Studies on Efficacy of Lidocaine for Status Epilepticus in Neonates

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Abstract

Purpose: Several reports indicate value for lidocaine (Lid) as an adjunctive agent in the treatment of neonatal seizures. The efficacy of Lid for status epilepticus (SE) in neonates was studied retrospectively.

Methods: In this study, SE included prolonged or frequently repeated seizures lasting more than 15 minutes and refractory to treatment with conventional anticonvulsants, such as diazepam, phenobarbital or phenytoin. Medical records of neonates aged less than 1 week who had received intravenous administrations Lid as treatment for SE were reviewed.

Results: Eleven neonates whose gestational ages and birth weights were 26 to 41 weeks and 550 to 3,400 g met the criteria and had received intravenous infusions of Lid as treatment for SE. The administration of Lid was effective in five of six patients with hypoxic-ischemic encephalopathy (HIE), and was ineffective in four patients with intraventricular hemorrhage, or lissencephaly. Maintenance dose of Lid and durations of Lid therapy for successfully treated patients were 2 to 4 mg/kg/hour, and 3 to 7 days, respectively. The blood concentrations of Lid after 24-hours administration were 3.3 to 5.5 \( \mu g/ml \). One remaining patient with HIE developed a bradycardia three hours after starting of Lid. This patient was classified as an ineffective case because administration of Lid was stopped due to toxicity.

Conclusions: Continuous intravenous administrations of Lid appeared effective in neonates with SE associated with HIE.

Key words
Status epilepticus, low-birth-weight infant, neonate, lidocaine, hypoxic-ischemic encephalopathy

Introduction

Status epilepticus (SE) occurs in children of all ages. Recent epidemiologic investigations of SE show heightened morbidity and mortality in newborns and young infants. However, the existing definition of SE in newborns is not precise and not easily applied in clinical investigations or in clinical practice. Several reports indicate value for lidocaine (Lid) as an adjunctive agent in the treatment of SE, intractable epilepsies and neonatal seizures. However, the efficacy of Lid for SE in neonates has not been adequately studied. In this study, we proposed criteria for SE in neonates and retrospectively evaluated the efficacy of Lid for intractable seizures in neonates.

Materials and Methods

The criteria for SE in neonates which we adopted were: prolonged or frequently repeated seizures lasting more than 15 minutes and refractory to treatment with conventional anticonvulsants such as phenobarbital (PB), phenytoin (PHT) or diazepam (DZP); no response to glucose, calcium or magnesium; and mechanical ventilation required during seizures. The seizures were observed and assessed by experts in neonatal intensive care. Treatment outcome for Lid was classified into four levels as follows: excellent: clinical cessation of seizures and adverse events were not reported; good: clinical cessation of seizures but manageable adverse events were reported, or seizures decreased more than 50%
following treatment and no adverse events were reported; **fair:** seizures decreased more than 50% following treatment but adverse events were reported; **ineffective:** no decrease in seizures, or seizures decreased 25–50% following treatment but serious adverse events were reported. Medical records of neonates aged less than 1 week who had received Lid as treatment for SE in neonates were reviewed retrospectively. The study was conducted with the approval of the St. Marianna University School of Medicine ethics committee (approval number 2618).

**Results**

Intravenous infusions of Lid were performed in 11 patients aged less than one week who completely fulfilled SE in neonate criteria. The gestational ages of patients were between 26 to 41 weeks and birth weights were 550 to 3,400 g. The administration of Lid was effective in five of six patients with hypoxic-ischemic encephalopathy (HIE) (**Table 1**), and was ineffective in four patients with intraventricular hemorrhage (IVH), or lissencephaly syndrome (**Table 2**). Two of five patients in whom administration of Lid was effective had also other etiology of seizure such as IVH and meningitis (**Table 1, 1-1, 1-4**). One patient with lissencephaly was diagnosed as Miller-Dieker syndrome by genetic tests (**Table 2, 2-4**). Maintenance dose of Lid and durations of Lid therapy for successfully treated patients were 2 to 4 mg/kg/hour, and three to seven days, respectively. The blood concentrations of Lid after 24 hours administration were 3.3 to 5.5 µg/ml. Five of six patients

**Table 1.** Lidocaine effective cases

<table>
<thead>
<tr>
<th>Patients</th>
<th>Etiology of Seizure</th>
<th>Underlying Condition</th>
<th>Maintenance Dose of Lid (mg/kg/hour)</th>
<th>Duration of Lid therapy (days)</th>
<th>Blood Concentrations (µg/ml)</th>
<th>Types of Seizure</th>
<th>Adverse Events</th>
<th>Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>HIE</td>
<td>None</td>
<td>3</td>
<td>4</td>
<td>3.3</td>
<td>GT</td>
<td>None</td>
<td>Excellent</td>
</tr>
<tr>
<td>1-2</td>
<td>HIE</td>
<td>None</td>
<td>3</td>
<td>3</td>
<td>3.5</td>
<td>GT</td>
<td>None</td>
<td>Excellent</td>
</tr>
<tr>
<td>1-3</td>
<td>HIE</td>
<td>Low birth weight</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>GC</td>
<td>None</td>
<td>Excellent</td>
</tr>
<tr>
<td>1-4</td>
<td>HIE</td>
<td>Meningitis</td>
<td>2</td>
<td>7</td>
<td>5.5</td>
<td>Clonic (multifocal)</td>
<td>None</td>
<td>Good</td>
</tr>
<tr>
<td>1-5</td>
<td>HIE</td>
<td>None</td>
<td>4</td>
<td>3</td>
<td>4.1</td>
<td>GT</td>
<td>None</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Table 2.** Lidocaine ineffective cases

