ORIGINAL ARTICLE

Neuroimaging, electroencephalography, response to treatment and outcome in Children with status epilepticus in a tertiary care hospital

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ABSTRACT

Background and Objectives: Status epilepticus (SE) is a pediatric neurological emergency which if not managed promptly, may result in significant neuro-morbidity and mortality. Our aim was to study the Neuro-imaging, Electroencephalography (EEG), response to treatment and outcome in children with SE.

Methods: It was an observational study conducted in post graduate Department of Pediatrics, Government Medical College, Srinagar. All patients between one month and 18 years who were admitted in PICU with SE constituted the study population. Treatment was given according to the standardized protocol followed in the hospital. Lorazepam, Phenytoin, valproate, Phenobarbitone, levetiracetam and midazolam infusion were given intravenous in that sequential order to control SE. Neuro-imaging and Electroencephalography were done after controlling SE. Outcome was assessed in terms of neuro-deficit and mortality. Statistical analysis was carried out with Statistical Package for Social Sciences (SPSS) 20.0 version. Results were presented as frequencies and percentages.

Results: MRI was done in fifty patients with 13 patients (26%) showing variable abnormality. The EEG was also done in 50 patients with electrographic seizures in 35 patients (70%). 12 patients (23.5%), 14 patients (27.4%), 12 patients (23.5%), 7 patients (13.7%) and 5 patients (9.8%) responded respectively to the sequential treatments. one patient (1.9%) needed midazolam infusion. There was no neuro-deficit in 36 patients (70.6%), neuro-deficit in 14 patients (26.5%) and mortality in 1 patient (2%).

Conclusions: Neuro-imaging and EEG abnormalities are common in children with SE. Prompt treatment is necessary to prevent morbidity and mortality associated with SE.

Key words: Status epilepticus neuroimaging, Electroencephalography, Neuro-deficit

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INTRODUCTION

Status epilepticus (SE) is a common pediatric neurological emergency which if not managed promptly, may result in significant neuro-morbidity and mortality and thus requires immediate and vigorous management [1].The International League Against Epilepsy (ILAE) Task Force on Classification of SE has updated the definition of SE in 2015 which is now defined as "a condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures [2]. After 30 minutes it can have long-term consequences which include neuronal death, neuronal injury, and altered neuronal networks [2]. In resource poor developing countries, the mortality and morbidity associated with Status epilepticus occurs at a higher rate than in the developed world [3-5]. Although mortality associated with SE has decreased from 6%-3% but the rates from India and other developing nations at short-term range between 10.5% and 28% [6,7]. Severe neurological or cognitive sequelae have been reported in 11–16% of patients with Convulsive SE (CSE) [7]. Factors associated with poor outcome after generalized CSE include: underlying etiology, de novo development of SE in hospitalized patients, older age, impairment of consciousness, duration of seizures, focal neurological signs at onset and the presence of medical complications [8]. SE is not a single entity and comprises different electro-clinical syndromes with various etiologies. Thus, the treatment of all SE by the same algorithm could have certain disadvantages [9]. Studies on management of status epilepticus in children have shown that laboratory parameters were often not checked and some results were available only after long delays.[10] Further in 23% of children with status epilepticus, dosing of benzodiazepine was outside usual dosing guidelines and the median time to administer a second-line anti-epileptic medication to a child with SE was 24 minutes and administration of anti-epileptic in children with refractory SE was substantially delayed [10-12]. It is recommended that to accelerate therapeutic decisions, a written management pathway with a clear structured time frame should be with all units [13]. Several examples of management pathways have been published and need to be adapted based on local resources and practices [14-17]. Costello and Cole highlighted the importance of giving an appropriate dose of the first- and second-line anticonvulsive medication in SE and recommended aggressive management of SE [18]. They found far less association of the excessive dose of initial medications with SE morbidity compared to prolonged seizure activity and treatment in intensive care unit (ICU) [18]. Suggestions to consult neurologists with Electroencephalography (EEG) knowledge during the early stage of SE treatment have been made [18]. In order to prevent the brain damage due to the direct

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effect of electrical activity of seizures, it has been highlighted to interrupt both clinical and electrical manifestation of seizures [19]. In a large multi-centric double-blind randomized study, Treiman et al. compared four ways of SE treatment in which they found lorazepam was effective in 52.2%, phenobarbital in 49.2%, combination of phenytoin and diazepam in 43.1% and phenytoin in 36.8% of patients [20]. There are multiple regimens for treating SE in children [20-22]. The choice of initial agent may depend on individual patient characteristics, prior antiepileptic drug therapy, and physician preference. However more information is to develop a structured treatment regimen based on an operational definition for SE. Our study presents the results of Neuroimaging and Electroencephalography in the patients who were admitted in the Pediatric Intensive Care Unit (PICU) of our hospital along with response to treatment and outcome in these patients.

