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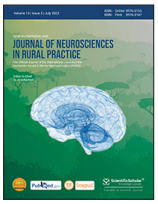

Original Article

Efficacy of a pre-specified timeline-based treatment protocol in children with acute repetitive seizures or seizure clusters

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ABSTRACT

Objectives: Acute repetitive seizures (ARSs) are one of the few commonly encountered neurological emergencies in children. There is a need for an appropriate timeline-based treatment protocol, which will be shown to be safe and efficacious in a clinical study.

Materials and Methods: This was a retrospective chart review to determine the efficacy of a pre-specified treatment protocol for the management of ARSs in children aged 1–18 years. The treatment protocol was specifically applied in children with a diagnosis of epilepsy and not critically ill, who met the criteria for ARSs, with the exemption of new onset of ARSs. The first tier of treatment protocol focused on intravenous lorazepam, optimization of dose of existing anti-seizure medications (ASMs), and control of triggers like acute febrile illness, while second-tier focused on adding one or two additional ASMs, commonly used in cases with seizure clusters or status epilepticus.

Results: We included the first 100 consecutive patients (7.6 ± 3.2 years, 63% boys). Our treatment protocol was successful in 89 patients (58 and 31 required first-tier and second-tier treatment). The absence of pre-existing drug-resistant epilepsy and the presence of acute febrile illness as a triggering factor ($P = 0.02$ and 0.03) were associated with the success of the first tier of the treatment protocol. Excessive sedation ($n = 29$), incoordination ($n = 14$), transient gait instability ($n = 11$), and excessive irritability ($n = 5$) were the most common adverse effects observed during the initial 1 week.

Conclusion: This pre-specified treatment protocol is safe and efficacious in controlling ARSs in cases with established epilepsy who are not critically sick. External validation from other parts of the world/centers and a more diverse epilepsy population are required before generalizing the protocol into clinical practice.

Keywords: Acute repetitive seizures, Seizure clusters, Epilepsy, Lennox-Gastaut syndrome, Epilepsy with myoclonic-atonic seizures, Treatment protocol

INTRODUCTION

Isolated seizures and status epilepticus (SE) can be considered as two ends of a clinical spectrum in terms of severity.[1,2] Acute repetitive seizures (ARSs) or sometimes called seizure clusters are often considered a relatively less well-defined and inconspicuously explored entity, lying in between these two extremes of the clinical spectrum.[3] However, it is one of the few clinical problems neurologists often come across in their practice.[4] The previous authors were of the view that more invasive management in the lines of SE is often not required in such cases and may even lead to increased morbidity.[5] Some author groups have previously attempted to define this entity and tried to determine the efficacy of various anti-seizure medications (ASMs).[6-8] While defining this entity, most author groups have stressed on acute and repetitive nature of seizures, in a patient who may or may not be already on ASMs.[9] While the management of a child with new onset ARSs or seizure clusters, mainly depends on the etiology and semiology of seizures and it is difficult to formulate a uniform protocol for new onset ARSs.[5,10] Moreover, in new-onset seizure cases, often neuroimaging, electroencephalogram (EEG), and genetic/metabolic testing are required to further characterize the nature of epilepsy and the choice of ASMs.[11]

However, for patients with an established diagnosis of epilepsy, there is some consensus in the existing literature about managing seizure clusters by first administering benzodiazepines (BZDs) and subsequently other ASMs.[12,13] Still, it is problematic to find an appropriate treatment protocol for ARSs, because it is an umbrella term, constituting a number of heterogeneous entities with varying prognoses.[3,14] Although BZDs are considered the core drugs

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used to stop ARSs, these medications are also not devoid of side effects.[15] Each repeat dose of BZDs increases the risk of respiratory depression.[16] On the contrary, untreated ARSs can proceed to SE.[17] This justifies the need for an appropriate timeline-based treatment protocol, which will be shown to be safe and efficacious in a clinical study and would facilitate the management of ARSs.

