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Assessment of Perinatal Factors, Eeg And Neuroimaging in the Prognosis of Term Asphyxiated Newborns

Dr.Y.Pradeep
[1,2,]*Dr.Y.Pradeep,Dr.Ravikumar, RICH Hospital,Pogathota ,Nellore, Andhrapradesh.*

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ABSTRACT: This research paper is about to deal with the assessment of perinatal factors, EEG and neuroimaging in the prognosis of term asphyxiated newborns with their immediate outcome at the time of discharge from the neonatal intensive care unit ,rich hospital,Nellore. Hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia remains a major cause of neonatal mortality and morbidity worldwide. Randomized control trials of therapeutic hypothermia (HT) for HIE have demonstrated a reduction in the death or severe disability at 18 months of age. However, death and disability continue to occur in 30% to 70% of infants with moderate-to-severe encephalopathy despite treatment with whole body/selective head cooling

KEYWORDS: 1.AED : Antiepileptic drugs
2.aEEG : Amplitude electroencephalogram
3.AMPA : Amino-3-hydroxy-5-methyl-4isoxazole propionate
4.AMP : Adenosine monophosphate
5.ARF : Acute renal failure
6.AS : Apgar score
7.ATP : Adenosine Triphosphate
8. BGT : Basalganglia Thalamus
9.CNS : Central nervous system
10.CP : Cerebral palsy
11.CPK-MBB : Creatinephospokinase Muscle,Brain,Bone
12. CS : Caesarean section
13.CT : Computerized tomography
14.DT : Diffusion tensor
15.DWI : Diffusion weighted imaging
16.EBM : Expressed breast milk
17.EEG : Electroencephalogram
18.HIE : Hypoxic Ischemic Encephalopathy 19.HI : Hypoxic insult
20. HT : Hypothermia treatment
21.LDH : Lactate dehydrogenase
22.LSCS : Lower Segment Caesarean Section
23.MOD : Multiorgan dysfunction
24.MRI : Magnetic resonance Imaging
25.MRS : Magnetic resonance spectroscopy
26.NEC : Necrotising enterocolitis
27. NE : Neonatal encephalopathy
28. NICU : Neonatal Intensive care Unit 29.NMDA : N-Methyl-D –Aspartate
30.NNPD : National neonatal perinatal database
31.NSG : Neurosonogram
32.NVD : Normal Vaginal Delivery
33.OLS :Oligodendrocytes
34.PLIC : Posterior limb of internal capsule
35.PRE-OLS : Premyelinatingoligodendrocytes
36.PVL : Periventricular leukomalacia
37. RDS : Respiratory distress syndrome 38.RNS : Reactive nitrate species
39.ROS : Reactive oxygen species
40. SIADH : Syndrome of Inappropriate secretion of Antidiuretic hormone
41.VEP : Visual evoked potentials

I. INTRODUCTION

DEFINITON: Hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia remains a major cause of neonatal mortality and morbidity worldwide. Randomized control trials of therapeutic hypothermia (HT) for HIE have demonstrated a reduction in the death or severe disability at 18 months of age. However, death and disability continue to occur in 30% to 70% of infants with moderate-to-severe encephalopathy despite treatment with whole body/selective head cooling.1-8 .The localization, distribution and severity of hypoxic-ischemic lesions detected by MRI can be graded and related to outcome. 9-12 However, one issue that remains unanswered is whether early MRI, performed in the first few days of life, in newborns reflects brain hypoxicischemic damage in all its extension.13 This question is crucial since there is a need for an early and accurate identification of infants who will have very severe impairment if they survive. As reported in the recent therapeutic Hypothermia trials, two-thirds of deaths in HIE infants followed withdrawal of life sustaining treatment.4,5 If decisions are delayed, there is a possibility that the infant will survive with very severe long-term disabilities, as end of life decisions are relying more and more on the results of MRI performed in the first days of life.14 The definition of perinatal asphyxia is variably indistinct. 31 The Apgar score has been

