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Original Research Article

To Study the Clinical Profile and Short-Term Outcomes of Whole-Body Therapeutic Hypothermia in Patients of Hypoxic Ischemic Encephalopathy

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Abstract:

Background: Neonatal encephalopathy (NE) is the clinical syndrome of disordered neurological function, and hypoxic ischemic encephalopathy (HIE) is NE that follows a perinatal hypoxic ischemic event. Strict criteria for making this diagnosis are constantly being developed but the essential components are the development of encephalopathy in a term/near term neonate soon after birth following an intrapartum event likely to cause hypoxia-ischemia.

Aim: To study the clinical profile and short-term outcomes of whole-body therapeutic hypothermia in patients of hypoxic ischemic encephalopathy.

Method: It was a prospective observational study conducted in a level IIIA NICU in Shri Shishu Bhawan Hospital, Bilaspur which is a tertiary care hospital from April – 2022 to March – 2023. It included all the newborn patients admitted with birth asphyxia with convulsions. Epidemiological data was collected, and patients were monitored for other complications. APGAR scores were recorded and Modified Sarnat and Sarnat staging was used to categorize HIE. Data was analyzed through SPSSv30.

Results: Out of 12 neonates with birth weight <2.5 kg, 10 (83.33%) neonates were discharged and 2 (16.67%) neonates died while out of 51 neonates with birth weight >2.5 kg, 34 (66.67%) neonates were discharged and 17 (33.33%) neonates died. Results also show mortality in low birth is less than birth weight >2.5 kg. Our study shows outcome is better and low death occur when therapeutic hypothermia starts before 6hrs as compared to initiated after 6hrs. This may be due to early start of therapy leads to early reversal of pathology, early resuscitations and supportive treatment.

Conclusion: Therapeutic hypothermia initiated before 6hrs had lesser complication like seizures, persistent acidosis, cardiac arrhythmia, hypotension, hypoglycemia and oliguria compared to initiate after 6hrs this may be due to early reversal of pathology during the first stage which is primary neuronal death and taking benefits of the latent period between primary and delayed neuronal death which is approximately 6 hours. Also, outcomes better if initiation of cooling is within 6hrs compared to after 6hrs mostly due to taking benefits of the latent period between primary and delayed neuronal death which is approximately 6 hours.

Keywords: Encephalopathy, Hypoxic Ischemic Encephalopathy, Therapeutic Hypothermia, Neonatal.

Introduction

Neonatal encephalopathy (NE) is the clinical syndrome of disordered neurological function, and hypoxic ischemic encephalopathy (HIE) is NE that follows a perinatal hypoxic ischemic event [1]. Strict criteria for making this diagnosis are constantly being developed but the essential components are the development of encephalopathy in a term/near term neonate soon after birth following an intrapartum event likely to cause hypoxia-ischemia [2]. The incidence throughout the world and even within the same country varies widely [3]. According to recent data, the estimated incidence of neonatal hypoxic-ischemic encephalopathy is 1.5 per 1000 live births in developed countries and in developing countries of 2.3-26.5 per 1000 live births [4,5].

In 2002-2003, the National Neonatal Perinatal Database (NNPD), a network of neonatal units in India comprising of 18 units across the country, reported that the incidence of HIE was 1.4% among institutional deliveries, and perinatal asphyxia was the commonest primary cause of neonatal mortality (28.8%) and stillbirth (45.1%) [6,7]. A recent systematic analysis of global, national, and regional causes of child mortality identified HIES as the third

important cause (20%) of neonatal deaths in India [8,9]

A systematic review concluded that therapeutic hypothermia is beneficial in neonates with HIE5 has a neuroprotective effect by modifying the cells programmed for apoptosis and reducing cerebral metabolic rate. As per current guidelines, it is mandatory to offer therapeutic hypothermia to all term neonates with evolving moderate or severe hypoxic-ischemic encephalopathy.

