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Effectiveness and adverse drug reactions of levetiracetam and midazolam in refractory neonatal seizure: A cross-sectional comparative study

Diptiman Jayswal, Uttam Kumar Roy[1], Taraknath Ghosh[2], Purnendu Mandal[1]

Department of Pharmacology, Burdwan Medical College and Hospital, Bardhaman, West Bengal, India, [1]Department of Pharmacology, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India, [2]Department of Pediatrics, Burdwan Medical College and Hospital, Bardhaman, West Bengal, India

Address for correspondence:
Dr. Uttam Kumar Roy, Dilip Das Sarani, Hill View Main, Paschim Bardhaman - 713 304, West Bengal, India.
E-mail: uroy951@gmail.com

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Abstract:

BACKGROUND: Neonatal seizure (NS) reflects serious underlying brain injury, requiring immediate evaluation and early treatment. In neonates, phenobarbitone and phenytoin are used primarily to control the seizures. If uncontrolled, widespread off-label use of midazolam and levetiracetam was practiced. These drugs gained popularity though there are no such studies available on literature search comparing them. The present study was designed to explore these lacunae using these two drugs in refractory cases. To study the efficacy and adverse drug reactions (ADRs) of midazolam and levetiracetam not responding to usual line of therapy.

MATERIALS AND METHODS: This was a prospective cross-sectional study conducted on 69 neonates in the NICU and Department of Pharmacology in Burdwan Medical College and Hospital, West Bengal. Patients receiving midazolam or levetiracetam when uncontrolled with first line antiepileptics, namely, phenobarbitone and phenytoin, were considered eligible. The study variables were time to control seizure, seizure recurrence and frequency, and treatment-related adverse events. analysis used Mann–Whitney U-test were applied Comparison with respect to time to control and Chi-square test were applied to detect difference in proportion for ADRs. The SPSS Statistics 17.0 was used for analysis.

RESULTS: We compared the time periods to control neonatal seizure for effectiveness between levetiracetam and midazolam showing no significant difference ($P = 0.190$). Comparing the portion of recurrences in two groups gives statistically nonsignificant ($P = 0.878$) result. Only respiratory depression was seen in the levetiracetam group (12.90%) and midazolam group (18.42%). All adverse events were 'probable' as per the WHO-UMC criteria, and there was no statistically significant difference between the two drugs ($P = 0.533$).

CONCLUSIONS: Both midazolam and levetiracetam are equally effective and safe in NS not responding to usual line of treatment.

Keywords:

Adverse drug reactions, levetiracetam, midazolam, neonatal seizure

Introduction

Seizure is defined clinically as a paroxysmal alteration in neurological function, i.e., motor behavior, and/or autonomic function.[1] Neonatal seizure (NS) patients are at a high risk of neonatal death or neurological impairment and seizure disorders in later life. With better availability of treatment options, mortality rate from NS has decreased from 40% to even as low as 7% in a study published in

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2006.[2] More recent data from a population-based study revealed that the incidence of NS was 78.6/100,000 persons-years (boys 88.1/100,000, girls 68.6/100,000). The same study revealed that the incidence of epilepsy after NS was 15.2% (8.2% for male, 23.5% for female, 16.3% in term, and 14.3% in preterm patients).[3] The prevalence of long-term neurodevelopmental sequel remains high in the patients of NS.[4,5]

NS frequently reflects serious underlying brain injury, so requires immediate evaluation and early treatment. Over the past few decades, etiological profile of NS s has altered depending on many factors including advances in obstetric/perinatal care, magnetic resonance imaging (MRI), diffusion-weighted MRI, and positron emission tomography scans which have helped raise the recognition of previously undiagnosed disorders. The increased use of electrodiagnostic techniques such as amplitude-integrated EEG (aEEG) or multichannel EEG monitoring in at-risk populations has improved our understanding of what constitutes a NS and therefore its incidence and treatment response.[6]

In NSs, phenobarbitone is a well-known first-line anticonvulsant agent (82% in US centers) according to international survey data.[7-9] In our setup, phenobarbitone and phenytoin are used primarily to control the seizures. The Cochrane Review found only one RCT that showed comparable seizure control rate with phenobarbitone and phenytoin (relative risk: 1.03, 95% confidence interval: 0.96 to 1.62), controlling seizures in only half of cases.[10] In the lack of clear-cut evidence or guidance, when no response is obtained with conventional antiseizure drugs, off-label agents are often administered, such as levetiracetam, topiramate, lidocaine, and midazolam.[11] However, if seizure remains uncontrolled, usually, the benzodiazepines such as lorazepam or midazolam have been also tried.[12] Midazolam has gained interest among the clinician due to shorter half-life and rapid onset of action as well as easy availability.[13,14] However, benzodiazepines in many cases are associated with respiratory depression which may be fatal if unmonitored there is also fall of BP following IV administration of benzodiazepines.[15] Studies show that midazolam was effective as a first-line abortive emergency treatment of NS, but there is lack of knowledge in this regard.[16] Levetiracetam, relatively new anticonvulsant, gained popularity in the recent past due to its efficacy in control of seizure disorder with safety profile and it is also associated with greater than 50% seizure reduction in 35% of cases.[17,18]

