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Management of generalised convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam – Pilot study

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ABSTRACT

Objective: This study was conducted to compare the efficacy of phenytoin, valproate and levetiracetam in patients with GCSE.
Methods: This randomised controlled prospective study was conducted on 150 patients to compare the efficacy of phenytoin ($n=50$), valproate ($n=50$) and levetiracetam ($n=50$) along with lorazepam in patients with GCSE. All recruited patients received i.v. lorazepam (0.1 mg/kg) followed by one of the 3 AEDs viz. phenytoin (20 mg/kg), valproate (30 mg/kg), and levetiracetam (25 mg/kg). Those who remained uncontrolled with 1st AED, received the other two AEDs sequentially. Clinical, imaging, EEG, etiological factors were analysed. Predictors of poor seizure control and outcome at discharge and at one month follow-up were assessed.
Results: In the phenytoin subgroup, the seizures could be controlled in 34 (68%) with lorazepam + phenytoin infusion. In the valproate subgroup ($n=50$), seizures could be controlled in 34 (68%) with lorazepam + valproate infusion. In the levetiracetam subgroup ($n=50$), seizures could be controlled in 39 (78%) with lorazepam + levetiracetam infusion. There was no statistically significant difference between the subgroups ($p=0.44$). Overall, following lorazepam and 1st AED, 107/150 (71.3%) were controlled; with addition of 2nd AED, 130/150 (86.7%) and by adding 3rd AED, 138/150 (92%) were controlled. Fifteen out of 110 (13.6%) expired within 1 month of SE: phenytoin-6; valproate-4; and levetiracetam-5. Interestingly, 3 patients in the levetiracetam had post-ictal psychosis.
Significance: Phenytoin, valproate, and levetiracetam are safe and equally efficacious following lorazepam in GCSE. The choice of AEDs could be individualised based on co-morbidities. SE could be controlled in 92% of patients with AEDs only and anaesthetics were not required in them.

Introduction

Status epilepticus (SE) is a common neurological emergency with significant mortality and morbidity (Logroscino et al., 2005; Rossetti et al., 2008). Benzodiazepines are drugs of choice in patients with convulsive status epilepticus (Treiman et al., 1998). The approved standard parenteral anti-epileptic drugs (AEDs) for the management of SE require have relative contraindications in those with systemic illnesses and hence require caution or require dose adjustment viz. phenytoin in patients with cardiac failure, and sodium valproate in patients with hepatic failure. Besides, they have several drug interactions with other medications. Intravenous levetiracetam has shown promising results in case reports and retrospective studies (Alvarez et al., 2011; Berning et al., 2009; Knake et al., 2008; Eue et al., 2009; Misra et al., 2012).

There are no systematic randomised controlled trials comparing phenytoin, valproate and levetiracetam in generalised convulsive SE (GCSE). The need for the same has been emphasised in

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many reviews (Yasiry and Shorvon, 2014; Prasad et al., 2007). As per the current guidelines, SE uncontrolled with benzodiazepines and another AED i.e. phenytoin or valproate, should be managed with anaesthetic agents like midazolam, thiopentone or propofol (Meierkord et al., 2010). Difficulties arise due to non-availability of ICU care in resource poor settings where there is a huge demand-supply gap.

This study was conducted to ascertain and compare the efficacy of phenytoin, sodium valproate and levetiracetam along with lorazepam in the management of GCSE, and to determine the possible causes of uncontrolled seizures.

Material and methods

This prospective randomised controlled single-centre study was carried out at a tertiary care University teaching hospital in south India. Patients of GCSE, aged 15–65 years, presenting to the neurological emergency services between September 2010 and November 2013 were recruited, irrespective of the aetiology, by a neurology resident (RC) under close supervision of an experienced faculty with special interest in epilepsy (SS). The exclusion criteria included (i) non-convulsive SE (NCSE), (ii) systemic disorders: hepatic/renal/cardiac disorder, (iii) pregnancy, (iv) neurosurgical disorders requiring urgent surgical intervention, (v) known allergy to AEDs, (vi) administration of parenteral AEDs for SE prior to study entry, (vii) lack of informed consent. New onset status epilepticus was noted in 62 (41.33%) patients while other patients ($n = 88$; 58.66%) were known to have seizures in the past. Among the latter group, 35 were either drug naïve or had stopped treatment before SE. Fifty three patients were on various oral AEDs viz. phenytoin: 24; phenobarbitone; 14; valproate and carbamazepine: 8 each; newer AEDs: 14. Fifteen were on multiple AEDs. No specific changes were made in the protocol if the patients on these oral medications; however we did not include patients if they had received any parenteral treatment for the said episode of SE before being referred to our centre for management of SE.

