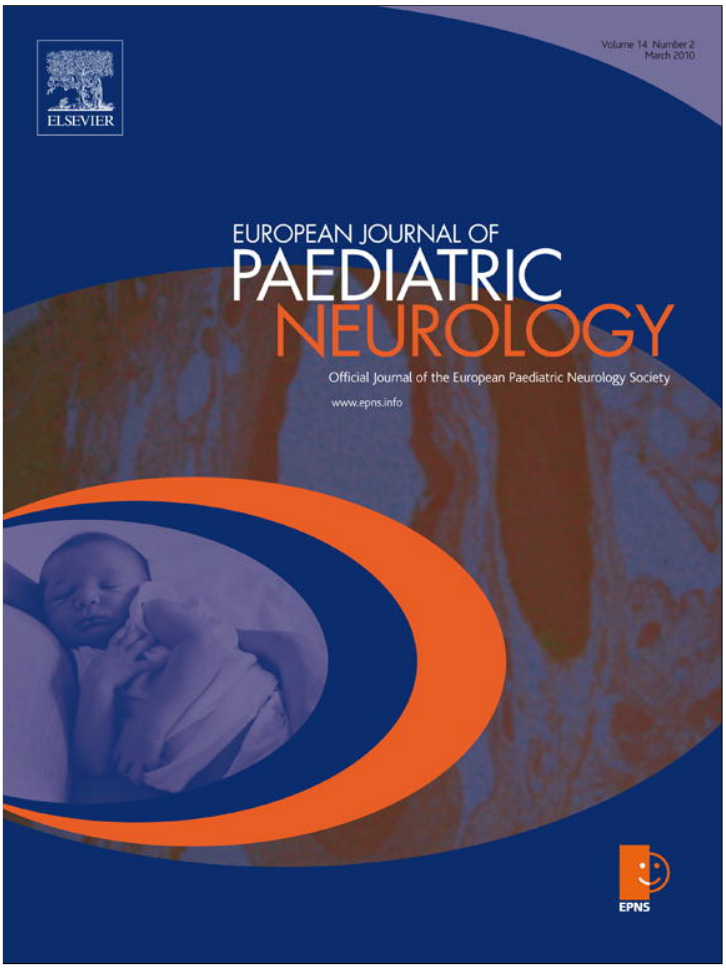

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 14 (2010) 162–168

Official Journal of the European Paediatric Neurology Society

Original article

Lorazepam versus diazepam–phenytoin combination in the treatment of convulsive status epilepticus in children: A randomized controlled trial

T.G. Sreenath[a], Piyush Gupta[a], K.K. Sharma[b], Sriram Krishnamurthy[a,*]

[a]Department of Pediatrics, University College of Medical Sciences and Guru Tegh Bahadur Hospital, Delhi 110095, India
[b]Department of Pharmacology, University College of Medical Sciences and Guru Tegh Bahadur Hospital, Delhi 110095, India

ARTICLE INFO

Article history:
Received 8 August 2008
Received in revised form
17 February 2009
Accepted 17 February 2009

Keywords:
Convulsive status epilepticus
Intravenous lorazepam
Intravenous diazepam
Phenytoin
Seizures
Children

ABSTRACT

Background: Convulsive status epilepticus demands urgent and appropriate management with anticonvulsants. Intravenous diazepam is an established drug in the management of convulsive status epilepticus in adults as well as in children. The efficacy of intravenous lorazepam has not been well established in children.

Objective: To determine whether intravenous lorazepam is as efficacious as diazepam–phenytoin combination in the treatment of convulsive status epilepticus in children.

Study design: Randomized controlled trial.

Methods: A total of 178 children were enrolled in the study; 90 in the lorazepam group and 88 in the diazepam–phenytoin combination group. Enrolled subjects were between 1 and 12 years with a clinical diagnosis of convulsive status epilepticus, presenting in pediatric emergency of a tertiary care hospital. They were randomized to receive either intravenous lorazepam (0.1 mg/kg) or intravenous diazepam (0.2 mg/kg)–phenytoin (18 mg/kg) combination at admission and were followed up for subsequent 18 h.