Aim: To study the clinical profile and short-term outcomes of whole-body therapeutic hypothermia in patients of hypoxic ischemic encephalopathy. The primary objective was to study the incidence of short-term outcome in therapeutic hypothermia. The secondary objective was to explore complication during therapeutic hypothermia.

Method and Material

It was a prospective observational study and all newborn patients fulfilling the inclusion criteria, admitted in NICU during the study period were enrolled in the study. It includes all the newborn patients admitted with birth asphyxia with convulsions in a level IIIA NICU in Shri Shishu Bhawan Hospital, Bilaspur. This study was conducted from April – 2022 to March – 2023.

Inclusion and Exclusion Criteria: Neonates more than 35 weeks gestational age, with low APGAR score <5 to 10 minutes of life, prolonged resuscitation at birth, chest compression and or prolonged intubation, and / or mask ventilation at 10 minutes, acidosis pH <7.1 from cord or patient blood gas within 60 minutes of birth, abnormal base excess <-10 mEq from cord gas or patient blood gas within 60 minute of birth, and less than 6hr post-delivery were included in the study. On the other hand, neonates with gestational age less than 35 weeks, IUGR < 1,750 grams, severe congenital anomalies /genetic syndrome / established metabolic disorder, major intracranial hemorrhage, overwhelming septicemia, uncorrectable clinically relevant coagulopathy were excluded. Also, moribund neonates or neonates with major congenital or genetic abnormalities, in whom no further aggressive treatment are planned, life-threatening abnormalities of the respiratory or cardiovascular system, E.g., diaphragmatic hernia requiring ventilation or complex congenital heart disease, significant chromosomal anomaly such as trisomy, death appears inevitable, and persistent pulmonary hypertension of the newborn (PPHN) is a relative contraindication were also excluded.

Data Collection: After obtaining ethical consideration, epidemiological data was collected from individual patients satisfying inclusion criteria. Patients were monitored for other complications. All the collected data, clinical observations were arranged in the form of Performa, so that tabulation and statistical analysis become easier later.

Procedure: After obtaining ethical consideration, epidemiological data was collected from individual patients satisfying inclusion criteria. The demographic details, clinical data including resuscitation details, APGAR score were recorded. Modified Sarnat and Sarnat staging was used to categorize HIE. Neonates with HIE were managed according to standard operating systems at the unit. These were followed up by a daily clinical examination and short-term outcome was recorded on day seven. The short-term outcomes of interest included died, alive without complications or alive with complications (requirement of respiratory support, absence of a nutritive suckling reflex, altered level of consciousness, presence of seizures, altered Moro reflex).

Results

A total of 63 enrolled neonates which received therapeutic hypothermia, 42.86% (27) were female and 57.14% (36) were male with P value 0.564. 57.14% (36) were delivered normal and 42.86% (27) were delivered by LSCS. Moreover, 19.05% (12) were Birth weight <2.5 and 80.95% (51) were Birth weight >2.5 with mean birth weight 2.79 kg with range from 1.8 to 3 kg. Additionally, 63 enrolled neonates which received therapeutic hypothermia, 69.84% (44) were discharged and 30.16% (19) were death.

