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Research Article

Study of Multiple Organ Failure in Birth Asphyxia and its Correlation with Immediate Neurological Outcome

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Abstract

Introduction: Perinatal asphyxia is one of the most devastating complications associated with the process of birth. It is due to lack of oxygen resulting in impending or actual cessation of life around the time of birth. It is a common disorder with an incidence of 2 - 4 per 1000 newborns. Infants who present with hypoxic ischemic encephalopathy (HIE) secondary to perinatal asphyxia have a high mortality with 15% - 20% of these infants dying during the newborn period. Out of the survivors, over 25% have permanent severe neurological deficits. The reasons being the associations of Multiple Organ Dysfunction Syndrome (MODS).

Materials and Methods: The study was conducted in the department of paediatrics, SCB Medical College and hospital and SVP PG Institute of Paediatrics, Cuttack from August 2016 to July 2018.

Result: Of the study population 11 (24%) developed HIE 1, 18 (41%) developed HIE 2 and 6 (13) developed HIE 3. There is slight male sex preponderance over female. The Apgar score for babies in the control group was 4.5 ± 0.7, HIE 1 was 3.8 ± 1.07, HIE 2 was 3.72 ± 1.13 and HIE 3 was 1.22 ± 1.5. Hence a low Apgar score correlates with a more severe grade of HIE.

Conclusion: Low Apgar scores was at 5 minutes correlates with more severe CNS involvement in the immediate newborn period. There was a proportionate increase in the number of organ systems involved with increasing grades of HIE and this correlation was confirmed by statistical analysis.

Keywords: *Multiple Organ Failure; Hypoxic Ischemic Encephalopathy; Apgar Score*

Background

The incidence of perinatal asphyxia is about 1 to 1.5% in most centres and is usually related to gestational age and birth weight [1]. It occurs in 9% of infants less than 36 weeks gestational age and in 0.5% of infants more than 36 weeks gestational age, accounting for 20% of perinatal deaths. It is a common disorder with an incidence of 2 - 4 per 1000 term newborns. National neonatology forum of India (NNF) has suggested that birth asphyxia should be diagnosed when 'baby has gasping and inadequate breathing or no breathing at 1 minute'. It corresponds to one minute APGAR score of 3 - 6. In 1952, Dr Virginia Apgar devised a scoring system that was a rapid method of assessing the clinical status of the newborn infants at 1 minute of age and the need prompt intervention to establish breathing [2]. Hypoxic ischemic encephalopathy (HIE) is defined as neonatal encephalopathy with intrapartum hypoxia in the absence of any other abnormality. Infants with severe encephalopathy frequently have an adverse outcome. The outcome of those with moderate encephalopathy is less certain.

The Sarnat grades of encephalopathy are commonly used [3]. Acute hypoxia usually affects all the vital organs and not just the brain but may occasionally occur without major dysfunction of other organs. Multisystem involvement may include acute bowel necrosis, renal failure, hepatic injury, cardiac damage, respiratory complications or haematological insult. This requires testing over the early neonatal period (within 24 hours) [4]. Therefore, intend to study the multiple organ dysfunction in birth asphyxia and correlate the immediate outcome of it.

Aim and Objective

To study the patterns of involvement of each major organ/system injury in infants with post-asphyxia HIE with the help of clinical, biochemical and haematological markers and correlate the dysfunction of each organ system with severity of HIE.

Materials

After obtaining the clearance from the institutional ethical committee the study was conducted in the department of paediatrics, SCB Medical College and hospital and SVP PG Institute of paediatrics, Cuttack from August 2016 to July 2018.

Methods

It is a case control study.

In this study all babies born in the Obstetrics and Gynaecology department of SCB Medical College and babies referred to SCB Medical College Hospital and SVP PG Institute of paediatrics within first 24 hours of life were taken into study.

The inclusion criteria are

1. APGAR score by attending paediatrician of ≤ 5 at the time of birth.
2. Foetal distress.
3. Any baby requiring mechanical ventilation at birth.

The exclusion criteria are

1. Preterm baby less than 37 weeks of postmenstrual age.
2. All babies with any severe congenital abnormality that would impact transition from foetal to neonatal life.
3. Neonates born to mother with toxaemia of pregnancy, diabetes mellitus, Rh incompatibility.
4. Neonates having evidence of septicaemia like positive blood culture, urine culture, evidence of meningitis, elevated band cell count, or elevated c-reactive protein value.

