Original Article

Experience of Therapeutic Hypothermia in Neonates with Perinatal Asphyxia in a Tertiary Care Center in North Karnataka, India

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Abstract

Introduction: Perinatal asphyxia contributes to 20%–30% of the neonatal deaths in India. In developed countries, therapeutic hypothermia (TH) is the established standard of care in asphyxiated neonates. In this study, we present our center experience in using TH for asphyxiated neonates using servo-controlled cooling machine. **Subjects and Methods:** This study was conducted in Level IIB Neonatal Intensive Care Unit (NICU) of Shri B M Patil Medical College Hospital Vijayapur, Karnataka, over a period of 1 year including neonates admitted in NICU with perinatal asphyxia. Babies with perinatal asphyxia (TOBY criteria) were enrolled in the protocol group and control group. In the protocol group, babies were cooled to 33.5°C using servo-controlled cooling machine within 6 h of birth for 72 h, followed by rewarming at 0.5°C/h to 36.5°C. In the control group, babies received standard supportive care as per unit protocol. Babies were enrolled in this study after taking verbal and written consent from parents. **Results:** Among 210 neonates included in the study, 92 in the protocol group received TH, whereas 118 neonates were in the control group. 10 neonates died/discharge against medical advice in the Protocol group whereas 22 neonates died/discharge against medical advice in the Control group. 35% and 19% had normal neurological examination at discharge in the protocol and control group, respectively. No statistically significant differences were observed among complications associated with TH between protocol and control group except for bradycardia and thrombocytopenia. **Conclusion:** TH resulted in better survival and neurodevelopmental outcomes at 18 months of age in our study. Developing training programs and improving infrastructure including neonatal transport are necessary for successful implementation of TH.

Keywords: *Neurodevelopmental outcomes, perinatal asphyxia, servo-controlled cooling, therapeutic hypothermia*

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Introduction

Perinatal asphyxia contributes to 20%–30% of the neonatal deaths in India as per Black *et al*.[1] Therapeutic hypothermia (TH) has been accepted as the standard of care for moderate-to-severe hypoxic–ischemic encephalopathy in the developed countries. Major randomized controlled trials (RCTs) have shown a beneficial effect of TH on survival and long-term neurological outcome for newborns with perinatal asphyxia using either selective hypothermia[2,3] or whole-body cooling.[4-7] However, TH has many limitations and practical problems in implementation, especially in resource-limited settings and low- and middle-income countries.[8] In this study, we present our center experience in using TH for asphyxiated neonates using servo-controlled cooling machine.

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Subjects and Methods

This study was conducted in Level IIB Neonatal Intensive Care Unit (NICU) of Shri B M Patil Medical College Hospital Vijayapur, Karnataka, India, over a period of 1 year including neonates admitted in NICU with perinatal asphyxia. Study design: Prospective, observational study involving neonates with asphyxia admitted in NICU. Study duration: 1 year. Babies with perinatal asphyxia (TOBY criteria) were enrolled in the protocol group and control group. In the protocol group, babies were cooled to 33.5°C using a servo-controlled cooling machine within 6 h of birth for 72 h, followed by rewarming at 0.5°C/h to 36.5°C. In the control group, babies received standard supportive care as per unit protocol. Babies were enrolled in this study after taking verbal and written consent from parents. Inclusion criteria: newborns born at ≥36 weeks of gestation with birth weight >1800 g were enrolled for treatment if presented with acute perinatal asphyxia with moderate or severe hypoxic–ischemic encephalopathy (HIE) (Sarnat and Sarnat staging criteria and arterial blood gas analysis with pH <7.1 and base deficit >16 mEq/L). Exclusion criteria: Gestation <36 weeks, birth weight <1800 g, severe chromosomal or congenital anomalies, major intracranial hemorrhage, and parents not willing for the treatment.

Baseline maternal and neonatal characteristics were documented. Demographic parameters (gestational age, birth, and sex) and neonatal features (mode of delivery, acute intrapartum events, Apgar score at 1, 5, and 10 min, and the need of neonatal resuscitation) were noted. Severity of HIE was assessed prior to cooling using Sarnat and Sarnat criteria. Associated complications such as bradycardia <90/min, need for ventilation, thrombocytopenia (platelet count <150,000/cumm), coagulopathy, hypotension, pulmonary arterial hypertension, intraventricular hemorrhage, hypoglycemia, hyperglycemia, leukopenia/neutropenia, and death were observed. Magnetic resonance imaging (MRI) brain was done after discharge and the result of the neurological examination at 6 months, 12 months, and 18 months was documented. We have documented the time of cooling initiation after birth, the rectal temperature monitoring, the adverse effects, and interventions during cooling for neonates in the protocol group.

