Neuro Developmental Outcome at 6 Months in a Cohort of Term Asphyxiated Newborns with Low APGAR Scores

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Abstract

Objective: This study was carried out to find the impact of APGAR scoring at 1', 5', 15' & 20' and HIE staging on development, its correlation with APGAR Scoring and HIE and to calculate their relative and attributable risks. **Study design:** Prospective cohort study with comparison. **Methodology:** The study group of 110 singleton term babies having birth asphyxia with APGAR score <7 or less at 1 minute was divided into 3 groups: mild, moderate and severe asphyxia according to APGAR scores and HIE staging. Sixty healthy term babies with APGAR score > 7 at 1 minute were enrolled as controls. A monthly developmental assessment was done for upto six months in both study and control groups using Woodside scale which includes following areas: 'Social', 'Hearing and Language', 'Vision and Fine motor' and 'Gross motor'. Statistical analysis consisted of x^2 evaluation for APGAR Score, HIE staging and other perinatal variables in relation to developmental score, with p value of < 0.05 considered significant. Also, the relative and attributable risks and correlation between birth asphyxia and developmental outcome were calculated. **Results:** There was statistically significant relationship between poor developmental outcome and APGAR score of <5 at 1 minute ($p<0.02$). There was statistically significant relationship between HIE staging and neonatal convulsions with developmental retardation ($p<0.001$). **Conclusion:** Patients with HIE stage II & III should be prognosticated with caution and regularly followed up for early detection of neurodevelopmental delay and necessary early intervention as it is a better foreteller than APGAR score for poor developmental outcome.

Introduction:

Perinatal asphyxia is an unchallenged cause of perinatal death, but whether sub lethal degrees of hypoxia result frequently in brain damage in surviving infants is less certain and questionable. Dweck and associates found no difference in Intelligence Quotient (I.Q.) between infants with low APGAR scores and those with 7 or more at 1 minute [1]. Misra et al showed that mortality and poor neuro-developmental outcome correlated inversely with the APGAR scores [2]. Broman reported 9.0% babies having delayed development in contrast to 2.7% by Agarwal et al in newborns with APGAR 0-3 at 1 minute [3,4]. Hence, this study was undertaken to find the impact of APGAR scoring at 1', 5', 15' & 20' and HIE staging on infant development, to find their relative and attributable risks and the correlation between birth asphyxia and developmental outcome.

Material and Methods:

This was a prospective cohort study done in level II NICU of a medical college, after taking approval from institutional review board. The study group comprised of 110

singleton term babies having birth asphyxia with APGAR score 7 or less at 1 minute. Sixty healthy term babies with APGAR score > 7 at 1 minute were enrolled as controls. Preterm, sick and those who had other significant neurological illnesses like CNS infection, congenital malformation and hyper-bilirubinemia requiring phototherapy were excluded.

The Study group was divided into 3 groups: mild, moderate and severe birth asphyxia with APGAR score of 5-7, 3-4 and 0-2 respectively. Gestational age was determined by modified Parkin's criteria [5] as the asphyxiated babies may have affected tone etc.. Antenatal, natal and postnatal risk factors were recorded on the specially designed Performa. HIE staging was done by using modified Sarnat and Sarnat's classification without an EEG [6].

Developmental assessment was done using Woodside scale of development [7] which is a simple screening test and gives the results in a graphic easy to interpret form. It includes following four areas: 'Social', 'Hearing and Language', 'Vision and Fine motor' and 'Gross motor'. In Woodside scale there are 4 charts for graphic representation of the developmental progress of the child. Development was considered satisfactory if the mark lied above the step, doubtful if it lied between the step and the dotted line and delayed if it lied on or below the dotted line. During serial observations a child may show fall off from satisfactory to doubtful or abnormal development. So we had 4 graphs one for each field of development. A scoring system was used to get one interpretation from 4 charts as follows:

Score 1 -If development is satisfactory in all 4 areas.

Score 2- If doubtful in one area.

Score 3 -If doubtful in 2 or more areas

Score 4- If abnormal in 1 or more areas.

Score 5- A fall of in one or more areas.

Cranial Ultrasonography [USG] was done in all cases through anterior, posterior fontanelle and temporo-squamal suture in different plains. First sonography was done within 48 hours of birth and was repeated at monthly intervals if significant abnormality was detected in first ultrasound to look for progression or resolution of abnormalities.

At monthly visits patients were routinely examined, assessed for development by Woodside Scale and cranial USG if any previous abnormality, and patients who were found to have developmental delay were referred for complete workup and early intervention.