Organ specific dysfunction criteria

Cardiovascular system: Hypotention treated with inotrope for more than 24 hours to main tan perfusion.

Respiratory system: Need for ventilator support with oxygen requirements FiO_2 > 40% for at least 4 hours after birth.

Hepatic system: Any one of the following:

1. Aspartate transaminase > 100 i.u. any time during first week.
2. Alanine transaminase > 100 i.u. any time during first week.

Haematological system: Nucleated red blood cells ≥ 26/100 wbcs.

Renal: Any 3 out of 4 of the following:

1. Urine output < 0.5 ml/kg/hr for 24 hrs or more.
2. Blood Urea Nitrogen (BUN) > 40 mg/dl.
3. Serum creatinine > 1 mg/dl or values that increase postnatally.
4. Significant hematuria (>10 rbcs/hpf in centrifuged sample) or proteinuria (2+ by heat coagulation method).

All the investigations were done in the central laboratory of SCB Medical College, Cuttack. Cord bloods collected from these babies were evaluated for routine haematological parameters with special reference to the nucleated RBC count. The peripheral sear was stained with Leishman's stain and studies under the microscope. BUN, Serum creatine were measured by using Systronic S-106 spectrophotometer. The method adopted for BUN estimation was enzymatic urease method and for creatinine alkaline picrate kinetic method employed. Serum aspartate transaminase and serum alanine transaminase were measured using Mod. IFCC UV Kinetic method.

For statistical analysis infants were grouped into case group, i.e. those infants who would go on to develop signs and symptoms of HIE and a control group, i.e. those baby who did not. Continuous variables were compared using the Students' t-Test. The incidence of the various organ involvements was calculated for both outcome groups.

Observation

All the data obtained from the study were compiled and tabulated and inferences were drawn.

Out of 45 babies enrolled in the study 10 (22%) did not developed any features suggestive of HIE and were placed in the controlled group. The rest 35 babies were the study group with 11 (24%) developing HIE 1, 18 (41%) developing HIE 2 and 6 (13%) developing HIE 3.

Gender	Control	HIE-1	HIE-2	HIE-3
Male	6	5	10	4
Female	4	6	8	2
Total	10	11	18	6

Table 1: *Gender distribution in various grades of HIE.*

It shows that 6 (60%) of the babies in the control group were male and 4 (40%) of the babies were female. In the study group 19 (54%) babies were male and 16 (46%) babies were female.

HIE	Control	HIE-1	HIE-2	HIE-3
< 3	1 (10%)	3 (27%)	8 (44%)	6 (100%)
> 3	9 (90%)	8 (73%)	10 (56%)	0 (0%)

Table 2: *Correlation of APGAR score with various grades of HIE.*

In the control group 10% had Apgar score less than 3 whereas 90% had score of more than 3. In the neonatal encephalopathy group 27% of the babies with HIE1, 44% of babies with HIE 2 and 100% of babies with HIE 3 had Apgar score of less than 3. The average Apgar score for babies in the control group was 4.5 ± 0.7, HIE 1 was 3.8 ± 1.07, HIE 2 was 3.72 ± 1.13 and in HIE 3 was 1.22 ± 1.5. It is inferred thereby that as the severity of the Sarnat grade for HIE increases the number of babies with low Apgar score also increases. Hence a low Apgar score correlates with a more severe grade of HIE.

	Routine	Oxygen	Bag and mask	ET tube
Control	2 (20%)	8 (80%)	-	-
HIE-1	-	2 (18%)	7 (64%)	2 (18%)
HIE-2	3 (27%)	1 (09%)	7 (38%)	7 (38%)
HIE-3	-	-	3 (50%)	3 (50%)

Table 3: *Mode of resuscitation in different group.*

Routine war care and stimulation or free flow oxygen were sufficient to resuscitate babies in the control group and babies with only grade 1 HIE. More invasive forms of resuscitation like bag mask ventilation or intubation with endotracheal intubation was required with more severe degrees of HIE with 100% of babies in grade 3 HIE, 76% of babies in grade 2 HIE and 82% of babies with HIE 1 requiring this form.