Results: The overall success rate of therapy was 100% in both the groups. There was no statistically significant difference in the two groups (lorazepam versus diazepam–phenytoin combination) in the median time taken to stop the seizure [20 s in both groups], the number of subjects requiring more than one dose of the study drug to stop the presenting seizure [lorazepam 6(6.7%) versus diazepam–phenytoin combination: 14 (15.9%); adjusted RR (95% CI) = 0.377 (0.377, 1.046); $P = 0.061$] and the number (%) of patients having respiratory depression [lorazepam 4(4.4%) versus diazepam–phenytoin combination 5 (5.6%)]. None of the patients in the two groups required additional anticonvulsant drug to stop the presenting seizure. No patient required mechanical ventilation and none of the patients in the two groups required cross-over to the alternative regimen.

Conclusion: Lorazepam is as efficacious and safe as diazepam–phenytoin combination. We recommend use of lorazepam as a single drug to replace the two drug combination of diazepam–phenytoin combination to control the initial seizure in pediatric convulsive status epilepticus.

* *Corresponding author.*
E-mail address: drsriramk@yahoo.com (S. Krishnamurthy).

1090-3798/$ – see front matter
doi:10.1016/j.ejpn.2009.02.004

1. Introduction

Convulsive status epilepticus is the most common neurological emergency of childhood and demands urgent and appropriate management with anticonvulsants. However, controversy exists regarding the best initial drug for treatment. According to the recommendations of the Epilepsy Foundation of Americas Working Group on Status Epilepticus,[1] either lorazepam 0.1 mg/kg or diazepam 0.2 mg/kg should be administered intravenously as the first line drug to terminate the presenting seizure. As initial therapy for all types of pediatric status epilepticus, intravenous diazepam was the treatment of choice in a European Expert Consensus Survey published recently.[2] A number of studies[3–6] suggest that lorazepam is superior to diazepam as first line therapy, with improved seizure outcome and less respiratory depression. However, most reports of lorazepam usage in status epilepticus refer to adults.[4,5,7,8] There is only one open prospective quasi-randomized study[3] comparing the efficacy of lorazepam and diazepam in treatment of status epilepticus in children. Nevertheless, lorazepam has recently been recommended as the first line intravenous drug in treating convulsive status epilepticus in children in a published consensus treatment.[9] The Cochrane Systematic Review 2008[10] opines that ''there remains a paucity of available data on the drug management of acute tonic–clonic seizures in childhood. Significant gaps remain in the evidence-base for the treatment of acute tonic–clonic convulsions and convulsive status epilepticus in childhood.'' These facts highlight the need for additional randomized controlled trials in treating convulsive status epilepticus. Therefore, we conducted a randomized controlled trial to compare the efficacy of intravenous lorazepam versus diazepam–phenytoin combination in the management of pediatric convulsive status epilepticus.

2. Subjects and methods

This randomized controlled trial was conducted at a tertiary care centre attached to a medical college in North India. A clearance from the ethical committee of the institute was obtained. Informed consent was taken prior to enrolment into the study.

Enrolled subjects were between 1 and 12 years and presenting with a clinical diagnosis of convulsive status epilepticus. For the purpose of this study, convulsive status epilepticus was defined as a continuous convulsive activity lasting for 5 min or more. Children were excluded from the trial if they had (i) received any antiepileptic medication in the preceding 4 weeks; (ii) sustained acute head trauma; (iii) jaundice, suspected renal failure (oliguria) or diarrhea presenting with seizures and (v) history of poisoning.

Simple randomization was done using a computer generated random number table on a master list, which was available to the principal investigator. Allocation was done by sealed envelope technique.

The study protocol is summarized in Fig. 1. When the patient was brought with convulsions, measures were taken to establish and maintain a patent airway, breathing and circulation. As soon as the cardiorespiratory status was stabilized, an IV access was established and blood samples were obtained to measure blood glucose, blood urea and serum electrolytes. Children were randomized to receive intravenously either (i) lorazepam (0.1 mg/kg) or (ii) diazepam (0.2 mg/kg). If IV access was not possible, the study drug was given rectally in the same dose. Children still convulsing after the initial dose received a second dose of the same drug. In the diazepam–phenytoin combination group, a loading dose of phenytoin (18 mg/kg) was administered, even if seizures had not recurred, 15–30 min after administration of diazepam. If seizure persisted after the second dose of the study drug, additional anticonvulsant drugs namely phenytoin, phenobarbitone and midazolam infusion were used in that order as summarized in Fig. 1. The child was monitored to see if there was any recurrence of seizure in the subsequent 18 h following seizure control with the study drug. In case of recurrence, the patient was crossed over to the alternative regimen as shown in Fig. 1. Treatment 'kits' consisting of two doses of study drug protocol and data entry sheets were available in the emergency room. After the completion of 18 h study period, appropriate maintenance antiepileptic drugs were started as per need of the individual case.

