Original Research Article

Neuro developmental outcome of preterm babies with hypoxic ischemic encephalopathy

Ramya H. S., Rajendra Prasad T. C.*, Nisar Ahamed A. R., Muragesh Awati, Maria George

Department of Pediatrics, Kempegowda institute of Medical sciences, Bangalore, Karnataka, India

Received: 11 March 2019
Accepted: 04 April 2019

*Correspondence:
Dr. Rajendra Prasad T. C.,
E-mail: rajendraprasadt@gmail.com

ABSTRACT

Background: Neonatal encephalopathy, following severe birth asphyxia or perinatal hypoxia is referred to as hypoxic ischemic encephalopathy (HIE). Cerebral ischemia occurs as a consequence of cerebral oedema and reduced cerebral perfusion due to myocardial dysfunction as a result of hypoxic cardiomyopathy. Sarnat stage I -100% recovery, HIE stage II - 80% normal and 20% mortality and HIE stage III - 50% mortality and 50% morbidity. Relatively few studies have been made on outcome in HIE affected preterm infants. The aims and objectives of this study was to find out the neurodevelopmental outcome in preterm infants with HIE.

Methods: This study is an observational clinical study, undertaken in Kempegowda Institute of Medical sciences and research centre, Bangalore, India. Study was performed between November 2016 to September 2018. 31 preterm infants with HIE were included in the study. Regular follow-up was done at 3, 6, 9, 12.15, 18 months by using Trivandrum development screening chart (TDSC) to stage II HIE infants.

Results: The incidence of abnormal neurological outcome was 12.9%. Out of 31 preterm babies, stage I were 24, stage II was 4 (100% morbidity) and stage III were 3 (100% mortality).

Conclusions: In present study, stage II HIE had 100% morbidity and moderate disability, stage III 100% mortality. Thus at 3-5 months of age during follow-up, when authors identify developmental delay, it is an ideal time to start interventional therapy to improve long term outcome.

Keywords: Early intervention, HIE, Neurodevelopment outcome, Preterm infants, Trivandrum development screening chart

INTRODUCTION

Neonatal encephalopathy, following severe birth asphyxia or perinatal hypoxia is referred to as hypoxic ischemic encephalopathy (HIE). Cerebral ischemia occurs as a consequence of cerebral oedema and reduced cerebral perfusion due to myocardial dysfunction as a result of hypoxic cardiomyopathy. Following severe birth asphyxia, 25% infants are likely to develop the syndrome of HIE.

Perinatal asphyxia is one of the predominant causes of neonatal mortality third only to sepsis and prematurity. It is also one of the leading causes of morbidity among children. According to the National neonatal perinatal database (NNPD) network report, the incidence of birth asphyxia is 1.4%.

Cerebral palsy, microcephaly, global developmental delay, seizure disorder is some of the neurological sequelae following hypoxic ischemic encephalopathy.
WHO defines perinatal asphyxia as “failure to initiate and sustain breathing”.

Babies born with birth asphyxia and showing features of hypoxic ischemic encephalopathy should be followed up at regular intervals to detect neurological abnormalities at the earliest and start early stimulation exercises so that their long-term outcome will be better.

The objectives of the study were to study the neurodevelopment outcome of surviving babies with hypoxic ischemic encephalopathy delivered in Kempegowda Institute of Medical sciences and Research Centre, Bangalore, India. Hypoxic-ischemic encephalopathy (HIE), and subsequent morbidity and mortality, is seldom reported in preterm infants. Criteria used in term infants to support a diagnosis of HIE occur for other reasons in preterm infants, where suboptimal Apgar scores, a need for respiratory support, and an inability to suck feed are common. Clinical seizures are often subtle in preterm and defining encephalopathy may be difficult. Few studies have evaluated neurodevelopment outcome, antecedent factors, brain injury patterns in preterm infants with signs of HIE. Basal ganglia and brainstem necrosis are reported following major hypoxia-ischemia (HI) in utero at 37 weeks gestation, but most studies of preterm ischemic brain injury suggest the commonest lesion is wide-spread white matter gliosis. Placental abruption is an identified antecedent factor.

METHODS

This study is an observational clinical study, undertaken in Kempegowda Institute of Medical sciences and Research Centre, Bangalore, Karnataka which is one among the largest teaching hospital in this region.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance.

