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Therapeutic Hypothermia with Phase-Changing Material in Neonates with Hypoxic-Ischemic Encephalopathy at a Tertiary Care Hospital

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Abstract: ***Phase-changing material is an alternative, effective and low-cost method of cooling babies sufficient to achieve and maintain the target rectal temperature with fewer adverse effects. The present study was done in a Tertiary care center to assess short-term neurological outcomes in neonates with HIE undergoing therapeutic hypothermia using the HINE score. In the present study, A total of 24 newborns were examined at discharge out of which 5 had abnormal HINE scores. At 1 month of age, 23 infants came for follow-up, of which 5 had abnormal HNNE scores, and 18 had normal scores whereas 1 infant was lost to follow-up. At 2 months of age, 22 infants came for follow-up, of which 4 had abnormal scores, and 18 had normal scores, 2 infants lost to follow-up. At 3 months of age, 22 infants came for follow-up of which 3 had abnormal HINE scores and19 had normal scores, 2 infants lost to follow-up. At 6 months of age, 18 infants came for follow-up of which one infant had abnormal HINE scores, 17 had normal scores, and 6 infants lost to follow-up at this visit. At 9 months of age, 18 infants came for follow-up all of them had normal HINE scores, and 7 infants lost to follow-up at this visit. At 12 months of age, 15 infants came for follow-up all of them had normal HINE scores, and 7 infants were lost to follow-up. A total of 5 babies who had abnormal HINE scores initially were found to be normal in the subsequent visits. To conclude, HINE sequential examination showed better neurological outcomes in asphyxiated newborns who underwent therapeutic hypothermia.***

Keywords: HIE, HINE, hypothermia, neonates, rewarming protocol

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) remains one of the leading causes of neonatal mortality and long-term disability worldwide with an incidence of 3-5 out of 1000 livebirths[1-3.] Asphyxia accounts for 45% of all intrauterine deaths and is the primary cause of neonatal mortality; accounting for 28.8% of all deaths.4 Morbidity associated with perinatal asphyxia includes motor disabilities, learning disabilities, visual & hearing impairments, behaviour abnormalities, and motor & cognitive disabilities.

Several neurological assessments are used as clinical tools to monitor developmental outcomes in infants at risk of developing neurodevelopment disabilities. In multiple studies, Hammer Smith Infant Neurological Examination (HINE) was proven to be a comprehensive and superior tool for the early diagnosis of neurological impairment in both low & high-risk infants. The present study aims to observe HIE neonates' neurological outcomes treated with hypothermia using the HINE score and possible complications during this process.

Aim

To monitor adverse events & assess short-term neurological outcomes in asphyxiated babies undergoing therapeutic hypothermia using Phase contrast material.

Primary Objective:

To assess short-term neurological outcomes in neonates with HIE undergoing therapeutic hypothermia using the HINE score.

Secondary Objective:

To monitor adverse events and possible complications that could occur secondary to therapeutic hypothermia.

1) Skin changes.
2) Thrombocytopenia.
3) Life-threatening coagulopathy.
4) Hypotension.
5) Cardiac arrhythmias.
6) Hepatic & Renal failure.
7) Persistent hypoxemia.
8) Electrolyte disturbances.
9) Sepsis.
10) Death.

2. Results

The study was done in the NICU & high-risk newborn clinics of NRI Hospital, chinakakani, mangalagiri for 2 years. Twenty-four newborn infants were recruited into the study (21 inborn and 3 out born) after informed consent was obtained from the parents in the investigator's presence. The

babies were admitted to the NICU and started cooling as per the protocol mentioned above.

Maternal Demographics

Table 1: Percentage of parity

Gravida	Frequency	Percentage
Primi	17	58.3
Multi	7	29.2
Total	24	100

Table 2: Antenatal Complications of pregnancy

Gestational Diabetes Mellitus	3 (12.5%)
Pregnancy Induced Hypertension	3 (12.5%)
None	18 (75%)

Table 3: Peripartum Complications

Fetal heart rate decelerations	7 (29%)
Heemorrage	2 (8%)
Meconium stained amniotic fluid	6 (25%)
Details incomplete	9 (38%)

Neonatal Demographics

Table 4: Gender

Gender	Inborn	Outborn	Total
Male	12 (50%)	2 (8.3%)	14
Female	9 (37.5%)	1 (4.2%)	10
Total	21	3	24

Table 5: Trend of variation in mean Heart rate and MAP

	0HRS	12HRS	24HRS	36HRS	48HRS	60HRS	72HRS	80HRS
HR	137.46±4.4	122.71±4.65	124.17±3.51	123.54±3.81	121.25±4.87	122.5±5.67	120.54±4.28	134.29±5.35
MAP	56.8±2. 24	50.3±8. 96	53±7.6	53.45±5.28	54.62±4.56	54.54±3.48	56.12±3.72	58.75±3.12

