Original Article

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Comparison of Injectable Phenytoin and Laveracetam in Control of Neonatal Seizure due to Hypoxic Ischemic Encephalopathy

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ABSTRACT

Objectives: To compare the efficacy of leviracetam and phenytoin as a sole agent in the control of neonatal seizure due to grade II HIE.

Methodology: A Prospective comparative study was conducted in the neonatal ICU of Combined Military Hospital Malir Cantt for 7 months from June 2020 to Dec 2020. Total 60 cases of grade II HIE due to perinatal asphyxia were reported during the study period and were enrolled using simple consecutive sampling technique. Their demographic data, clinical features and frequencies of the selected known risk factors for perinatal asphyxia were recorded. The samples were randomized into two groups using alternate sampling technique. Group A was given I/V Phenytoin while group B was given I/V Laveracetam. The response was measured in terms of seizure control with single drug.

Results: Out of 60 neonates 35(58.33 %) were preterm. Observed risk factors for perinatal asphyxia included gestational diabetes 14(23.3%), pregnancy induced hypertension 10(16.7%), meconium stained liquor 9(15%), fetal bradycardia 8(13.3%) and maternal infections 2(3.3%). Phenytoin alone controlled seizures in 22 (73.3%) cases and was found significantly better than Laveracetam which alone controlled seizures in 19(63.3%) cases. (P-value < 0.001)

Conclusion: Perinatal asphyxia is more common in preterm neonates. Gestational diabetes is the most common risk factor for perinatal asphyxia. Phenytoin is significantly better first line sole antiepileptic agent than Laveracetam.

Keywords: Neonatal seizures, leviracetam, Phenytoin, risk factors

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Introduction

Neonatal seizures are a common neonatal problem with a reported incidence of 1-5.5/1000 live births in term infants, while higher incidence of up to 10-130/1000 live births have been reported in preterm babies.[1] Besides being a frightening incidence for the family, these are associated with significant morbidity and mortality. Reported mortality is as high as 20%.[2] Surviving neonates are at risk of developing intellectual impairment, developmental delay, cerebral palsy, and epilepsy.[3] Various identified causes of neonatal seizure are hypoxic ischemic encephalopathy (HIE) due to birth asphyxia, metabolic derangements, cerebral malformations, central nervous infections, ischemic strokes and inborn error of metabolism[4]. Out of all these most common etiology in term infants is HIE while in preterm neonates it is periventricular hemorrhage.[5]

Underlying etiology, seizures frequency and duration are most significant factors predicting long term CNS consequences in survivors of neonatal seizures. Where HIE, CNS infections, bleed and cerebral malformations are associated with more adverse outcome. [6]

Seizures due to metabolic derangements need only their correction to resolve. While all other fits need anticonvulsants to settle down. Phenobarbitone is the recommended first line antiepileptic drug which due to its difficult availability is being replaced by phenytoin. As a single drug their use is associated with almost 50% failure rate and serious adverse effects like neuroapoptosis.[7] Additionally, phenytoin has difficult availability, has narrow therapeutic index (10-20mg/L), causes cardio toxicity with parenteral use (bradycardia, hypotension), neurotoxicity (cerebellar symptoms), hypersensitivity and rarely purple glove syndrome.[8]

Laveracetam is relatively newer antiepileptic drug with safer profile, good tolerability and has no neurotoxic effects at therapeutic doses. Even with long term use reported side effects include drowsiness, mild fever, headache, and upper respiratory tract infection.[9] Because of good efficacy, laveracetam is now recommendation as a first line antiepileptic agent in management of some forms of childhood epilepsies.[10] However to our knowledge data regarding its use in neonatal seizure is limited.

All the above facts led us to plan a prospective study to compare the efficacy of leviracetam and phenytoin as a sole first line drug to treat neonatal seizure using a therapeutic protocol. HIE being the most common etiology, was used for case enrolment to ensure uniformity and transparency of results. The objectives of our study were to compare the efficacy of leviracetam and phenytoin as a sole agent in control of neonatal seizure due to grade II HIE.

Methodology

This prospective comparative study was carried out in neonatal intensive care unit of Combined Military Hospital Malir cantt Karachi from 1st June 2020 to 31st December 2020 after taking approval from institutional Ethical Review Committee number 1440/2019/Trg/adm. During the study period 60 neonates of grade II HIE, who had clinically observed seizures were reported and enrolled using consecutive sampling method after taking written consent from their parents. All enrolled patients had history of birth asphyxia which was labeled on the basis of poor apgar score (<6) at 5 minutes, or had umbilical cord blood Ph of <7 or who had evidence of intrapartum asphyxia in the form of persistent fetal bradycardia. Although there is no standardized methodology for clinical staging of encephalopathy but Sarnat staging chart (introduced by Sarnat M.S and Sarnat H.B in 1976) was used to identify stage II HIE, characterized by lethargy, hypotonia, meiosis, poor neonatal reflexes and bradycardia (HR < 100 beats/min). (doi.10.137/journal.pone.0122116.t002).