<table>
<thead>
<tr>
<th>Patients</th>
<th>Etiology of Seizure</th>
<th>Underlying Condition</th>
<th>Types of Seizure</th>
<th>Adverse Events</th>
<th>Treatment Outcome</th>
<th>Finally Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>HIE</td>
<td>Low birth weight</td>
<td>Clonic (focal)</td>
<td>Bradycardia</td>
<td>Fair</td>
<td>PTB</td>
</tr>
<tr>
<td>2-2</td>
<td>IVH</td>
<td>None</td>
<td>GT</td>
<td>None</td>
<td>Ineffective</td>
<td>PTB</td>
</tr>
<tr>
<td>2-3</td>
<td>IVH</td>
<td>Low birth weight</td>
<td>Clonic (focal)</td>
<td>None</td>
<td>Ineffective</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>2-4</td>
<td>Lissencephaly</td>
<td>Miller-Dieker Syndrome</td>
<td>GT</td>
<td>None</td>
<td>Ineffective</td>
<td>PTB</td>
</tr>
<tr>
<td>2-5</td>
<td>Epileptic syndrome</td>
<td>None</td>
<td>Myoclonic (multifocal)</td>
<td>Decreased urine output</td>
<td>Ineffective</td>
<td>PTB</td>
</tr>
<tr>
<td>2-6</td>
<td>Lissencephaly</td>
<td>None</td>
<td>GT</td>
<td>None</td>
<td>Ineffective</td>
<td>PTB</td>
</tr>
</tbody>
</table>

Abbreviations: Lid; lidocaine, HIE; hypoxic-ischemic encephalopathy, IVH; intraventricular hemorrhage, GT; generalized tonic, GC; generalized clonic.

Abbreviations: IVH; intraventricular hemorrhage, GT; generalized tonic, PTB; pentobarbital.
who were classified as ineffective case were finally effectively treated by pentobarbital (Table 2, 2-1, 2-2, 2-4, 2-5, 2-6) and the other one was treated by zonisamide (Table 2, 2-3). One remaining patient with HIE developed a bradycardia three hours after starting of Lid. This patient was classified as ineffective case because administration of Lid was stopped due to toxicity (Table 2, 2-1). Decreased urine output was observed in one other patient who was classified as an ineffective case (Table 2, 2-5).

Discussion

Previously reported incidence rates of neonatal seizures were 4% at 30 to 34 weeks of gestational age, more than 10% at less than 30 weeks of gestational age, and more than 12% after 38 weeks gestational age respectively. Clancy reported that the duration of single seizures is usually less than two minutes and continuous SE is rare. Common causes of neonatal seizures include HIE, IVH, central nervous system (CNS) infections and CNS abnormalities. HIE was also the most common etiology in neonatal SE in that study.

Although treatment protocols exist for SE in older children and adults, no standard definition or treatment procedures exist for SE in neonates. The lack of accepted recommendations and supporting clinical data are reflected in the opinions of experts, which are divided fairly equally among the different options at the various stages of treatment. Neonates can tolerate relatively prolonged seizures without suffering massive cell death, but neonates are vulnerable to changes induced by seizures. In neonates, SE could be synonymous with intractable seizures, as we noted in our multi-center collaborative study. Selection of infants for treatment with anticonvulsants or related medication depends on accurate identification of infants with epileptic seizures.

Diagnosis of neonatal seizures without ictal electroencephalography (EEG) studies may be uncertain and questionable. A recent ictal video-EEG study shows that paroxysmal events that were considered to be seizures by clinicians were often non-epileptic paroxysmal events. Ictal EEGs are necessary to distinguish as reliable as feasible between epileptic seizures and non-epileptic events. However, the absence of EEG seizures activity in a newborn may not rule out an epileptic origin for the observed clinical activity. As we could not obtain ictal EEG records from each patient, the seizures were inspected and judged by experts in neonatal intensive care units. In future studies, it will be desirable to differentiate epileptic seizures confirmed by EEG from other epileptiform clinical events. The exclusion of non-epileptic seizures is important for appropriate treatment decisions and evaluating the effects of treatment.

The value of Lid as an adjunctive agent in the treatment of neonatal seizures has previously been reported. In one study, approximately 75% of patients who did not respond to PB and DZP were reported to experience cessation of neonatal seizures within 10 minutes of the start of intravenous administration of Lid. Similar to our current findings, continuous intravenous Lid appeared effective in certain cases of premature infants and neonates with intractable seizures mainly associated with HIE. Hypotension, decreased urine output and arrhythmia were the most general adverse effects in Lid and were identified in 7.3% of patients previously reported. Although two out of eleven patients (18.2%) showed the adverse effects in this study, the extent of events was not serious. Lid was an useful and safe drug for the treatment of neonatal SE.

Several papers from other countries have documented the efficacy of Lid as a second or third line agent in the treatment of neonatal seizures. Our previous collaborative study showed that approximately 10 to 15% of neonates with seizures did not respond to the sequential administration of PB, PHT and DZP, and further treatment was needed. Approximately 15 minutes are needed to observe and to assess the efficacy of drug treatment such as with PB, PHT or DZP, as mentioned in the criteria of SE in neonates used in our survey. Experts in various countries recommend intravenous PB as treatment of choice and intravenous lorazepam or fosphenytoin as additional first-line options for initial therapy in neonatal seizures. If the initial treatment with a benzodiazepine fails to stop seizures, experts intravenous PB is often recommended as treatment of choice, with intravenous fosphenytoin, another first-line option, as the next choice. In summary, we found that continuous intravenous administration of Lid appeared effective in neonates with SE associated with HIE. However, Lid was ineffective in patients with IVH, lissencephaly syndromes or chromosomal abnormalities.

References