Statistical Analysis consisted of x^2 evaluation for APGAR Score, HIE staging and other perinatal variables in relation to developmental score, with p value < 0.05 considered significant. Also the relative and attributable risks and correlation between birth asphyxia and developmental outcome were calculated.

Results:

The study group (Group A) comprised of 110 singleton term asphyxiated babies with APGAR score 7 or less at 1 minute of which 85 (77 %) could be followed up at monthly

intervals for 6 months and rest 25(23%) were lost to follow up. Sixty healthy term babies with APGAR score > 7 at 1 minute were initially enrolled as controls (Group B) out of which 54 (90 %)could be followed up and rest 6 were lost.

More males than females were brought for follow up, in our study. The original male: female ratio was 1.22 : 1 & 1.29 : 1 in control and study group whereas among those followed up it was 1:1 and 2.3 :1 respectively. The abnormal mode of delivery was more commonly associated with low APGAR scores. There was no significant difference in the mean weight and head circumference in control and study groups.(Table I).

Table 1: Patient distribution in the study and control groups

Parameters	Study (Group A) n=85	Control (Group B) n=54	p Value
Male: Female	2.2:1	1:1	p<0.05
Mode of delivery:NVD/LSCS/Breech/Forceps	59%,29%,2%,10%	76%,20%,0,4%	p<0.05
Mean weight	2.75±0.98	2.73±0.84 kg	p>0.05
Mean Head Circumference.	34.00±2.44 cm	34.31±1.70 cm	p>0.05
HIE none	0	54	
HIE Stage I	45(53%)	0	
HIE Stage II	34(40%)	0	
HIE Stage III	6(7%)	0	
1' APGAR >7	0	54	
1' APGAR 5-7	29(34%)	0	
1' APGAR 3-4	41(48%)	0	
1' APGAR <3	15(18%)	0	
Convulsions	19/85(22.3%)	0	

In our study, majority 56 (66%) of asphyxiated newborns had APGAR score <5 at 1 minute. 47% of the neonates with low APGAR had HIE II & III and convulsions were present in 22.3%.

Among the newborns with APGAR Score 5-7, 3-4 and 0-2 at one minute 13.2%, 14.6% and 6.6% respectively had abnormal cranial USG findings whereas 2.1%, 17.6% and

50% neonates with HIE Stage I,II and III had abnormal cranial USG findings. Abnormal USG findings were more commonly associated with increasing severity of hypoxic ischemic encephalopathy rather than to low APGAR scores as per te available data in the study.The only baby with delayed development in the control group was affected in all the four fields of development. Out of 8 babies with delayed development in the study group, 89.5% each were affected in 'Gross motor'and in 'Social, Vision & Fine motor fields', 75% in 'Hearing & Language' and 75% in all the four fields of development.

In our study, prevalence of developmental delay among neonates with 1 minute APGAR score >7 was 1.85%, and 9.4% in babies with low APGAR. There was no significant relationship between mode of delivery and developmental outcome. Similarly, no significant effect of birth weight and head circumference at birth on developmental outcome was noted. There was statistically significant relationship between developmental outcome and APGAR score of <5 at 1 minute ($p<0.02$).T he Relative risk (and attributable risk) of low APGAR Scores at 1 min, 5 min, 15 & 20 min were 5.21(80.8%), 2.53 (60%), 2.45 (50%) & 2.58 (61.2%).Correlation coefficient (r) for APGAR scores and development score as shown in Table II reveal that statistically developmental delay is related to APGAR Score to a very small degree varying from 1.11% to 4.53% at 1 & 20 minutes respectively thereby indicating poor correlation as per the data available.

Table II: Relationship of developmental scores to various parameters

S.No	Parameter	Delayed development	Normal development	P value	RR	AR
1.	1' APGAR <5	7	49	<0.02*	5.21	80.8%
APGAR	n=56					
	1' APGAR ≥5	2	81			
	n=83					
	5' APGAR <5	2	12	<0.5	2.53	60%
	n=14					
	5' APGAR≥5	7	118			
	n=125					
	15' APGAR ≤7	3	23	P<0.5	2.45	50%
	n=26					
	15'APGAR	6	107			

	>7 n=113					
	20'APGAR≤7 n=21	3	18	P<0.5	2.58	61.2%
	20' APGAR >7 n=108	6	102			
2.HIE	HIE II / III n=34 / 6	5/2	29/4	<0.001**	8.75	88.57%
	HIE I / Controls n=45 / 54	1/1	44/53			
3. Convulsion	Convulsions present n=19	6	13	<0.001**	12.6	92.06%
	Convulsions absent n= 120	3	117			

Among the neonates with HIE II & III, 20.2% had developmental delay on follow up (p<.001). There was statistically significant relationship between HIE staging and neonatal convulsions with developmental delay (p<0.001). The Relative risk, Attributable Risk and correlation values between HIE staging and developmental score were 8.75, 88.57% and 10.92 respectively.