2.1. *Primary outcome*

The primary outcome of interest was the overall success rate of therapy. Treatment was considered successful, if all clinical evidence of seizure activity stopped within 10 min of the first intervention and there was no recurrence of seizure over next 18 h.

2.2. *Secondary outcome*

Secondary outcome measures included (a) time taken for initial (presenting) convulsion to stop after administration of the first dose of drug, (b) number of doses of the study drug required to treat the initial convulsion, (c) the use of additional anticonvulsant drugs, (d) the total number of seizures occurring in the first 18 h following administration of the study drug, (e) the development of respiratory depression (defined as requiring either endotracheal intubation, a poor respiratory effort or reduced respiratory rate following cessation of the convulsion; or oxygen saturation $<92\%$); (f) the number of patients requiring transfer to ICU for mechanical ventilation; and (g) the number of patients requiring cross-over to alternative regimen.

The duration of the seizure was recorded on the basis of information provided by the parent or accompanying relative. The time taken to stop the convulsion following drug administration was measured by a staff nurse using a stopwatch, from the onset of intravenous drug administration to the end of the seizure activity (tonic or clonic movements). Data on patient characteristics, seizure type and duration, diagnosis, previous use of antiepileptic drugs, vitals signs, frequency of convulsions before and after infusion of study drug and other relevant details were recorded. Blood pressure,