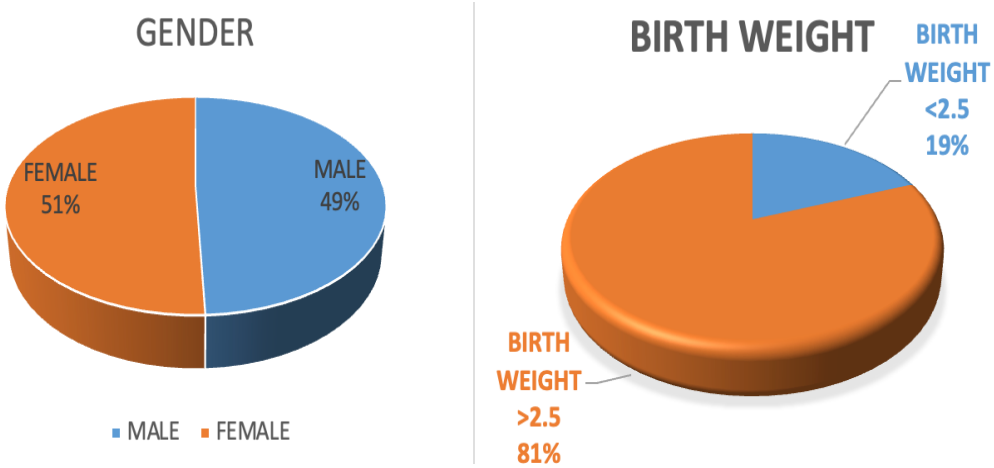

Figure 1: Distribution as per gender and birth weight

Table 1: Association Between Time of Initiation of Cooling and Complications

Complications	Body Cooling Initiation	Absent	Present	Total
Seizure	Before 6hrs	35 (76.09%)	11 (23.91%)	46
	After 6hrs	6 (35.29%)	11 (64.71%)	17
Cardiac Arrhythmia	Before 6hrs	36 (78.26%)	10 (21.74%)	46
	After 6hrs	8 (47.06%)	9 (52.94%)	17
Persistent acidosis	Before 6hrs	29 (63.04%)	17 (36.96%)	46
	After 6hrs	8 (47.06%)	9 (52.94%)	17
Hypotension	Before 6hrs	31 (67.39%)	15 (32.61%)	46
	After 6hrs	7 (41.18%)	10 (58.82%)	17
Hypoglycemia	Before 6hrs	33 (71.74%)	13 (28.26%)	46
	After 6hrs	7 (41.18%)	10 (58.82%)	17
Oliguria	Before 6hrs	32 (69.57%)	14 (30.43%)	46
	After 6hrs	11 (64.71%)	6 (35.29%)	17

As per table 1, during cooling out of 46 neonates, to whom initiated whole body cooling within 6hrs, 35 (76.09%) neonates were shows no seizures and 11 (23.91%) neonates were shows seizures, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 6 (35.29%) neonates were shows no seizures and 11 (64.71%) neonates were shows seizures. Association between time of body cooling initiation and incidence of seizures in neonates is statistically significant with P value 0.002572, Chi square statistic = 9.0888 and df =1.

Further, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 36 (78.26%) neonates were shows no cardiac arrhythmia and 10 (21.74%) neonates were shows cardiac arrhythmia, while out of 17 neonates to whom initiated whole body cooling after 6 hrs, 8 (47.06%) neonates were shows no cardiac arrhythmia and 9 (52.94%) neonates were shows cardiac arrhythmia. Association between time of body cooling initiation and incidence of cardiac arrhythmia in neonates is statistically significant with P value 0.016608, Chi square statistic = 5.7373 and df =1.

Also, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 29 (63.04%) neonates were shows no persistent acidosis and 17 (36.96%) neonates were shows persistent acidosis, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 8 (47.06%) neonates were shows no persistent acidosis and 9 (52.94%) neonates were shows persistent acidosis. Association between time of body cooling initiation and incidence of persistent acidosis in neonates is statistically significant with P value 0.252664, Chi square statistic = 1.3085 and df =1.

Moreover, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 31 (67.39%) neonates were shows no hypotension and 15 (32.61%) neonates were shows hypotension, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 7 (41.18%) neonates were shows no hypotension and 10 (58.82%) neonates were shows hypotension. Association between time of body cooling initiation and incidence of hypotension in neonates is statistically significant with P value 0.059051, Chi square statistic = 3.5638 and df =1.

Furthermore, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 35 (76.09%) neonates were shows no hypoglycemia and 13 (28.26%) neonates were shows hypoglycemia, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 7 (41.18%) neonates were shows no hypoglycemia and 10 (58.82%) neonates were shows hypoglycemia. Association between time of

body cooling initiation and incidence of hypoglycemia in neonates is statistically significant with P value 0.025318, Chi square statistic = 5.002 and df =1.