Nucleated RBC /100WBC	Cases	Controls
0 - 25	19 (54%)	9 (90%)
26 - 50	10 (28%)	1 (10%)
51 - 75	2 (7%)	-
76 - 100	3 (8%)	-
Mean ± SD	30.77 ± 25.95	10.1 ± 8.98
Range	4 to100	2 to28

Table 4: *Distribution of nucleated RBC's in both group.*

The babies in the case group had significantly higher number of NRBCs/100 WBC (mean 30.77 ± 25.95) when compared to the control group (mean 10.1 ± 8.98) and this observation is highly statistically significant (p = < 0.001). The mean ± SD for the nucleated RBC counts in the various stages of HIE were 18.27 ± 20.65 for HIE 1, 23.98 ± 10.26 for HIE 2 and 74.33 ± 23.98 for HIE 3. It is seen that the NRBC counts increased progressively with the greater severity of HIE. Hence NRBC count is directly proportional to the stage of HIE.

HIE stage	N	Sr Urea	Sr Creatinine
Control	10	25.9 ± 7.84	0.66 ± 0.51
HIE-1	11	27.18 ± 13.42	0.54 ± 0.38
HIE-2	18	44.86 ± 18.29	1.13 ± 0.52
HIE-3	6	59 ± 14.91	1.85 ± 0.69
Case	35	41.71 ± 19.45	1.07 ± 0.67

Table 5: *Urea and Creatinine values correlated with the different stages of HIE.*

The mean ± SD of serum urea and creatinine in the control group was 25.9 ± 7.84 while in the case group it was 41.71 ± 19.45. This difference observed was statistically significant. Further it is seen that the serum urea values increase as the grade of HIE increases with a value of 27.18 ± 1342 in HIE 1, 44.86 ± 18.29 in HIE 2 AND 59 ± 14.91 in HIE 3. The mean ± SD of serum creatine in the control group was 0.66 ± 0.51 while in the case group was 1.07 ± 067. This difference observed was statistically significant. Further it is seen that the serum creatinine correlates with the severity of HIE with a value of 0.54 ± 0.38 in HIE 1, 1.13 ± 0.52 in HIE 2 and 1.85 ± 0.69 in HIE 3.

System involvement	Control	Cases
Present	3 (30%)	20 (57%)
Absent	7 (70%)	15 (43%)
Total	10 (100%)	35 (100%)

Table 6: *System involvement in the two groups.*

This table shows that at least one and more system involvement was present in only 3 (30%) of babies in the control group, while it was present in 20 (57%) of babies among the cases. On the other hand, 7 (70%) of babies in the control group and 15 (43%) of babies in the case group did not show signs of any organ system involvement. The difference observed in the two groups was statistically significant ($p < 0.05$) the figures in the parenthesis represent percentages.

	Hematology	CVS	Renal	Hepatic	Pulmonary
Control	1 (10%)	0 (0%)	1 (10%)	2 (20%)	0 (0%)
Cases	16 (45%)	12 (35%)	20 (57%)	9 (26%)	7 (20%)

Table 7: *Patterns of organ specific involvement in the two groups.*

It shows the frequency of different organ system involvement. The renal system was most frequently involved 57% cases, followed by the hematological system 45%, cardiovascular system 35%, hepatic system 26% and the least frequently involved system was the pulmonary system 20%. In the control group, 10% had hematological involvement, 10% renal and 20% had hepatic involvement probably due to co morbid factors.

	Hematology	CVS	Renal	Hepatic	Pulmonary
HIE-1	3 (27%)	0 (0%)	2 (18%)	0 (0%)	1 (%)
HIE-2	7 (39%)	6 (33%)	12 (66%)	4 (22%)	2 (11%)
HIE-3	6 (100%)	6 (100%)	6 (100%)	5 (83%)	4 (66%)

Table 8: *Organ specific involvement in various grades of HIE.*

It is seen that in each system, as the severity of CNS insult i.e. HIE grading increases, there is more involvement of all other organ systems. There is a striking 100% involvement of Hematological system, CVS system and Renal system in HIE 3. In each group the pulmonary system is least frequently involved whereas the renal system is most frequently involved.

	< 3 systems	≥ 3 systems
HIE-1	10 (91%)	1 (9%)
HIE-2	11 (62%)	7 (38%)
HIE-3	0 (0%)	6 (100)

Table 9: *Pattern of multisystem involvement in various grades of asphyxia.*

The difference observed in the occurrence of multiple organ dysfunction (≥ 3 system involvement) between HIE groups 1 and 2 was found to be statistically significant ($p < 0.05$). However, it is clearly evident from the above table that multiple organ dysfunctions have been envisaged in all the babies who manifested symptoms of HIE 3.