The following assumptions on data is made assumptions

- Dependent variables should be normally distributed, Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group.

Statistical analysis

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

The study was conducted between November 2016 to August 2018. 1500 babies delivered during this period were studied of which, 421 were preterm deliveries of which, 31 Preterm infants fulfilling inclusion criteria were included in the study. Antenatal and perinatal data were also collected, and developmental assessment was done using Trivandrum development screening chart (TDSC).

Figure 1: Trivandrum development screening chart (TDSC).

Inclusion criteria

- Gestational age (GA) <36 completed weeks,
- Apgar scores< 5 at 1 and <7 at 5 min,
- Major resuscitation (intubation/cardiopulmonary resuscitation/adrenaline) at birth,
- Cranial ultrasonogram.

Exclusion criteria

- Metabolic disorders,
- Congenital malformations/ infections,
- Genetic abnormalities.

Neurodevelopmental outcome

Outcome was assessed at 3, 6, 9, 12, 15, 18 months corrected age. Developmental quotients (DQ) were determined using the Trivandrum developmental screening chart. A structured neurologic exam was performed. Cerebral palsy (CP) was defined.

Outcome classification is as follows

- Normal: normal neurologic exam/DQ >85;
- Mild: delay in motor milestones but no CP and/or DQ 75-85,
- Moderate: athetoid/diplegic CP, DQ >75.
• Severe: spastic/dystonic CP, DQ<50 if assessable, + seizures,
• Death: from severe neurologic problems.

Preterm babies with birth asphyxia admitted in our hospital were first observed for features of hypoxic ischemic encephalopathy. Staging of HIE done with Sarnat and Sarnat staging. At the time of discharge parents were advised to come for follow up, every 3 months. During follow up babies were examined at child development clinic in our hospital.

USG cranium is done to all babies with hypoxic ischemic encephalopathy. If USG cranium is abnormal or neurological examination is abnormal, MRI brain is also done. In babies with abnormal neurological examination, early stimulation exercises are started, and these babies are regularly followed up at our high risk new born clinic.

RESULTS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance.

In the present study 1500 babies delivered in our hospital were enrolled, of which 421 were preterm deliveries of which 31 preterm babies had low apgar score of <5 at 1 minute and <7 at 5 minutes taken as a feature of HIE. 71% of the patients studied were male and 29% were female as per gender distribution.

Table 1: Gender distribution of patients studied.

| Gender | No. of patients | %   |
|--------|----------------|-----|
| Female | 9              | 29.0|
| Male   | 22             | 71.0|
| Total  | 31             | 100.0|

About 3.2% of the babies were of birth weight <2 kg and 96.8% were between 2-2.5 kg, with Mean SD:2287.10±189.28.

Table 2: Gestational age distribution of patients studied.

| Gestational Age | No. of patients | %   |
|-----------------|-----------------|-----|
| 30-33           | 7               | 22.6|
| 33-36           | 24              | 77.4|
| Total           | 31              | 100.0|

Mean±SD: 34.29±1.27

Table 3: Birth weight (grams) distribution of patients studied.

| Birth weight (grams) | No. of patients | %   |
|----------------------|-----------------|-----|
| <2000                | 1               | 3.2 |
| 2000-2500            | 30              | 96.8|
| Total                | 31              | 100.0|

Mean±SD: 2287.10±189.28

There were 22.6% of the babies were between 30-33 weeks gestation and 77.4% were between 33-36 weeks with Mean±SD: 34.29±1.27. 32.3% of the preterm babies

Figure 2: Gender distribution of patients studied.

Figure 3: Birth weight (grams) distribution of patients studied.

Figure 4: Gender distribution of patients studied.

Table 3: Birth weight (grams) distribution of patients studied.
had convulsions on day 1, 54.8% on day 2 and 12.9% on day 3.

Figure 5: Gender distribution of patients studied.

Table 4: Stages of HIE distribution of patients studied.

| Stages of HIE | No. of patients | %   |
|---------------|-----------------|-----|
| 1             | 24              | 77.4|
| 2             | 4               | 12.9|
| 3             | 3               | 9.7 |
| Total         | 31              | 100.0|

Figure 6: Stages of HIE distribution of patients studied.