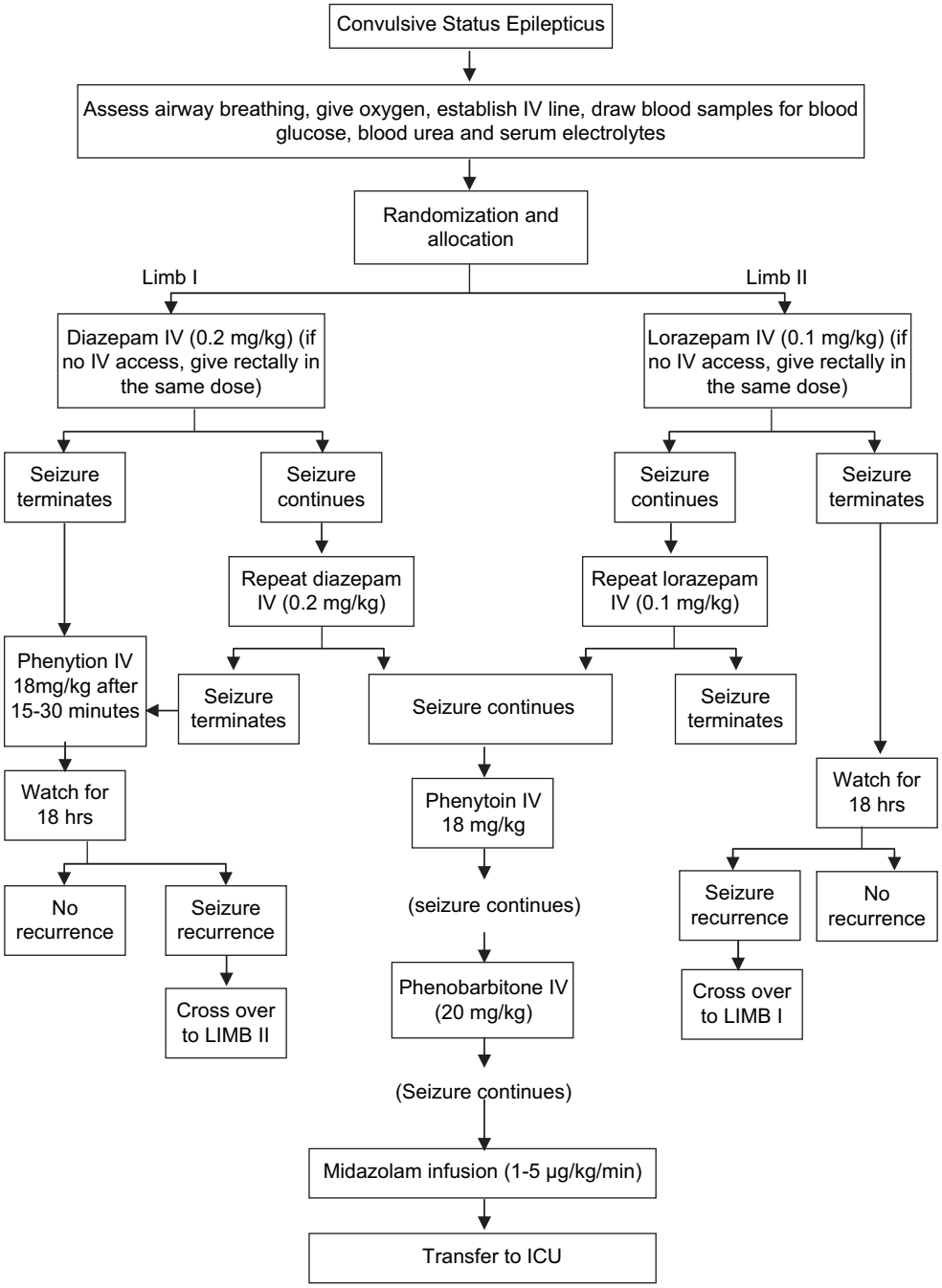

Fig. 1 – Study protocol for the treatment of children with convulsive status epilepticus.

heart rate, respiratory rate, level of consciousness (Glasgow Coma Scale) and convulsive activity were monitored during the 18 h follow-up period.

2.3. *Sample size*

According to sample size testing for equivalence studies, the sample size in each treatment group was estimated to be 88 taking an α error of 0.05, β error of 0.20, meaningful difference of 10% between the two treatment arms, and the efficacy of diazepam–phenytoin combination group and lorazepam group as per a previous study being 56% and 65%, respectively.[4] Hence, a total of 178 children were enrolled in the study.

2.4. *Statistical analysis*

Analysis was performed on an intention to treat basis. Chi square test was used to compare categorical variables. All quantitative variables were compared by unpaired *t* test or analysis of variance. Multivariate analysis was conducted with multiple regression and logistics models. The alpha error was set at 0.05.

3. Results

Fig. 2 depicts the inclusion and follow-up of the study subjects in a flowchart. There were 90 subjects in the lorazepam group and 88 subjects in the diazepam–phenytoin combination group. One of the patients had inadvertently received lorazepam in spite of being assigned diazepam–phenytoin group, thus resulting in difference in number of subjects enrolled in the two groups.

Both study groups (lorazepam versus diazepam–phenytoin combination) were similar in the baseline characteristics such as age, sex distribution, anthropometric measurements, type of seizure, and cause of seizure. Except for the difference in venous blood glucose, both the study groups were comparable in the vital state, initial biochemical profile (blood urea, serum sodium and potassium), and presence of provoking or predisposing factors, i.e. presence of fever, signs of meningeal irritation, developmental delay and presence of contact with tuberculosis (Table 1).

The overall success rate of therapy was 100% in both the groups. There was no statistically significant difference in the two groups in the time taken to stop the seizure after intravenous drug administration, the number of subjects requiring more than one dose of the study drug to stop the presenting seizure and the number (%) of patients having respiratory depression. None of the patients in two groups required additional anticonvulsant drug to stop the presenting seizure. None of the patients in the two groups required transfer to the ICU for mechanical ventilation and none of the patients in the two groups required cross-over to the alternative regimen. The outcome measures in two groups are summarized in Table 2.

