Original Article

Predictors of Outcome in Children with Status Epilepticus during Resuscitation in Pediatric Emergency Department: A Retrospective Observational Study

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Abstract

Objectives: To study the clinical profile and predictors of outcome in children with status epilepticus (SE) during resuscitation in pediatric emergency department. **Materials and Methods:** This retrospective study was carried out in a tertiary care teaching hospital. Admission and resuscitation data of children, aged between 1 month and 12 years, treated for SE, between September 2013 and August 2014, were extracted using a standard data collection form. Our SE management protocol had employed a modified pediatric assessment triangle to recognize and treat acute respiratory failure, cardiovascular dysfunction (CD), and subtle SE until all parameters resolved. Continuous positive airway pressure, fluid boluses based on shock etiology, inotropes, and cardiac safe anticonvulsants were the other modifications. Risk factors predicting mortality during resuscitation were analyzed using univariate and penalized logistic regression. **Results:** Among 610 who were enrolled, 582 (95.4%) survived and 28 (4.6%) succumbed. Grunt odds ratio (OR): 3.747 (95% confidence interval [CI]: 1.035−13.560), retractions OR: 2.429 (95% CI: 1.036−5.698), rales OR: 10.145 (95% CI: 4.027−25.560), prolonged capillary refill time OR: 3.352 (95% CI: 1.339−8.388), and shock requiring >60 mL/kg fluids OR: 2.439 (95% CI 1.040−5.721) were associated with 2−3 times rise in mortality. Inappropriate prehospital treatment and CD were the significant predictors of mortality OR: 7.82 (95% CI 2.10−29.06) and 738.71 (95% CI: 97.11−999), respectively. Resolution of CD was associated with improved survival OR: 0.02 (95% CI: 0.003−0.17). **Conclusion:** Appropriate prehospital management and treatment protocol targeting resolution of CD during resuscitation could reduce mortality in children with SE.

Keywords: Cardiovascular dysfunction, Pediatric assessment triangle, prehospital care, status epilepticus

Introduction

Prehospital emergency care is still in its infancy in India. Although nationwide ambulance services were established in 2009, most children with status epilepticus (SE) reaching our hospital had not received protocol-based care. Children were reaching late with respiratory failure and shock.[1] Most children presented with features of acute respiratory failure (ARF) and cardiovascular dysfunction (CD), low systolic blood pressure, and low mean arterial pressure (MAP). These children with SE may develop neurogenic pulmonary edema (PO), characterized by the acute onset of PO following significant central nervous system injury.[2] Described as secondary to a catecholamine surge that changes cardiopulmonary hemodynamics and Starling forces, the clinical patterns impact diagnosis, cardiac evaluation, fluid management, and choice of inotropic or vasoactive substances.[3,4]

An academic 837-bedded public hospital, our institution provides free care to over 700,000 children who registered at the outpatient department every year. Around 7000−8000 patients were critically ill on arrival. Blood gas analysis and invasive monitoring were unavailable in emergency room settings.

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Post-resuscitation access to mechanical ventilation was also scarce.[5] Hence, the conventional SE protocol was modified to recognize and resolve ARF and CD.[5] Implementation of this modified SE protocol consistently reduced hospital mortality to 2%−6% since 2006 [Table 1]. This study aimed to study the clinical profile and predictors of outcome in children with SE during resuscitation in pediatric emergency department.

Materials and Methods

Children with seizures lasting for more than 5 min in duration and children with subtle signs such as eye deviation, roving eye movements, or focal or multifocal face or limb motor movements with altered mental status following overt seizures were included in the study. Retrospective data of children with SE, aged between 1 month and 12 years, admitted to the PED between September 2013 and August 2014, were entered in a predesigned proforma. Children with abnormal movements other than SE were excluded from the study. Our objectives were to describe the clinical profile of children resuscitated for SE in the PED and second, to find the predictors of outcome in these children during resuscitation. Institutional review board approval was obtained.

Modified status epilepticus protocol

On arrival, of the convulsing child, a focused history was elicited while addressing the airway and breathing. Duration of seizure activity was computed based on the time of onset and distance traveled to reach the hospital. We hypothesized that risk of ARF/CD was high if seizures lasted for more than 30 min, or if altered level of consciousness (ALOC) was noted between precipitating events (fever, focus of infection, breathlessness, or diarrhea) and generalized tonic–clonic seizures (GTCS). ALOC between the precipitating event and GTCS was presumed as secondary to severe hypoxia or shock carrying increased risk of ARF and CD. SE that occurred suddenly was less prone to ARF/CD. Developmental status, history of epilepsy, antiepileptic drugs, and nature of prehospital management were also reviewed. The second responder, concurrently, performed the rapid cardiopulmonary cerebral assessment. Clinical signs of ARF and cardiac dysfunction and signs of subtle SE (SSE) were incorporated into the modified pediatric assessment triangle (PAT) to enable decision-making.[5]

Table 1: Incidence and mortality for children presenting with status epilepticus to our pediatric emergency department between 2006 and 2010 (medical records department data from ICH and HC)

Year	Number of children presenting with SE to the PED	Mortality, *n* (%)
2006	656	36 (5.48)
2007	653	17 (2.60)
2008	744	25 (3.36)
2009	756	14 (1.85)
2010	571	10 (1.75)

SE = Status epilepticus, PED = Pediatric Emergency Department, ICH = Institute of Child Health, HC = Hospital for Children