A recent survey among pediatric neurologists suggests quite widespread off-label use of levetiracetam for refractory NS despite lack of evidence on the safety, pharmacokinetics, and efficacy of its use in neonates.[19] No respiratory or cardiac adverse effects were reported or detected.[17] However, there are limited data that compare midazolam with levetiracetam used in this situation.

Therefore, our aim was to compare relative safety and efficacy of midazolam with levetiracetam in Neonatal seizure not controlled with phenobarbitone and phenytoin.

Materials and Methods

This was a prospective cross-sectional study conducted in the Neonatal Intensive Care Unit (NICU) and the Department of Pharmacology of Burdwan Medical College and Hospital. Duration of our study was 19 months, of which data were collected for 16 months (February 2018 to May 2019). We used a predesigned case record form (CRF) for the purpose of data collection. After approval from the Institutional Ethics Committee, we started recruitment of participants through consecutive sampling method, and the data were collected using a predesigned CRF.

Sixty-nine NS patients when not controlled with first-line antiepileptics, namely phenobarbitone and phenytoin, and had received midazolam or levetiracetam were considered eligible for data collection. The dose of phenobarbitone was 20 mg/kg/IV slowly over 20 minutes (not faster than 1 mg/kg/min). If seizures persisted after completion of this loading dose, an additional dose of phenobarbitone 10 mg/kg was used every 20–30 min until a total dose of 40 mg/kg has been given. Phenytoin was indicated if the maximal dose of phenobarbitone (40 mg/kg) fails to resolve seizures or earlier and if adverse effects such as respiratory depression, hypotension, or bradycardia ensue with phenobarbitone. The dose was 20 mg/kg IV at a rate of not more than 1 mg/kg/min under cardiac monitoring. Phenytoin was diluted in normal saline as it is incompatible with dextrose solution. A repeat dose of 10 mg/kg was given in refractory seizures. Midazolam was used as 0.15 mg/kg IV bolus followed by infusion of 0.1 to 0.4 mg/kg/h.[20] Levetiracetam was used in loading dose: 40 mg/kg iv infused over 15 min.[21] They were observed for at least 48 hrs. Term neonates having birth weight >2.5 Kg who have completed 37 weeks of gestational age presented with seizure in the NICU were included in this study. Babies having seizure due to correctable metabolic abnormalities (hypoglycemia and hypocalcaemia) were excluded.

The study variables were time to control seizure, seizure recurrence and frequency, and adverse drug reactions (ADRs) observed in the study period. All demographic variables of neonates like age, gender,

gestational age, mode of delivery, and birth weight were recorded. D ata of the clinical condition of the baby were recorded including heart rate and respiration rate on admission. Blood biochemistry including plasma bilirubin, plasma calcium, blood sugar on admission and complete hemogram were checked on admission. Seizure related information like time to control seizure and seizure recurrence were recorded. We also observed. Treatment-related adverse events including evidence of clinical signs of apnea, cyanosis, respiratory depression, need of ventilation. Other information such as involuntary abnormal movement (restlessness, shivering, and shaking), hypotension, fever, soreness of mouth, and skin rash were documented. All neonates were observed for ADRs 48 h after receiving midazolam or levetiracetam.

The collected data were tabulated for descriptive statistics as well as for inferential statistics. Comparison of time taken in each group by Mann–Whitney U-test was done. Chi-square test was applied to detect difference in proportion for ADRs. Alpha level was set at 0.05 before data collection. $P < 0.05$ was considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 17.0 was used for the purpose of statistical analysis.

Results

A total of 69 patients were recruited as per availability during the study period who matched the inclusion and exclusion criteria by consecutive sampling method. All of these patients received levetiracetam and midazolam in NS not controlled with phenobarbitone and phenytoin in the NICU in the Department of Paediatrics, Burdwan Medical College and Hospital.

The sociodemographic profile of all patients belonged to the age group of neonates is depicted in Table 1.

