

# Severity of Hypoxic Ischaemic Encephalopathy in Neonates with Birth Asphyxia

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## Abstract

**Background:** To compare the severity of Hypoxic Ischaemic Encephalopathy (HIE) in neonates with birth asphyxia born in Holy Family Hospital (in-cases), and those born at places other than this hospital (out-cases).

**Methods:** This prospective study was carried out in the neonatal unit of Holy Family Hospital, Rawalpindi, from 1st January 2003 to 30th June 2003. One hundred neonates with birth asphyxia were enrolled of which fifty were in-cases and fifty out-cases. They were selected by simple random sampling. The severity of HIE was staged according to Sarnat criteria and these neonates followed daily till discharge and then on fourteenth day of life. At that time HIE outcome was determined as recovered or improved and worsened or died.

**Results:** According to Sarnat's criteria, majority of the neonates were in stage II or stage III at the time of admission of which 38 (76%) were in-cases and 48 (96%) out-cases, (p value 0.006). On univariate and multivariate analysis neonates admitted in stage III had treatment failure twenty-four times more than those neonates who were in stage I and II.

**Conclusion:** Severity of HIE is significantly more in out-cases and is detected earlier in hospital settings.

## Introduction

Birth asphyxia is defined as a severe disturbance of oxygen supply to the fetus which develops during the first or second stage of labour<sup>1</sup>. It is considered in the presence of fetal acidosis, a 5 minute apgar score of less than 7<sup>2</sup> as well as functional disturbance as a result of hypoxic damage to multiple organs including central nervous system<sup>3,4</sup>.

Birth asphyxia is a worldwide problem and its contribution to cerebral palsy and mental retardation constitutes significant morbidity and mortality. Incidence in Pakistan is very high and varies from one centre (60% of admission in neonatal unit)<sup>5</sup> to another<sup>6</sup>. Perinatal events observed in a community based study in Lahore, showed that it affected 2.16% cases with case mortality of 65%<sup>4</sup>. Birth asphyxia is the most common cause of fetal/neonatal injury or death in up to 50 to 60% of cases<sup>7</sup>. Over all it is estimated that it affects 2.9 to 9 neonates per 1000 births and causes 1 million deaths annually on a global basis with an equal number of infants left with serious neurological sequelae<sup>7</sup>. Incidence of birth asphyxia has been reported as 3% in a study<sup>8</sup> and accounts for 7% of neonatal morbidity in another trial<sup>9</sup>.

This study was done to compare the severity of Hypoxic Ischemic Encephalopathy (HIE) in babies with birth asphyxia delivered at Holy Family Hospital (HFH) and those brought from other places.

## Patients and Methods

This prospective comparative study was conducted at Neonatal intensive care unit of the Department of Paediatrics, Holy Family Hospital, Rawalpindi (HFH) from 1st January to 30th June 2003. One hundred neonates with birth asphyxia, 50 born at HFH and 50 born at other places were selected by simple random sampling. Those born in the hospital were called "in-cases" and those born at home or places other than HFH as "out-cases". In-cases and out-cases formed the two comparison groups.

Neonates with birth asphyxia, fulfilling two out of the following four criteria were included in the study: (1) History of fetal distress as reported by obstetrics record (2) Birth history of delayed cry >5 minutes, limpness, cyanosis, apnea for > 1minute (3)

Apgar score < 7 at 1 and 5 minutes of life (4) Need for resuscitative efforts at the time of birth.

Neonates with major systemic malformations, pre-maturity (gestational age < 37 weeks) and weight < 2000gm were excluded from the study. Information was recorded on study proforma at the time of admission. The presence of hypoxic ischaemic encephalopathy was staged using the Sarnat criteria (Table 1) at the time of admission. Neonates were observed daily, using Sarnat criteria till their discharge to see improvement in the stage of HIE. They were followed up and recalled at 14th day of life. At that time HIE outcome was determined as a) Recovered or improved if there was no neurological deficit or when HIE staging improved compared with the stage on admission. This was considered as treatment success. b) Worsened, if there was deterioration of stage compared to that on admission, any neurological deficit or if they died. This was considered as treatment failure.

