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Original article

Treatments with midazolam and lidocaine for status epilepticus in neonates

Hitoshi Yamamoto [a,*], Masao Aihara [b], Shinichi Niijima [c], Hideo Yamanouchi [d]

[a] *Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan*
[b] *Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan*
[c] *Department of Pediatrics, Juntendo University Nerima Hospital, Tokyo, Japan*
[d] *Department of Pediatrics, Dokkyo Medical University School of Medicine, Tochigi, Japan*

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Abstract

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. To evaluate the underlying conditions, clinical features and treatment of SE in neonates in Japan, a retrospective multi-center study was performed. In the initial investigation, questionnaires were sent to pediatric neurologists in 194 neonatal intensive care units of university hospitals, children's hospitals, and general hospitals throughout in Japan. The questionnaires sought information on the background of each case, types of seizures, etiology of SE, treatments, results and adverse effects of treatment for patients less than 1 week old who had prolonged or frequently repeated seizures lasting more than 15 min and who are refractory to treatment with conventional anticonvulsants, such as diazepam (DZP), phenobarbital (PB) or phenytoin (PHT). As a secondary investigation, 65 cases from nine institutes, which completely fulfilled these criteria and were treated with midazolam (MDL) or lidocaine (Lid) to stop seizures were examined more fully. Subtle seizure and generalized tonic–clonic seizure were the most frequent seizure types. Neonatal SE was most frequently associated with hypoxic–ischemic encephalopathy, followed by intraventricular hemorrhage, central nervous system infections, and cerebral infarction. The final treatment outcome was available for 72.7% and 81.3% of MDL- and Lid-treated patients, respectively. Adverse effects of MDL and Lid were identified in 7.3% and 6.3% of patients, respectively. To reveal electroclinical seizures, clinical seizures without ictal discharge or other non-epileptic movements in neonates was important for appropriate treatment. MDL and Lid were useful drugs for the treatment of neonatal SE.

Keywords: Neonatal status epilepticus; Midazolam; Lidocaine; Multi-center survey; Neonates

1. Introduction

SE occurs at all ages, but particularly in the neonatal period. The definition of SE in newborns is not precise and not easily applied in clinical investigations or in clinical practice. Underlying etiologies are very different in infants compared with older children. Treatment modalities for infants are different from those for other ages. This paper discusses the results of a recent questionnaire survey of neonatal SE in Japan, the criteria of neonatal SE which the authors propose and the recent general problems of neonatal seizures.

2. Materials and methods of multi-center survey

To evaluate the underlying conditions, clinical features and treatment of neonatal SE in Japan, a

* Corresponding author. Tel.: +81 44 977 8111x3321; fax: +81 44 976 8603.
E-mail address: h3yama@marianna-u.ac.jp (H. Yamamoto).

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retrospective multi-center study was performed. In the initial investigation, questionnaires were sent to pediatric neurologists in 194 neonatal intensive care units of university hospitals, children's hospitals, and general hospitals in Japan. The questionnaires sought information on the background of each case, types of seizures, etiologies of SE, treatments, results and adverse effects of treatment for patients less than 1 week old. The criteria of SE which we adopted were prolonged or frequently repeated seizures lasting more than 15 min and refractory to treatment with conventional anticonvulsants, such as DZP, PB or PHT, no response to glucose, calcium and magnesium, mechanical ventilation required during seizures, and further therapeutic options for MDL or Lid needed. Primary answers were received from 123 institutes from which we selected nine institutes (65 cases) in which MDL or Lid were used in multiple cases. As a secondary investigation, 65 cases from the nine institutes with infants having gestational ages raging from 25 to 41 weeks and birth weights from 580 and 3280 g (which completely fulfilled these criteria), were examined more fully. The seizures were inspected and judged by experts in neonatal intensive care units. In these 65 cases (MDL only, 49 cases; Lid only, 10 cases; both, 6 cases), the efficacy of MDL and Lid, which have been used as a further treatment for neonatal SE, was particularly examined. Treatment outcome for MDL and Lid was classified into four levels as follows; *excellent*: seizures were well controlled and adverse events were not reported, *good*: seizures were well controlled but manageable adverse events were reported, or seizures decreased more than 75% 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.

3. Results

Subtle seizure and generalized tonic seizure were the most common types of neonatal seizures. The distribution of types of seizures and the efficacy of further therapeutic options (MDL and Lid) in respective type are shown in Figs. 1 and 2. Frequently repeated seizures were the most common type in neonatal SE. In etiologies of neonatal SE, HIE was most common. PB was still commonly used in neonatal seizures as a treatment prior to MDL or Lid in Japan. Treatments prior to

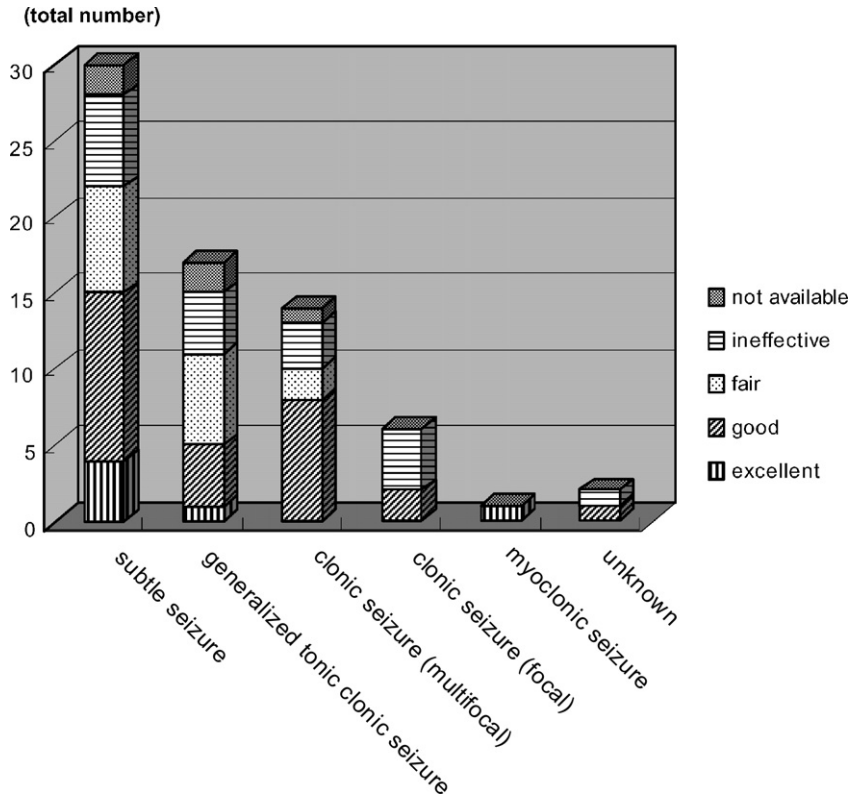

Fig. 1. The seizure types of neonatal seizures and the efficacy of MDL. (*excellent*: seizures were well controlled and adverse events were not reported, *good*: seizures were well controlled but manageable adverse events were reported, or seizures decreased more than 75% following treatment and no adverse events were reported, *fair*: seizures decreased more than 50% following treatment but adverse events were reported, *ineffective*: no decreased in seizures, or seizures decreased 25–50% following treatment but serious adverse events were reported).