MATERIALS AND METHODS

This was a retrospective chart review to determine the efficacy of a pre-specified treatment protocol for the management of ARSs or seizure clusters in children aged 1–18 years who were not critically ill, presenting to a tertiary care teaching hospital in North India between August 2019 and June 2022. The primary objective of our study was to determine the proportion of patients who achieved control of ARSs at 24 h after initiating the pre-specified protocol (complete seizure freedom without any evidence of non-convulsive status epilepticus (NCSE) in EEG in patients who had no clinical seizures within 1 week before the onset of ARSs or reached baseline seizure frequency). The secondary objective was to determine the proportion of patients who achieved control of ARSs with intravenous BZD (first stage of the pre-specified treatment protocol) and intravenous ASMs (second stage of the pre-specified treatment protocol). The study also intended to determine the safety parameters of these pre-specified treatment protocols in terms of the nature and frequency of adverse effects and also the proportion of patients who had a recurrence of ARSs, within a follow-up period of 6 months.

This study included all consecutive patients in the above-mentioned age group with acute ARSs. We excluded those patients aged <1 year, with inadequate clinical details of follow-up till 3 months, those who had convulsive or NCSE, and who were critically ill. We also excluded those patients who became critically sick (pSOFA score>2) and required intensive care unit care, as many of these patients required mechanical ventilation and BZD infusion for purposes other than seizures.[18] This subset of patients had also several systemic confounders and limitations for administering intravenous medications like intravenous valproate in patients with liver failure and intravenous levetiracetam in patients with acute kidney injury. We also excluded patients with neurodegenerative diseases such as progressive myoclonic epilepsy and subacute sclerosing panencephalitis. We assumed an efficacy rate of at least 60% of the pre-specified treatment protocol. With a precision of 90% and power of 90%, the minimum sample size was calculated to be 93. We decided to enroll at least 100 consecutive children satisfying the inclusion criteria in our study after taking approval from the institutional ethics committee and informed consent from the parents. The treatment protocol was specifically applied in children with a diagnosis of epilepsy and not critically ill, who met the criteria for ARSs, with the exemption of new onset of ARSs.

At our center, during the study period, we followed a uniform definition of "acute repetitive seizures," mentioned in the article by Cereghino[3] We defined "acute repetitive seizures" as a chronobiological entity with seizures irrespective of etiology that are severe and occurring repetitively (at least 3 times in 24 h), but not satisfying the definition of SE (patient recovery between seizures), historically distinct from the patient's other seizures in type, frequency, severity, or duration, have an onset that is easily recognized by the family and physician, have a consistent component (such as an aura, prodrome, or characteristic single or multiple seizures) that is predictably and temporally linked to subsequent seizures. Moreover, the criteria also included that patient needed to be receiving stable ASM regimens, with good compliance and the heralding consistent component might even be a non-convulsive symptom, such as vomiting.

For our study purpose, we only included patients with an established diagnosis of epilepsy and not those patients with new onset ARSs, without the previous unprovoked seizures.

For the treatment of ARSs, we followed a two-tier approach initially [Figure 1]. First, we administered injectable lorazepam q8hourly for 24–48 h. Once the seizures are controlled, we introduced oral clobazam or clonazepam (BZD), if the patient was not previously receiving or hiked the maintenance dose of oral BZD, if the patient was already receiving the same. Simultaneously, we also converted the existing ASM regimen from oral to intravenous route (because oral bioavailability is sometimes compromised during acute febrile illness with vomiting), and tried to optimize the dose of the existing ASM regimen guided by the feasibility and results of therapeutic drug monitoring. We also tried to alleviate or treat the triggering condition if feasible such as acute febrile illness or vomiting or gastroenteritis. If seizures remained uncontrolled at 24–48 h, we introduced 1–2 new intravenous ASMs (one among the following six medications: valproate, phenytoin, levetiracetam, brivaracetam, lacosamide, or phenobarbitone) or topiramate loading through nasogastric or oral route at 10 mg/kg followed by maintenance at 5 mg/kg/day, This ASM was decided by the treating pediatric neurologist taking into account epilepsy and patient characteristics as well as existing ASM regimen. We added the second new intravenous ASM only after the first ASM was administered for 24 h and still, the seizures remained uncontrolled. The sequence and choice of the intravenous ASM were decided by the treating pediatric neurologist. If the patient still didn't respond to the addition of this new ASM after 24–48 h, then we considered it to be a failure of our treatment protocol and subsequent decision for starting intravenous midazolam,