Table 6: Trend of Mean Oxygen Saturation during WBC

	0HRS	12HRS	24HRS	36HRS	48HRS	60HRS	72HRS	80hrs
Spo2	97.75±1.48	97.96±1.37	97.79± 1.56	97.63± 1.47	98.21± 1.35	98.08±1.32	98.21±1.35	98.79±1.22

Table 7: Metabolic Parameter Trend Over 72 Hours

	Baseline	24HRS	48HRS	72HRS
S. Sodium (mEq/L)	134.67±2.78	133.83±3.09	134.67±2.33	135.92±3.67
S. Potassium (meq/l)	4.49±0.26	4.12±0.42	4.18±0.52	4.11±0.29
S. Urea (mg/dl)	20.75±4.1	28.37±7.19	23.21±7.47	19.83±6.94
S. Creatinine (mg/dl)	1.16±0.11	0.82±0.29	0.66±0.11	0.54±0.12
Blood Glucose (mg/dl)	103±23	139±58	114±39	80±19

Table 8: Hematology Trend Over 72 Hrs

	Baseline	24 Hrs	48 Hrs	72 Hrs
Total leucocyte count (cumm)	22793±4523	15644±4273	13086±3656	11489±3586
Neutrophils (%)	69±8	85±6	76±5	67±2
Platelet Count (Lacs)	2.08±0.36	1.62±0.40	1.35±0.38	1.36±0.41
PT (SEC)	21.79±6.44	27.45±8.37	--	17.20±9.45
PTT (SEC)	55.5±15.07	50.33±14.59	--	33.54±15.80
INR	1.44±0.35	1.84±0.10	--	1.16±0.40

Table 9: Serious adverse events during WBC

Adverse Events	NO (%)
Cardiac arrhythmias	nil
Hypoglycemia*	3 (12.5)
Hyperglycemia requiring insulin**	2 (8.3)
Thrombocytopenia#	5 (20.8)
Bleeding$	1 (4.1)
Skin changes	4 (16.6)
oliguria[at]	Nil
Hepatic dysfunction+	1 (4.1)
Death	none

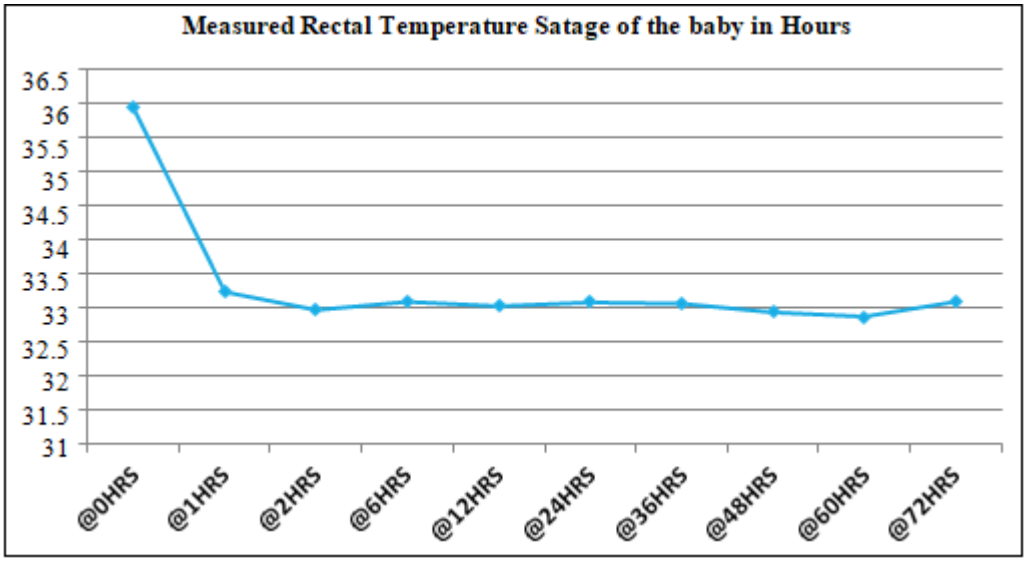

Figure 1: Rectal Temperature Vs hours of cooling

Hammer Smith Infant Neurological Examination:
All the babies who underwent therapeutic hypothermia were discharged after stabilization and performing Hammer smith's neurological examination. Subsequent neurological assessment was done at high-risk newborn clinics by two independent examiners with a minimum of 2 years experience in newborn assessment along with objective scoring with Hammersmith infant neurological exam.