4. Discussion

In this study, we defined convulsive status epilepticus as a continuous convulsive activity lasting for 5 min or more. This is based on the operational definition stated by Lowenstein and Bleck.[11] The rationale for this revised, operational definition is that defining status epilepticus based on the theoretical concept of neuronal injury, as done in the past, is of questionable value because the relationship between status epilepticus and neuronal injury in humans is complex and influenced by various factors besides duration of seizure activity, which are poorly understood in children. Practically speaking, any person who exhibits persistent seizure activity or who does not regain consciousness for 5 min or more after a witnessed seizure should be considered to have status epilepticus.[11]

Both intravenous lorazepam and diazepam–phenytoin combination were equally effective in the management of convulsive status epilepticus, each with a success rate of 100%. There was no statistical difference in the two groups in the time taken to stop the seizure after drug administration, number of doses of the study drug required to treat the initial convulsion or proportion of patients with respiratory depression. Patients in both the groups did not require any additional anticonvulsant for upto 18 h after control of the initial seizure. No patient in either of the study groups required mechanical ventilation or cross-over to the alternative regimen.

The main strength of the present study is its robust design, including a large sample size. The only other study in children on lorazepam versus diazepam–phenytoin combination was not adequately randomized.[3] In that study, children were assigned to receive either diazepam or lorazepam on an 'odd and even' date basis. The study population was small and there were substantial differences in the size of the two treatment groups [lorazepam 33 (38%) subjects and diazepam 53 (61%) subjects]. There were a relatively large number of protocol violators (16% of the total study population) who were excluded from the analysis. The analysis was therefore not an 'intention to treat' analysis. In our study, these lacunae were avoided.

Our study has certain limitations. Though we ascertained the etiologies of these seizures, data regarding further follow up were not collected for study purposes, as this was not the primary objective. Children of age less than 1 year were excluded from our study as metabolic abnormalities account for a major proportion of seizures occurring in this age group, where the seizures tend to recur in spite of anticonvulsant therapy until the underlying metabolic derangement has been corrected. This limits the applicability of the findings to the younger age groups where the incidence of SE is very high. Children who had received anticonvulsant medication in the preceding 4 weeks were also excluded from the study, with the intention to avoid the possibility of drug–drug interactions causing variations in the outcome variables. Nevertheless, this exclusion criterion also reduces the generalizability of the study. Patients with history of acute head trauma were excluded from the study as most of them would require prompt neurosurgical intervention. Similarly, children with jaundice, suspected renal failure (oliguria) or diarrhea presenting with seizures were excluded.

The assessment of the efficacy of benzodiazepines in the management of acute seizures and status epilepticus is mainly based on nonrandomized uncontrolled trials. The efficacy of intravenous diazepam has ranged from 54 to 100% in various studies, while it was 82–100% for intravenous lorazepam.[12] The success rate in our study was 100% which is in conformity with that reported in literature. The definitions used for measuring efficacy of benzodiazepines have been variable in different studies, which may contribute to variable efficacies reported in the literature. In the study by Appleton et al.,[3] treatment was considered efficacious if seizure or episode of status stopped within 7 or 8 min of administration of the first dose of the study anticonvulsant. In that study, one or two doses of lorazepam stopped the convulsion in 19 of 27 (70%) lorazepam and 22 of the 34 (65%) diazepam–phenytoin treated subjects (RR = 1.09; 95% CI: 0.77, 1.54). In another 12 month single centre randomized study comparing intranasal midazolam and intravenous diazepam in the treatment of prolonged febrile seizures (a seizure of at least 10-min duration) in children aged 6 months to 5 years, treatment was successful if the clinical features of the seizure stopped within 5 min.[13]