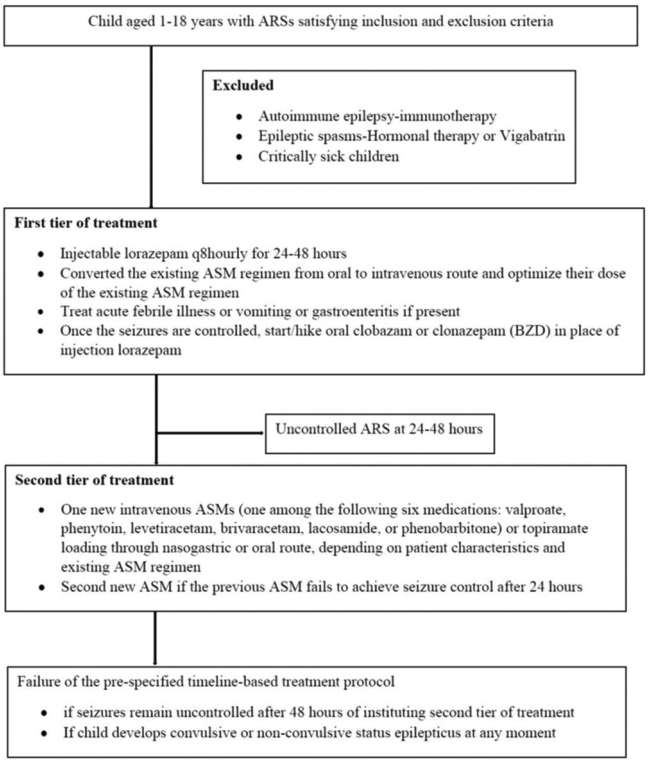

Figure 1: Flowchart showing the prespecified timeline-based proposed treatment protocol for acute repetitive seizures.

or phenobarbitone infusion or other oral medications such as oxcarbazepine, perampanel, and cannabidiol ketogenic diet or immunotherapy with corticosteroid or intravenous immunoglobulins or work up for epilepsy surgery was taken by the treating neurologist. Similarly, if patients developed convulsive or NCSE at any time during treatment, then also this was considered a failure of the treatment protocol. Although intravenous preparation of oxcarbazepine is currently approved by FDA, it is not easily available in our setting. Hence, we could not include this in our treatment protocol, but for focal onset seizures with/without impaired awareness, we preferred to start oxcarbazepine as the initial ASM if no other contraindication is present. However, in patients with a previously confirmed diagnosis of autoimmune epilepsy, we included immunotherapy in the first tier of treatment, as results of repeat workup for autoimmune etiology often have a turnaround time of >24 h. Another exception, we followed was in patients with epileptic spasms, in whom we tried hormonal therapy or vigabatrin in the first tier of treatment, if they have not already exhausted that option previously. Hence, the majority of patients with focal epilepsy who developed ARSs were already on oxcarbazepine. If ARSs recurred again during the follow-up of 6 months, we followed the same treatment protocol and we continued the ketogenic diet if the child was already receiving the diet during the execution of this abovementioned treatment protocol, unless and until other contraindications were present.

We documented all the sociodemographic, clinical, electrographic, neuropsychological, and pharmacological details of patients who became a part of our study. The list of variables included age of onset of seizures, age at presentation with ARS, gender, baseline seizure semiology, frequency, National Hospital Seizure 3 severity score, abnormalities in magnetic resonance imaging (MRI) of the brain, EEG, single-photon emission computerized tomography brain, epilepsy gene panel, chromosomal microarray, and neurometabolic work up, developmental and intelligence quotient, details of the perinatal adverse event, abnormalities on neurological examination, behavioral abnormalities, triggers/precipitating factors for ARSs, history of similar episodes or history of convulsive or NCSE, family history of seizure, existing ASM regimen, and compliance. We also noted the details of ARSs in terms of seizure semiology, aura, post-ictal events, duration and frequency of seizures, time since onset of ARSs to presentation, recent EEG findings, etc. During the time treatment protocol was initiated we noted down both safety, efficacy, and tolerability parameters. After the ARSs was controlled, these children were followed as part of our routine clinical outpatient follow-up protocol at monthly interval for the first 3 months and subsequently at 3 months. During these follow-up outpatient visits, we noted any breakthrough seizure, recurrence of "acute repetitive seizures" adverse effects related to the ASM regimen or ketogenic diet, cognition, and behavioral parameters.