The Institute Ethics Committee (IEC), approved the study to obtain written informed consent for participation in the study from a family member or accompanying person (surrogate), since patients were not competent to give informed consent. The state and IEC regulations regarding surrogate consent were adhered.

Initial management and randomisation

All the patients were managed emergently for stabilising airway, breathing and circulation, and intravenous lorazepam (0.1 mg/kg; 4–6 mg) was administered within 5 min of arrival. None of the patients developed respiratory depression following lorazepam. Consecutive patients with GCSE ($n = 188$) presenting to the emergency services, satisfying the inclusion criteria were screened. Thirty-eight (M:F = 22:16; age: 42.4 ± 21 years) were excluded due to the following reasons: received AEDs before screening [$n = 22$; one of the patient in this subgroup had psychogenic non-epileptic seizures (PNES)], hepatic dysfunction ($n = 6$), lack of consent ($n = 5$), cardiac disorder ($n = 3$), renal dysfunction ($n = 2$). The cohort included 150 patients (M:F = 88:62; age: 33.71 ± 17.0 years), 50 in each arm. A quick bedside evaluation was performed and patients were randomised (computer generated randomisation) to one of the following three arms within 10 min. Patients whose seizures were uncontrolled with the 1st AED were sequentially given the 2ndAED and similarly 3rdAED according to a predesigned protocol (Fig. 1):

(i) Group I: Phenytoin → uncontrolled → valproate → uncontrolled → levetiracetam
(ii) Group II: Valproate → uncontrolled → phenytoin → uncontrolled → levetiracetam
(iii) Group III: Levetiracetam → uncontrolled → phenytoin→ uncontrolled → valproate

Following injection lorazepam, the first line AED infusion was started within 10 min and was administered over 15–30 min, and 30 min after completion of the infusion decision of requirement of second line AEDs was taken and similarly for 3rd line AED. The loading dose of phenytoin was 20 mg/kg (800–1600 mg) in 100 ml normal saline infused intravenously at 50 mg/min followed by maintenance dose (5 mg/kg/day in 3 divided doses). Likewise, the loading dose of valproate was 30 mg/kg (1200–2400 mg) in 100 ml normal saline) infused over 15 min followed by maintenance dose (30 mg/kg/day in 3 divided doses). The loading dose of levetiracetam was 25 mg/kg (1000–2000 mg) in 100 ml normal saline over 15 min followed by maintenance dose (25 mg/kg/day in 3 divided doses). Patients with adequate seizure control as per defined criteria were given maintenance doses of AEDs. When seizures were uncontrolled with these three AED, midazolam (0.1 mg/kg), followed by thiopentone (3–7 mg/kg), was administered in the ICU under close monitoring and mechanical ventilation. The requirement of ICU was primarily decided based on the stability of vitals like SPO_2, and patients with falling SPO_2 were shifted to ICU irrespective of the stage of AED infusion. Oxygen saturation was monitored as part of A, B, C of emergency care.

Definitions

GCSE: continuous generalised seizures of ≥10 min or ≥2 discrete seizures without complete recovery of consciousness in between (Treiman et al., 1998). *NCSE after CSE*: lack of improvement in sensorium following AED therapy/non-convulsive clinical symptomology and EEG features of focal/generalised ictal rhythm or PLEDs responsive to lorazepam (Shorvon, 2007). *Control of SE*: no recurrence of seizures after 30 min of completion of AED infusion with substantial improvement in sensorium over next 24 h or sensorium didn't improve substantially but EEG excluded NCSE. *Uncontrolled SE*: seizure recurrence after ½ h of AED infusion till 24 h or lack of substantial improvement in sensorium and EEG evidence of NCSE. *Refractory SE (RSE)*: seizures uncontrolled after initial lorazepam and 1st AED (Hanley and Kross, 1998; Mayer et al., 2002). *Super RSE*: recurrent SE ≥ 24 h after initiation of anaesthetic therapy, including those that recurred with reduction or withdrawal of anaesthetic agents (Shorvon and Ferlisi, 2011).