Therapeutic hypothermia protocol

Asphyxiated neonates were enrolled in the protocol group and treated with servo controlled TH as per unit TH protocol (TOBY criteria).[9,10] Inclusion criteria: newborns born at ≥36 weeks of gestation with birth weight >1800 g were enrolled for treatment if presented with acute perinatal asphyxia with moderate or severe HIE (Sarnat and Sarnat staging criteria and arterial blood gas analysis with pH <7.1 and base deficit >16 mEq/L). Exclusion criteria: gestation <36 weeks, birth weight <1800 g, severe chromosomal or congenital anomalies, major intracranial hemorrhage, and parents not willing for the treatment.

Cooling was initiated before 6 h of life. Phases of cooling: (1) Induction phase: to attain target core temperature of 33.5°C, it takes around 30 min. Rectal temperature was checked every 15 min for the 1st h and then hourly. (2) Maintenance phase: characterized by maintenance of core (rectal) temperature between 34°C and 35°C (33.5°C) for 72 h. (3) Rewarming phase: Controlled rewarming was initiated gradually after 72 h of hypothermia at 0.5°C/h (6 h) from 33.5°C to 36.5°C. Continuous monitoring of vitals (blood pressure/heart rate/respiratory rate/SpO_2) and glucose monitoring every 8 h was done. Laboratory parameters were assessed as follows: complete blood count – 0, 48 h, and 72 h; renal function tests – 0, 24 h, and 72 h; coagulation profile – 0, 24 h, and 72 h; and liver function tests (serum glutamic–oxaloacetic transaminase and serum glutamic pyruvic transaminase) – 0 and 72 h.

Statistical analysis

SPSS Version 23.O (IBM, NY, USA) was used for statistical analysis. Chi-square or Fisher's test for qualitative variables and nonparametric Mann–Whitney test for quantitative variables were used. Statistical difference was considered statistically significant if $P < 0.05$.

Results

Among 279 neonates hospitalized for perinatal asphyxia in NICU, 210 neonates fulfilled the criteria and were included in the study. The remaining 69 were excluded from the study because they did not meet the TH inclusion criteria (<36 weeks, birth weight <1800 g, chromosomal or genetic abnormalities, life-threatening bleeding, and parents not willing).

Among 210 neonates included in the study, 92 received TH in protocol group whereas 118 neonates were in the control group. Reasons for the 118 neonates who were not cooled include admission beyond 6 h of life in 61%, mild encephalopathy in 15%, cooling contraindication in 15%, and the nonavailability of the cooling machine in 9%. For the control group, we continued to manage the neonates as per standard supportive care for neonatal perinatal asphyxia as per unit protocol.