Exclusion criteria included neonates having seizure due to any other etiology like infection, cranial malformation, metabolic derangements, neonates having hypoxic ischemic encephalopathy needing ventilator support (grade III HIE), neonates who died during study due to any reason and those who had other comorbidities like septicemia, severe metabolic derangements. Selection of cases for administration of any type of anticonvulsant was used on alternate basis. Intravenous route was used for first and second dose administration followed by oral maintenance therapy. (If seizures were controlled). Group A (30 cases) received Intravenous phenytoin given at 20mg/kg slow over 30min while group B (30 cases) received intravenous laveracetam at 15mg/kg. In both study groups same dose of same anticonvulsant was repeated once if fits were not controlled with first dose. If fits were not controlled with a single drug (total 3 I/V doses) till 24 hours adjuvant therapy was used to control them. No significant adverse effects of phenytoin or leviracetam were observed in the two study groups. A predesigned Performa was used to record observations. It contained demographic features of enrolled cases like gender, birth weight, age at onset of fits, gestational age at birth, maternal parity, risk factors for HIE, cranial ultrasound findings, development of cerebral edema, response to I/V anticonvulsant and need for adjuvant therapy. Data was analyzed using SPSS version 20. Descriptive statistics like frequencies and percentages were calculated. Comparison of drug efficacy was done using independent sample t- test. Significance level was set at $p < .05$.

Results

Total 60 cases of grate II hypoxic ischemic encephalopathy were enrolled. Out of them 1(1.7%) newborn was extreme premature (born at gestational age of < 28 weeks), 8 (13.3%) were very preterm (gestational age 28-32 weeks), 26 (43.3%) were preterm (gestational age 32-37 weeks) and 25(41.7%) were born full-term. So total 58.33% of study participants were born premature. Age of onset of clinically noticeable seizures was < 24hrs in 27(45%), 24-48hrs in 22(36.7%) and > 72 hours in 11(18.3%) presenting newborns. Type of seizures is shown in table I, tonic fits being most common of all

types of seizures noticed in 31(51.7%) cases. Total 28(46.7%) neonates born to primigravida mothers while 32(53.3%) mothers were multiparous. Table II shows the Identifies risk factors for HIE in the study population. Ultrasound brain was done in each study case which showed showed no significant findings in 45(75%) patients, cerebral edema was seen in 11(18.3%) and hydrocephalus in 4(6.7%) cases. Cerebral edema was also noticed clinically in 13(21.7%) cases. Response of fits to phenytoin and leviracetam in the two study groups has been shown in table III. Group A received phenytoin alone as a first line drug and fits were controlled in 22(73.3 %) cases while 8(26.6 %) cases needed adjuvant therapy. Group B received leviracetam alone as a first line therapy. Fits were controlled in 19(63.3%) cases while 11(36.6%) cases second line or adjuvant therapy. Comparison of the two drugs using independent sample t-test revealed a p-value of <0.01, which showed that phenytoin was better anticonvulsant in controlling fits alone as a first line therapy.

Table I: Types of seizures.(n=60)

Types of Seizure	N(%)
1) Tonic	31 (51.7%)
2) Clonic	5 (8.3%)
3) Myoclonic	9 (15%)
4) Subtle	15 (25%)

Table II: Risk Factors for HIE.(n=60)

Identified Risk features for Birth Asphyxia	N(%)
1) None	1(1.7%)
2) Pregnancy induced hypertension	10(16.7%)
3) Gestational diabetes	14(23.3%)
4) Placental Abruption	6(10%)
5) Meconium stained liquor	9(15%)
6) Decreased Fetal movements	3(5%)
7) Fetal bradycardia	8(13.3%)
8) Cord prolapse	4(6.7%)
9) Maternal infection	2(3.3%
10) Multiple	3(5%)

Table -III: Comparison of Response to anticonvulsant in the two study groups

Response as a single drug	Group A phenytoin (n=30)	Group B Leviracetam (n=30)	p-value
Fits completely controlled Mean+ SD	22(73.3%) 0.727 ± 0.105	19(63.3%) 0.727 ± 0.140	<0.01

Discussion

The predominance of premature neonates in the study population, the type of fits observed, gestational diabetes as the most commonly identified risk factor for HIE, and the superiority of phenytoin over leviracetam in the control of neonatal seizures due to HIE were all notable findings of our study. The results of our study are quite comparable with other studies conducted previously on same subjects.