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used as a marker for perinatal asphyxia but it has low sensitivity, specificity and predictive value for future outcome. 31-37 A shift to a 23 multiple marker definition was made during the last 20 years using a combination of low Apgar scores, biochemical markers and the need for neonatal resuscitation. These markers reflect intrapartum fetal and neonatal distress33-44 , which can lead to a process of neurological cell injury and brain damage. "Failure to initiate or sustain respiration after birth" has been defined as criteria for the diagnosis of asphyxia by WHO .16 As per the AAP (American academy of Pediatrics) and ACOG (American college of Obstetrics and Gynecology), all the following must be present for designation of asphyxia (a) Profound metabolic or mixed acidemia (pH< 7.00) in cord blood. (b) Persistence of Apgar scores 0-3 for longer than 5 minutes. (c) Neonatal neurologic sequelae (eg, seizures, coma, Hypotonia). (d) Multiple organ involvement (eg, kidney, lungs, liver, heart, intestine) Definitions based on Apgar scores may be useful as it can be used for formulating guidelines for post-asphyxial treatment of neonates. Apgar scores are also useful for predicting long term outcome in infants with perinatal asphyxia. 165,166 These studies address different aspects of Hypoxic-Ischemic Encephalopathy (HIE) as a consequence of acute perinatal asphyxia .These markers reflect disturbances in gas exchange, hypoxia, hypercarbia and 24 acidosis. The infant has delayed onset of breathing and neurological signs of encephalopathy. 15 Hypoxic –ischemic cerebral injury results from a combination of hypoxemia and ischemia, which often is associated with impaired cerebrovascular autoregulation and exacerbated by diminished cerebral glucose substrates, lactic acidosis, the accumulation of free radicals and excitotoxic aminoacids (especially glutamate) and other metabolic derangements .The localization and the extent of the perinatal Hypoxic – Ischemic cerebral injury is determined principally by the maturity of the brain at the time of the insult.17 All the observation raises and suggest the possibilities that an insult that originated much earlier during gestation may predispose some infants to subsequent Hypoxic –ischemic insult at the time of delivery .Anyway, there are extensive experimental, clinical ,and neuroimaging and electrodiagnostic data that provides a compelling evidence that acute intrapartum Hypoxic – ischemic insult is an important etiological factor for neonatal brain injury.17 . Incidence HIE is a serious condition resulting in high morbidity and mortality rates in newborn infants all over the world. 31, 43, 46-49 The incidence of acute neurological symptoms within in the first hour of life with HIE is 1-3 per 1000 live births .In low socio-economic areas the rate is approximately 10 times higher, accounting for one million intrapartum related deaths per year . The incidence of HIE varies between countries and different studies depending on the inclusion criteria and study population.15 According to World Health Organization estimates, in the developing countries 3% of all infants (3.6 25 millions) suffer from moderate to severe birth asphyxia, of which 23% (840,000) die and approximately the same number develop serious sequelae.19 Prevention is more important than treatment. In a developing country like India, the need for risk assessment of perinatal asphyxia is thus obvious. 20 Indian data.

II. SOLENOIDS AS A VALVES IN 2 STROKE ENGINE

A solenoid is simply a specially designed electromagnet. A solenoid usually consists of a coil and a movable iron core called the armature. Here's how it works. When current flows through a wire, a magnetic field is set up around the wire. If we make a coil of many turns of wire, this magnetic field becomes many times stronger, flowing around the coil and through its center in a doughnut shape. When the coil of the solenoid is energized with current, the core moves to increase the flux linkage by closing the air gap between the cores. The movable core is usually spring-loaded to allow the core to retract when the current is switched off. The force generated is approximately proportional to the square of the current and inversely proportional to the square of the length of the air gap.

When an electrical current is passed through the coils windings, it behaves like an electromagnet and theplunger, which is located inside the coil, is attracted towards the centre of the coil by the magnetic flux setup within the coils body, which in turn compresses a small spring attached to one end of the plunger. The force and speed of the plungers movement is determined by the strength of the magnetic flux generated within the coil.