Also, out of 46 neonates, to whom initiated whole body cooling within 6 hrs, 32 (69.57%) neonates were shows no oliguria and 14 (30.43%) neonates were shows oliguria, while out of 17 neonates to whom initiated whole body cooling after 6 hrs, 11 (64.71%) neonates were shows no oliguria and 6 (35.29%) neonates were shows oliguria. Association between time of body cooling initiation and incidence of oliguria in neonates is not statistically significant with P value 0.713029, Chi square statistic = 0.1353 and df =1.

Table 2: Association Between Rewarming and Incident of Complications

Complications	Rewarming in Body Cooling Initiation	Absent	Present	Total
Seizure	Before 6hrs	36 (78.26%)	10 (21.74%)	46
	After 6hrs	7 (41.18%)	10 (58.82%)	17
Cardiac Arrhythmia	Before 6hrs	35 (76.09%)	11 (23.91%)	46
	After 6hrs	7 (41.18%)	10 (58.82%)	17
Persistent Acidosis	Before 6hrs	39 (84.78%)	7 (15.22%)	46
	After 6hrs	8 (47.06%)	9 (52.94%)	17
Hypotension	Before 6hrs	39 (84.78%)	9 (19.57%)	46
	After 6hrs	9 (52.94%)	8 (47.06%)	17
Hypoglycemia	Before 6hrs	38 (82.61%)	8 (17.39%)	46
	After 6hrs	11 (64.71%)	6 (35.29%)	17
Oliguria	Before 6hrs	36 (78.26%)	10 (21.74%)	46
	After 6hrs	10 (58.82%)	7 (41.18%)	17

Table 2 shows that during cooling out of 46 neonates, to whom initiated whole body cooling within 6hrs, 36 (78.26%) neonates were shows no seizures and 10 (21.74%) neonates were shows seizures, while out of 17 neonates to whom initiated whole body cooling after 6hrs 7 (41.18%) neonates were shows no seizures and 10 (58.82%) neonates were shows seizures. Association between time of body cooling initiation and incidence of seizure in neonates is statistically significant with P value 0.005003, Chi square statistic = 7.8783 and df =1.

Further, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 35 (76.09%) neonates were shows no cardiac arrhythmia and 11 (23.91%) neonates were shows cardiac arrhythmia, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 7 (41.18%) neonates were shows no cardiac arrhythmia and 10 (58.82%) neonates were shows cardiac arrhythmia. Association between time of body cooling initiation and incidence of cardiac. arrhythmia in neonates is statistically significant with P value 0.009077, Chi square statistic = 6.8075 and df =1.

Moreover, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 29 (63.04%) neonates were shows no persistent acidosis and 7 (15.22%) neonates were shows persistent acidosis, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 8 (47.06%) neonates were shows no persistent acidosis and 9 (52.94%) neonates were shows persistent acidosis. Association between time of body cooling initiation and incidence of persistent acidosis in neonates is statistically significant with P value 0.002263, Chi square statistic = 9.3231 and df =1.

Also, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 39 (84.78%) neonates were shows no hypotension and 9 (19.57%) neonates were shows hypotension, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 9 (52.94%) neonates were shows no hypotension and 8 (47.06%) neonates were shows hypotension. Association between time of body cooling initiation and incidence of hypotension in neonates is statistically significant with P value 0.029092, Chi square statistic = 4.7622 and df =1.

Furthermore, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 38 (82.61%) neonates were shows no hypoglycemia and 8 (17.39%) neonates were shows hypoglycemia, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 11 (64.71%) neonates were shows no hypoglycemia and 6 (35.29%) neonates were shows hypoglycemia. Association between time of body cooling initiation and incidence of hypoglycemia in neonates is statistically not significant with P value 0.129225, Chi square statistic = 2.3018 and df =1.