Investigations

STESS (Status Epilepticus Severity Scale) was computed. The etiologies of SE were assessed based on standard clinical practice with neuroimaging (CT/MRI), various blood investigations (hemogram, serum glucose, liver/kidney function tests, electrolytes, and in some patients immunological tests) and CSF studies (routine and infective workup if clinically indicated). EEG was performed in all the patients within 24 h, but it could be carried out in those with suspected NCSE ($n = 12$) before the initiation of 2nd or 3rd line AED infusion. EEG was reviewed by two neurologists. In case of disagreement, a consensus was arrived at by discussion.

Follow up

Patients were discharged only after a minimum of 24 h after controlling seizures and excluding NCSE. They were followed up after one month for seizure control, SE recurrence, changes in AED requirement, and AEDs side effects. Functional outcome at

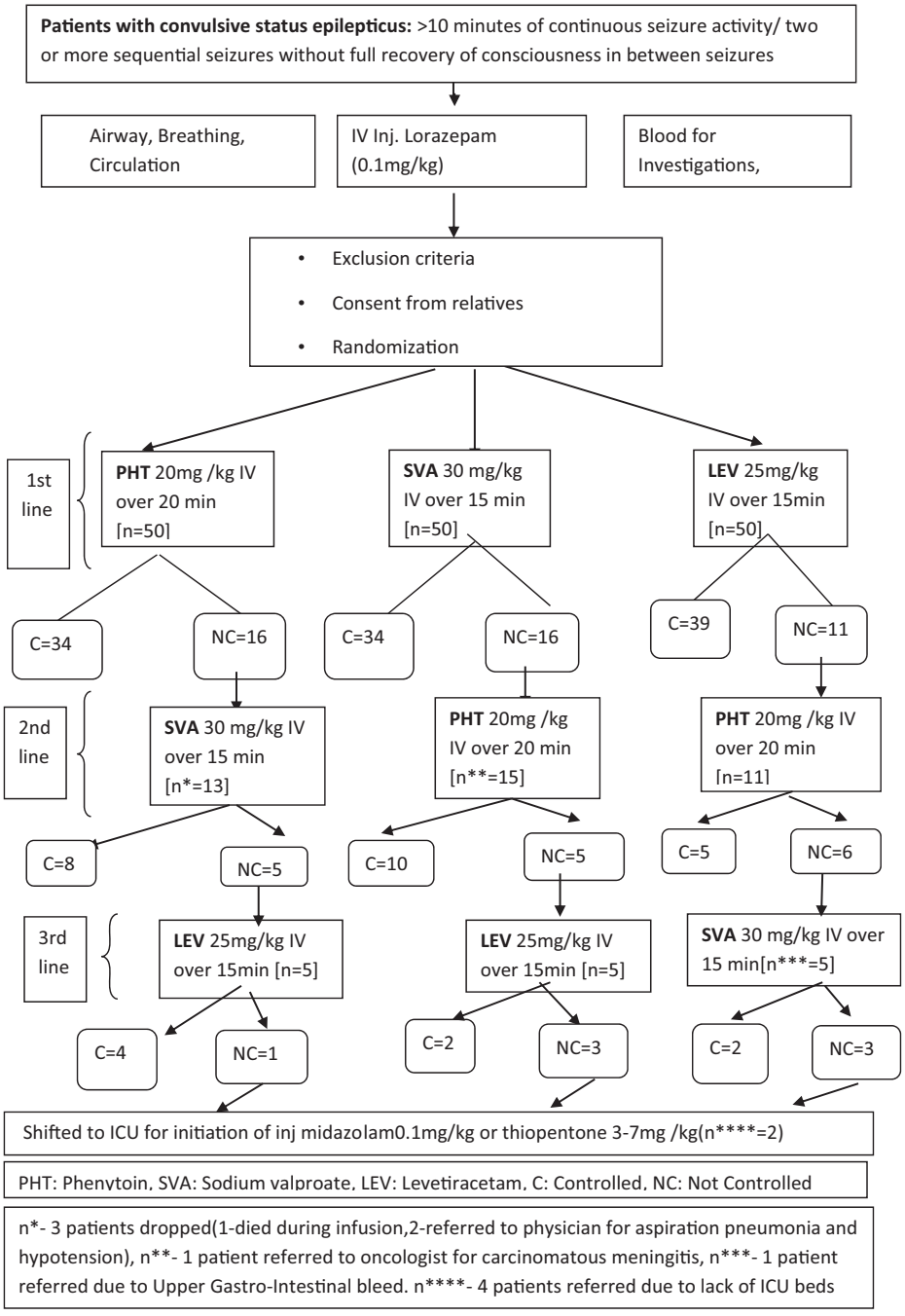

Figure 1. Flow chart of methodology

discharge and after a month of follow-up was assessed using Glasgow outcome scale (GOS) and modified Rankin scale (mRS).

