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Research Article

Factors Affecting Short Term Outcome of Therapeutic Hypothermia in Neonatal Hypoxic Ischemic Encephalopathy-A Cross Sectional Study

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Abstract

Background: Perinatal Hypoxic Ischemic Encephalopathy (HIE) is an important cause of Neonatal Encephalopathy, and contributes to both infant mortality and long term disability in children. Therapeutic hypothermia (TH) has transformed clinicians treatment approaches and improved clinical outcomes.

Objective: We studied the Factors affecting short term outcome of therapeutic hypothermia in Neonatal Hypoxic Ischemic Encephalopathy and factors contributing to these morbidity and mortality in these neonates in Neonatal Intensive Care Unit (NICU) at tertiary care hospital.

Method: It is a hospital-based, cross-sectional study conducted over 18 months. A total of 90 neonates were included in this study which satisfy the inclusion criteria. Before starting therapeutic hypothermia, clinical and outcome parameters and existence of co-morbidities was recorded, according to a predesigned proforma.

Results: Out of 90 babies, 82 (91.1%) were born by vaginal route, 8 (8.8%) were of lower segment cesarean section. More of babies who delivered by vaginal route undergone therapeutic hypothermia, 67 (74.4%) babies required bag and mask ventilation, 21 (23.3%) babies required endotracheal intubation and 2 (2.2%) babies required drugs in the delivery room for resuscitation. 60 (66.6%) babies had moderate encephalopathy and 30 (33.3%) babies had severe encephalopathy. Mean gestational age was 38.3 weeks in our study, mean birth weight in our study was 2.79 kilograms, mean temperature at admission was 34.48°C in our study, mean depth of cooling of 33.53°C in our study.

Conclusion: Our study shows that hypothermia treatment is feasible in resource limited settings and outcome of asphyxiated neonates can be improved.

Keywords: *Neonatal Hypoxic Ischemic Encephalopathy; Perinatal Asphyxia; Therapeutic Hypothermia; Neonates*

Abbreviations

HIE: Hypoxic Ischemic Encephalopathy; TH: Therapeutic Hypothermia; NICU: Neonatal Intensive Care Unit; APGAR: Appearance, Pulse, Grimace, Activity and Respiration

Introduction

Hypoxic Ischemic Encephalopathy (HIE) is a serious condition secondary to decreased cerebral blood flow and oxygen supply to the foetal brain at the time of birth. HIE is a main cause for neonatal mortality and morbidity across the globe. HIE is seen in 1 - 3 per 1000 live births in developed countries and 20 per 1000 live births in underdeveloped and developing countries [1]. Report from National Neonatal Perinatal Database showed that incidence of HIE is 1.5% live birth and is responsible for 20% neonatal mortality [2]. According to National Neonatal Perinatal Database report from India HIE incidence is 1.4% among institutional deliveries and it constitutes 28% of neonatal deaths [2].

But this data may not reflect the real scenario and represents only the tip of the iceberg. There is no accurate data on incidence of HIE in India. Inspite of many efforts of reducing HIE through training in neonatal resuscitation [3], it remains a major cause of neonatal mortality and morbidity with long term neuromotor disability. Perinatal asphyxia is the common reason for the mortality.

Therapeutic hypothermia (TH) has been shown to reduce death and disabilities among neonates with HIE and increase the number of survivors without neurodevelopmental disabilities.

Several studies have shown that cerebral function monitoring using non-invasive techniques, such as electroencephalogram within six hours of birth, cranial ultrasonography, cranial topography, doppler measurements of cerebral blood flow, somato-sensory evoked potentials, magnetic resonance imaging and estimation of neurophysiological markers such as creatine kinase - brain, brain specific lactate dehydrogenase isomer, glutamate and neuron specific enolase in the cerebrospinal fluid are all useful in predicting both the immediate dysfunction and the long term outcome. But none of these facilities are routinely available except in few tertiary hospitals and in some of the teaching hospitals of our country. Other factors like poverty, ignorance and lack of medical facilities and obstetric care contributes significantly to magnitude of the problem in our country [4].

Only a third of deliveries in India are institutional and many asphyxiated babies are brought late to hospitals. The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia [4].

Therapeutic hypothermia has now become the standard of care in HIE as it has been proven to be effective in decreasing morbidity and mortality associated with it [5,6]. In underdeveloped and developing countries TH is still in beginning process even though incidence is more common in these countries. This is due to non availability of expensive devices used for cooling in these countries.

Therapeutic hypothermia initiated within 6 hours of birth that is before the initiation secondary energy failure after hypoxic insult showed improvement in neurodevelopmental outcome [6]. Usually, it is continued for 72 hours for better neuroprotection. It has shown to be effective in decreasing combined outcome of death or neurodevelopmental outcome.

Objective of the Study

Hence the present study was carried out with an objective to study the short term outcome in babies treated with therapeutic hypothermia for Hypoxic Ischemic Encephalopathy and to study the factors contributing to morbidity and mortality in these neonates.

Materials and Methods

The present study is a cross sectional study done in neonatal intensive care unit, carried out in S N Medical College and Hanagal Shri Kumareshwar Hospital and Research Centre (An Institute of National Importance) with a study period of eighteen months from 01/04/2021 till 31/10/2022.