The primary outcome measure was the success rate in aborting the ARSs with the above-mentioned treatment protocol. Secondary outcome measures were efficacy of the first tier and second tier of the above-mentioned protocol, adverse effects noted with the treatment protocol, recurrence rate over the following 6 months, and factors determining the success of the treatment protocol.

Statistical analysis

We used SPSS software version 29.0 for performing the statistical analysis. We presented the distribution of continuous variables and categorical variables as mean, standard deviation/median, interquartile range, and frequency with a 95% confidence interval respectively. We checked the difference between the distribution of two continuous variables using the Wilcoxon rank sum test or student's *t*-test, respectively. For the corresponding purpose, we used the Chi-square test or student's *t*-test. Two-tailed $P < 0.05$ was considered statistically significant. For determining the predictors associated with response to the suggested treatment protocol (dependent variable), we first checked the relevant independent sociodemographic, clinical and neurodiagnostic variables by univariate analysis

and then we subjected those variables to multivariate analysis subsequently.

RESULTS

We included the data of the first 100 consecutive patients (7.6 ± 3.2 years, 63% boys) with adequate follow-up details, satisfying inclusion criteria. For this, we screened records of 135 patients (35 excluded, only 3 were lost to follow-up, 23 required critical care for systemic illness such as severe pneumonia, shock including mechanical ventilation, eight children had a breakthrough seizure due to poor compliance with advised ASM regimen, and one child was suffering from neuronal ceroid lipofuscinosis).

The demographic, clinical, and epilepsy characteristics of the sample population have been described in [Tables 1 and 2], respectively. Most patients belonged to rural areas and middle/lower socioeconomic status. While 59 patients had a structural abnormality in neuroimaging, the rest had probable or definite genetic epilepsy. Lennox Gastaut syndrome (LGS) (n = 43) was the most common epilepsy syndrome followed by epilepsy with sleep-related hyper motor epilepsy (n = 15), myoclonic atonic seizures (n = 14), and Dravet syndrome (n = 10). Multiple viable parenchymal neurocysticercoses with structural epilepsy (n = 4), structural epilepsy due to hypoglycemic brain injury during the neonatal period (n = 5), focal cortical dysplasia (n = 6), and focal epilepsy due to perinatal hypoxia and cerebral gliosis (n = 4) were other etiologies. While 31/43 patients with LGS (72%) had structural etiology due to perinatal asphyxia or hypoglycemia or postnatal insult like meningoencephalitis, the rest 12 patients had probable genetic cause (cryptogenic LGS). Among 41 patients with probable genetic etiology, a definite genetic diagnosis could be established in 22 patients (SCN1A, n = 10, CHD2, n = 3, GRIN2A, n = 2, ADGRV1, n = 2 were the most common genes, in which pathogenic mutation was identified in our cohort) [Table 3]. While 34 patients had purely focal seizures during their lifetime and during the episode of ARSs, 41 patients had both generalized and focal seizures and mostly pleomorphic seizure semiology (tonic, tonic-clonic, atonic seizure, etc.). Rest 25 patients had mainly generalized seizures, although a significant subset of these patients also had pleomorphic seizure semiology before the onset of ARSs in the form of tonic, myoclonic, atonic, atypical absence, and myoclonic-atonic seizures. Before presenting with ARSs, 79 patients had no seizure episode within the previous month, whereas 21 patients had a median of 4 (IQR: 2–11 seizures) in the previous month and the monthly median seizure frequency was 1/month (IQR-0.5–3/month). A total of 13, 23, 53, and 11 patients were on 1, 2, 3, and 4 ASMs, respectively. Sodium valproate, oxcarbazepine, levetiracetam, and BZDs were commonly used ASMs in 61, 35, 47, and 41 patients, respectively. Topiramate, lacosamide, phenytoin, zonisamide, perampanel, brivaracetam, and lamotrigine were other ASMs used in a small proportion of patients. Eleven patients with

Table 1: Socio-demographic variables of study participants.

