Phenobarbitone in Neonatal Seizures: Controversies

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Received date: July 19, 2016; Accepted date: August 03, 2016; Published date: August 08, 2016

Abstract

Seizures are defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behaviour and/or autonomic function. Seizures are the most important signal of neurological disease in the neonatal period. They occur in 1-5% of the new-borns [2]. The incidence is higher during this period than in any other period in life. It is important to treat seizures because of the potential adverse effects of seizure on respiratory function, circulation, cerebral metabolism and brain development. If aEEG is being used, termination of all electrical seizure activity should be the goal of therapy. Though mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long term neurodevelopmental sequel has remained almost unchanged at around 30%. This signifies that the treatment of neonatal seizures is still inappropriate and there is a potential for improvement. Current guidelines are based on limited clinical data. The controversies regarding the best first line agent, second line agent, dose and duration, monitoring the drug levels still continue.

Keywords: Depolarisation; EEG; Electrical seizures; GABA; Phenobarbitone; Seizure

Neonatal Seizures

Seizures are defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behaviour and/or autonomic function [1]. Seizures are the most important signal of neurological disease in the neonatal period. They occur in 1-5% of the new-borns [2]. The incidence is higher during this period than in any other period in life.

Seizures can be classified as [3]:

**Epileptic seizures:** Phenomenon associated with corresponding EEG seizure activity, e.g. tonic seizures. 2. Non-epileptic seizures: Clinical seizures without corresponding EEG correlate, e.g. subtle and generalised tonic seizures. 3. EEG seizures: Abnormal EEG activity with no clinical correlation (electroclinical dissociation).

Neonatal seizure activity results from an excessive synchronous electrical discharge (i.e., depolarization) of neurons within the central nervous system. The process of depolarization occurs by the inward migration of sodium (Na+), and repolarization by the efflux of potassium (K+) [3].

Certain clinical seizures (e.g. subtle seizures), most generalized tonic seizures and the focal and multifocal types of myoclonic seizures in the new-born originate from electrical seizures in deep cerebral structures (limbic regions), or in diencephalon, or brain stem structures and thereby are either not detected by surface-recorded EEG or inconsistently propagated to the surface. Treating such phenomenon is still a controversial issue. Electroclinical dissociation is the occurrence of only electrographic seizures not accompanied by clinical seizure activity. This dissociation is especially common in the most immature infants and in those treated with anticonvulsant drugs especially phenobarbitone. The main reason behind this is GABA acting as excitatory rather than inhibitory neurotransmitter in the developing brain. And the usual AEDs which are GABA agonist are unable to diminish the electrical seizure activity completely. The common causes of seizures include hypoxic ischemic encephalopathy, metabolic disturbances (hypoglycaemia, hypocalcemia and hypomagnesemia) and meningitis. Table 1 shows the frequency, time of onset of seizures and typical clinical symptoms for each of them [3].

It is important to treat seizures because of the potential adverse effects of seizure on respiratory function, circulation, cerebral metabolism, and brain development. If an EEG is being used, termination of all electrical seizure activity should be the goal of therapy [3]. Though mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long term neurodevelopmental sequel has remained almost unchanged at around 30% [1]. This signifies that the treatment of neonatal seizures is still inappropriate and there is a potential for improvement. Current guidelines are based on limited clinical data. The controversies regarding the best first line agent, second line agent, dose and duration, monitoring the drug levels still continue.

Phenobarbitone has been historically recommended and popularly used as first choice drug for neonatal seizures in loading dose of 20 mg/kg/dose @1 mg/kg/min. Phenobarbitone acts by facilitating GABA and raising the levels of the drug [4]. Besides this phenobarbitone causes decrease in the effect of paracetamol, increase
in clearance of steroids, rifampicin, theophylline, propranolol and metronidazole [5]. Respiratory effort should be monitored during administration of phenobarbitone.

Despite being most commonly used, various trials have shown limitation of phenobarbital in control of seizures in neonatal period. Moreover, there are concerns regarding its adverse effects on brain. The Cochrane review [6] found only one RCT that showed comparable seizure control rate with phenobarbital and phenytoin (RR 1.03, 95% CI 0.96 to 1.62), controlling seizures in only half of cases. A recent trial by Pathak et al. demonstrated phenobarbitone to be more effective than phenytoin as first line drug in control of clinical seizures [7]. The study by Perveen et al. demonstrated that phenobarbitone is more efficacious than levetiracetam in treatment of clinically apparent neonatal seizures in term and late preterm neonates with seizures due to perinatal asphyxia [8]. Table 2 summarises the various studies comparing the efficacy of phenobarbitone. Based on available evidence, the WHO guidelines on neonatal seizures currently recommend phenobarbitone as the first line agent for management of neonatal seizures [9].