There were 77.4% of the preterm babies had HIE stage I, 12.9% had stage II, and 9.7% stage III. 38.7% of the preterm babies had maternal history of placental abruption, 61.3% of them had no antenatal risk factors.

Table 5: Day of neonatal seizures distribution of patients studied.

| Day of neonatal seizures | No. of patients | %   |
|--------------------------|-----------------|-----|
| D1                       | 10              | 32.3|
| D2                       | 17              | 54.8|
| D3                       | 4               | 12.9|
| Total                    | 31              | 100.0|

Figure 7: Material history distribution of patients studied.

Table 6: Material history distribution of patients studied.

| Material history          | No. of patients | %   |
|---------------------------|-----------------|-----|
| Nil                       | 19              | 61.3|
| Placental abruption       | 12              | 38.7|
| Total                     | 31              | 100.0|

Figure 8: Outcome distribution of patients studied.

There were 38.7% had meconium staining. USG cranium was done for all babies of which only one had IVH and remaining were normal. Outcome of the present study showed 12.9% of moderate cerebral palsy, 9.7% died and 77.4% were normal. All the babies at birth had normal head size.

Table 7: Outcome distribution of patients studied.

| Outcome       | No. of patients | %   |
|---------------|-----------------|-----|
| Normal        | 24              | 77.4|
| Death         | 3               | 9.7 |
| Moderate      | 4               | 12.9|
| Total         | 31              | 100.0|
Vision and hearing tested clinically were normal in all 31 babies. The mean birth weight of the baby studied was 2.25 kg and mean gestational age was 32 weeks. Out of 31 babies studied, 4 babies had abnormal tone with hypertonia. Detecting it early and starting early intervention can improve the tone and neurological outcome of the baby.

**DISCUSSION**

The 31 babies were followed up till 18 months of age. Incidence of abnormal neurodevelopmental outcome was 12.9%. In the study conducted by Baburaj S et al, developmental delays due to birth asphyxia was 16.7%. In another study conducted by Padayachee N et al, 11.5% had cerebral palsy and 5.3% had developmental delay. Follow up was done till 18 months of age as abnormal neurological outcome can be detected early as early as 3 months and starting early intervention can improve the outcome. In a study conducted by Zafar M et al, developmental delay was found in 9.5% of the healthy children as early as 3 months of age, using Trivandrum development screening chart and 15% were due to birth asphyxia. In a study conducted by Kaye et al, antenatal risk factors identified were ante partum hospitalization, anaemia, ante partum hemorrhage, preeclampsia, and augmentation of labour with oxytocin, MSAF, instrumental delivery and malpresentations. But in present study placental abruption was a maternal risk factor. In this study, an attempt was made to detect abnormal neurological behavior at an early age so that early intervention could be started to improve the outcome. Measurements of head circumference at regular intervals will help to monitor and detect microcephaly. Hence counselling of the parents regarding the follow up visits should be done to detect abnormalities early. These high-risk babies are followed up at 3 months regular intervals to detect subtle neurological abnormalities later. Long term follows up of these babies is necessary to detect subtle neurological abnormalities, and the follow up in this study was done for 18 months.

**CONCLUSION**

In present study the incidence of abnormal neurological outcome was 12.9%. Stage II HIE had 100% morbidity and moderate disability, stage III 100% mortality. The

---

**Table 8: Head circumference (cm).**

| Head circumference (cm) | Min-Max | Mean±SD | Difference | t value | P value |
|-------------------------|---------|---------|------------|---------|---------|
| 1                       | 30.00-35.00 | 33.29±1.35 | -          | -       | -       |
| 3                       | 39.00-42.00  | 40.61±0.74  | -7.321     | -26.875 | <0.001**|
| 6                       | 42.00-44.00  | 43.46±0.64  | -10.179    | -43.129 | <0.001**|
| 9                       | 44.00-48.00  | 45.46±0.84  | -12.179    | -45.523 | <0.001**|
| 12                      | 45.00-48.00  | 46.50±0.69  | -13.214    | -52.057 | <0.001**|
| 15                      | 46.00-49.00  | 47.64±0.62  | -14.357    | -63.680 | <0.001**|
| 18                      | 47.00-50.00  | 48.75±0.70  | -15.464    | -69.936 | <0.001**|

Student t test
early markers predicting neurological sequelae identified were, antenatal risk factors, low apgar scores and hypoxic ischemic encephalopathy. It could be inferred from the study that abnormal neurological outcome could be predicted as early as 3 months of age. Thus at 3-5 months of age during follow-up, when we identify developmental delay, it is an ideal time to start interventional therapy, to improve long term outcome. Long term follow up of these babies is needed to detect subtle neurocognitive abnormalities. Early intervention with physiotherapy results in good prognosis among infants with HIE.