When the supply current is turned "OFF" (de-energised) the electromagnetic field generated previously by the coil collapses and the energy stored in the compressed spring forces the plunger back out to its original rest position. This back and forth movement of the plunger is known as the solenoids "Stroke", in other words the maximum distance the plunger can travel in either an "IN" or an "OUT" direction, for example, 0 to 30 mm

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III. EXPERIMENTATION

This study was carried out in ASRAM hospital over a period of 1 and half year i.e January 2013 to August 2014.The study was enrolled with 451 cases in which 70 asphyxiated neonates were selected on the basis of fulfilling the inclusion and exclusion criteria.In these neonates 5 cases were excluded as non-HIE neonates. Hence forth the study included 65 cases on the basis of fulfilling the inclusion and exclusion criteria with HIE. The total number of neonates which were admitted in ASRAM hospital, Eluru during the study period were 451 in which the neonates with asphyxia were 70 in number which comprises of 15.5 % on the whole number of neonates admitted in NICU. And the remaining 381 with a percentage of 84.5%neonates which were admitted with multiple etiologies like low birth weight, sepsis , hyaline membrane disease, hyperbilirubinemia ,necrotizing enterocolitis. The term neonates which were asphyxiated were 70 in number in these neonates are demarcated based on neurological effects , 5 neonates were non-HIE neonates and 65 HIE neonates . A study conducted by Sitthivuddhi Futrakul et al which was a retrospective study of 17,706 newborns, who were admitted to the Neonatal Unit of King Chulalongkorn Memorial Hospital, from July 1999 till the end of December 2000. In them, 84 infants with perinatal asphyxia were enrolled. All of the possible risk factors that have contributed to asphyxia were identified 86 and recorded HIE was diagnosed based on the Modified Sarnat-Sarnat Score for the diagnosis of neonatal encephalopathy(NE). The categorical data were analyzed for statistical significance ($p < 0.05$) by Chi-square test were performed. Stepwise multiple logistic regression analysis was used to determine the independent factors that may predispose an infant to HIE .167 This study comprises totally of 65 HIE neonates, in them 61.5% males were predominant in number when compared to the 38.5% females included in the study. Sitthivuddhi Futrakul et al study conducted in Neonatal Unit of King Chulalongkorn Memorial Hospital, is coinciding with the present study in describing that male neonates were a significant risk factor for HIE .167 In the present study showing that males and female neonates have percentages of 37.5% and 40% of poor prognosis and good prognosis of 55% and 52%. The death percentage in females is 8% when compared to 7.5% in males.And the p value has been suggested that it is insignificant as there is no relation of the sex with the prognosis of the neonate. In the present study, primigravida mothers have 50.9% of good prognosis and the remaining 39.6% have a poor prognosis , with 9.4 % of deaths.Multigravida mothers have 67% of good prognosis and 33% of poor prognosis and no deaths. A study performed showing that the neonates born to 30% of primigravida mothers and 12% in multigravida mothers have neonatal complications in the form of perinatal asphyxia.179 87 In the present study ,HIE neonates born with meconium staining has 52% of good prognosis and 40% of poor prognosis and 8% of death.Further taking into consideration that the HIE neonates which has been born without the exposure of meconium staining has almost equal prognosis.Hence forth describing in a nut shell that meconium staining of the HIE neonate doesn't change the prognosis of the neonate. And the stastically insignificant p value as been noticed supporting the present study. In a study with meconium stained amniotic fluid was present in 50% of cases which is similar to the finding of Martin-Ancel etal. 174 meconium staining of liquor did not affect the progression to different stages of HIE in neonates with perinatal asphyxia.175This study is correlating with the present study. Cord entangled twice around the neck have 83.4% of poor prognosis and have 16.6% deaths.Cord entangled once around the neck have 75%poor prognosis,25% good prognosis. when the neonates doesn't have cord entanglement 31% have poor prognosis,61.8% have good prognosis. Even though cord around the neck are common and occur 25% -35% of the time ,rarely a neonates cord will be wrapped so tightly around their neck that their body is compressed and oxygen delivery to the neonate is compromised.when this occurs, a caesarean is prudent and in its absence, perinatal asphyxia/death could occur.A cord around the neck mostly are of single and are loosely coiled and less commonly they are tightly coiled.Mercer et al study shows that cord around the neck of 10% - 37% of births, shown to be having short term morbidity.Although studies have shown 88 a clear evidence that not cutting a tight cord around the neck before ,or immediately after birth can result in serious brain injuries and even death.185,186,187 The present study describes that any neonates born with an APGAR score of 5 have 100% good prognosis.Statistically significant p value is supporting this study. Few studies supporting the present study are as follows: Only a 5-minute Apgar score was significantly associated with HIE .167 Persistence of an Apgar score of < 7 and/or intrapartum fetal distress on cardiotocograph could be used as indicators of fetal hypoxia in the absence of arterial cord blood analysis.177 In a study by Shah et al, APGAR score at 5 minute was less than 5 in 63.12% neonates.184 89 The present