About 58.33% of our study population consisted of preterm neonates. Literature also advocates that incidence of hypoxic ischemic insult is higher in preterm babies and follow more complex and adverse neurological outcome as compared to the term infants.[11] Since survival rate of the preterm babies is increasing with holistic care of pregnancy and labor, there is a parallel increase in the incidence of periventricular leucomalasia which is a grave neurological consequence of hypoxic ischemic insult. Numerous studies have been conducted in past on the frequency of identified risk factors for HIE. Tosew and his colleagues concluded in their study that maternal illiteracy, primiparous status, low birth weight prematurity and meconium stained liquor were intrapartum risk factors for birth asphyxia.[12] Antepartum risk factors identified by Lilijestrome were null parity, previous cesarean delivery, short stature, overweight, gestational age; occipito-posterior and birth weight.[13] We observed frequency of different identified maternal and fetal risk factors for birth asphyxia. Gestational diabetes was most frequently observed risk factor. Possible reasons for HIE in gestational diabetes are prolong labor and fetal macrosomia which can obstruct labor and cause asphyxia. [14] Other identified risk factors in our study with decreasing frequency included pregnancy induced hypertension, meconium stained liquor, fetal bradycardia, cord prolapse and maternal infections. However, since it was a hospital-based study with labor conducted in a controlled environment these frequency figures may not depict the true prevailing situation at community level and many significant factors like unskilled birth attendant, lack of antenatal care, unavailability of a person trained in performing neonatal resuscitation were not assessed.

Cerebral edema is a well- known neurological complication of HIE. In our study 21.7% neonates had clinical and 18.3% neonates had sonological evidence of cerebral edema. Similar finding was observed in Humsene`s study where 74% of neonates with HIE developed cerebral edema diagnosed on cranial ultrasound. [15] Hydrocephalous is a late sequel of HIE but in our study 6.7% neonates were found to have

hydrocephalous. Most frequently observed type fits in our study were tonic, followed by myoclonic. Although subtle seizures are most frequent type of clinically observed seizures among neonates. Previous data regarding type of seizures in HIE is limited as in most studies seizures have been monitored through continuous electroencephalography recording and type of seizures were not observed clinically.

The essence of our study was the comparison of Phenytoin and Laveracetam as first line and sole therapeutic agent to control of seizures. Phenytoin alone controlled seizures in 73.3% of cases while Leviracetam controlled seizures alone in 63.3% cases. Phenytoin was proved significantly better first line antiepileptic agent in control of neonatal seizures as a sole agent and disproved our null hypothesis that both drugs have equal efficacy. In a study from India efficacy of intravenous Phenytoin and Leviracetam was compared in pediatric age group 3-12 years, irrespective of the cause of fits and no significant difference was observed in control of fits after 24 hours, though bioavailability of Leviracetam was found better than Phenytoin.[16] Similar results were obtained from Turkey where Laveracetam was found even better than Phenytoin in status epilepticus.[17] Gowhar Wan and his colleagues also found Laveracetam more effective than Phenytoin in status epilepticus.[18] Data regarding neonatal seizures is limited. In most studies efficacy of Laveracetam and Phenobarbitone was compared and Phenobarbitone was found superior to laveracetam as first line drug in neonatal seizures due to perinatal asphyxia. [19, 20] While in Gobbhar`s study both drugs were found equally effective.[21] So no conclusive decision regarding superiority of any anticonvulsant can be made. A vast difference in our study and those conducted previously was the dose discrepancy for Laveracetam. Maximum dose of Laveracetam used in our study was 45mg/kg/day. While in other studies upto 60mg/kg of Laveracetam was used before trying other anticonvulsant. Dose increment can change the scenario altogether but at the risk of adverse effects.

Our research had a few limitations. EEG record of the fits could not be obtained. The sample size was too small to generalise and give some conclusive evidence because it was conducted during the COVID-19 pandemic period with relatively lesser patient influx in hospital. Studies with larger sample size and long term follow up are required to accurately assess the drug efficacy and monitor short and long term adverse effects.

Conclusion

Neonatal seizures resulting from type II HIE were more common in preterm as compared to term neonates. Tonic type was most frequently clinically observed form of fits while gestational diabetes was most common identified risk factor for perinatal asphyxia. Phenytoin and laveracetam were both compared for control of neonatal seizures. A significant difference was noted between two groups (p<.001). Phenytoin being better as first line drug to control neonatal seizures .Both drugs can be used as single drug or adjuvant therapy to control neonatal seizures. Both are safe with no noticeable side effects seen in neonatal age groups.

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