MATERIALS AND METHODS

The present study was conducted in the post graduate Department of Pediatrics, Government Medical College, Srinagar. This was an observational study conducted over a period of one year from April 2015 to March 2016. The study was approved by the ethical committee of Government Medical College, Srinagar. Informed consent was taken from the parents/guardian. All the patients between one month and 18 years who were admitted in PICU with SE constituted the study population. Patients with seizure duration less than five minutes, age < 1 months or >18 years and whose parent/ guardian didn't give the consent where excluded from the study. Treatment was given according to the standardized protocol followed in our hospital. Lorazepam, phenytoin, valproate, phenobarbitone, levetiracetam and midazolam infusion were given intravenous in that sequential order to control SE. Neuro-imaging and EEG were done after controlling SE. Outcome was assessed in terms of neuro-deficit and mortality at the time of discharge from hospital. Data collected was entered in a Microsoft Excel spreadsheet. Statistical analysis was carried out with Statistical Package for Social Sciences (SPSS) 20.0 version using descriptive statistics and results were presented as frequencies and percentages.

RESULTS

MRI was done in fifty patients with 13 patients (26%) showing variable abnormality. 3 MRI's showed infarct, 2 showed brain abscesses, 2 showed tuberculomas,1 MRI showed corpus callosal agenesis, 1 revealed schiezencephaly,1 revealed dilatation of cerebral vessels on MRA, 1 showed sub-ependymal tubers, 1 revealed cystic encephalomalacia and 1 revealed disseminated hyperintense lesions in bilateral cerebral hemispheres. CT was done in 15 patients of which 2 scans revealed cerebral abcess,1 revealed Tuberculoma, 3 scans showed stroke and 9 scans were normal. (Table 1 and Table 2). The EEG was done in 50 patients with electrographic seizures in 35 patients (70%) and Normal EEG in 15 patients (30%). Focal sharp waves were present in 17 patients (34%), Background slowing in 05 patients (10%), Moderate to high amplitude, generalized 10-25 Hz spikes in 06 patients (12%), Polypiles in 04 patients (08%) and Hypsarrhythmia type of discharges in 03 patients (06%). (Table 3). 12 patients (23.50%) responded to lorazepam, 14 patients (27.40%) responded to second line drug phenytoin, 12 patients (23.5%) responded to third line drug Valproate while 7 patients (13.7%) responded to fourth line drug Phenobarbitone 9.80% and 5 patients (9.8%) responded to fifth line drug levetiracetam. one patient (1.9%) needed midazolam infusion. (Table 4). There was no neuro-deficit in 36 patients (70.6%), neuro-deficit in 14 patients (26.5%) and mortality in 1 patient (2%). (Table 5)

Table 1: MRI Findings.

MRI finding	Number of Patients	Percentage
Normal MRI	37	74
Infarct	03	06
Brain Abscesses	02	04
Tuberculomas	02	04
Corpus callosum agenesis	01	02
Shiezencephaly	01	02
Dilatation of cerebral vessels	01	02
Sub-ependymal tubers	01	02
Cystic encephalomalacia	01	02
Hyper intense lesion	01	02
Total	50	100

Table 2: CT Findings.

Number of Patients	CT finding
1	Tuberculoma
2	Cerebral abcess
3	Stroke
9	Normal

Table 3: EEG Findings.

EEG pattern	No. of patients	Percentage
Normal	15	30
Focal sharp waves	17	34
Background slowing	05	10
Moderate to high amplitude, generalized 10-25 Hz spikes	06	12
Polyspikes	04	08
Hypsarrythmic type of discharges	03	06
TOTAL	50	100

Table 4: Drugs used in a sequential manner to achieve control of the status.