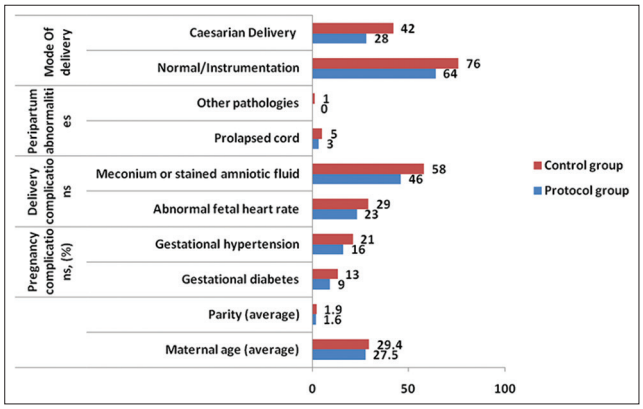

Figure 1: Baseline maternal characteristics in both groups

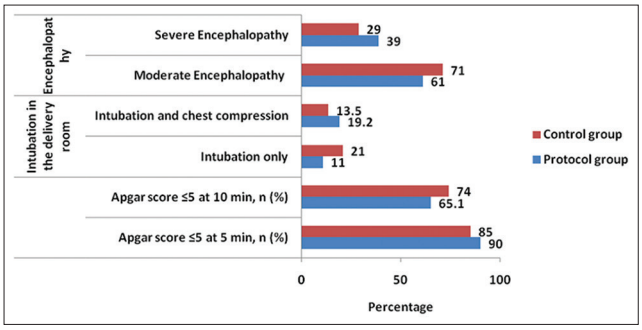

Figure 2: Baseline neonatal characteristics in both groups

Characteristics

Maternal and neonatal characteristics [Figures 1 and 2] were similar in both protocol and control groups. The neonatal perinatal asphyxia was suspected when fetal heart rate abnormalities were noted (bradycardia and decelerations) in both groups. The HIE was classified as per Sarnat and Sarnat Staging criteria. As per criteria, moderate encephalopathy was seen in 61% of protocol group and 71% of control group, whereas severe encephalopathy in 39% of protocol group and 29% of control group [Figure 2].

Asphyxiated neonates were admitted at 3.6 ± 2.6 h of life in the NICU. TH was initiated at 3.8 ± 1 h of life in the protocol group. At admission, average rectal temperature was 35.4 ± 0.6 C. Induction time required was 24 ± 4.6 min.

Observations of laboratory parameters in the protocol and control group were documented. It shows significant differences in hemoglobin/total count and coagulation profile after 72 h of TH in the protocol group, which was similar to the control group [Tables 1 and 2].

Complications

No statistically significant differences were observed among complications associated with TH between protocol and control group except for bradycardia and thrombocytopenia. Bradycardia (<90/min) and thrombocytopenia (platelet count <150,000/cumm) were statistically significant complications in the protocol group [Table 3]. Indicators of sepsis such as leukopenia/neutropenia were observed in both groups, which was not statistically significant.

Course of newborns

Hospital stay (mean duration) was longer in the protocol group. 11% neonates died/discharge against medical advice in the Protocol group whereas 19% neonates died/discharge against medical advice in the Control group. 35% and 19% had normal neurological examination at discharge in the protocol and control group, respectively [Table 4].

Eighty neonates in the protocol group and 93 neonates in the control group underwent MRI brain after discharge. No HIE changes in MRI brain was seen in 35% of cases in the protocol group, whereas 19% in the control group. Severe HIE changes was seen in 19% and 26% of cases in the protocol and control group, respectively. Regional specific HIE changes in MRI brain were observed in 20% and 16% of cases in the protocol and control group, respectively, which was statistically significant [Table 5].

The follow-up rate at the age of 18 months was almost similar in the protocol and the control group (87%). 67% from the protocol group had normal neurological examination at 18 months of age, 18% had psychomotor delay, but 15% presented with neurosensorial abnormalities, which was statistically significant [Table 6].

Discussion

In developed countries, TH has been the standard of care in neonates with perinatal asphyxia. Data of developed countries with TH cannot be extrapolated to resource-limited developing countries like India.[11] Major randomized controlled studies have shown a beneficial effect of controlled hypothermia on survival and long-term neurological outcome for newborns with perinatal asphyxia using either selective hypothermia or whole-body cooling. In this study, our aim was to observe the outcomes of neonates with perinatal asphyxia with introduction of whole-body cooling with servo-controlled cooling machine. Our results are encouraging with respect to the feasibility and safety of whole-body cooling and the beneficial effect in terms of survival and neurodevelopmental outcome at 18 months of age.

Two principal methods of TH exist: selective head cooling and the whole-body cooling. Whole-body cooling is favored as a reduction of systemic temperature

is necessary to achieve deep brain cooling and the distribution of the intracerebral temperature is more homogeneous in the case of total body cooling.[12-14] In this study, we used the whole-body cooling for TH.

Current recommendations require TH to begin before 6 h of life as shown in animal studies, as there is still a "therapeutic window" where secondary neuronal injury could be prevented or reduced by brain cooling.[15,16]

Thoresen M *et al*.[17] suggested that TH started within 3 h of birth improves motor outcome in asphyxiated neonates, and in the TOBY study, hypothermia was more effective in neonates treated during the first 4 h after birth.[6] In this study, average time for starting TH was 3.8 ± 1 h of birth.

The need to start TH before 6 h of life has been a major limitation in this protocol since 41% of newborns referred to this center arrived late. This problem has been discussed in other studies analyzing the feasibility of hypothermia in low- and middle-income countries,[18] in which the therapeutic time-window for administering beneficial cooling may be passed, due to delayed hospital admissions and lack of neonatal transport facilities. It therefore seems necessary to promote rapid transfer policy to level III centers of newborns with HIE by creating awareness among peripheral centers.