Inclusion criteria:

1. Birth asphyxiated neonates with age less than 6 hours, birth weight more than 1.8 kilograms, gestational age more than 36 weeks (Based on reported last menstrual period or ultrasound).
2. Need for continued resuscitation at 5 minutes of age and/or 5 minutes APGAR score less than 6 (for babies born at hospital) or lack of crying by 5 minutes of age (for out born babies).
3. Sarnat and Sarnat staging for neonatal HIE with stage 2 and stage 3.

Exclusion criteria:

1. Absent heart rate at 10 minutes of age despite adequate resuscitation or imminent death.
2. Age more than 6 hours of life.
3. Major life-threatening congenital malformations.
4. Neonates whose attenders did not give consent for treatment.

Sample size calculation

According to the study conducted by Massaro [7], Proportion of Neonates with moderate Hypoxic Ischemic Encephalopathy following birth asphyxia was 69% which was taken as prevalence. At 10%, Absolute precision, Sample size estimated is 83 which is rounded off to 90.

Data collection

- Obtained ethical clearance from institution ethics committee on human subjects research. Written informed consent (in English and local language) was taken from all study subjects (parents) before enrolment in the study and before starting therapeutic hypothermia. The following parameters was estimated.
- Baseline parameters: Birth weight, date of birth, age at admission, sex, gestational age, birth order, inborn/outborn, maternal history, mode of delivery, complaints at presentation, general physical examination, systemic examination, lab investigation.

Parameters monitored are:

- Inborn/outborn, birth weight, gender, APGAR score, seizures, HIE stage II and III Sarnat and Sarnat staging, electroencephalogram, inotropic support, myocardial dysfunction, persistent pulmonary hypertension, pulmonary hemorrhage, anticonvulsants, sedatives/analgesics, neuromuscular blocking agents, arterial blood gas parameters, sepsis, gastric bleeds, acute kidney injury, necrotizing enterocolitis, neuroimaging.

Statistical analysis

Statistical analysis was done using SPSS software19.0. Proportions was used for qualitative data. Student t test for quantitative data was used. Chi-square test for proportions in qualitative data. Other appropriate statistical tests was applied. $P<0.05$ was considered statistically significant.

Results

In this study total of 90 participants were present. Neonates with moderate and severe encephalopathy, (Table 1) shows neonates with moderate encephalopathy 60 (66.6%) and neonates with severe encephalopathy 30 (33.3%).

Characteristics	No of Cases (n = 90)	Percent (%)
Neonates with Moderate Encephalopathy	60	66.6
Neonate with Severe Encephalopathy	30	33.3
Total	90	100

Table 1: *Neonates with moderate and severe encephalopathy.*

Based on the anticonvulsant requirement for seizures, 61 (67.7%) infants required the anticonvulsants and 29 (32.2%) didn't required the anticonvulsant drugs (Table 2).

Clinical Seizures Requiring Anticonvulsants	No of cases (n = 90)	Percent (%)
Present	61	67.7
Absent	29	32.2
Total	90	100

Table 2: *Based on anticonvulsant requirement for seizures.*

Seizures free by 72 hours only in 52 (85.2%) infants (Table 3).

Seizures free by 72 hours	No of cases (n = 61)	Percent (%)
Yes	52	85.2
No	9	14.7
Total	61	100

Table 3: *Seizures free by 72 hours.*

Out of 90 infants 59 (65.6%) were completely recovered with normal, infants Survived with neurological deficit 23 (25.6%) and died were 8 (8.9%) (Table 4).

Outcome	No of cases (n = 90)	Percent (%)
Normal	59	65.6
Survived with neurological deficit	23	25.6
Death	8	8.9
Total	90	100

Table 4: *Distribution based on outcome.*

Parameters of therapeutic hypothermia (Table 5) shows 3.43 hours is the mean age of babies when cooling was started. Mean age when target temperature first achieved is 4.17 hours. Mean temperature of babies at admission is 34.48 degree celsius. Depth of cooling 33.53 degree celsius. Mean Duration of cooling 72.39 hours.

Parameters	Mean	Standard Deviation
Age when cooling started	3.43 hours	1.15
Age when target temperature first achieved	4.17 hours	1.02
Temperature at admission	34.48°C	1.27
Depth of cooling	33.53°C	0.14
Duration of cooling	72.39 hours	2.61

Table 5: *Parameters of therapeutic hypothermia.*

Parameters monitored in the present study were out of 90 participants, inotropic support was present in 23 (25.6%) participants, PPHN present in 2 (2%) participants, pulmonary hemorrhage present in 11 (12.2%), anticonvulsants given to 61 (67.7%) participants, sedatives/analgesics given to all participants, arterial blood gas (acidosis) present in all participants, sepsis present in 28 (30%) participants, gastric bleeds present in 12 (12.4%) participants, acute kidney injury present in 8 (8.9%) participants, necrotizing enterocolitis present in 12 (13.3%) participants, neuroimaging done in all participants.