Of the neonates with normal cranial sonography findings only 4 % had developmental delay whereas 40%, 80% and 100% neonates with ICH, ventriculomegaly alone and ventriculomegaly with periventricular leucomalacia respectively had developmental delay.

Discussion:

In our study, more males than females were brought for follow up in the study group ie. when the parents were expecting some risk to the baby in the long term, changing male:female ratio from 1.29:1 initially to 2.3:1 in the follow up. This is in agreement with the overall bias towards males in provision of health care as has been observed by

Singh et al [8].This factor also explained 23% loss of patients on follow up in the study group, majority (92%) being females.

There was statistically significant difference between the mode of delivery in control and study group with 'other than a normal' mode of delivery being more commonly associated with asphyxia ($p<.05$) probably because fetal distress lead to emergency intervention.

In our study, none of the baby in the control group had convulsions against 22.3% in study group. Finer et al [9], reported seizures in as many as 69.4% of asphyxiated neonates. However in study by Singh et al [10], seizures occurred in only 7.3% neonates. This can be explained by difference in sample composition and whether asphyxiated neonates who expired were included in the study.

In comparison to 2.1%, 17.6% and 50% neonates with HIE Stage I,II and III who had abnormal sonographic finding in our study, Soni et al & Merchant et al reported a hgher incidence of abnormal cranial USG findings[11,12]. Difference in incidence of sonographic abnormalities can be explained by whether expired cases were included in the study or not.

No significant effect of birth weight and head circumference at birth on developmental outcome was observed as only term babies were included in the study.

In our study, 1.85 % of the neonates with 1 minute APGAR score >7 were having developmental delay on follow up. The reported prevalence by other authors were Broman et al, Drage et al and Nelson et al were 4.9%, 1.7% & 0.2% respectively [3,13,14]. This variation can be explained by differences in the methods of developmental assessment and age at which development is assessed.

In the current study there was significant effect of low APGAR scores at 1 minute on development but no significant effect of APGAR Scores at 5',15' & 20'. Similarly, Drage et al [13] correlated a low 5 minute APGAR score with 4 year development of the child and found no relationship to 4 year IQ scores. Dweck et al [1] found no IQ difference between babies with APGAR scores < 3 at 1 minute and $\geq$7 1 minute. In contrast, in the collaborative Perinatal Project [14], for the infants above 2.5 kg prolongation of low APGAR Score was associated with increasingly high rates of cerebral palsy. Misra et al [2] reported that babies with low APGAR scores at 10 minutes had worse mortality and neurodevelopmental outcome than those with low APGAR scores at 5 minutes

Among the neonates with HIE II & III 20.2% were having delayed development on follow up ($p<0.001$). Similarly, Levene et al [15], Finer et al [9], Merchant et al [12] & Brown et al [16] reported that of the neonates with HIE stage II & III 25.8%, 48%, 55.5% & 63% respectively on follow up revealed delayed development. Similarly Carli et al [17] reported that 36% of the neonates with moderate HIE had either Cerebral Palsy with or without developmental delay or were so severely impaired that they died by 1 year age.Thus, all above studies agree with the greater effect of HIE on infant development. Barnett et al [18] followed 80 term infants with neonatal encephalopathy due to asphyxia and used Griffith scales for developmental testing at 1-2 years of age and

followed up till school age. It was found that a poor score on Griffiths scales at 1-2 year is a good predictor of impairment at school age. However a normal score in early years can't preclude later neurological, perceptual-motor or cognitive abnormality. Bayley Scale is another tool to evaluate infants and toddlers development. Woodside scale is a simple tool can be instituted by a trained nurse and gives a graphic interpretation.Early identification of develpomental delay led to the institution of early interventions available in the form of milestone enhancing exercises in our institute.

In our study, developmental delay was noted in 40%, 80% and 100% of the neonates with ICH, ventriculomegaly and ventriculomegaly with periventricular leucomlacia, respectively. In comparison, Merchant et al [12] reported delay in 62.5% and 60% of neonates with ICH and cerebral hypodensities, respectively. Similarly, Floodmark et al [19] & Azzopardi [20] reported that cerebral hypo-densities correlated well with later developmental outcome. Among newer imaging modalities MR spectroscopy is considered more sensitive and specific than conventional MRI in predicting neuro-developmental impairment. The basal ganglia lactate/ N acetyl aspartate peak/ area ratio is considered an important predictor of developmental outcome [21].But cranial USG has the advantage of portability, in house availability, low cost, not requiring sedation and it requires less time and is feasible during NICU stay.