Also, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 36 (78.26%) neonates were shows no oliguria and 10 (21.74%) neonates were shows oliguria, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 10 (58.82%) neonates were shows no oliguria and 7 (41.18%) neonates were shows oliguria. Association between time of body cooling initiation and incidence of oliguria in neonates is not statistically

significant with P value 0.122881, Chi square statistic = 2.3802 and df =1.

Table 3: Association Between Post Rewarming and Finding of Complications

Complications	Post Rewarming in Cooling Initiate	Normal	Abnormal	Total
VIDEO EEG	Before 6hrs	37 (80.43%)	9 (19.57%)	46
	After 6hrs	6 (35.29%)	11 (64.71%)	17
USG CRANIUM	Before 6hrs	41 (89.13%)	5 (10.87%)	46
	After 6hrs	9 (52.94%)	8 (47.06%)	17
MRI BRAIN	Before 6hrs	40 (86.96%)	06 (13.04%)	46
	After 6hrs	11 (64.71%)	06 (35.29%)	17

In this study, during post rewarming out of 46 neonates, to whom initiated whole body cooling within 6hrs, 37 (80.43%) neonates were shows normal Video EEG and 9 (19.57%) neonates were shows abnormal Video EEG, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 6 (35.29%) neonates were shows normal Video EEG and 11 (64.71%) neonates were shows abnormal Video EEG. Association between video EEG and Outcome in neonates is statistically significant with P value 0.00, Chi square statistic = 11.6731 and df =1

Further, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 41 (89.13%) neonates were shows normal USG cranium and 5 (10.87%) neonates were shows abnormal USG cranium, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 9 (52.94%)neonates were shows normal USG cranium and 8 (47.06%) neonates were shows abnormal USG cranium. Association between USG cranium and Outcome in neonates is statistically significant with P value 0.0016, Chi square statistic = 9.9264 and df =1

Also, out of 46 neonates, to whom initiated whole body cooling within 6hrs, 40 (86.96%) neonates were shows normal MRI brain and 06 (13.04%) neonates were shows abnormal MRI brain, while out of 17 neonates to whom initiated whole body cooling after 6hrs, 11 (64.71%) neonates were shows normal MRI brain and 06 (35.29%) neonates were shows abnormal MRI brain. Association between MRI brain and Outcome in neonates is statistically significant with P value 0.045, Chi square statistic = 3.9855 and df =1.

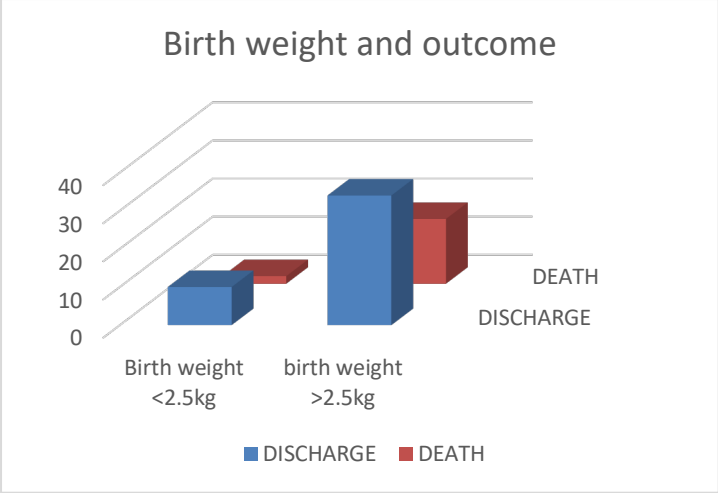

Figure 2: Association Between Outcomes and Birth Weight

Out of 12 neonates with birth weight <2.5 kg, 10 (83.33%) neonates discharged, and 2 (16.67%) neonates died while out of 51 neonates with birth weight >2.5 kg, 34 (66.67%) neonates discharged, and 17 (33.33%) neonates died. Association between birth weight and incidence of outcome in neonates is statistically not significant with P value 0.257695, Chi square statistic = 1.2811 and df =1.