Sample size

The sample size was chosen based on site feasibility, single centre study and duration of the study of 38 months. Intent to treat analysis of all the recruited 150 patients (50 in each arm) was performed.

Statistics

The data was analysed using the SPSS version 15.0. Chi-square test was used to find association among qualitative measurements; quantitative data was analysed using descriptive statistics, independent sample *t* test, analysis of variance followed by post hoc test. Fisher's exact test was done to calculate *p* value when the numbers were small. Binary logistic regression was used to predict poor seizure control.

Results

The clinical, EEG and imaging features of recruited 150 patients and the 3 subgroups are summarised in Table 1.

Therapeutic details

In phenytoin subgroup ($n = 50$) patients, seizures were controlled in 34. Of the 16 patients with uncontrolled seizures, 13

Table 1
Various characteristics in the 3 groups of the cohort of patients with GCSE.

Parameters	Total ($n=150$)	Phenytoin group I ($n=50$)	Valproate group II ($n=50$)	Levetiracetam group III ($n=50$)	p value (Chi/Fisher's exact)
M:F	88:62	28:22	28:22	32:18	0.644
Mean age (years)	33.71 ± 17.0	33.24 ± 13.39	33.12 ± 11.99	34.78 ± 13.64	0.77
Duration of SE in hours	8.08 ± 8.08	6.7 ± 6.53	7.38 ± 8.39	10.18 ± 9.33	0.08
Past h/o seizures – yes:no	88:62	25:25	30:20	33:17	0.26
CT of brain	149	49	50	50	NA
Abnormal CT brain	89 (59.7%)	36 (73.47%)	29 (58%)	24 (48%)	0.03
Focal CT abnormalities	60 (40.26%)	32 (65.3%)	23 (46%)	18 (36%)	0.01
Brain MRI	60	12	21	27	NA
Abnormal MRI brain	49 (81.6%)	12 (100%)	18 (85.7%)	19 (70.3%)	0.07
Focal MRI abnormalities	47 (78.3%)	12 (100%)	17 (80.9%)	18 (66.7%)	0.06
EEG	139	48	44	47	NA
EEG-abnormal	87 (62.6%)	26 (59.09%)	31 (64.58%)	30 (63.82%)	0.27
NCSE after CSE	16 (10.67%)	5 (11.36%	6 (12.5%)	5 (10.63%)	0.89
PLEDS	13 (8.67%)	4 (09.09%)	7 (14.58%)	3 (06.38%)	0.33
Aetiology					
Vascular	37 (24.67%)	16	9	12	0.10
Infective	32 (21.33%)	10	11	11	
Metabolic	25 (16.67%)	10	4	11	
Other structural	23 (15.33%)	8	12	3	
Autoimmune	3 (2%)	0	1	2	CNBD
Neoplastic	3 (2%)	0	3	0	
Acute symptomatic SE	65 (43.33%)	25	17	23	0.35
Remote symptomatic SE	58 (38.67%)	19	23	16	
Cryptogenic SE	27 (18%)	6	10	11	
STESS	2.43 ± 0.5	2.5 ± 0.5	2.4 ± 0.5	2.4 ± 0.5	0.24
Medical complications	31	8	15	7	0.07
Mortality	15 (10%)	6	4	5	0.94
Major side effects (acute)	6 (4%)	Cardiac arrest – 1 Hypotension – 2	Nil	Post ictal psychosis – 3	0.25

CNBD, could not be done due to small numbers; NA, not applicable; STESS, Status Epilepticus Severity Scale; SD, standard deviation.

received valproate (2nd AED) following which seizures could be controlled in eight. Five patients who remained uncontrolled, received levetiracetam (3rd AED) and 4 were controlled. One patient had uncontrolled seizures after three AEDs. In valproate subgroup ($n=50$), seizures were controlled in 34. Of remaining 16 patients with uncontrolled seizures, 15 received phenytoin (2nd AED) and seizures could be controlled in 10. The remaining five patients with uncontrolled SE, received levetiracetam (3rd AED) and seizures were controlled in two. Three patients had uncontrolled seizures with 3 AEDs. In the levetiracetam subgroup ($n=50$), 39 patients attained seizure control with the first AED. Eleven patients whose seizures were not controlled, received phenytoin (2nd AED), resulting in seizure control in five. Five out of the remaining six patients received valproate (3rd AED) with seizure control in two. Three had uncontrolled seizures in this sub-group.