study doesn't show the p value statistical significance in the prognosis of the neonate in relation to modes of delivery (LSCS,NVD). There is a study showing to be effective in preventing prolonged NVD and in reducing operative intervention and in improving the neonatal outcome.179 Another study performed by Agarwal et al shows that modes of delivery did not affect the progression to different stages of HIE in neonates with perinatal asphyxia.175 The present study shows that how important a pediatrician presence for a neonatal resuscitation, showing a varied change in prognosis of the neonate.The death percentage in the absence of the pediatrician for a neonatal resuscitation is 80% and in the presence of pediatrician it is only 20%.stastitically significant p value is observed. Sitthivuddhi Futrakul et al study conducted in in Neonatal Unit of King Chulalongkorn Memorial Hospital,Thailand shows that the presence of a Paediatrician during the neonatal resuscitation has shown the importance in prognosis of neonates. All the HIE neonates in the present study are staged into 4 parameters based on Sarnat and sarnat staging clinically ,than those staged neonates are related with the prognosis of the neonates.The neonates with stage I have good prognosis and the neonates which were staged under stage 2 and stage 3 have a higher incidence of poor prognosis and deaths. A study performed by Charlene MT Robertson et al showing that the surviving neonates with stage 3 HIE, as well as those with stage 2 and 90 feeding and swallowing difficulties, should be referred to a developmental therapist.Neonates with continuing seizures or difficult to treat neonatal seizures should have post discharge medical supervision by a physician with knowledge of epilepsy.Newborns with HIE who are adequately feeding on discharge majority fall in stage 1 encephalopathy,including hyperalertness and no hypotonia, these neonates have good prognosis.in newborns surviving with the stages 2 and stages 3 HIE, as well as those with encephalopathic signs persisting at discharge. The neuroimaging and EEG studies which are required for describing the prognosis of the neonate is helpful. Neonates with diffuse echogenicity in the brain parenchyma has 45% of poor prognosis and 55% with good prognosis. Totally 75.3% neonates underwent neurosonogram study in which remaining neonates were expired or were not investigated depending on the clinical correlation. In the present study 61.5% of the neoantes have an abnormal pattern of neurosonogram. MRI is a very good investigation for detection and prognostification of the neonates with HIE.In this study totally 80% of the neonates underwent the investigation. The neonates with the abnormal pattern of BGT involvement are 67.3%. Remaining 32.6% were having a normal pattern of MRI.MRI radiological picture has a stastical significance of p value. Advanced methods of neuroimaging, such as magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and diffusion-weighted MRI, have identified patterns of damage after ischemic insult to the newborn brain. This has been explained Metka Derganc et al in a study of 104 children 91 with evidence of bilateral hypoxic-ischemic brain damage, at least three different patterns were observed with the use of MRI. These patterns are dependent on the gestational age of the infant, because certain neuron groups exhibit age-specific vulnerability.Lesions in the basal ganglia and thalamus occurred in full-term babies who had profound asphyxia. Multicystic changes were seen in a minority of infants who had severe encephalopathy but only a mild hypoxic-ischemic event; this group may include babies who had underlying fetal infections or metabolic disorders that had eluded diagnosis. These data suggest that injury is related to the gestational age at the time of the insult, although the severity or chronicity of the insult may be a better indicator of eventual outcome.170 Several studies performed in the latter years have shown importance of MRI in early diagnosis as well as in follow-up studies of newborns with HIE. Perinatal lesions are best detected between the first and second week of life. Very early MRI, performed within the first three days of life is of clinical importance when deciding whether to continue with treatment or not in the artificially ventilated newborns, but the MRI changes are subtle.170 Standard T1 weighted MRI performed with a 1–1.5 T or stronger machine is best for evaluation of basal ganglia and posterior end of the capsula interna, while T2 weighted MRI imaging is better for early detection of ischemic lesions and imaging differentiating between white and grey matter.170 Diffusion weighted imaging is best for detection of ischemic lesions within the white matter.170 With the use of MRI in newborns with HIE, it is possible to predict the pattern of the later neurodevelopmental deficit.170 92 A study found a high correlation between early and late sequential MRI in HIE infants treated with hypothermia.There data suggest that MRI in the first days of life may be a useful prognostic tool for clinicians and can help in medical issues such as end of life decisions. Further studies evaluating the outcome of these patients and the use of advance imaging techniques, may help to determine the timing for imaging in this population. 176 EEG also helps in prognostication of the neonates and