Variable	Distribution (n=100)
Age at presentation (years)	7.6±3.2
Age at onset of seizure	2.3±2.1
Gender	
Male	63 (63%, 52–73%)
Female	37 (37%, 27–47%)
Socioeconomic status	
Lower	29 (29%, 20–38%)
Middle	69 (69%)
Higher	02 (2%, 0.2–7%)
Residence	
Rural	73 (73%, 63–81%)
Urban	27 (27%, 15–32%)

Table 2: Clinical variables of study participants.

Variable	Distribution (n=100)
Etiology of epilepsy	
LGS	43 (43%, 33–52%))
EMAS	14 (14%, 7–22%)
SRHE	15 (15%, 8–23%)
Dravet syndrome	10 (10%, 4–17%)
Multiple viable parenchymal neurocysticercosis	4 (4%, 1.1–9.9%)
Hypoglycemic brain injury during neonatal period	5 (5%, 1.6–11.2%)
FCD	6 (6%, 2.2–12.6%)
Focal epilepsy due to perinatal hypoxia and cerebral gliosis	4 (4%, 1.1–9.9%)
Number of ASMs	
One	13 (13%, 7.1–21.2%)
Two	23 (23%, 15.1–32.4%)
Three	53 (53%, 42.7–63.0%)
Four	11 (11%, 5.6–18.8%)
Seizure frequency (per month) (median, IQR)	1 (0.5–3)
Well-controlled epilepsy (no seizures within previous 1 month)	
Yes	79 (79%, 69.7–86.5%)
No	21 (21%, 13.4–30.2%)
Seizure semiology	
Only focal onset seizure	34 (34%, 24.8–44.1%)
Only generalized onset seizure	25 (25%, 16.8–34.6%)
Both focal and generalized onset seizure	41 (41%, 31–52%)
Developmental delay/intellectual disability	75 (75%, 65–83%)
Neuromotor impairment	56 (56%, 45–66%)
Behavioral abnormalities	59 (59%, 48–69%)

LGS: Lennox Gastaut syndrome, EMAS: Epilepsy with myoclonic-atonic seizures, SRHE: Sleep-related hyper motor epilepsy, ASMs: Anti-seizure medications

Table 3: Neuroimaging, EEG, and genetic work up findings in our study participants.

Variable	Distribution (*n*=100)
Normal MRI brain	41 (41%, 31–42%)
Abnormal MRI brain	59 (59%, 48–69%)
EEG	
Features of LGS (SSW, PFA etc)	43 (43%, 33–54%)
Generalized spike wave or polyspike wave discharges	29 (29%, 20–39%)
Focal/multifocal discharges	27 (27%, 18–36%)
Normal EEG	1 (1%, 0.1–5.4%)
Genetic aetiology (*n*=22)	
SCN1A	10 (10%, 4.9–17.6%)
CHD2	3 (3%, 0.6–8.5%)
GRIN2A	2 (2%, 0.2–7.0%)
ADGRV1	2 (2%, 0.2–7.0%)
Others	5 (5%, 1.6–11.2%)

EEG: Electroencephalogram, MRI: Magnetic resonance imaging, LGS: Lennox Gastaut syndrome, SSW: Slow spike-wave, PFA: Paroxysmal fast activity

a diagnosis of LGS, epilepsy with myoclonic-atonic seizures (EMAS), and Dravet syndrome were receiving a ketogenic diet. EEG showed features of LGS (slow spike-wave, paroxysmal fast activity, etc.) in 43 patients, generalized spike-wave or polyspike wave discharges in 29 patients, and focal/multifocal discharges in 27 patients. One patient with multiple neurocysticercoses had normal baseline EEG, but at the time of ARSs, all of them had some epileptiform abnormality in EEG, including this patient, who also had focal discharges during the episode. Moreover, 11 patients showed additional findings of focal fast activity in EEG and more prominent background slowing in 36 patients. In a total of 56 patients, the discharges in EEG were more frequent as compared to the previous EEG, but the site of origin of epileptiform abnormalities remained the same in patients with focal discharges [Table 3].