Overall, seizures could be controlled in 138/150 patients (92%), while 5 patients could not complete the study, 7 remained uncontrolled even after usage of three AEDs. Among these 7 patients, 2 patients were provided ICU care. One of them received injection midazolam (0.1 mg/kg) while another received inj. midazolam (0.1 mg/kg) followed by inj. thiopentone (3 mg/kg) infusion in another patient. Both the patients improved without any deficits. The remaining 5 patients were referred to other hospitals due to non-availability of ICU beds and 4 of them expired within 7 days. Out of 150 patients, 28 patients required endotracheal intubation during the course of treatment. Ten of them were in the group of patients controlled after LZM+ 1 AED, 5 patients were in group controlled with LZM+ 2 AEDs and rest of them were in the group not controlled with LZM+ 2 AEDs.

The control of SE after 1st AED was possible in 68%, 68%and 78% in groups I, II and III respectively. Eventhough, there was 10% better control in the levetiracetam subgroup, it was not significant (p value: 0.44). The details are shown in the Table 2. The control of SE following the three first line AEDs were also compared between all 3 pairs separately with Chi square test didn't show any significant difference among the groups.

In 43 patients, seizures were uncontrolled with the 1st AED. Four patients could not receive the second AED as they were referred elsewhere due to carcinomatous meningitis ($n=1$) and lack of ICU beds ($n=2$), and death during phenytoin infusion ($n-1$). Thirty-nine received second AED and seizures were controlled in 15/26 and 8/13 with phenytoin and valproate respectively ($p=0.8$). There was no statistically significant difference among groups ($p=0.54$). Fifteen out of 16 patients who had uncontrolled SE after second AED; received third AED and seizures were controlled in 6/10 and 2/5 with levetiracetam and valproate respectively. One patient could not receive third AED and was referred elsewhere due to upper gastrointestinal bleed. Statistical analysis could not be done due to small numbers in each subgroup (Fig. 1).

Outcome

One month follow-up data was available for 110 patients (73.33%): group I: 35; group II: 38; group III: 37. Seizure recurrence was noted in 19/95 (20%) patients: group I: 5/29; group II:

Table 2
Comparative analysis of outcome of first AED (phenytoin vs valproate vs levetiracetam).

Subgroups	Controlled after 1st AED	Un-controlled after 1st AED	χ^2 with 2 df (p value)
Phenytoin ($n=50$)	34 (68%)	16 (32%)	1.63 (0.44)
Valproate ($n=50$)	34 (68%)	16 (32%)	
Levetiracetam ($n=50$)	39 (78%)	11 (22%)	

Table 3
Functional outcome at discharge and after 1 month.

Scales	Outcome	Phenytoin Group I	Valproate Group II	Levetiracetam Group III	χ^2 with 2 df (p value)
mRS at discharge	Good (0–3)	37/50 (74%)	39/50 (78%)	43/50 (86%)	2.27 (0.3203)
	Poor (4–6)	13/50 (26%)	11/50 (22%)	7/50 (14%)	
GOS at discharge	Good (4–5))	30/50 (60%)	26/50 (52%)	30/50 (60%)	0.872 (0.464)
	Poor (1–3	20/50 (40%)	24/50 (48%)	20/50 (40%)	
mRS at 1 month of follow up	Good (0–3)	29/35 (82.9%)	34/38 (89.5%)	31/37 (89.8%)	0.766 (0.681)
	Poor (4–6)	06/35 (17.1%)	04/38 (10.5%)	6/37 (16.2%)	
GOS at 1 month of follow up	Good (4–5)	29/35 (%)	32/38 (84.2%)	29/37 (78.4%)	0.466 (0.792)
	Poor (1–3)	06/35 (17.1%)	06/38 (15.8%)	8/37 (21.6%)	

6/34; group III: 8/32. The functional outcome was similar in all three groups (Table 3). One-month mortality was 13.6% (15/110) including 11/43 patients with RSE. Twelve had died within 7 days. Six patients had acute symptomatic seizures, while nine had remote symptomatic cause (Table 1).