Table 4: Time of Initiation of Cooling

Time of initiation of cooling	Discharge	Death	Total
Body cooling initiation <6hrs	34 (73.91%)	12 (26.09%)	46
Body cooling initiation >6hrs	10 (58.82%)	7 (41.18%)	17

Out of 46 neonates with Body cooling initiation <6hrs, 34 (73.91%) neonates discharged, and 13 (36.11%) neonates died while out of 17 neonates with Body cooling initiation >6hrs, 10 (58.82%) neonates discharged, and 7 (41.18%) neonates died. Association between time of body cooling initiation and incidence of outcome in neonates is statistically not significant with P value 0.246, Chi square statistic = 1.3418 and df =1.

Discussion

Out of 12 neonates with birth weight <2.5 kg, 10 (83.33%) neonates discharged, and 2 (16.67%) neonates died while out of 51 neonates with birth weight >2.5 kg, 34 (66.67%) neonates discharged, and 17 (33.33%) neonates died. The CoolCap study Wyatt JS, Gluckman et al. (2010) [10] has noted that there is an interaction between hypothermia and birth weight, infants with lower weight had better outcomes with cooling. Our study also shows mortality in low birth is less than birth weight >2.5 kg.

In our study show low birth weight (<2.5kg) shows less death and better outcome as compared to more birth weight (>2.5kg). Coolcap study also shows mortality low in low birth weight less than birth 2.5kg. This might be due to low birth weight get lower degree hypoxic ischemic injury. Out of 46 neonates with Body cooling initiation <6hrs, 34 (73.91%) neonates discharged, and 13 (36.11%) neonates died while out of 17 neonates with Body cooling initiation >6hrs, 10 (58.82%) neonates discharged, and 7 (41.18%) neonates died.

Jia, et al. (2018) [11] shows that in newborns with moderate HIE, both time windows (< 6 h and 6–12 h) for starting hypothermia treatment showed curative effects. The treatment effects were better when the treatment was started early. Meanwhile, newborns with severe HIE only showed a therapeutic effect for hypothermia treatment beginning within 6 h.

Sabir et al. (2012) [12] shows that in the neonatal rats with moderate HIE, the effectiveness of TH was maximal immediately after brain injury and decreased linearly with delay in time of initiation

Guillot et al. (2019) [13] shows that if the outcome is similar in the 'Early' versus 'Late' groups of Guillot et al, this would suggest that earlier treatment is more effective, since the infants who were cooled earlier had a more severe hypoxic-ischemic insult as demonstrated by a significantly higher resuscitation score.

Multicenter studies [14,15] also indicated that hypothermia treatment can significantly improve the prognosis of newborns with moderately severe HIE, as well as the time window of treatment < 6 h after birth. Our study shows outcome is better and low death occur when therapeutic hypothermia started before 6hrs as compared to initiated after 6hrs. Our findings were similar all above study this may be due to early start of therapy leads to early reversal of pathology, early resuscitations and supportive treatment.

Conclusion

Therapeutic hypothermia initiated before 6hrs had lesser complication like seizures, persistent acidosis, cardiac arrhythmia, hypotension, hypoglycemia and oliguria compared to initiate after 6hrs this may be due to early reversal of pathology during the first stage which is primary neuronal death and taking benefits of the latent period between primary and delayed neuronal death which is approximately 6 hours. Rewarming during therapeutic hypothermia had lesser incidence of complications as compared to during cooling. This was mostly due to cooling induce bradycardia and decrease metabolism.

MRI, EEG and USG cranium findings mostly normal in neonates initiates therapeutic hypothermia within 6hrs as compared to after 6hrs due to taking benefits of the latent period. Outcomes in low birth weights (<2.5kg) neonates better than more weight neonates receiving therapeutic hypothermia, mostly due to lower birth weights associated with lesser degree of hypoxic ischemic encephalopathy. Also, outcomes better if initiation of cooling is within 6hrs compared to after 6hrs mostly due to taking benefits of the latent period between primary and delayed neuronal death which is approximately 6 hours.

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