To determine the effectiveness between levetiracetam and midazolam, we compared the time periods to control seizure but the time distribution was not normally distributed (Shapiro–Wilk test). We performed Mann–Whitney U-test. Significance level (alpha) was set at 0.05 and as *P* value was = 0.190 null hypothesis was retained. There was no difference in time to respond in two groups statistically. The mean time duration and Hypothesis Testing revealed no statistically significant difference (P = 0.190) [Tables 2 and 3].

Effectiveness in the two groups was measured by comparing the proportion of recurrences in two groups using Chi-square test of proportion. Recurrence of seizure was almost similar in the two groups. In the levetiracetam group, recurrence rate was 22.58%, wherein in the midazolam group, it was 21.05%. Chi-square value with df = 1 comes to 0.23, $P = 0.878$ signifying no difference in proportion of recurrences in two arms statistically [Table 4].

During the study period, only respiratory depression was seen in both the groups. In this study, in the levetiracetam group, the number of respiratory depression cases was 4 (12.90%) and in the midazolam group, it was 7 (18.42%) [Table 5].

No patients needed ventilator support. All adverse events were 'probable' as per the WHO-UMC causality assessment criteria.[22]

Adverse Drug Reactions (ADRs) in two in the two groups

Table 1: Baseline characteristics of demography

Category	Groups	Frequency, *n* (%)
Age (days)	1	49 (71.01)
	2-7	17 (24.64)
	7-21	2 (2.89)
	21-28	1 (1.46)
Gender	Male	41 (59.42)
	Female	28 (40.58)

Table 2: Time to control seizure in two different drug groups

Drug	Number of patients	Time to control seizure (s), mean±SD	95% CI
Levetiracetam	31	387.10±67.241	362.43-411.76
Midazolam	38	361.58±81.92	334.65-388.51

SD=Standard deviation, CI=Confidence interval

Table 3: Mann-Whitney U-test of two different drug groups

Hypothesis test summary			
Null hypothesis	Test	Significant	Decision
The distribution of Time_ (sec) is the same across categories of group	Independent-samples Mann-Whitney U-test	0.190	Retain the null hypothesis

Asymptotic significances are displayed. The significance level is 0.05 (two-tailed)

Table 4: Recurrence of seizure in two different drug groups

Drug group	Recurrence		Total
	Yes	No	
Levetiracetam	7	24	31
Midazolam	8	30	38
Total	15	54	69

Table 5: Number of adverse reactions in two different drug groups

Drug group	Adverse reaction		Total
	No	Yes	
Levetiracetam	27	4	31
Midazolam	31	7	38
Total	58	11	69

were tested by comparing the proportion of ADRs in the two groups using Chi-square test of proportion which revealed no significant difference between two groups statistically. In case of the proportion of ADRs , Chi-square value with df = 1 comes to 0.388, $P = 0.533$. Other ADRs such as involuntary abnormal movement (restlessness, shivering, and shaking), hypotension, fever, soreness of mouth, and skin rash were not reported in both groups.

Discussion

In our study, we assessed the effectiveness and ADRs of midazolam and levetiracetam in NS cases not controlled with phenobarbitone and phenytoin. In this research procedure, out of 69 patients, male preponderance was more (59.42%) than females (40.58%) and the mean age was 1 day. Effectiveness and ADR were compared between the two drug groups. To compare the time to control seizure between these two groups, namely levetiracetam and midazolam, we used Mann–Whitney U-test, as data were nonnormally distributed. There was no significant difference in the two groups with respect to time to control seizure. Effectiveness in the two groups was also measured comparing number of recurrences using Chi-square test of proportion and found no significant difference. Another study variable measured was adverse events between the two arms. Here, also, no statistically significant difference was found in terms of safety parameter.

A study done by van Rooij *et al*.[23] reviewed the NS treatment with midazolam and turned out to be effective (0% to 100%) in phenobarbitone and phenytoin refractory seizures. Similarly, in our study, there was good response nearly 80% and recurrence occurred in only 20% cases within 48 h. Both studies found midazolam to be relatively safe in NS. Our finding was consistent with the study done by Sirsi *et a*l.,[24] where three neonates with status epilepticus with different etiologies remain unresponsive to phenobarbitone and phenytoin, responded to midazolam infusion as seen in continuous EEG monitoring. However no significant cardiovascular or respiratory side effects seen with this study[24], we found 7 respiratory depression events with midazolam therapy.

A retrospective, observational cohort study of prehospital patients done from 2010–2014[25] proved the safety and effectiveness of midazolam for benzodiazepine-treated seizures in prehospital clinical practice was also consistent with RAMPART[26] trial.