The duration of ARSs from onset to presentation at our institute was a median of 3 days (IQR: 2–7 days) and the frequency of seizures during this episode was a median of 7/day (IQR: 4–16/day). The seizure semiology grossly matched with previous seizure semiology in all of these patients and the majority of patients with pleomorphic seizures also had pleomorphic seizures during the current illness. A total of 47 patients had a temporally correlated acute febrile episode before the onset of ARSs and 38 of these patients showed irritability, lethargy, excessive drowsiness, and poor appetite, probably related to the repeated seizures, but none of them had NCSE in EEG, nor any of those seizures satisfied the criteria for SE. Most of these seizures were self-aborted or aborted at home by intranasal midazolam spray. The median duration of those seizures was 1 min (IQR: 0.5–2 min) [Table 4].

Table 4: Characteristics of ARS and response to suggested treatment protocol.

Variable	Distribution (*n*=100)
Duration of ARS before presentation (in days) (median, IQR)	3 (2–7)
Frequency of seizures (median, IQR)	7 (4–16)
Duration of seizures (minutes) (median, IQR)	1 (0.5–2)
Temporally correlated acute febrile episode	47 (47%, 36–57%)
New onset symptoms related to ARS	38 (38%, 28–48%)
ARS control with suggested treatment protocol	89 (89%, 81–94%)
ARS responsive to first tier of treatment protocol	58 (58%, 47–68%)
ARS responsive to second tier treatment protocol	31/42 (73%, 57–68%)
Duration required by patient for controlling ARS (hours) (median, IQR)	30 (18–41)
Number of doses of BZD required for controlling ARS (hours) (median, IQR)	2 (1–3)
Time required for controlling the fever (hours) (median, IQR)	10 (5–22)
Response to immunotherapy	1 (1%, 0.1–5%)
Response to ketogenic diet	2 (2%, 0.2–7%)
Progression to convulsive SE	2 (2%, 0.2–7%)
Progression to NCSE	0 (0%)
Recurrence of ARS within 6 months	7 (7%, 2.8–13.8%)

ARS: acute repetitive seizure, SE: Status epilepticus, NCSE: Non-convulsive status epilepticus, BZD: Benzodiazepine

The first tier of our treatment protocol (management of acute febrile illness, including fever control, converting existing ASM regimens to the intravenous route, and optimizing their dose as per feasibility and intravenous lorazepam) was successful in controlling ARSs in 58 patients. Out of the 42 patients, who required a second tier of treatment including the addition of one or two new intravenous ASM or topiramate loading orally/through a nasogastric tube, 31 patients achieved control of ARSs (17 after adding one new ASM and 14 after adding another ASM). Hence, 89 patients could be successfully brought to their baseline seizure frequency/complete seizure control using our pre-specified protocol. On follow-up, seven patients had a recurrence of similar episodes within 6 months (LGS-3, Dravet syndrome-2, EMAS-1) and 5 of them could be controlled using a similar protocol.

Overall, the median duration required by the patient for controlling ARS was 30 (18–41) h and the number of doses of BZD required for controlling ARS was 2 (1–3), whereas, the time required for controlling the fever was 10 (5–22) h. The cause of fever was respiratory illness in 35 cases, gastrointestinal illness in the rest of the seven cases, and Dengue fever in five cases. The maximum time point

cutoff for determining the success or failure of the first tier of treatment was 48 h and the second tier of treatment was 96 h since starting the protocol or (48 h since beginning the second tier of treatment, whichever was earliest).