Commencement of TH protocol before 6 h of life requires early assessment of the severity of HIE and early recognition of hypoxic–ischemic nature. Repetitive clinical assessment (every 1–2 h during the first 6 h) is required for these neonates to determine the stage and progression of HIE from Stage I→II→III.

Detailed neurological examination of an asphyxiated newborn according to criteria defined by Sarnat and Sarnat was followed to assess the severity of HIE. However,[19] it may be defective in some urgent assessment circumstances such as painful or sedated newborn.[20,21]

Clinical monitoring and laboratory tests are essential in neonates with HIE regardless of the mode of treatment, but TH requires additional procedures such as umbilical arterial and venous catheterization for blood draw and

Table 1: Observations of lab parameters in the protocol group

Parameters	At admission	AT 72 h	*P*
Hemoglobin	18.55±1.048	14.90±2.64	0.004 (S)
Total leukocytes	16,996±8771	11,428±5960	0.005 (S)
PT	24.63±16.23	42.90±29.34	0.002 (S)
APTT	49.83±28.24	66.16±31.22	0.003 (S)
Serum creatinine	0.82±0.16	0.99±0.44	0.11 (NS)
pH	7.15±0.78	7.35±0.17	0.001 (S)
PO_2	77.31±51.8	98.25±40.79	0.24 (NS)
PCO_2	32.90±33.71	29.92±11.01	0.58 (NS)
BD	−16.9±4.40	−11.26±9.6	0.0004 (S)
HCO_3	9.94±5.13	14.03±8.27	0.003 (S)

Results based on Mann–Whitney U-test comparison.
NS – Not significant; S – Significant; PT – Prothrombin time; APTT – Activated partial thromboplastin time

Table 2: Observations of lab parameters in the control group

Parameters	At admission	AT 72 h	*P*
Hemoglobin	17.45±2.048	15.90±2.64	0.05 (S)
Total leukocytes	17,996±4771	13,428±5960	0.05 (S)
PT	21.63±16.23	29.52±17.51	0.05 (S)
APTT	44.83±18.68	66.16±31.22	0.03 (S)
Serum creatinine	0.68±0.16	0.89±0.44	0.11 (NS)
pH	7.11±0.88	7.25±0.19	0.065 (NS)
PO_2	86.56±31.8	94.50±39.69	0.24 (NS)
PCO_2	42.07±33.15	39.37±13.16	0.85 (NS)
BD	−17.4±3.40	−13.66±9.6	0.064 (NS)
HCO_3	8.94±6.13	12.03±9.27	0.072 (NS)

Results based on Mann–Whitney U-test comparison
NS – Not significant; S – Significant; PT – Prothrombin time; APTT – Activated partial thromboplastin time

Table 3: Complications observed among protocol and control group

	Protocol group (*n*=92), *n* (%)	Control group (*n*=118), *n* (%)	Value
Bradycardia <90/min	81 (88)	19 (16)	S
Need for ventilation	39 (42.3)	58 (49)	NS
Thrombocytopenia (platelet count <150,000/cumm)	47 (51)	34 (29)	S
Coagulopathy	33 (36)	37 (31)	NS
Hypotension	50 (54)	67 (57)	NS
PAH	14 (15)	22 (19)	NS
IVH	5 (5.4)	8 (7)	NS
Hypoglycemia	17 (18.4)	27 (23)	NS
Hyperglycemia	38 (41)	41 (35)	NS
Leukopenia/neutropenia	26 (28)	27 (23)	NS

Results based on Chi-square test. NS – Not significant; S – Significant; PAH – Pulmonary arterial hypertension; IVH – Intraventricular hemorrhage

Table 4: Newborn course during hospitalization in both groups

	Protocol group (*n*=92), *n* %	Control group (*n*=118), *n* (%)	*P*
Average of hospital stay	13.8	9.8	S
Death/DAMA	10 (11)	22 (19)	NS
Normal neurological exam at discharge	32 (35)	23 (19)	NS

Results based on Mann–Whitney U-test comparison and Chi-square test. NS – Not significant; S – Significant; DAMA – Discharge against medical advice

Table 5: Characteristics of magnetic resonance imaging brain among protocol and control group