Table 10: Normal and abnormal HINE groups followup

No. of Infants (N=24)	1 month	2 months	3 months	6 months	9 months	12 months (N=21)
Normal group on Follow up	18	18	19	17	18	15
Normal group who lost to follow up	1	2	2	6	7	7
Abnormal group	5	4	3	1	0	0
Abnormal group who lost to follow up	none	none	none	none	none	none
Abnormal group improved to normal		1	2	4	5	

A total of 24 newborns were examined at discharge out of which 5 had abnormal HNNE scores. At 1 month of age, 23 infants came for follow-up, of which 5 had abnormal HNNE scores, and 18 had normal scores whereas 1 infant was lost to follow-up. At 2 months of age, 22 infants came for follow-up, of which 4 had abnormal scores, and 18 had normal scores, 2 infants lost to follow-up. At 3 months of age, 22 infants came for follow-up of which 3 had abnormal HINE scores and 19 had normal scores, 2 infants lost to follow-up. At 6 months of age, 18 infants came for follow-up of which one infant had abnormal HINE scores, 17 had normal scores, and 6 infants lost to follow-up at this visit. At 9 months of age, 18 infants came for follow-up all of them had normal HINE scores, and 7 infants lost to follow-up at this visit. At 12 months of age, 15 infants came for follow-up all of them had normal HINE scores, and 7infantswere lost to follow-up. A total of 5 babies who had abnormal HINE scores initially were found to be normal in the subsequent visits.

3. Discussion

Hypothermia is a proven neuroprotective strategy in newborns. Many studies have shown the benefits of whole-body cooling in reducing mortality and long-termmorbidity[5, 6]. This study demonstrated hypothermia benefits, particularly in reducing neurological morbidity in asphyxiated babies and monitoring any adverse events and complications in our setting. The sample size obtained was 24 for 15 months, and follow-up was done in these infants for up to 1 year period. The analysis of data was done on the IBMSPSS 21 Version. Mean, median, mode, standard deviation, frequency, Pearson's coefficient, student t-test, and the Mann-Whitney U test were used.

Inclusion Criteria:
This study included infants with evidence of encephalopathy based on the modified Sarn at staging. Twenty-four new born infants were recruited into the trial over 15 months after fulfilling the inclusion criteria. Most other studies on hypothermia for perinatal asphyxia included babies with similar clinical profiles asours.[5-8] A control group was not included in the study as the intervention's efficacy had already been proven in randomized control trials. It is unethical to deny cooling to any infant. Mira cradle with phase-changing materials was used in our unit to achieve target cooling temperatures, and the rectal temperatures were monitored closely. Vitals were monitored closely & continuously using multi-parameter monitors. The target temperature in this trial was a rectal temperature of 33±0.5°C. The temperature range used in this trial is termed moderate hypothermia. The duration of hypothermia was 72 hours in our study as it was in all other trials mentioned in the table.

Table 11: Important Characteristics of Other Trials Till Date

Study	Method of cooling	Target temperature	Rewarming protocol	Duration of cooling
Akisu 2003[9]	Servo controlled Cooling Cap	Rectal temp: 36-36.5°C		72 hrs
Eicher 2005[10, 11]	Iceto head and body for 2 hours and servo-controlled cooling blanket	Rectal temp: 32.5-33.5°C	0.5°C/hour	48 hrs
Gluckman2005[12]	Servo controlled Cooling Cap	Rectal temp: 34-35°C	0.5°C/hour	72 hrs
Gunn1998[13]	Cooling cap	Groups with rectal temp in (i) 36-36.5°C (ii) 35.5-35.9°C (iii) 34.5-35.4°C		72hrs
ICE2011[14, 15]	Hot/Cold Gelpacks	Rectal temp: 33.5-34.5°C	0.5°C/2hours	72 hrs
Shankaran 2002[16]	Servo controlled cooling blanket	Oesophageal temp: 34.5°C	0.5°C/hour	72 hrs
Linn 2006[8]	Cooling cap	Rectal temp: 34-35°C	Rewarm Spontaneously.	72 hrs
Thayyil 2010[17]	Phase Changing material	33.5±0.5°C	0.24°C/hr	72 hours

In our study 17 (70.8%) babies achieved target rectal temperature within 1hour of initiation of cooling. All 24 babies reached the target rectal temperature within 2hours of initiation of cooling. Many studies did not give data on how long it took to cool the infants to the target temperature. The available data suggests that an upper limit of 90 minutes is more feasible. Using this criterion of 90 minutes, almost all of our newborn infants reached the target rectal temperature.

Standard equipment like Tecotherm and Blanketrol III system is expensive. The cost of whole-body cooling apparatus with phase-changing material (PCM) is about INR 3000. The mattress and PCM were reusable and lasted for at least 20 babies making it more economically feasible. Other low-cost systems used include cool gel/ icepacks, cooling fans & water bottles are associated with increased fluctuations in the temperature, the need for frequent changes, more manpower, and the potential for increased skin changes.