All data was double entered using Statistical Package for Social Sciences (SPSS) version 10, to minimize data entry errors and for validation. Data analysis was performed using the same software. Chi-square test and logistic regression analysis was done. Odds Ratio (OR) obtained through logistic regression was converted into Relative Risk (RR) using the following formula:

$$RR = OR / [(1-PO) + (PO * OR)]^*$$

Baseline characteristics were expressed as percentage and were compared using Chi-square tests considering the  $p \leq 0.05$  as significant. Univariate analysis was carried out for various important variables and Relative Risk with 95% confidence intervals were calculated. All those variables with a p-value of  $\leq 0.02$  in the Univariate analysis were entered for multiple logistic regression analysis, to assess the independent effect of each variable on HIE outcome. Some interaction terms were entered in the model to see the combined effect of variables on outcome of the treatment.

## Results

Comparisons of demographic characteristics of both groups are presented in Table 2. There was preponderance of male neonates in both groups with 26 (52%) in-cases and 31 (62%) out-cases. The female neonates were more in the in-cases group, 24 (48%) versus 19 (38%) in out-cases. Majority were appropriate for gestational age in both in-cases and out-cases, 44 (88%) versus 40 (80%), where as small for gestational age were 3 (6%) versus 7(14%). Large for gestational age constituted the smallest group 3 (6%) in each group.

**Table 1: Sarnat Criteria**

<i>Signs</i>	<i>Stage I</i>	<i>Stage II</i>	<i>Stage III</i>
<i>Level of consciousness</i>	<i>Hyperalert</i>	<i>Lethargic</i>	<i>Stuporous, coma</i>
<i>Muscle tone</i>	<i>Normal</i>	<i>Hypotonic</i>	<i>Flaccid</i>
<i>Posture</i>	<i>Normal</i>	<i>Flexion</i>	<i>Decerebrate</i>
<i>Tendon reflexes/ clonus</i>	<i>Hyperactive</i>	<i>Hyperactive</i>	<i>Absent</i>
<i>Myoclonus</i>	<i>Present</i>	<i>Present</i>	<i>Absent</i>
<i>Moro reflex</i>	<i>Strong</i>	<i>Weak</i>	<i>Absent</i>
<i>Pupils</i>	<i>Mydriasis</i>	<i>Miosis</i>	<i>Unequal, poor light reflex</i>
<i>Seizures</i>	<i>None</i>	<i>Common</i>	<i>Decerebration</i>
<i>Duration</i>	<i>&lt; 24 hr if progress; otherwise, may remain normal</i>	<i>24 hr- 14 days</i>	<i>Days to weeks</i>
<i>Outcome</i>	<i>Good</i>	<i>Variable</i>	<i>Death, severe deficits</i>

Regarding the weight of neonates which was divided into 4 groups, the maximum number fell into weight group of 3-3.4kg constituting 24 (48%) and 14 (28%) in-cases and out-cases respectively, followed by 3.5-4 kg comprising of 11 (22%) versus 15 (30%), then weight of 2.5-2.9 kg comprising 12 (24%) versus 15 (30%), while only 3 (6%) versus 6 (12%) had the weight of 2-2.4 kg. Spontaneous vertex delivery was higher in out-cases 17 (34%) versus 42 (84%) where as caesarean section was higher in the in-cases i.e. 33 (66%) versus 8 (16%) in out cases.

The variable which showed a significant difference was stage on admission. The maximum number of neonates admitted were in stage II

\* OR=Odds Ratio/adjusted Odds Ratio  
RR=Relative Risk/adjusted Relative Risk  
PO=Prevalence of Outcome in the un-exposed groups

according to Sarnat’s criteria, 36 (72%) versus 41 (82%), both in-cases and out cases forming a big group. There were 12 (24%) in-cases in stage I and 2 neonates as out cases were admitted, where as in stage III there were only 2 (4%) in-cases compared to 7 (14%) out-cases respectively. The p value for both groups was 0.006.