Prognostic markers for poor seizure control

Chi-squared test revealed that female gender, rural background, past history of seizures, focal MRI abnormalities, abnormal EEG, NCSE after CSE, remote symptomatic aetiology, associated medical complications were associated with poor response to 1st AED (Table 4). Subanalysis of those with or without past history of seizures revealed that 19 out of 88 (21.6%) patients with past history of seizures presented after 12 h of onset of SE whereas 9 out 62 (14.5%) patients with without past history of seizures presented after 12 h of onset of SE though this difference was statistically not significant ($p = 0.38$). Binary logistic regression analysis showed that female gender ($p = 0.02$, OR: 4.5), focal imaging abnormalities ($p = 0.02$, OR: 4.9), medical complications ($p < 0.001$, OR: 66.1), NCSE after CSE/PLEDS in EEG ($p = 0.005$, OR: 3.3), have high risk of uncontrolled seizures with first AED. In view of uneven distribution of some of the variables in the 3 subgroups, further logistic regression analysis was carried out for the three medication subgroups separately with focal CT abnormalities as the predictor. In this subanalysis, focal CT abnormality was not found to be a significant predictor for poor outcome.

Discussion

This study attempted to compare the combined efficacy of parenteral phenytoin, valproate and levetiracetam along with initial lorazepam in the management of generalised convulsive SE. This study results have practical implications for clinicians managing such patients with GCSE.

Seizures were controlled in 107 (71.33%) patients with lorazepam + 1st line AEDs, while it was uncontrolled in the rest 43 (28.66%) patients. Following administration of the second AED, seizures were controlled in 23/39 patients (58.9%), while 16 patients remained uncontrolled. After third AED, seizures could be controlled in 8/15 patients (53.3%), while 7 remained uncontrolled. In this cohort, SE could be controlled in 92% of patients by adding second and third AEDs and introduction of anaesthetics could be avoided. Though the exact reason of overall better seizure control in this cohort after 3 AEDs cannot be ascertained

Table 4
Prognostic markers for poor seizure control.

Parameters	Controlled SE (lorazepam + 1st AED) ($n = 107$)	Not controlled (lorazepam + 1st AED) ($n = 43$)	χ^2 with 1 df (p value)
Age (years)			
15–30	55 (51.4%)	19 (44.2%)	3.203 (0.201)
31–50	37 (34.6%)	21 (48.8%)	
51–65	15 (14.0%)	03 (07%)	
Gender			
M	67 (62.6%)	20 (46.5%)	3.26 (0.07)
F	40 (37.4%)	23 (53.5%)	
Rural vs urban	49 (45.8%)	31 (72.1%)	8.52 (0.003)
	58 (54.2%)	12 (27.9%)	
Poor socio-economic status	51 (47.7%)	19 (44.2%)	0.149 (0.699)
Past h/o seizures			
Yes	58 (54.2%)	30 (69.8%)	3.06 (0.08)
No	49 (45.8%)	13 (30.2%)	
Duration of SE before treatment (mean ± SD)	7.53 ± 7.62	9.47 ± 9.60	1.187 (0.240)
Mean STESS ± SD	2.4 ± 0.5	2.3 ± 0.4	1.628 (0.1)
New onset SE vs SE	49/107 (45.8%)	12/43 (27.9%)	4.067 (0.04)
with history of seizures	58/107 (54.2%)	31/43 (72.1%)	
Acute symptomatic SE	51/107 (47.6%)	14/43 (32.55%)	4.15 (0.12)
Remote symptomatic	36/107 (33.64%)	22/43 (51.16%)	
Cryptogenic	20/107 (18.69%)	7/43 (16.27%)	
Focal CT abnormality	48/107 (44.9%)	25/43 (58.1%)	2.165 (0.141)
PHT	20	12	0.63 (0.426)
SVA	16	7	0 (1.00)
LVM	12	6	1.2 (0.172)
Focal MRI abnormality	27/38 (71.1%)	20/22 (90.9%)	3.236 (0.07)
EEG abnormal	71/100 (71%)	34/39 (87.2%)	3.975 (0.04)
PLEDS	9/100	4/39	0.69 (0.75)
NCSE	7/100 (7%)	12/39 (30.8%)	13.43 (0.0002)
Medical complications	6/107 (5.6%)	25/43 (58.1%)	51.62 (<0.001)