Eleven patients who could not reach the baseline seizure frequency were subjected to the addition of other intravenous/oral ASMs. Out of these, two children had subsequently a prolonged seizure lasting >5 min (satisfying the definition of SE). But only two children reached baseline seizure frequency with these ASMs after about 2 weeks, only one child responded to immunotherapy and two children reached baseline seizure frequency after 2 months of initiating a ketogenic diet. Although the rest of the six children never reached their baseline seizure frequency on follow-up at 6 months, all of them had at least a 50% reduction in seizure frequency as compared to the frequency at the time of presentation with ARSs.

Subsequently, we tried to determine factors associated with response to the first tier of the treatment protocol, that was the absence of pre-existing drug-resistant epilepsy (one or two ASMs) and the presence of acute febrile illness as triggering factors ($P = 0.02$ and 0.03, respectively). However, we could not identify any factor other than the number of baseline ASMs for response to the second tier of our treatment protocol. Numerically, the response was slightly higher with phenobarbitone (85%), as compared to valproate (63%), levetiracetam (59%), lacosamide (49%), phenytoin (56%), topiramate (51%), and brivaracetam (58%), when used as additional first or second ASM over and above the existing ASM regimen. However, the difference between individual groups didn't reach statistical significance, probably because there were only a few patients in the phenobarbitone, brivaracetam, and topiramate group ($P = 0.11$).

Excessive sedation ($n = 29$), incoordination ($n = 14$), transient gait instability ($n = 11$), and excessive irritability ($n = 5$) were the most common adverse effects observed during the initial 1 week, but all of them were self-resolving and none required discontinuation of the protocol. No serious adverse effect or mortality was observed in any patient. During the 6-month follow-up, behavioral abnormalities ($n = 12$), the asymptomatic elevation of liver transaminases ($n = 5$), thrombocytopenia ($n = 3$), hyperammonemia ($n = 4$), weight gain ($n = 6$), and excessive sedation ($n = 10$) were predominant adverse effects. But all of them could be managed by reducing the dose of ASM, most likely responsible for the adverse effect or they resolved spontaneously over time.

DISCUSSION

Our study showed that merely by using intravenous BZD, optimizing the dose of existing ASMs, and treating the triggers such as acute febrile illness, around half of children with ARSs can be controlled. Around three fourth of the remaining children can be brought to baseline seizure frequency by adding one or two properly chosen intravenous ASMs. Still around one-tenth of patients will require other more cumbersome interventions or immunotherapy and still have a minimal probability of reaching baseline seizure frequency.

The definition of ARSs for our study is similar but slightly different to the definition used by Mesraoua *et al*.[7] for "seizure clusters" in 2021, which states "seizure clusters" are closely grouped seizures over minutes to 2 days, representing an increase in seizure frequency compared with baseline. However, we removed the time limit as in a setting like ours in a low-medium income country (LMIC), often the patients present after 2 days of acute increase in seizure frequency. Szklener *et al*.[9] used a criterion of 3 or more seizures within 24 h, which we also included in our definition.

The protocol we used in our study was based on the results of previous studies enrolling patients with ARSs or seizure clusters. McTague *et al*.[19] in their study found that intravenous levetiracetam was effective in 23 out of 39 patients with ARSs, comparable to our study results. Our study was a retrospective chart review and the choice of selecting the additional ASM was according to the treating pediatric neurologist. Phenobarbitone and brivaracetam were selected only in a few patients, probably because of the significant adverse effects of phenobarbitone and the higher cost of injectable brivaracetam. Topiramate was selected in a smaller number of patients as it can be loaded only through the oral or nasogastric route and no intravenous preparation was available. Our study analysis was mainly limited to the first one or two additional ASMs and if the ARS still remained uncontrolled, then it was considered a failure of the protocol.

Overall, the treatment protocol suggested by us seems to be efficacious in most cases. However, we have excluded new onset ARSs cases and those children who were critically sick. This could have falsely heightened the success rate of our protocol. In new-onset ARSs cases, initially, the neurologist may not have access to MRI brain and video EEG records in all the cases, unlike in our study population, where the neurologist was aware of the definite structural or genetic etiology in all the cases. This avoided choosing improper ASM such as phenytoin in cases with Dravet syndrome. We also excluded cases who developed ARSs following poor compliance with the advised ASM regimen. However, this constitutes one of the most important causes of ARSs in LMICs like India. In such cases our protocol might not be helpful completely, as reinstituting the previous ASM regimen may achieve seizure control in the majority of cases.