In a study published by Kawaguchi *et al*.,[27] 39 patients with NSs were retrospectively studied. It was administered to 22 neonates by bolus injection and/or continuous infusion and was effective in 71% and 76%, respectively, and was considered relatively safe for the management of NSs. In the study by Hu *et al*., of 32 neonates with seizures refractory to diazepam, phenobarbitone, and phenytoin, midazolam was successful in terminating status epilepticus in all.[28] In another non-randomized study by Castro Conde *et al*.[29] which observed major outcome in 45 neonates to evaluate electrical control of the seizures. Seizures were rapidly controlled with midazolam in all non-responders to phenobarbitone/phenytoin (17 out of 32 patients). These study results are quite similar with our study results of midazolam group where all 38 neonates not responding to phenobarbitone/phenytoin were controlled well up to 48 h. Respiratory depression was seen as adverse effects in both studies although it was not severe. Midazolam, thus, may be considered a safe and effective antiepileptic drug in refractory NSs of diverse etiologies.

Despite published data in children, there are few studies evaluating the safety and efficacy of levetiracetam in NSs.

A 2007 survey showed that 47% of pediatric neurologists preferred levetiracetam off-label use for NS treatment.[19] Recent retrospective cross-sectional studies done by Khan *et al*.,[30] have reported levetiracetam to be an effective and well-tolerated adjunctive antiepileptic agent for seizure control in neonates and infants. In this study, response to treatment was determined both clinically and electroencephalographically. Seizures were clinical at onset and then prolonged on follow-up evidenced by continuous electroencephalogram monitoring. Fifteen patients (68%) began receiving levetiracetam because of continued seizures on phenobarbital, three (14%) because of adverse reactions to a previous antiepileptic drug, and one (5%) because of continued seizures on fosphenytoin. Three patients (14%) were initially started on levetiracetam. Nineteen of 22 patients (86%) manifested immediate seizure cessation. One patient exhibited increased irritability while on the study medication. No clinical side effects were evident in the remaining 21 patients. In comparison, our study which assessed seizure control clinically found that all 31 patients had well control of seizure activity in short time period with only 7 recurrences during next 48 h. Only adverse event seen was respiratory depression in four cases. Another retrospective cohort study by Rao *et al*.,[31] in 2018 suggests that levetiracetam exhibits superior efficacy in comparison with phenobarbitone in the treatment of NSs associated with HIE in term newborns as measured by primary outcome parameter of seizure control and measured time to seizure freedom. In our study, levetiracetam was able to control phenobarbitone- and phenytoin-resistant Neonatal Seizure effectively up to 48 h, as seen by measuring time to control seizure and incidence of seizure recurrence , which also indicates superior efficacy of livetiracetam.

The safety profile of levetiracetam is advantageous as showed by many studies,[32,33] with a very low rate of adverse effects reported (most often somnolence and sedation and rarely agitation and thrombocytopenia).[34] In 2013, a study with 280 infants with comparable seizure etiology and cranial imaging results , increased exposure to Phenobarbitone found out to be associated with poor BSID cognitive and motor scores (8.1- and 9-point decrease per 100 mg/kg; $P = 0.01$). The effect was less with levetiracetam (2.2–and 2.6-point decrease per 300 mg/ kg levetiracetam ($P = 0.01$)).[35]

A prospective observational study published[36] in 2017 shows the efficacy and safety of levetiracetam as first-line treatment of NSs. The total number of NS patients was 16 as diagnosed by clinical signs and video-EEG and underwent levetiracetam therapy. All patients responded to treatment, with a variety range of seizure resolution periods (mean hours 96 ± 110) without requiring any second anticonvulsant drug. In contrast to that, in our study, levetiracetam has achieved quicker control of seizure in 387 ± 67.241 seconds, although it is used as a second-line agent to phenobarbitone and phenytoin. Thus, our study also supports the use of levetiracetam.

Limitations include small sample size. This study would yield better result if more participants were recruited. Being cross-sectional in nature, long-term follow-up was not done and the study periods were restricted to 48 hrs. Seizure control was assessed only clinically. EEG and aEEG were not available in our study setup. Low birth weight babies were excluded from the study.

Conclusions

Both midazolam and levetiracetam found to be effective and safe in NS not controlled with phenytoin and phenobarbitone in this study. Studies can be done using large sample size. Long-term follow-up as well as randomized trial is needed to explore the strength of our findings. Preterm babies are also to be recruited. Seizure control assessment should not only be done clinically but also with the help of EEG and aEEG. All these may open a new window in refractory seizure cases.

Although midazolam and levetiracetam are used frequently by clinicians, recent works favor the use of levetiracetam as a first-line drug and considered it a safe alternative to phenobarbitone in NS. Some workers have proposed to draft a guideline for multicentric trial for its use. Preterm babies have also received levetiracetam in few trials. All these invite further research in these cases.

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Conflicts of interest

There are no conflicts of interest.

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