Sequential drugs used to Control Status Episode	Number of Patients	Percentage
Lorazepam	12	23.50
Phenytoin	14	27.40
Valproate	12	23.50
Phenobarbitone	7	13.70
Levitiracetam	5	9.80
Midazolam infusion	1	1.90
Total	51	100

Table 5: Outcome.

Outcome	Number	Percentage
No deficit	36	70.60
Neuro-deficit	14	27.50
Death	1	2.00
Total	51	100

DISCUSSION AND CONCLUSION

MRI was done in fifty patients with 13 (26%) patients showing some abnormality. CT was done in fifteen patients with six showing abnormality. A wide range of abnormalities were found in those with abnormal study. Three of the patients who had CT documented stroke also confirmed the same on MRI. Two patients revealed lesions suggestive of Tuberculomas as reported by a radiologist while other two patients had multiple cerebral abscesses. One patient had corpus callosal agenesis and one MRI revealed Shiezencephaly. One patient had dilatation of cerebral vessels suggestive of moyamoya disease. One patient showed findings suggestive of tuberous sclerosis as reported by a radiologist. One MRI showed bilateral gliosis and cystic encephalomalacia with cortical atrophy of fronto-parietal lobes with laminar necrosis/hemorrhage with hemorrhagic infarcts of thalami. One MRI also revealed hyper intense lesions. Khalid et al. reported abnormal CT in 23% and abnormal MRI in 43% of patients [23]. Mytal et al. said neuroimaging abnormalities have been reported in 30% of children with SE [24]. Bhalla et al. reported abnormal radiological study in 67.5% of subjects and normal study in 32.5% [25]. While it is agreed that patients with new-onset SE require neuroimaging, but the timing of imaging is of less consensus [26]. The American Academy of Neurology's Practice Parameter states that once SE has been controlled and child stabilized, neuroimaging should be done [27]. According to Neuro-critical Care Society's guideline, neuro-imaging is to be done on "urgent" basis and performed within the first 60 min of SE onset [8]. Ultimately it is at the discretion of the treating clinician with regard to the necessity and timing of neuro-imaging. Immediate neuro-imaging can be abandoned in cases where the cause of SE is clearly established. In other cases, such as when the SE etiology is unknown or in trauma patients, neuroimaging should be considered on urgent basis. The EEG was done in 50 patients, out of which 25 were done within 72 hours of SE episode, while 16 were done within 1 week of the SE episode and in 9 patients it was done after 1-week period. 17 patients showed epileptiform discharges with focal sharp waves and 5 patients showed background slowing of the electrical activity. 6 patients revealed moderate to high amplitude generalized 10-25 Hz spikes. 4 patients had EEG consisting of polyspikes. 3 patients revealed the Hypsarrythmic type of discharges. 15 patients revealed normal EEG pattern. Thus, this study shows that the electrographic seizures occurred in 35 patients after having convulsive SE. This finding although differs from many other studies but the EEG findings vary temporally in relation to the status event and also depends upon the type of the SE [28]. The principal goal in the management of SE is cessation of both clinical and electrographic seizure activity [8]. However, an immediate EEG is usually not done during the initial stage of treatment of CSE. The indications for emergency EEG include unexplained altered consciousness (to exclude Non-convulsive SE); elimination of convulsive movements by neuromuscular paralysis for SE which does not stop the electrographic seizure activity; or when refractory SE (RSE) needs continuous intravenous (IV) therapy [29]. In the resource poor countries like India, EEG monitoring should be targeted to patients at highest risk for non-convulsive SE with a goal to identify and manage the electrographic seizures for improved patient outcome. In our study the first line drug used in patients of SE for control of seizure was intra-venous (I.V.) Lorazepam in all cases and 12 patients (23.5%) responded to it. Those in whom seizures were uncontrolled even after I.V. Lorazepam, I.V. Phenytoin was used as second line drug and 14 patients (27.4%) responded to it. I.V. valproate was used as third line drug and 12 patients (23.5%) responded to it. I.V. Phenobarbitone was used in those who didn't respond to above three drugs and 7 patients (13.7%) responded to it. Intravenous levetiracetam was the next drug used and 5 patients (9.8%) responded to it. Only one patient (1.9%) needed I.V. midazolam infusion to control the seizures. Our results are similar to the results of Kumar et al. who in their study found 16 patients (22.7%) responded to I.V. lorazepam. Intravenous Phenytoin was needed in 27 (38.5%) patients as second line drug while intravenous Phenobarbitone was used in 18 (25.7%) patients of SE not responding to lorazepam and phenytoin. Nine patients required intravenous midazolam infusion and intravenous levetiracetam [30]. Menon et al. also support our results by finding majority of patients (79%) with SE responding to first- and second-line drugs [31]. Our results are also supported by Gulati et al. who in their study reported that a combination of diazepam and phenytoin was used in 93% of the patients and more than 3 drugs were required to control SE in 33.3% of the patients [32]. Kalita et al. used a different protocol for controlling SE in children. They used either phenytoin or valproate as the first line drug followed by intravenous lorazepam, diazepam, midazolam or intramuscular paraldehyde. They found that SE was well controlled following the first antiepileptic drug in 66.7% children [33]. Khalid et al. from Pakistan found that a minimum of 2 and maximum of 8 anti-epileptics were used with a mean of 4.33 and 62% of patients required continuous midazolam infusion. Their contradictory results to our study could be explained as they had >60% of patients with refractory SE which they admitted is higher than other studies [23]. Saz et al. also used a different protocol for treating SE. Two repeated doses of 0.5 mg/kg of rectal diazepam was used in Step I followed by one of the following second line drug (1) 20 mg/kg of intravenous phenytoin or (2) a bolus of midazolam (0.15 mg/kg iv) in Step II followed by intravenous midazolam every 5 min up to 0.6 mg/ kg/min in Step III. In Step IV: If seizures continued for 60–90 min after the initiation of therapy propofol infusion (1 mg/kg/h) was introduced. Only 2 of their 27 (7.5%) episodes of SE were controlled by step I. 95% of SE were arrested after midazolam infusion (step III) [34]. Although they used a different protocol, but their study also showed that most of the patients required more than one drug to control an episode of SE. Several RCTs and systematic reviews have concluded that Benzodiazepines are first line drugs for treatment of SE in children and lorazepam is the agent of choice among the benzodiazepines [20,35,36]. Phenytoin is one of the preferred second-line anticonvulsant [20]. Intravenous Phenobarbitone is