ACKNOWLEDGEMENTS

Authors would like to thank all the studied participant.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Jehan I, Harris H, Salat S, Zeb A, Mobeen N, Pasha O, et al. Neonatal mortality, risk factors and causes: a prospective population-based cohort study in urban Pakistan. Bull World Health Org. 2009;87:130-8.
2. Ekwochi U, Ndu IK, Nwokoye IC, Ezenwosu OU, Amadi OF, Osuorah DI. Pattern of morbidity and mortality of newborns admitted into the sick and special care baby unit of Enugu State University Teaching Hospital Enugu state. Nigerian J Clinic Practice. 2014;17(3):346-51.
3. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing Panorama of cerebral palsy in Sweden XI. Prevalence and origin in birth period 1995-98. Acts Paediatr. 2005;94:287-94.
4. Cordes I, Roland EH, Hill A, Lupton BA. Early prediction of the development of microcephaly after hypoxic-ischemic encephalopathy in the full-term newborn. Pediatr. 1994;93(5):703.
5. Levene MI. Management and outcome of birth asphyxia. Fetal and neonatal neurology and neurosurgery, London: Churchill Livingstone. 1995:427-2.
6. Mizrahi EM, Kellaway P. Characterization and classification of seizures. Neurol. 1987;37:1837-44.
7. Robertson CMT, Perlman M. Follow up of the term infant after hypoxic Ischemic encephalopathy. Pediatr Child Health. 2006;11(5):278-82.
8. Barkovich AJ, Sargent SK. Profound asphyxia in the premature infant: imaging findings. Am J Neuroradiol.1995;16:1837-46.
9. Keeney SE, Adcock EW, McArdle CB. Prospective observations of 100 high-risk neonates by high-field (1.5 Tesla) magnetic resonance imaging of the central nervous system: I. Intraventricular and extracerebral lesions. Pediatr. 1991;87(4):421-30.
10. Salhab WA, Perlman JM. Severe fetal acidaemia and subsequent neonatal encephalopathy in the larger premature infant. Pediatr Neurol. 2005;32:25-9.
11. Cohen M, Roessmann U. In utero brain damage: relationship of gestational age to pathological consequences. Develop Med Child Neurol. 1994;36(3):263-8.
12. Yokochi K. Thalamic lesions revealed by MR associated with periventricular leukomalacia and clinical profiles of subjects. Acta Paediatri. 1997;86:493-6.
13. Marín-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II: white matter lesions of the neocortex. J Neuropathol Exp Neurol. 1997;56(3):219-35.
14. Squier M, Keeling JW. The incidence of prenatal brain injury. Neuropathol Appl Neurobiol. 1991;17:29-38.
15. Mercuri E, Guzzetta A, Laroche S, Ricci D, Cowan FM, Dubowitz LM. 2003 Neurological examination of preterm infants at term age: comparison with term infants. J Pediatr. 2003;142:647-55.
16. Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy. Dev Med Child Neurol. 2005;47:571-6.
17. Baburaj S, Abraham B, Vasant PV, Raj S, Mohandas MK. Growth and development of high-risk graduates till one year from a rural neonatal intensive care unit in South India. Int J Biomed Res. 2013;4(12):695-700.
18. Padayachee N, Ballot DE. Outcome of neonates with perinatal asphyxia at a tertiary academic hospital in Johannesburg, South Africa. SAJCH. 2013;7:89-4.
19. Zafar M, Sheela L. A study on prevalence and antecedents of developmental delay among children less than 2 years attending well baby clinic. People’s J Sci Res. 2009;2(1):9-12.
20. Kaye D. Antenatal and Intrapartum Risk Factors for birth asphyxia among emergency obstetric referrals in Mulego Hospital. East African Med J. 2003;80(3):140-3.
21. Senthilkumar K. Neurodevelopmental outcome of babies with hypoxic ischemic encephalopathy. Int J Res Med Sci. 2017;5(7):3197.