using the CMJAH Neonatal Unit database (REDCap) and hospital records. The data sheet will capture demographic information, adverse birth history, Initial APGARs, biochemical parameters and treatment interventions.

Data Analysis

Data collected will be entered into a Microsoft excel spreadsheet and basic statistical analysis will be performed using IBM SPSS Version 23. Appropriate descriptive statistical analysis using percentages and means or medians will be used. Continuous data will be presented as medians with first and third interquartile (Q1 to Q3) or means with standard deviations, depending on the distribution, and categorical data will be presented as percentages. All statistical assessments will be considered significant for a p-value below 0.05.

Limitations

The study is a retrospective study and therefore study data will be collected from an existing database. In case of unavailable data, participants will still be included in order to attain a true representation

Timeline

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
LITERATURE REVIEW												
PREPARING PROTOCOL												
PROTOCOL ASESSMENT												
ETHICS APPROVAL												
DATA COLLECTION												
DATA ANALYSIS												
WRITE-UP												

Funding

The researcher, will be responsible for all the funding of this dissertation, which includes mainly the use of stationary and printing, at a cost of approximately R650.

Ethical considerations

As this is a retrospective study, no informed consent from the study participants' parents can be obtained. However, confidentiality will be maintained, as all recorded data will remain anonymous. No names, hospital or ID numbers, or any other data that would lead to patient identification will be captured. There will be no additional study investigations, inconvenience or risk is involved for the participants. Permission has been granted by the CEO of CMJAH to conduct this research and the Human Research Ethics Committee of the University of the Witwatersrand has approved the ethics application, Clearance no. M170549.

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Appendix 2: Data Sheet

Data Sheet

Study no.	GA	AGA/ SGA/ LGA	Birth weight	Sentinel event	Apgars	Resus at birth	ABG		HIE Grade	Initial Thomson's Score	Ventilation			Criteria met Y/N	Cooled Y/N	Appropriately cooled Y/N	Time to cooling	Site of cooling	Reason for not cooling	MRI/aEEG	Cranial U/s finding	Outcomes
							pH	**BE**			**CPAP**	**CMV**	**HFOV**									

Appendix 3: Ethics Clearance Certificate

R14/49 Dr KN Sebetseba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170549

NAME: (Principal Investigator)	Dr KN Sebetseba
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The use of therapeutic hypothermia in neonates with perinatal asphyxia at Charlotte Maxege Johannesburg Academic Hospital: a retrospective review
DATE CONSIDERED:	26/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	Change of project title approved 15/08/2017
SUPERVISOR:	Professor D Ballot
APPROVED BY:	Professor CB Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/05/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **May** and will therefore be due in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 4: Acceptance letter for publication

Decision Letter (THER-2017-0040)

From: ddietrich@miami.edu

To: drsebetseba@gmail.com

CC: hbramlett@miami.edu

Subject: Therapeutic Hypothermia and Temperature Management - Decision on Manuscript ID THER-2017-0040

Body: 12-Oct-2017

Dear Dr. Sebetseba:

It is a pleasure to accept your manuscript entitled "THE USE OF THERAPEUTIC HYPOTHERMIA IN NEONATES WITH PERINATAL ASPHYXIA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL:
A Retrospective Review" in its current form for publication in Therapeutic Hypothermia and Temperature Management.

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Thank you for your fine contribution. On behalf of the Editors of Therapeutic Hypothermia and Temperature Management, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. W. Dietrich
Editor-in-Chief, Therapeutic Hypothermia and Temperature Management
ddietrich@miami.edu

Date Sent: 12-Oct-2017

Appendix 5: Plagiarism (TURNITIN Report)