CNBD, could not be done due to small numbers; SE, status epilepticus.

from the present analysis, there could be few possible explanations: (a) the design of the study allowed us to assess efficacy of combined inj. lorazepam + 1 AED, (b) the overall outcome assessment was based on sequential use of 3 AEDs, (c) the present cohort consisted of predominantly young patients (mean age: 33.71 ± 17.0 years) with relatively lesser medical comorbidities and (d) treatment of underlying cause might have contributed to better control of SE. If one treats RSE as per current guidelines, all 43/150 with RSE might require ventilation and additional anaesthetic medication. In the current study, only 7/145 patients remained uncontrolled after administration of three parenteral AEDs. In the study by Misra et al. (2006), by switching over between phenytoin and valproate, seizures were controlled in 55/68 (80.88%) patients with SE. This might be due to action of multiple AEDs with possible synergism between various drugs. This is an encouraging observation, especially in 'resource poor setting' or 'state funded public hospitals' where there is a huge demand-supply gap. Hence, patients can be tried on multiple AEDs sequentially provided patients and their vitals parameters (SPO2, BP) are monitored adequately, especially in resource limited settings. In this cohort, 29% had refractory SE. This is similar to the reported prevalence 20% to 30% in previous studies (Mayer et al., 2002; Novy et al., 2010). New onset refractory SE was found in 13 (8.67%). In another study from our centre, seizures could be controlled after a mean of 2 days in 66/98 subjects with RSE (Sinha et al., 2010a).

Seizures could be controlled with a single AED following lorazepam injection in 68%, 68% and 78% of subjects in groups I, II, and III, respectively. Overall, seizures could be controlled with the sequential addition of three AEDs in 92% of patients in each of the three groups. The efficacy of the individual AED in controlling SE has been studied in previous studies. Different protocols have been employed: benzodiazepines alone, or in combination with other AED like phenytoin, SVA, and phenobarbitone. Treiman et al. (1998) showed that lorazepam was successful in 64.9%, phenobarbital in 58.2%, diazepam and phenytoin in 55.8%, and phenytoin in 43.6% in controlling SE. But the present study did not intend to analyse the efficacy of lorazepam alone. Seizures were controlled 42% of patients by phenytoin as the initial AED in a study by Misra et al. (2006). Alvarez et al. (2011) showed that seizures were not controlled in 29/70 (41.42%) patients after lorazepam and phenytoin. The efficacy of valproate in controlling seizures is reported to be higher compared to phenytoin, and ranges from 66% to 85% (Alvarez et al., 2011; Misra et al., 2006). The reported efficacy of levetiracetam varies from 51.7% to 94% (Alvarez et al., 2011; Berning et al., 2009; Knake et al., 2001). A recent meta-analysis of eight studies that included 294 patients with SE showed that the mean efficacy of phenytoin was 50.2% (95% CI: 43.2–66.1%), valproate was 75.7% (95% CI: 63.7–84.8%), and levetiracetam was 68.5% (95% CI: 56.2–78.7%) (Yasiry and Shorvon, 2014). The efficacy of valproate and phenytoin in controlling seizures in the current study was less compared to that by Agarwal et al. (2007) who showed that valproate and phenytoin were effective in 88% and 84% ($p > 0.05$) of benzodiazepine resistant SE respectively.

In the current study, slightly better seizure control in the levetiracetam group compared to phenytoin and valproate subgroups was noted, but this was not statistically significant ($p = 0.44$). Moreover, patients in the levetiracetam group reported to the emergency services after a mean delay of 10.18 ± 9.33 h which was more than the other 2 treatment groups. This might indirectly suggest a slight edge to the levetiracetam arm. Randomisation of a larger number of patients may establish/refute the superiority of levetiracetam over phenytoin and valproate in controlling SE. Intravenous levetiracetam as add-on treatment in 26 patients (after benzodiazepines plus phenytoin, valproate or both) had an efficacy of 46.1%; when used early (pre-treatment with benzodiazepines or nothing) in 14 patients the efficacy was 78.5% (p 0.048) (Aiguabella et al., 2011).