Outcome	Control	HIE-1	HIE-2	HIE-3
Discharge	10 (100%)	11 (100%)	14 (82%)	-
Death	-	-	4 (18%)	6 (100%)

Table 10: *Outcome of HIE.*

This table shows that all the babies with HIE 3 expired, while there was a mortality rate of 18% in HIE 2 group. All babies in the control group and HIE 1 survived.

Discussion

Out of 45 babies enrolled in the study, the control of 10 babies constituted 22% of the total. Of the study population, 11 (24%) developed HIE 1, 18 (41%) developed HIE 2 and 6 (13%) developed HIE 3. The higher incidence of more severe HIE grades i.e. grade 2 and 3 (54%) in our study was probably due to the fact that our institute being a tertiary level hospital gets good number of referred cases due to pregnancy complications wherein there is increased chances of fetal asphyxia prior to the birth of the baby.

Table 1 shows the gender distribution in various grades of HIE. It was found that 6 (60%) of babies in the control group were male and 4 (40%) of babies were female. In the study group 19 (54%) babies were male and 16 (46%) babies were female. The male sex preponderance over female was not very much marked as the ratio of Male:Female was 1.18:1 in the case group and 1.5:1 in the control group.

The recent guideline for the diagnosis of birth asphyxia by the American task force has essential criteria like metabolic acidosis, early onset neonatal encephalopathy, cerebral palsy of spastic or dyskinetic type and exclusion of other criteria.it further has some indirect evidences like sentinel hypoxic event, fetal heart rate variability, Apgar score of 3 or less beyond 5 minutes, onset of multisystem involvement within 72 hours of birth and early imaging abnormality [5]. However, it has been reported Martin., *et al.* [6] that the Apgar score at 1 and 5 minutes were the only perinatal factors related to the number of organ involved and the severity of involvement; the apgar score at 5 minutes had the strongest independent association. No relationship with organ dysfunction was found with the umbilical cord arterial blood pH, meconium stained amniotic fluid, umbilical cord abnormalities, presentation, or type of delivery. They have concluded that Apgar score at 5 minutes, is the perinatal marker that may best identify infants at risk of organ dysfunction. Based on this study, we have taken indirect evidences of asphyxia like fetal distress, Apgar score of less than 5 at 5 minutes of life and requirement of mechanical ventilation at birth.

Table 2 shows the correlation of Apgar scores with severity of HIE. All babies had an Apgar score of less than or equal to 5 at 5 minutes as it was an entry criteria. The average score for babies in the control group was 4.5 ± 0.7, HIE 1 was 3.8 ± 1.07, HIE 2 was 3.72 ± 1.13 and HIE 3 was 1.22 ± 1.5. It is inferred from here that a low Apgar score correlates with a more severe grade of HIE. The criteria to ascertain multiple organ dysfunction in birth asphyxia used in our study has been drawn from various studies. The emphasis has been to use clinical and easily available laboratory criteria. Most of the criteria have been drawn from a study Hankins., *et al.* [7] which is similar to our study. Another study by Shah., *et al.* [4] on multiorgan dysfunction also have similar finding as our study. The criteria adopted by Gupta., *et al.* [8] and Mishra., *et al.* [9] have nearly same type of finding as ours.

Table 3 shows a cord nucleated RBC count of ≥ 26 was considered significant to attribute it to the asphyxia process as proposed by Hankins., *et al* [7].

Table 4 shows the babies in the case group had significantly higher number of NRBC/100 WBC (mean 30.77 ± 25.95) when compared to the control group (mean 10.1 ± 8.98) and this observation is highly significant (p value < 0.001). Korst LM., *et al.* [10], Phelan JP., *et al.* [11] and Hanlon-Lundry KM., *et al.* [12] also have made similar observations.

Table 5 shows a rising trend in concentration of blood urea and creatinine was observed as HIE staging of neonate progressed and the difference was statistically significant between babies with no HIE and those with HIE stage 3 ($p < 0.05$). Gupta., *et al.* [8] reported similar trends.

Table 6 shows it is evident that one or more organ system injury is more likely to occur in babies who sustain CNS involvement than in those who do not. Hence a multisystem approach to the management of perinatal asphyxia would help to minimize the morbidity and mortality in such patients.

