Indian Journal of Emergency Pediatrics
Volume 3 Number 4, October - December 2011

Clinical question

Management of Neonatal Emergencies: Current Evidence

Clinical Question: First line drug for treatment of neonatal seizures

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Abstract

Neonatal seizures are usually an acute manifestation of disturbance of the developing brain and are very common in the first weeks of life (1-5 per 1000 live births). The outcome of neonates with neonatal seizures has changed in recent years due to improved prenatal care, better obstetrical care and intensive neonatal care. However, it still remains an important contributor to future neurological complications. Based on this, immediate and aggressive anticonvulsant therapy seems reasonable, but standardized approaches to the treatment of neonatal seizures remain undeveloped. There is a paucity of strong clinical evidence on the efficiency of anticonvulsants and their effects on neurodevelopment. In particular, few studies address the issues related to the use of antiepileptic drugs (AEDs), as first-line and second-line agents. Nevertheless, despite concern about diagnosis, most physicians choose to treat neonates who have seizures, most commonly with either phenobarbital or phenytoin as first line drug. In the current clinical query we have tried to address the unresolved issue of first line drug treatment for neonatal seizures, which would benefit the clinician in taking an evidence based decision for the treatment of neonatal seizures. Development of a safe and effective treatment strategy for neonates with seizures remains an important priority for future research.

Key words: Seizures; Neonate; Phenytoin; Phenobarbitone.

Case scenario

You are newly appointed resident in neonatal intensive care and are emergently called by the nursing staff on duty as she see a 36 weeks baby who suffered perinatal insult with abnormal movements. Even though you are slightly dogmatic about these abnormal movements as seizures or not, you assign the abnormal movements as seizures and decide to treat them as an emergency. The staff prepares the phenytoin in meantime but you order her to give phenobarbitone. She is surprised and asks you, which is the preferred drug to abort the neonatal seizures, as they use phenytoin.

You are now confronted with the following questions:

1. How can the staff think of giving phenytoin as first drug as I remember giving phenobarbitone as first line drug for neonatal seizures? Is it not a 'standard practice' to use phenobarbitone for neonatal seizures?
2. Are there any studies available, which have compared use of phenobarbitone with other antiepileptic drugs for neonatal seizures?
3. If there are any studies, which is the preferred drug for neonatal seizures?

You inform her that you will answer her query after reviewing the available literature.

Clinical questions

Is phenytoin better than phenobarbitone as first line drug for treating neonatal seizures?

Is there any other antiepileptic drug better than phenobarbitone to treat neonatal seizures?

Background

Neonatal seizures represent a distinctive medical emergency. It is a representative signal of severe brain pathology in the neonate which may be a hypoglycemic episode, hypoxic ischemic insult or severe brain malformation.[1] The incidence of this medical emergency varies with gestation and weight with incidence of 57.5/1000 in VLBW babies and 2.8/1000 in

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Table 1 : Observational trials evaluating drug therapy for neonatal seizures

Name	Design	Population	Intervention	Outcome	Comments
Nunnes etal[6] 2008 Arq Neuro psiquiatr	Prospective observational	Preterm and term neonates with seizures N=101	Outcome of neonatal seizures	Phenobarbitone as monotherapy controlled 62% of seizures.	No control group Heterogenous population (preterm and term)
Boylan 2002[7] ADCFN	Observational	Preterm and term neonates with seizures N=14	Effect of phenobarbitone on neonatal seizures	Phenobarbitone as first line drug responded in only 4/14(28%) newborns	No control group. Small sample size Heterogenous population (preterm and term)
Boylan 2004[8] Neurology	Observational	Preterm and term neonates with seizures N=22	Treatment of phenobarbitone failed seizures with second line drug (lidocaine or midazolam)	Phenobarbitone as first line drug responded in only 11/22 (50%)newborns	Small sample size. Heterogenous population (preterm and term)

babies with birth weight more than 2500 gm.[2] It is important to recognize seizures, evaluate for etiology and treat them, as Improper and inadequate management of seizures leads to severe neurological damage.[3] Various categories of drugs (phenobarbitone, phenytoin, lorazepam, lidocaine and newer antiepileptics) have been used for the management of seizures but current management is empiric and untested by well-designed clinical trials.[4] There is a need to develop evidence based guidelines for management of neonatal seizures, both for the neonatologists and pediatric neurologists. To address this paucity of clinical evidence for treatment of seizures, we would try to discuss the evidence based approach for the first line drug management for neonatal seizure. This review would hopefully lay the foundation for future randomized trials and systematic reviews for management of neonatal seizures.