an effective alternative to phenytoin in benzodiazepine unresponsive seizures [20,37]. The efficacy of valproic acid is similar to phenytoin after failure of benzodiazepines though a recent meta-analysis found it to have superior efficacy [37,38]. Levetiracetam is another emerging drug in the management of status epilepticus but presently there are no randomized trials reporting its use in children [39]. Intravenous Anesthetic Agent Midazolam infusion is the most preferred initial treatment in children with refractory status epilepticus, effective in seizure control in 76% of these patients [40]. In our study, there was no neuro-deficit in 36(70.6%) patients, neuro-deficit in 14 (26.5%) patients and mortality in 1 (2%) patient. Jan et al. in their study didn't found a gross neuro-deficit in about 70% of their patients after treatment which is consistent with our study [41]. They reported higher mortality (16.6%) than our study but they admitted that their results are higher than the recently published studies [41]. Although Kumar et al. in their study had 60% of patients without any neuro-deficit after treatment which is in accordance with our study but the mortality rate in their study was high (31.4%) [30]. The high mortality in their study could be explained by the fact that their study had many patients who were referred from peripheral centers and were having refractory status epilepticus [30]. Our results are also supported by many other studies which have reported majority of patients without any neuro-deficit [23,42,43]. The inpatient mortality rate in this study is comparable to other studies on children with SE which have shown lower mortality rates [44]. The short-term (within 30 days) mortality rate in a systematic review of population-based studies was 3-9% in children [45]. The variability in mortality rates across different studies is expected because of differences in causes and increases significantly due to symptomatic reasons [46,47]. However, the mortality rate in our study was low which is in accordance with the tendency towards a decrease during last decade which is probably multi-factorial being helped by advances in childhood medical and nursing practices with acute life support, critical care management and evolving anti-epileptic drug therapies [32,48-50]. In conclusion, neuro-imaging and EEG abnormalities are common in children with SE. Rapid treatment of both clinical and electrographic seizures is necessary to prevent morbidity and mortality associated with SE. Prompt treatment with benzodiazepines is the first-line treatment of SE, but many patients will need additional treatment with additional medications including phenytoin, valproic acid, phenobarbital, or levetiracetam.

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