Table 7 shows using the criteria for hematological system as proposed by Hakins., *et al.* [7], we found an incidence of 45% involvement in our study which is comparable to 54% to their study. The rate of cardiovascular system involvement in the present studies was 35% which is comparable to Goodwin., *et al.* [13] who found it in 35% of their cases and Martin., *et al.* [6] who reported it in 29%. However, Hakins., *et al.* [7] report a much higher frequency of 78.2% as do Shah., *et al.* [4] with 62%. The difference probably due to the different definition criteria adopted by the various studies. Renal system involvement was most frequently observed with 57% which is similar to Perlman., *et al.* [14] with 50% and Martin., *et al.* [6] of 42%. Again Hakins., *et al.* [7] have reported higher incidence of 72% and Shah., *et al.* [4] of 70%. Using similar criteria for Hepatic dysfunction as Shah., *et al.* [4] the rate of affliction was 26% whereas they reported 82% involvement. This difference could be probably due to difference in the timing of sampling of blood. Using Shah., *et al.* [4] criteria for pulmonary system, it was found to be least affected with an incidence of 20% as compared to 86% in their study.

Table 8, 9 and 10 shows Shah., *et al.* [4] in their study followed up their patients looking for adverse outcomes up to 12 months of age. They reported that the rates of adverse outcomes increased as the number of additional organs involved increased from one to three but decreased when an additional four organ were involved. In our study, we have found that the immediate neurological outcome progressively detoriates with more than 2 systems involvement. Only 9% babies in HIE 1 had more than 2 system involved whereas all babies in HIE 3 group had multisystem involvement. it is reasonable to conclude that severe CNS involvement is always associated with involvement of other system.

The outcome of the study shows that HIE 3 carried the highest mortality of 100% and HIE 2 had a 18% mortality with all babies of HIE 1 having uneventful outcome.

Summary

Out of 45 babies enrolled in the study the control of 10 babies constituted 22% of the total. Of the study population 11 (24%) developed HIE 1, 18 (41%) developed HIE 2 and 6 (13) developed HIE 3. There is slight male sex preponderance over female. The Apgar score for babies in the control group was 4.5 ± 0.7, HIE 1 was 3.8 ± 1.07, HIE 2 was 3.72 ± 1.13 and HIE 3 was 1.22 ± 1.5. Hence a low Apgar score correlates with a more severe grade of HIE. Nucleated RBCs were directly proportional to the stage of HIE being 18.27 ± 20.65 for HIE 1, 23.89 ± 10.26 for HIE 2 and 74.33 ± 23.98 for HIE 3. Blood urea and serum creatinine were significantly higher in asphyxiated babies compared to the control group. A rising trend in concentration of blood urea and creatinine was observed as HIE staging of neonates progressed and the difference was statistically significant between babies with no HIE and those with HIE stage 3 ($p < 0.05$). hence there was direct correlation of severe renal injury with more severe CNS insult. One or more organ system injury is more likely to occur in babies who sustain CNS involvement than in those who do not. In our study the pattern of organ involvement was follows in asphyxia injury sufficient to result in CNS damage: the renal system was most frequently involved 57% cases, followed by the hematological system 45%, cardiovascular system 35%, hepatic system 26%, and the least frequently involved system was the pulmonary system 20%. The higher the grade of asphyxia the more chance of involvement of multiple organs. We found that the immediate neurological outcome progressively deteriorates with more than 2 systems involvement. Only 9% of babies in HIE 1 had more than 2 systems involved whereas all babies in HIE 3 group had multisystem involvement. The outcome of our study shows that the HIE 3 carried the highest mortality of 100% and HIE 2 had a 18% mortality, all babies of HIE 1 having an uneventful course.

Conclusion

Low Apgar scores was at 5 minutes, correlates with more severe CNS involvement in the immediate newborn period. There was a proportionate increase in the number of organ systems involved with increasing grades of HIE and this correlation was confirmed by statistical analysis. This leads to conclude that the asphyxia process that is severe enough to produce central nervous system dysfunction, more often than not has already led to dysfunction in the other organ systems. The renal system was most frequently involved and the pulmonary system was least involved. There was no difference in the involvement of essential and non-essential organs. The outcome of babies with more severe grades of HIE was found to be poor.

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