Duration of stay of neonates in the hospital was 1-3 days in 23 versus 16 (46% versus 32%), 4-7 days in 16 vs 20 (32% vs 40%) and 8 or more days in 11 vs 14 (22% versus 28%) in in-cases and out-cases respectively. Most of the neonates stayed for less than 7 days in both groups.

HIE outcome assessed as failure or success on the 14th day of life was 11 vs 13 (22% vs 26%) and 39 vs 37 (78% vs 74%) in in-cases and out-cases respectively. There was no significant difference with regard to outcome at this time.

8 or more days	11 (22)	14 (28)
<b>HIE Outcome</b>		
Failure	11 (22)	13 (26)
Success	39 (78)	37 (74)

**Table 2: Characteristics of Newborns by “In” and “Out” Cases**

Characteristic	In-Case (n=50) # (%)	Out-Case (n=50) # (%)	p-Value
<b>Sex</b>			
Male	26 (52)	31 (62)	0.313
Female	24 (48)	19 (38)	
<b>Weight for Gestational Age</b>			
Appropriate	44 (88)	40 (80)	0.409
Large	3 (6)	3 (6)	
Small	3 (6)	7 (14)	
<b>Weight of Newborn</b>			
2.0 – 2.4 kg	3 (6)	6 (12)	0.205
2.5 – 2.9 kg	12 (24)	15 (30)	
3.0 – 3.4 kg	24 (48)	14 (28)	
3.5 kg and above	11 (22)	15 (30)	
<b>Mode of Birth</b>			
SVD	17 (34)	42 (84)	< 0.001
C-Section	33 (66)	8 (16)	
<b>Stage on Admission</b>			
Stage I	12 (24)	2 (4)	0.006
Stage II	36 (72)	41 (82)	
Stage III	2 (4)	7 (14)	
<b>Duration of Stay</b>			
1-3 days	23 (46)	16 (32)	0.640
4-7 days	16 (32)	20 (40)	

Univariate analysis is given in Table 3. In this analysis association of HIE outcome failures was seen with significant enrolment variables. The only statistically significant association was seen with the Stage on admission. Out of 100 neonates, 12 neonates in Stage I recovered compared to 2 cases that deteriorated (RR 1). Neonates in stage II were 77, out of them 63 improved while 14 did not. RR 1.33 (95% CI 0.27- 5.97). Neonates in stage III were 9 of which only 1 improved while 8 failed to. RR 24.74 (95% CI: 3.52- 46.35). After adjusting for other variables and taking care of the confounding factors, none showed any significant association with treatment failure except variable stage on admission. Stage III showed statistical significance (Table 4).

similar association.

## **Discussion**

This study included full term neonates (> 2kg and > 37wks gestation) admitted in the in-patient and out patient nurseries. There was predominance of male sex in both groups. Ibrahim<sup>10</sup> identified weight of more than 2.5kg and full term neonates, as risk factors leading to birth asphyxia in an analysis of 235 cases. A study done by Abbasi et al reported an incidence of 70% for male neonates presenting with HIE<sup>6</sup>. There was also preponderance of male sex (72%) in a study by Chishty<sup>7</sup>.

More of the Appropriate for gestational age (AGA) neonates in both groups suffered from HIE in this study again with no statistical significance. Chishty<sup>7</sup> in a study at Lahore found 170 AGA neonates out of 200 (85%) suffering from HIE.

Spontaneous vaginal delivery (SVD) was the most common mode of delivery in 42 (84%) out-cases with p value less than 0.001. Chishty<sup>7</sup> noted 166 (83%) SVDs in all out-cases with HIE, in-cases were not included by them due to lack of obstetric unit. Ibrahim<sup>10</sup> noted that SVD was the predominant mode of birth in 202 (86%) neonates admitted with birth asphyxia. Caesarean section (CS) was more in our in-cases, and it has statistical significance. High number of CS in in-cases show skills of detecting perinatal asphyxia in a tertiary care hospital and going for early intervention. CS has also been identified as a risk factor having significant influence, OR = 8.7, (95% CI 3.4, 24. 6) on birth asphyxia with HIE. Studies done by Milsom<sup>11</sup> and Itoo<sup>12</sup> noted a