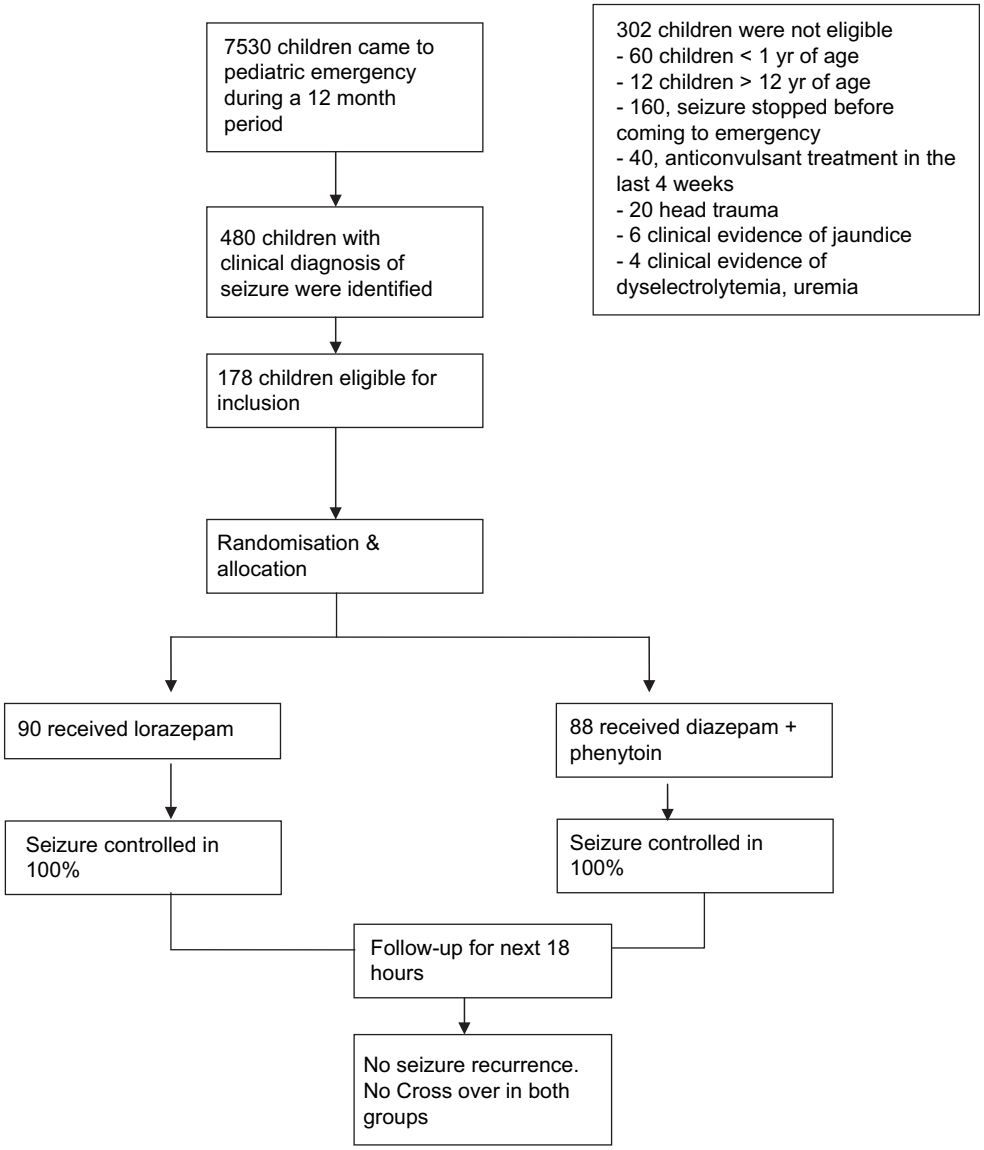

Fig. 2 – Flowchart depicting the inclusion and follow-up of the study subjects.

In our study, treatment was considered successful, if all clinical evidence of seizure activity stopped within 10 min of the first intervention and there was no recurrence of seizure over next 18 h.

Our study is notable for only a small percentage of subjects requiring a second dose of the study drug to control the initial seizure (6.7% lorazepam versus 15.9% diazepam–phenytoin group). No subject required the use of additional anticonvulsant drug in both the groups. These differences could have probably arisen due to the difference in mean duration of initial convulsion before arriving in the hospital. In the study by Appleton et al.,[3,9] the mean time taken the presenting convulsion to stop was 29 s in the intravenous lorazepam group and 26 s in the intravenous diazepam group. The median time taken to seizure termination in our study was approximately 20 s, which is in conformity with these data. It has also been mentioned that activity of diazepam is noticeable in as little as 10–20 s after administration, which has been explained on the basis of high lipid solubility of benzodiazepines, as a result of which they enter cerebral tissue rapidly.[14]

In the present study, none of the patients in both groups had seizure recurrence in the ensuing 18 h follow-up period. This was in contrast to the study by Appleton et al.,[3] where 6/27 (22%) patients in the lorazepam group and 35% patients in the diazepam group had seizure recurrence in 24 h follow-up period. This variation in the results could be explained by the fact that in that study,[3] none of the patients in the diazepam group was given a loading dose of long-acting anticonvulsant after the cessation of initial seizure. Diazepam being a short-acting drug, seizures are likely to recur. Also the follow-up period in our study was 18 h in contrast to 24 h follow-up period in the study by Appleton et al.[3] As the duration of action of lorazepam is 18 h, the seizures might have probably recurred in the last 6 h of the 24 h follow-up period in that study.