75.3% neonates were performed with the investigation, in which 69.3 % neonates have got an discontinuous pattern or a burst suppression pattern and the remaining 30.6% has a normal interictal or rapid resolution EEG pattern. This EEG tests have a significant p value. In the study of Pappas et al., EEG recordings showing a discontinuous pattern with voltage suppression or rapid bursts of sharp and slow waves are associated with poor outcome.Rapid resolution of EEG and normal interictal EEG pattern would have a good neurological outcome. 170 Neurophysiologic testing was shown to be useful in helping to predict the outcome in neonatal asphyxia. A study extends several points previously made about the role of EEG in prognostication of the asphyxiated newborns. It is recommended that neurophysiologic testing should be carried out as soon as possible after the acute insult since on monitoring the progress of the EEG and it was found that improvement occurs with time.178 HIE neonates have an higher incidence of ventilator requirement in which 54.6% of neonates have poor prognosis and the mortality is at 93 22.7%.Non-ventilated HIE neonates have good prognosis.There is also a stastical p value significance. A study conducted in Sweden by BoubouHallberg have shown the cortical activity has been shown to be influenced by many factors such as ventilatory management , medication and body temperature. 15 The number of AED's used in the neonates for controlling the seizures also decide the prognosis of the neonates.The neonates with the early usage of AED's has a good prognosis.Usage of multiple AED's in neonates have poor prognosis.Usage of three AED's in a neonates with controlled seizure has higher mortality and moribidity.The neonates in which an AED is not used and when there is no clinical appearance of seizures those neonates have good prognosis. Luis Fernando Garcias da Silva et al study shows, high doses of phenobarbital (40 mg/kg) immediately after birth were related to a better neurodevelopmental outcome of newborns with HIE.169 The authors speculated that allopurinol administration to the fetus with (imminent) hypoxia via the mother during labor might be more effective in reducing free radical induced post-asphyxial brain damage.169 The present study shows that the neonates in whom AED's were continued at the time of discharge have 59.5% poor prognosis and 40.5% good prognosis.In neonates in whom AED's were not continued at the time of discharge have 100% good prognosis.

Ethical issuses and stastiscal analysis methods: Approval for the study has been obtained from the ASRAM medical college Ethics Committee .Ethics committee clearance certificate has been issued. All the data were been taken from the history and the consent has been taken from the parents.The complete data has been kept in the form of a master sheet in the Microsoft word excel 2013 format and the statistical data tables were procceded using the SPSS 17.0 version software. The formula for the p values used for calculation are as follows : Pearson's Chi square test is a statistical test applied to sets of categorical data. Calculate the chi-square test statistic, which resembles a normalized sum of squared deviations between observed and theoretical frequencies. Determine the degrees of freedom of that statistic , which is essentially the 63 number of frequencies reduced by the number of parameters of the fitted distribution. Chi- square test formula : In a statistical significance testing , the p-value is the probability of obtaining a test statistic result at least as extreme or as close to the one that was actually observed , assuming that the null hypothesis is true. And the p values are interpreted as follows: p >0.05 - not significant 0.05<p<p<p

IV. CONCLUSION

1.The incidence of the HIE in neonates in the present study is 15.5%. 2. In the present study ,cord entanglement around the neck has shown a poor prognosis and deaths were noticed. 3. In the present study the neonates having Apgar score

SOME OF THE ADVANAGES FROM THE ABOVE RESULTS

1.The presence of a Paediatrician for a delivery during the neonatal resuscitation has shown a good prognostic value. 2.Prognosis of neonates at the time of discharge is helpful in follow up of the infant to subside the morbidity.

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