	Protocol group (*n*=92), *n* (%)	Control group (*n*=118), *n* (%)	*P*
Number of MRI brain	80 (87)	93 (79)	S
No HIE	28 (35)	18 (19)	S
Suspicion of HIE	21 (26)	36 (39)	S
Severe HIE	15 (19)	24 (26)	S
Regional specific HIE	16 (20)	15 (16)	S

Results based on Chi-square test. S – Significant; HIE – Hypoxic-ischemic encephalopathy; MRI – Magnetic resonance imaging

Table 6: Neurological assessment at 18 months of age of protocol and control group

	Protocol group (*n*=72), *n* (%)	Control group (*n*=84), *n* (%)	*P*
Normal neurological exam	48 (67)	44 (52)	NS
Psychomotor delay	13 (18)	16 (19)	NS
Neurosensorial disorders	11 (15)	24 (29)	S

Results based on Chi-square test. S – Significant; NS – Not significant

urinary catheterization for urine output measurements. Full monitoring includes heart rate, respiratory rate, blood pressure, core temperature, surface temperature, and SaO_2. The core temperature was recorded by rectal probe.[22] Laboratory monitoring included complete hemogram, coagulation profile (prothrombin time/international normalized ratio with activated partial thromboplastin time), and renal function and liver function tests.

In the protocol group, specialized servo-controlled cooling equipment (Criticool MTRE) was used; the hypothermia was attained using body wraps with circulating cold water placed on the body of the neonate. The average rectal temperature at admission in TH protocol group was 35.4°C ± 0.6°C. The average time taken to reach the target temperature of 33.5°C was 24 ± 4.6 min (induction time).

During the process of TH, minimal temperature fluctuations were noticed at 0.5°C in the range of 33°C–34°C. Achieving and maintaining target temperature required the nurse's constant attention and vigilance to ensure that the temperature probes (rectal and surface) remained within the proper position.[22]

Complications related and secondary to perinatal asphyxia were similar for both groups; except for bradycardia and thrombocytopenia. Bradycardia (<90/min) and thrombocytopenia (platelet count <150,000/cumm) were statistically significant complications in the protocol group.

Hospital stay was longer in the protocol group, which was also found in the randomized study of Shankaran *et al*.[23] 19% of neonates died/DAMA in the control group whereas only 11% died/DAMA in the protocol group, which was not statistically significant.

Neurological examination at discharge was done using Hammersmith Neonatal Neurological Examination. Subsequent neurodevelopmental follow-up at 18 months was performed on the babies using Developmental Assessment Scales for Indian Infants-III. Normal neurological examination at discharge was observed in 67% in the protocol group and 52% in the control group, which was not statistically significant, whereas 29% presented with neurosensorial abnormalities, which was statistically significant in the control group.

Hypothermia is known to cause some degree of immunosuppression with decreased leukocyte number and impaired functions,[24,25] as also reported in the latest Cochrane meta-analysis.[26] Indicators of sepsis such as leukopenia/neutropenia were observed in both groups, which was not statistically significant.

Severe HIE changes were seen in 19% and 26% of cases in the protocol and control group, respectively, which was not statistically significant. Regional-specific HIE changes in MRI brain were observed in 20% and 16% of cases in the protocol and control group, respectively, which was statistically significant.

Newborn follow-up rate was similar in the TH and control group, reaching 87%. A significant decrease in death rates and neurological morbidity at the age of 18 months in children who have moderate or severe HIE was found in newborns of protocol group.

Limitation of study

Data presented here are derived from a single center and are assessed for short-term follow-up at 18 months of

age. The further RCT studies in lower middle-income countries with larger population and long-term follow-up at 5 years of age are desirable.

Conclusion

TH is established standard of care in the developed countries. TH resulted in better survival and neurodevelopmental outcomes at 18 months of age in our study. Implementation of TH is facing a lot of problems in lower middle-income countries like India where the rates of neonatal perinatal asphyxia and HIE are high. The generalization and easy approach of this practice needs to be guided by standardized protocols. Developing training programs and improving infrastructure including neonatal transport are necessary for successful implementation of TH.

What is already known

TH is established standard of care in the developed countries.

What does this study add?

TH is safe, effective, feasible, and can be implemented in lower middle-income countries with better survival and neurodevelopmental outcomes at 18 months of age in asphyxiated neonates.

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Conflicts of interest

There are no conflicts of interest.

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