The usefulness of intravenous lorazepam was highlighted in a recently published prospective, population-based study

Table 1 – Baseline comparison of subjects in lorazepam versus diazepam–phenytoin group.

Parameter	Lorazepam group ($n = 90$)	Diazepam + phenytoin group ($n = 88$)	P-value
A. Patient characteristics			
1. Mean age (SD) in months	84.0 (36.8)	78.7 (32.5)	0.31
2. Sex:			
Male (%)	55 (61.1)	47 (53.4)	0.30
Female (%)	35 (38.8)	41 (46.5)	
3. Mean weight (SD) in kg	21.4 (6.9)	20.7 (6.3)	0.50
4. Mean height (SD) in cm	116.7 (16.9)	114 (16.0)	0.26
5. Mean head circumference (SD) in cm)	52.2 (2.3)	52.6 (3.0)	0.34
6. Presence of fever (%)	30 (33.3)	22 (25)	0.22
7. Presence of signs of meningeal irritation (%)	9 (10)	6 (6.8)	0.44
8. Presence of upper respiratory tract infection (%)	30 (33.3)	30 (34.01)	0.91
9. Presence of contact with tuberculosis (%)	1 (1.1)	2 (2.2)	0.54
B. Seizure characteristics			
1. Type of seizure			
(a) Generalised			
Generalised tonic	11 (12.2%)	8 (9.0%)	0.40
Generalised clonic	12 (13.3%)	7 (7.9%)	
Generalised tonic clonic	51 (55.5%)	61 (69.3%)	
Generalised myoclonic	1 (1.1%)	0 (0%)	
(b) Partial			
Simple partial	1 (1.1%)	3 (3.4%)	0.71
Complex partial	10 (11.1%)	8 (9%)	
Partial with secondary generalised	4 (4.4%)	3 (3.4%)	
2. Duration of seizure (min) [median, IQR]	20 (15–21)	17 (15–20)	0.77
3. Presence of past history of seizures	6 (6.6%)	8 (9.09%)	0.54
C. Vital status			
1. Mean systolic blood pressure (SD) mmHg	94.6 (12.7)	94.5 (15.0)	0.94
2. Mean diastolic blood pressure (SD) mmHg	63.6 (9.3)	66.7 (10.3)	0.95
3. Mean temperature (SD) °F	99.9 (1.5)	99.7 (1.4)	0.31
4. Mean SPO_2 (SD) %	95.3 (2.3)	95.5 (2.3%)	0.63
5. Mean Glasgow Coma Scale (SD)	11.4 (6.4)	11.0 (1.6)	0.59
D. Biochemical profile			
1. Mean venous blood sugar (SD) mg/dL	87.4 (11.3)	96.4 (14.2)	<0.001
2. Mean blood urea (SD) mg/dL	30.4 (7.8)	30.0 (6.5)	0.73
3. Mean serum sodium (SD) mEq/L	139.6 (7.0)	139.1 (5.3)	0.57
4. Mean serum potassium (SD) mEq/L	4.2 (0.6)	4.2 (0.6)	0.69
E. Apparent cause of seizure at presentation			
1. Unprovoked seizure	60 (66.6%)	64 (72.7%)	
2. Simple febrile seizure	15 (16.6%)	7 (7.9%)	
3. Atypical febrile seizure	3 (3.3%)	7 (7.9%)	
4. Pyogenic meningitis	4 (4.4%)	3 (3.4%)	
5. Tuberculous meningitis	2 (2.2%)	1 (1.1%)	
6. Viral meningoencephalitis	4 (4.4%)	3 (3.4%)	
7. Microcephaly	2 (2.2%)	0	
8. Cerebral palsy	0	2 (2.2%)	
9. Hypertensive encephalopathy	0	1 (1.1%)	

Table 2 – Outcome in the lorazepam vs. diazepam–phenytoin group with respect to recurrence of seizure and respiratory depression.