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
<th>Typical clinical symptoms</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic-ischaemic encephalopathy</td>
<td>30-53%</td>
<td>History of delayed cry, poor Apgar, dull baby</td>
<td>1st 6-12 h</td>
</tr>
<tr>
<td>Intracranial haemorrhage (arachnoid hemorrhage)</td>
<td>7-17%</td>
<td>Well baby with seizures CT is diagnostic</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>6-17%</td>
<td>Decrease movement of opposite side but this may not be visible in acute period</td>
<td>Variable</td>
</tr>
<tr>
<td>Cerebral malformations</td>
<td>3-17%</td>
<td>Well baby with seizures head size may be abnormal</td>
<td>Variable</td>
</tr>
<tr>
<td>Meningitis/septicemia</td>
<td>2-14%</td>
<td>Associated with fever, bulging fontanelle</td>
<td>After 3 days</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>0.1-5%</td>
<td>IUGR, preterm, infant of diabetic mother. Exclusive breast feed baby with excess</td>
<td>1st 48 h</td>
</tr>
<tr>
<td>Hypocalcaemia, hypomagnesemia</td>
<td>4-22%</td>
<td>weight loss and decrease urine output</td>
<td></td>
</tr>
<tr>
<td>Hypo-/hypernatraemia</td>
<td></td>
<td></td>
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<tr>
<td>Hyematremia</td>
<td></td>
<td></td>
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<tr>
<td>Inborn errors of metabolism</td>
<td>3-4%</td>
<td>Refractory seizures with no often predisposing factor or consanguinity.</td>
<td>Variable</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>1%</td>
<td>Severe jaundice</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Table 1: Seizure etiology and their frequency.

Painter et al. showed that the dose of 20 mg/kg is necessary to achieve a blood level of about 20 mcg/ml [14]. Jalling et al. reported that convulsion ceased at serum levels between 12 and 30 mcg/ml, although there was a subgroup of convulsing patients whose seizures could not be controlled despite achievement of therapeutic levels [15]. Ouvrier and Goldsmith have also documented seizure control with phenobarbitone levels in range of 7 to 15 mcg/ml [16]. Wasim et al. performed a prospective observational study in 99 neonates and reported clinical seizure cessation in 44 neonates (44%) after a single loading dose of 20 mg/kg of phenobarbital. The study demonstrated that more than a third of neonates with sub-therapeutic serum phenobarbital levels also had clinical control of seizures. This finding indicates that the seizure control may be somewhat independent of serum levels of phenobarbitone. However, the minimum serum phenobarbitone level at which seizure was controlled was 6 mcg/ml. Also, the study recommended serum level monitoring in cases of suspected side effects of this drug, or if multiple doses have been given [17].

The data on safety and efficacy of phenobarbitone in relation to its dosage and blood levels is limited. Following the loading dose of phenobarbitone, giving maintenance doses has been a conventional practice. Twenty-four hours after the loading dose, starting maintenance doses at 3-6 mg/kg/day is the most commonly followed practice. Its purpose is to maintain the serum levels built by the loading dose. Also, it has long half-life of about 72-100 h, which covers the period of maximum probability of seizure recurrence in most cases.

Table 2: Different trials comparing efficacy and control rate of phenobarbitone.

Historically, phenobarbitone prophylaxis has been used for weeks to months even after control of neonatal seizures, to minimize the risk of recurrence [18,19]. However, there is accumulating evidence that its long term use may be associated with neuronal apoptosis that can lead to impairment of behaviour, intelligence, cognition, learning and memory [3]. It has also been demonstrated that early phenobarbitone discontinuation in clinically stable neonates does not lead to increase in breakthrough seizures [20]. There is data to suggest that phenobarbitone administration after seizure control does not improve
neurological outcome [21]. Though WHO has recently recommended stoppage of phenobarbitone within 3 days of loading dose [9], timing of phenobarbitone discontinuation after control of seizure is a matter of debate and needs further research. Theodore et al. [22] have reported that little correlation exists between the rate of phenobarbitone withdrawal and seizure control. He observed no significant difference in recurrence of seizures, irrespective of maintenance therapy after discharge. He also reported that abnormal neurological outcome and cerebral palsy were more common in children discharged on phenobarbitone. A recent trial at our institute by Saxena et al. evaluated the withholding of maintenance doses of phenobarbitone altogether, in a RCT in 154 babies. The study demonstrated that the clinical breakthrough seizures till discharge are not likely to increase on withholding phenobarbitone maintenance after the loading dose. It was observed that mortality and abnormal neurodevelopmental outcomes till 3 months were slightly higher in placebo group, though it was not statistically significant [13].

Due to encouraging results of trials on early cessation of phenobarbitone coupled with well documented adverse effects of drug, WHO has recommended reduction in duration of maintenance therapy to three days after seizure control [9].

Considering the magnitude of seizures in the neonatal period, further studies are warranted for studying the side effect profile, serum drug levels of phenobarbitone and other antiepileptics and long term neurodevelopmental outcomes with different AEDs.

References