The factors associated with the success of our proposed treatment protocol were mainly the absence of drug-resistant epilepsy previously. It is natural to expect those with drug-

resistant epilepsy are more likely to have an unfavorable response to adding further ASMs.[2] In the majority of those children, who had a recurrence of ARSs during the follow-up period, the same protocol was efficacious. It suggests that the same treatment protocol can be used multiple times in the same patient when episodes of ARSs occur. Immunotherapy was not a part of our protocol, as existing literature yet does not have enough evidence to universally use immunotherapy in patients with ARSs. However, future studies need to carefully explore the probability of using immunotherapy in patients with ARSs.

The previous studies have shown around 10–15% of patients with ARSs develop SE.[5] This proportion was less among our study participants, probably due to the inclusion of a more selective population. The choice of ASMs in the second tier of protocol did not have a significant impact on the efficacy of our protocol. Although phenobarbitone had relatively higher efficacy, it was selected only in a few patients because it has more adverse effects and it is not an appropriate choice of ASM for most cases such as LGS, EMAS, and Dravet syndrome in our study population.[20,21]

Recently, Pfeiffer *et al*.[22] found in a study that parenteral long-acting ASMs are used more often to treat seizure clusters rather than SE. This shows the magnitude of the clinical burden of ARSs on neurological practice. Phenytoin and levetiracetam were the most commonly used parenteral long-acting ASMs in this study, which was among the commonly chosen ASMs in our study too.[22,23] However, that study did not mention in detail the use of short-acting parenteral ASMs.

Our study has several limitations. Therapeutic drug monitoring was not available in all cases. Serum valproate level often does not correlate with anti-seizure efficacy. We do not have a facility at our center to test for blood levels of levetiracetam, and brivaracetam, and testing the blood level of the active metabolite of oxcarbazepine was possible only in a few cases. Second, it was a retrospective study, and the choice of ASM was arbitrary and according to the choice of neurologist in the second tier of the protocol. Prospective studies with a more uniform treatment protocol need to be explored in future cases. We could not check the compliance with the previously advised ASM regimen in all cases and could not rule out subtherapeutic ASM levels in participants. A randomized controlled trial in this regard assessing the efficacy of the proposed regimen in a center with uniform starting of ASM regimen and easily available therapeutic drug level monitoring will be ideal for formulating a stronger recommendation. The protocol also needs to be checked in cases with new onset ARSs, and in critically sick children with continuous EEG monitoring (to rule out NCSE). The majority of children in our study suffered from LGS or Dravet syndrome, in which such ARSs have been reported frequently, which responds to BZDs or hiking ASMs. Our study did not include any patient with definite autoimmune epilepsy, West syndrome. Our study was not powered enough to compare the efficacy of individual ASMs used in the second tier of the protocol, although it was powered enough to check for the efficacy of the overall treatment protocol.

Still, this is one of the first studies which attempt to formulate a treatment protocol for this well-known yet clinically less well-defined entity, for which no definite treatment protocol is available yet. Although neurologists agree that cases with ARSs cannot be managed on the same line as isolated seizures or SE, due to heterogeneous etiology, the above-mentioned protocol after external validation from other parts of the world can help neurologists in managing these patients.

CONCLUSION

This pre-specified treatment protocol is safe and efficacious in controlling ARSs in cases with established epilepsy who are not critically sick. External validation from other parts of the world/centers and a more diverse epilepsy population are required before generalizing the protocol into clinical practice.

Author contributions

PKP, AE, AT, AR, VK, and IKS were involved in data acquisition and analysis. PKP and IKS did inter-observer assessments. PKP, AE, AT, VK, and AR wrote the initial draft of the manuscript and was critically revised by AR and IKS. PKP, AR, and IKS performed statistical analysis. All authors have approved the final article.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent.

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Conflicts of interest

There are no conflicts of interest.

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