We had limitations of small sample size and shorter follow up of six months only which can be overcome by further studies of a longer follow up. Also 23% of the study group was lost to follow up especially females which is alarming and requires patient sensitization towards importance of females in the society

Recommendations: On the basis of results of this study, it is suggested that patients with HIE stage II & III should be prognosticated with caution and regularly followed up for early detection of neurodevelopmental delay and necessary intervention as it is a better foreteller of poor developmental outcome .

References:

1.Dweck HS, Huggins WA, Dorman LP, Saxon SA, Benton JW, Cassady G. Developmental sequelae in infants having suffered severe perinatal asphyxia. *Am J obstet Gynecol* 1974, 119:811.

2.Misra PK, Srivastava N, Malik GK, Kapoor RK, Srivastava KL, Rastogi S. Outcome in relation of APGAR score in term neonates. *Indian pediatr* 1994, 31: 1215-1218.

3.Broman S. Perinatal anoxia and cognitive development in early childhood, infants born at risk, NewYork 1979 Spectrum publications.

4. Agarwal S, Chopra K, Gupta S. Asphyxia neonatorum. Indian J Pediatr 1973, 40:422.

5. Parkin JM, Hey EN, Clowes JS. Rapid assessment of gestational age at birth. *Arch Dis Child* 1976, 57:259.

6. Sarnat H, Sarnat M. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographic study. Arch Neurol 1976, 33:696. Modified form copyright 1976, American Medical Association.

7. B SL Eu.Evaluation of a developmental screening systemfor use by child health nurses. *Arch Dis Child* 1986, 6:34-41.

8. Singh RN, Goyal RK. A clinical study of status of girl child in rural area of western Rajasthan. A thesis submitted to University of Rajasthan for the degree of M.D. (Paediatrics), 1992.(Unpublished data)

9. Finer NN, Roberton CM, Kathryn LP, Coward JH.Factors affecting outcome in Hypoxic Ischemic Encephalopathy in term infants. *Am J Dis child* 1983, 137:21.

10. Singh M, Deorari AK, Paul VK. Birth Asphyxia and Neurodevelopmental outcome. *Indian Pediatr* 1989, 26:793-799.

11. Soni JP, Gupta BD, Soni M, Gupta M, Dabi DR, Nemal KR. Ultrasonic diagnosis of intracranial hemorrhage in high risk neonates. *Indian Pediatr* 1995, 32: 453-460.

12. Merchant RH, Khare MD. Diagnostic and prognostic value of CT brain scan in term neonates with moderate and severe birth asphyxia. *Indian Pediatr* 1990, 27:267.

13. Drage J, Berendes H, Fisher P. APGAR scores as they relate to performance on the four-year psychological examination. *Pan Am Health Org. Sci Pub* 1969, 185:222.

14. Nelson KB, Ellenberg JH. APGAR scores as predictors of chronic Neurologic disability. *Pediatrics* 1981, 68 :36-44.

15.Levene MI, Sands C, Grindulis H, Moore JR. Comparison of two methods of predicting outcome in perinatal asphyxia. *The Lancet* 1986, 67.

16.Brown JK, Purvis RJ, Forfar JO, Cockburn F. Neurologic aspects of perinatal asphyxia. *Dev Med Child Neurol* 1974, 16:567-571.

17.Carli G, Reiger I, Evans N (2004) One-year neurodevelopmental outcome after moderate newborn

18.Barnett AL, Guzzetta a, Mercuri E, Henderson SE, Haataja L, Cowan F, DubowitzL (2004) Can the Griffiths scales predict neuromotor and perceptual motor impairment in term infants with neonatal encephalopathy? Arch Dis Child 89:637-643.

19.Floodmark O, Fitz CR, Harwood Nash DC.Computed tomographic diagnosis and Short-term prognosis of intracranial hemorrhage and hypoxix/ ischemic brain damage in neonates. *J Comput Assist Tomogr* 1980, 4:775-787.

20.Azzopardi D. Neuroimaging in infants with Birth Asphyxia. *Pediatr Res* 1989,25:445.

21.Thayyil S, Chanrasekaran M, Taylor A et al. Cerebral magnetic resonance biomarkers for predicting neurodevelopmental outcome following eonatal encephalopathy: a meta analysis. Pediatrics. 2010; 125(2). Available at www.pediatrics.org/cgi/content/full/125/2/e382.