Evidence

As of today, there is only one randomized controlled trail and small observational trials available to address this issue

Randomised controlled trial

The study by Painter et al, 1999, enrolled 59 newborns with electrographic confirmed seizures and compared phenytoin versus phenobarbitone as first line drug.[5] The primary outcome of this study was control of electrographic seizures. Results revealed that both drugs were similarly effective in controlling seizures (RR 1.03 95% CI 0.96 to 1.62), although either of the two drugs was effective in only 45 percent of cases. When either drug was used in conjunction with other, combining resulted in abolishing nearly 70-80% of seizure episodes. This study did not report mortality and short or long term neurodevelopmental outcome.

Other small observational trials (Table 1)

Study done by Nunnes et al[6] while evaluating the outcome of newborns with neonatal seizures, recorded that phenobarbitone alone could control neonatal seizures in as many as 62% of newborns. This study did not compare phenobarbitone with phenytoin as first line agent. Other studies done by Boylan et al in 2002[7] and 2004[8] reported that phenobarbitone as monotherapy controlled seizures in 28% and 50% of cases of neonatal seizures, respectively.

To summarize, using phenobarbitone or phenytoin as monotherapy

- Either of the two drugs did not result in complete cessation of seizures although each responded in nearly 45 % of cases.
- Combining the two resulted in aborting nearly 70-80 % of seizures.
- Effect on mortality and long term outcomes of either drug is not known.

DISCUSSION

The available evidence seems to come from only one RCT which does not favor either of the two drugs and few observational trials. But there are concerns regarding the studies and accepting the validity of the results. The concerns include:

Methodological issues

The only RCT done addressing this issue is not blinded. This could have result in bias as phenobarbitone has been used in most of the neonatal intensive care units since long time and more comfortable in using phenobarbitone as compared to phenytoin. Though the author did not report any bias in level of care provided but non-blinding could result in different level of care in the two groups thus affecting the results.

Heterogeneity of the study population

The RCT as well as the observational trials, enrolled both preterm and term newborns which ranged from <28 weeks gestation to 41weeks. The causes of seizures are different in preterm babies, like intraventricular hemorrhage (IVH) as compared to term babies, like hypoxic ischemic encephalopathy (HIE). Severe IVH may respond differently as compared to severe HIE. There needs to be homogenous study population while enrolling for the study and the results to be interpreted with caution when extrapolating to other study population.

Lack of short term and long term neurological outcome

This is the one of the most important outcomes while addressing the issue of neonatal seizures. Unfortunately the issue of short term outcome –mortality as well as long term neurological outcome were not addressed in this study

Generalization of results

Since this study was done in developed country, the result may not apply to the developing countries where the causes of neonatal seizures may be altogether different. So extrapolating the results in developing countries would not be a good decision.

Currently there is no hard evidence from randomized controlled trials to support the use of any of the anticonvulsant drugs for first line drug therapy in neonatal seizures. Phenobarbitone is still the first choice of drug used in most of the neonatal units, despite its concerns about adverse effects on developing brain. The American academy of pediatrics neurology group proceedings, 2006,[9] on phenobarbitone treatment trial warned that "phenobarbitone might work well in mild seizures but, It is possible that seizures might respond to phenobarbitone differently in other circum-stances such as for severe HIE, in the premature infant, or in those infants whose seizures arise from develop-mental abnormalities such as tuberous sclerosis". There is an urgent need for well designed, multicenter, randomized trial to answer this neonatal medical emergency.[9]

CONCLUSION

To conclude, there is pressing need to develop safe and effective treatment for the neonatal seizures which relies on future studies of high quality and of sufficient sample size to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability in addition to short term gains in reduction of seizures.

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