S. No.	Outcome variable	Lorazepam ($n = 90$)	Diazepam + phenytoin ($n = 88$)	Difference
1.	Overall success rate of therapy	100%	100%	Nil
2.	Time taken to stop seizure (s) median (interquartile range)	20 (15–23)	20 (15.3–24)	$P = 0.29$
3.	Number of subjects requiring more than one dose of anticonvulsant to stop seizure	6 (6.7%)	14 (15.9%)	Adjusted RR = 0.377 (0.377, 1.046), $P = 0.061$
4.	Additional anticonvulsant	None	None	Nil
5.	Total number of additional seizure in 18 h after control of initial seizure	None	None	Nil
6.	Number (%) having respiratory depression	4 (4.4%)	5 (5.6%)	RR = 0.810 (3.690, 0.177), $P = 0.785$
7.	No. of patients requiring transfer to the ICU for mechanical ventilation	None	None	Nil
8.	No. of patients requiring cross-over to alternative regimen	None	None	Nil

on the treatment of community-onset, childhood convulsive status epilepticus, in which analysis with multivariate models showed that treatment with intravenous lorazepam in the accident and emergency department was associated with a 3.7 times greater likelihood of seizure termination than was treatment with rectal diazepam.[15]

Although there was no statistically significant difference between the lorazepam group and diazepam–phenytoin combination group in our study, in terms of the outcome measures discussed above, it may still be inferred that lorazepam can be used as the drug of choice to treat convulsive status epilepticus in children instead of diazepam–phenytoin combination because of the fact that a long-acting anticonvulsant like phenytoin need not be loaded after administration of lorazepam, since lorazepam has a long duration of action. Also, though not statistically significant, the number of subjects in the lorazepam group requiring more than one dose of anticonvulsant to stop the seizure was half that of the number in the diazepam–phenytoin group [6 (6.7%) cases lorazepam versus 14 (15.9%) cases in diazepam-phenytoin group].

Our study adds to knowledge regarding optimum emergency treatment of pediatric convulsive status epilepticus. We recommend that intravenous lorazepam should be the drug of choice for the management of convulsive status epilepticus in children.

Authors' contribution

TG Sreenath participated in protocol preparations, review of literature, collection of data and drafting of the manuscript. Piyush Gupta was the principal investigator, conceived and designed the study, reviewed the literature, analysed the data, finalized the draft and shall act as guarantor of the paper. KK Sharma participated in protocol preparations, analysis of data and finalizing the manuscript. Sriram Krishnamurthy reviewed the literature and assisted in drafting of the manuscript. All authors approved the final version of the manuscript.

Funding

None.

Competing interests

None stated.

REFERENCES

1. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the epilepsy foundation of America's working group on status epilepticus. *JAMA* 1993;**270**:854–9.
2. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion. *Epileptic Disord* 2007;**2007**(9):353–412.
3. Appleton R, Sweeney A, Choonara T, Robson I, Mohyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol* 1995;**37**:682–8.
4. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments of generalised convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998; **339**:792–8.
5. Aldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam and placebo for the treatment of out of hospital status epilepticus. *N Engl J Med* 2001;**345**:631–7.
6. Uthman Basim M, Wilder BJ. Emergency management of seizures: an overview. *Epilepsia* 1989;**30**(Suppl. 2):33–7.
7. Cock HR, Schapitra AVH. A comparison of lorazepam and diazepam as initial therapy in convulsive status epileptics. *Q J Med* 2002;**95**:225–31.
8. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;**249**:1452–4.
9. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The Status Epilepticus Working Party. The treatment of conclusive status epilepticus. *Arch Dis Child* 2000; **83**:415–9.
10. Appleton R, Macleod S, Martland T. Drug management for acute tonic–clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev* 2008;**3**: CD001905.
11. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;**40**:120–2.
12. Rey E, Tréluyer JM, Pons G. Pharmacokinetic optimization of benzodiazepine therapy for acute seizures. Focus on delivery routes. *Clin Pharmacokinet* 1999;**36**:409–24.
13. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomized study. *BMJ* 2000;**321**:83–6.
14. Aschenbrenner DS. Drugs treating seizure disorders. In: Aschenbrenner DS, Venable SJ, editors. *Drug therapy in nursing*. 3rd ed. Philadelphia: Lipincott Williams and Wilkins; 2009. p. 344–8.
15. Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *Lancet Neurol* 2008;**7**:696–703.