Table 12: Comparison of Serious Adverse Events with Other Published Trials

Adverse events	Gluckmann2005[43] (n=112)	Gunn1998[36] (N=13)	Shankaran2002[45] (n=9)	Shankaran2005[54] (n=103)	Current study (n=24)
Cardiac arrhythmias	0	1 (7.6%)	0	2 (1.9%)	0
Hypoglycemia	14 (13%)	3 (23%)	-	12 (11.6%)	3 (12.5%)
Hyperglycemia	-	-	-	-	2 (8.3%)
Bleeding	1 (0.8%)	4 (31%)	1 (11.1%)	3 (2.9%)	1 (4.1%)
Skin changes	1 (0.8%)	-	-	4 (3.8%)	4 (16.6%)
Hypoxemia	-	4 (31%)	3 (33.3%)	25 (23.1%)	0
Hepatic dysfunction	42 (38%)	0	1 (11.1%)	20 (19.4%)	1 (4.1%)
death	36/108 (33%)	1 (7.60%)	2 (22.2%)	45 (44%)	0

Table 13: Comparison of Minor Adverse Events with Other Published Trials

Adverse events	Gluckmann2005	Gunn1998	Shankaran2005	ICE2002	Akisu2003	Current study
	N=112	N=13	N=103	N=7	N=11	N=24
Sinus bradycardia	10 (8.9%)	1 (7.6%)	1 (0.9%)	-	0	5 (21%)
Hypotension requiring inotropic support	74 (66%)	3 (23%)	55 (53%)	3 (42.8%	-	3 (13%)
leukopenia	2 (1.7%)	1 (7.6%)	-	-	-	0
Thrombocytopenia	39 (34.8%)	7 (53.8%)	3 (2.9%)	-	-	5 (21%)
Coagulopathy with hemorrhage	0	2 (15%)	3 (2.9%)	1 (14.2%)	-	1 (4%)
hypokalemia	71 (63.3%)	8 (61.5%)	-	-	-	0
Sepsis	3 (2.6%)	1 (7.6%)	5 (4.8%)	-	1 (9%)	0
Oliguria	24 (21.4%)	13 (100%)	24 (23%)	3 (42.8%)	-	0

The results of our study are on par with other pilot studies where hypothermiais not associated with adverse events like cardiac arrhythmias, prolonged acidosis, life-threatening bleeding, or thrombosis. When the target rectal temperature was reached, the heart rate fall was consistent with other reports and the cold physiologic effects. The mean arterial pressure decreased after whole-body cooling and increased to normal levels after the baby was rewarmed. Monitored biochemical and hematological parameters over the 72 hours of cooling. There was thrombocytopenia in five of the infants as a result of cooling. However, there were no bleeding manifestations in 4 of the babies. One baby had a deranged coagulation profile with thrombocytopenia and considerable bleeding requiring transfusion with blood products. One baby developed culture-positive sepsis and was treated with antibiotics. No leucopenia or neutropenia was noted. Impaired leucocyte mobility and phagocytosis were reported in adult studies. However, there is no evidence of sepsis in any of the newborn infants who underwent whole-body cooling. There was no evidence of hypokalemia and persistent metabolic acidosis. Hypoglycemia was seen in three infants requiring higher carbohydrate content. They returned to normal levels in the next hours and did not require any further treatment. Hyperglycemia was seen in two babies &was treated with insulin. Deranged hepatic function was evident in most of the babies due to hypoxic-ischemic damage. In our study, one infant had normal liver enzymes at the start of WBC but

showed a worsening trend as the cooling progressed. Skin changes were seen in 4 babies, particularly within 24 hours of initiation of cooling, and resolved spontaneously after rewarming. The small sample size precludes any definite conclusion on adverse events. All babies who underwent therapeutic hypothermia were examined regularly to assess neurological and developmental outcomes and intervene early for abnormal HINE scores. Hammersmith neonatal examination showed 5 babies had abnormal neurological scores at discharge. In subsequent visits at 1, 2, 3, 6, 9&12 month, almost all babies were found to be neurologically normal. In previous studies, Bayley-II, General Motor Function Assessment (GMF), and vine land follow-up scales were used to assess hypothermia babies' neuro-developmental outcomes. In recent years, HINE has been identified as one of the best and simplest neurological examinations for the early diagnosis of neurological impairment in low and high-risk infants. However, limited studies have used HINE to predict neuro developmental outcomes from birth in new borns with HIE treated with TH.

4. Conclusion

1) Phase-changing material is an alternative, effective and low-cost method of cooling babies sufficient to achieve and maintain the target rectal temperature.
2) It is feasible to obtain informed consent and start the procedure within the acceptable time frame of 6 hours following birth.
3) Achieve a target rectal temperature within 2 hours of initiation of whole-body cooling.
4) Maintain the target rectal temperature for 72 hours.
5) HINE sequential examination showed better neurological outcomes in asphyxiated new borns who underwent therapeutic hypothermia.

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