Parameters		No of cases (n = 90)	Percent (%)
Inotropic Support	Absent	67	74.4
	Present	23	25.6
Myocardial Dysfunction	Absent	90	100
Persistent Pulmonary Hypertension	Present	2	2.2
	Absent	88	97.8
Pulmonary hemorrhage	Present	11	12.2
	Absent	79	87.7
Anticonvulsants	Given	61	67.7
	Not given	29	32.2
Sedatives/Analgesics	Given	90	100
Neuromuscular blocking agents	Not given	90	100
Arterial blood gas (Acidosis)	Present	90	100
Sepsis	Absent	62	70
	Present	28	30
Gastric bleeds	Absent	78	87.6
	Present	12	12.4
Acute kidney injury	Absent	82	91.1
	Present	8	8.9
Necrotizing enterocolitis	Absent	78	86.6
	Present	12	13.3
Neuroimaging	Present	90	100

Table 6: *Parameters monitored during the study.*

Discussion

In hypoxic ischemic encephalopathy (HIE), mortality is more due to perinatal asphyxia. Perinatal asphyxia is a devastating clinical condition because of its potential for causing permanent damage, even death of the fetus or newborn infant. The APGAR score has a limited role in predicting the immediate outcome, such as that of HIE and the long-term sequelae.

Regarding the effect of the lower APGAR score at birth, other studies showed that acidemia and lower APGAR scores were associated with a worse outcome of HIE infants [8].

In the present study, the comparison of surviving and non surviving newborns showed by using therapeutic hypothermia. This is the first cross sectional study to conduct with large sample size on HIE.

In the present study 90 participants were included in which neonates with moderate to severe HIE treated with selective therapeutic hypothermia, in which 59 (65.6%) were responded good with the treatment, 23 (25.6%) infants survived with neurological deficit and died 8 (8.9%) infants with severe encephalopathy.

In the present study, 61 (67.7%) participants showed Clinical Seizures Requiring Anticonvulsants, after the treatment 52 (85.2%) Seizures free by 72 hours.

In a study done by Srinivasakumar., *et al*. [9] demonstrated therapeutic hypothermia was associated with a decrease in electroconvulsive seizures in neonates with moderate HIE.

In studies done by Srinivasakumar., *et al*. [9] and Gluckman., *et al*. [10] hypothermia appears to be less protective in infants with the most severe HIE. The study done by Shankaran., *et al*. [11] demonstrated 24% in the hypothermia group and 37% in the control group died. In comparison to these studies our study had very less deaths which is suggestive of increased survival rate after therapeutic hypothermia.

Therapeutic hypothermia for perinatal asphyxia in low and middle income countries has not been shown to be associated with a statistically significant reduction in neonatal mortality or neurodevelopmental morbidity [11]. The results of a multicenter study (HELIX trial) from low and middle income countries was recently published.

Brain imaging and the severe HIE can provide a more accurate assessment of neurological complications. In the present study we observed other organ complications like acute kidney injury, sepsis, pulmonary haemorrhage.

In the present study 60 (66.6%) babies had moderate encephalopathy and 30 (33.3%) babies had severe encephalopathy in other studies like Jacob., *et al*. [12] study 57% babies had moderate encephalopathy and 27% of babies had severe encephalopathy and Rao., *et al*. [13] study 68% of babies had moderate encephalopathy and 26% of babies had severe encephalopathy.

Mean temperature at admission was 34.48°C in our study this is comparable to other studies like Jacob., *et al*. [12] mean temperature at randomization was 35.3°C.

Mean age when cooling started is 3.43 hours compared to other studies like Zhou., *et al*. [14] where the age at therapy was 4 hours and Sinha., *et al*. [15] where the age at therapy was 3.8 hours.

Mean age when target temperature achieved in our study is 4.17 hours compared in other studies like Azzopardi., *et al*. [16] the age was 6 hours and in Sinha., *et al*. [15] study the age was 5.2 hours.

Mean depth of cooling of 33.53°C in our study which is comparable with other studies like Eunice Kennedy Shriver National Institute of Child Health and Human Development cooling trail where mean depth of cooling is 33.5°C and Bharadwaj., *et al*. [17] study the mean depth of cooling was 33.7°C.

TH increases the survival rate if initiated within 6 hours of birth and continued for 72 hours, which is consistent with previous reports published by Jacob., *et al*. [12]. This is comparable to current study.

The strength of the study is the more sample size and more survival rate of the infants for the therapeutic hypothermia which is also comparable to the previous above mentioned studies and the limitation of the study is there is no follow up of the survived participants.

Conclusion

To conclude, moderate or severe encephalopathy due to perinatal asphyxia was an important reason for admission to the NICU among late preterm and term infants. In the present study 90 infants received TH, in that Survival to discharge among infants is high compared to other studies. This is the first prospective cross sectional study done in HIE in the North Zone of Karnataka. Findings may reflect the relationship between brain injury severity and the integrity of autonomic control, and suggest that whole body cooling techniques could be further optimized and perhaps tailored to the severity of hypoxic ischemic encephalopathy. Our study shows that hypothermia treatment is feasible in resource limited settings and outcome of asphyxiated neonates can be improved.

Conflict of Interest

None.

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