As a second AED in RSE, phenytoin controlled SE in 15/26 (57.69%) and valproate in 8/13 (61%), the difference was not statistically significant. As a third AED in RSE, valproate controlled SE in 2/5 (40%) and levetiracetam in 6/10 (60%), statistical analysis could not be performed due to small numbers. Direct comparison of the results of this study with others may not be plausible due to differences in methodology, AEDs, and operational definitions of SE and control of seizures. The key message from this study is that a clinician can choose any of the three parenteral AEDs as the initial step in the management of SE given the fact there was no statistically significant difference in their efficacy.

The indicators for poor seizure control in this cohort after 1st AED were female gender, rural background, past history of seizures, focal MRI abnormalities, abnormal EEG, NCSE, remote symptomatic aetiology, associated medical complications. Binary logistic regression analysis showed that female gender, focal imaging abnormalities, medical complications, NCSE in EEG, have high risk of uncontrolled seizures after usage of first AED. Most of these factors are in accordance to the published literature. Interestingly, patients with past history of seizures had poorer outcome in this study which is in contradiction to previous studies. The exact reason could not be ascertained based on the present analysis but the possibilities could be patients with known epilepsy presented late to the emergency services than patients without history of seizures in the past.

Functional outcome as assessed by mRS and GOS at one month follow up was good in majority (95/110) irrespective of the treatment group. This suggests that depending on the aetiology, survivors of SE have good functional outcome including patients with RSE. Seizure recurrence was noted 20%: 17% each in phenytoin and valproate and 25% in levetiracetam subgroups. Seizure recurrence was more in levetiracetam subgroup could be due to poor compliance in some patients due to its high cost.

One month mortality was 13.6% in the current study and was higher in those with RSE (25.6%). This was related to the underlying aetiology and medical complications. Chin et al. (2004) reviewed various studies and found short and long term mortality of 7.6–22% and 43%, respectively. The reported mortality in RSE ranges from 15 to 60% in different studies (Sutter et al., 2013). A prior study from our centre identified prior history of epilepsy in 35% and discontinuation of treatment in 71.4% of patients with fatal SE. The common etiological factors were neuroinfection ($n = 34$) and stroke ($n = 16$) (Sinha et al., 2010).

One patient died due to sudden cardiac arrhythmia immediately following phenytoin infusion and could not be successfully resuscitated. Two patients developed hypotension and respiratory failure with phenytoin. Misra et al. (2012) reported phenytoin resulted in hypotension and respiratory depression in two patients each and cardiac arrhythmia in none. Treiman et al. (1998) reported hypotension (27%), respiratory depression (9.9%), and cardiac arrhythmia (6.9%) following phenytoin in SE. There were no apparent adverse reactions due to valproate in this study. Valproate monotherapy was associated respiratory suppression in 1 and reversible liver dysfunction in 3 (Misra et al., 2012). Three patients in the levetiracetam arm developed post-ictal psychosis with hallucinations, which resolved within 3–4 days, however two of these patients also had history of alcohol dependence. Adverse effects with levetiracetam in SE by Misra et al. (2006) included agitation: 4, rash: 1, and thrombocytopenia: 4.

The limitations of the study were small cohort, not double blinded, and continuous EEG monitoring was not done. Adequate monitoring was not undertaken especially while administration of injection phenytoin in this study carried out in a non-ICU setting which may have its own risk. The small cohort was due to the fact of hospital record regarding the number of patients with SE likely to visit this centre during the study period of 38 months. Even

though the sample size was small, it is one of the largest single centre prospective randomised controlled study involving three drugs. Nevertheless, this study, the first of its kind, is one of the largest single centre prospective randomised study. The efficacy of phenytoin, valproate and levetiracetam in controlling SE with lorazepam was compared. Levetiracetam is safe and efficacious in the management of GCSE. This study also provides an important observation that sequential administration of intravenous AEDs is beneficial when one AED does not control SE. The key message is that a clinician can choose any of the three parenteral AEDs as the initial step in the management of SE given the fact there was no statistically significant difference in their efficacy. In the event of uncontrolled seizures, a second parenteral AED can be given before considering the use of anaesthetic agents. Overall, 92% patients could be controlled without anaesthetics thereby obviating need for ICU care and the associated complications.

Conflict of interest

None.

Financial disclosure

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