**Table 3: Univariate Analysis: Association of HIE Outcome Failures with Significant Enrolment Variables**

Variable	Success (n=76)	Failure (n=24)	RR* (95% CI**)
<b>Sex</b>			
Male	42	15	1
Female	34	9	1.26 (0.61 - 2.60)
<b>Weight for Gestational Age</b>			
Appropriate	63	21	1
Large	4	2	1.04 (0.73 - 3.51)
Small	9	1	0.80 (0.25 - 1.09)
<b>Weight of Newborn</b>			
2.0 - 2.4 kg	8	1	0.42 (0.05 - 1.96)
2.5 - 2.9 kg	22	5	0.69 (0.22 - 1.66)
3.0 - 3.4 kg	27	11	1.07 (0.45 - 1.99)
3.5 kg and above	19	7	1
<b>Mode of Birth</b>			
SVD	44	15	1
C-Section	32	9	0.85 (0.40 - 1.60)
<b>Stage on Admission</b>			
Stage I	12	2	1
Stage II	63	14	1.33 (0.27 - 5.97)
Stage III	1	8	24.74 (3.52 - 46.35)
<b>Duration of Stay</b>			
1-3 days	26	13	1
4-7 days	27	9	0.69 (0.27 - 1.65)
8 or more days	23	2	0.19 (0.04 - 0.86)
<b>Case Type</b>			
In	37	13	1
Out	39	11	1.18 (0.59 - 2.38)

\* RR - Relative Risk

\*\* CI - 95% Confidence Interval

**Table 4: Final Multivariate Model showing Predictor(s) of Treatment Failure**

Variable	RR	95% CI
<b>Stage on Admission</b>		
Stage I	1	
Stage II	1.32	0.27-5.97
Stage III	24.74	3.52-46.35

We found a larger number of stage II and stage III in out-cases as compared to in-cases (p value 0.006). As HIE is detected immediately at the time of birth or just afterwards, hence the severity of HIE at admission is less in the in-cases. This supported our study hypothesis. Studies done by Chishty<sup>7</sup> and Ayyapan<sup>13</sup> showed 73% and 64% neonates with HIE (in stage II and III) respectively.

In Univariate analysis (Table 3) stage III HIE is the only variable more than 24 times likely to result in treatment failure (RR 24.74; 95% CI: 3.52 - 46.35). In a study by Thonberg all infants with severe HIE died or developed neurological damage, where as 50% with moderate HIE and all with mild HIE showed a favourable outcome<sup>2</sup>.

In multivariate analysis (Table 4) again only stage III was found to be significant predictor of bad outcome. Neonates in Stage III failed the treatment more than 24 times. Chishty identified Stage III as a risk factor towards mortality<sup>14</sup>. Strongest association in the prediction of neonatal death was seen by comparing Sarnat grade III with grade II (Common odds ratio 24; 95% confidence interval 13-45), by Van de Riet<sup>15</sup>. Also in the prediction of cerebral palsy, the strongest associations were found for Sarnat grade III versus grade II. In factors affecting outcome in HIE Sarnat staging was significantly correlated with outcome in term infants<sup>16</sup>.

There is no statistically significant difference with regard to HIE outcome. The reason may be that most of the neonates in in-cases were delivered by unbooked mothers coming to our hospital for deliveries at the eleventh hour. In booked cases at tertiary level hospitals there is better chance of detecting intrapartum as well as peripartum asphyxia.

Concluding, hypoxic ischemic encephalopathy is more severe in out-cases and detected earlier in hospital settings. It reflects the poor perinatal services offered in those maternity homes or hospitals which are the origin of these out-cases. This stresses the need for strengthening obstetric services at primary and community level nation wide to detect intrapartum asphyxia which is more disastrous than perinatal asphyxia. These services include antenatal monitoring of high-risk pregnancies, timely referral and resuscitation to reduce increasing sequelae related to birth asphyxia reflected as multisystem involvement

and higher mortality.

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