Intravenous or intraosseous access was established simultaneously. Blood and tissue fluids were collected for appropriate testing. An initial bolus of 10 mL/kg normal saline was administered if shock was recognized. Hypoglycemia and dyselectrolytemia were corrected. Antipyretic was administered if needed. The rapid cardiopulmonary cerebral assessment was repeated after each intervention and incorporated into the PAT, thereby guiding therapy until therapeutic goals were achieved.[5] Fluid boluses were interrupted, inotrope infusion was initiated, and intubation was performed if signs of ARF or CD were unmasked during shock correction.[2] SE requiring phenobarbitone or raised intracranial pressure was other indications for intubation. Shock was managed appropriately with inotropes. Following inotrope infusion and intubation, if shock persisted, further fluids were given based on etiology. If septic, hypovolemic, or anaphylactic shock was identified, large volumes (>60 mL/kg) of fluid boluses were planned.[5] If severe traumatic brain injury, submersion injury, envenomation, or toxin ingestion had preceded SE, the total volume of fluids needed to correct shock was restricted to 20−30 mL/kg.[5]

Ceftriaxone was initiated in PED as per hospital infection control policy, if septic shock was associated with leukocytosis. If malaria, scrub, leptospirosis, H1N1, or herpes simplex was suspected, the appropriate antimicrobial drug was administered in the PED. Anticonvulsants were administered simultaneously during resuscitation as per our PED protocol shown in Figure 1.[5] Phenytoin and fosphenytoin were avoided if duration of SE was more than 30 min, history suggestive of septic shock or evidence of PO or vasodilatory shock was noted during resuscitation. Alternatively, levetiracetam (60 mg/kg) was initiated after benzodiazepines, followed by sodium valproate (20–40 mg/kg) if seizures were refractory. Airway positioning, provision of continuous positive airway pressure (CPAP), bag valve mask ventilation/intubation, fluid boluses, inotropes, and anticonvulsants were continued until PO, shock, convulsive SE, or SSE were corrected.[5]

Sample characteristics were analyzed using descriptive statistics. The predictive association of different variables for mortality was analyzed using univariate logistic regression with constant in all the analyses. Variables, which were clinically significant, were analyzed using penalized logistic regression analyses. Analyses were performed using SPSS (version 21) and MedCalc (version 12.2.1.0). Penalized logistic regression was analyzed using R 3.1.2.

Results

Of 610 children who were resuscitated for SE, 582 (95.4%) survived and 28 children (4.6%) succumbed. Baseline history and characteristics of our cohort are shown in Tables 2 and 3. Mean duration of SE before reaching our PED was 2.51 h, while mean distance traveled was 39 km. Although 195 (31.9%) had

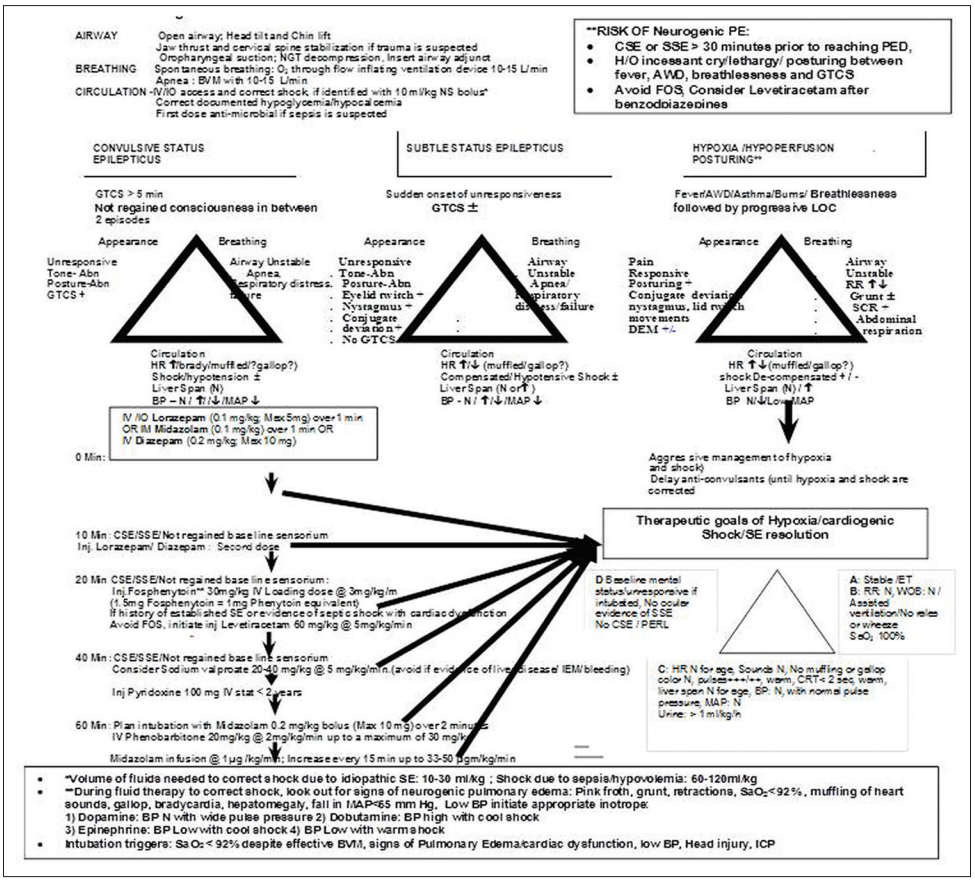

Figure 1: Modified status epilepticus protocol for the management of children with convulsive and subtle status epilepticus in our pediatric emergency department NGT = Nasogastric tube, IV = Intravenous, IO = Intraosseous, NS = Normal saline, CSE = Convulsive status epilepticus, SSE = Subtle status epilepticus, FOS = Fosphenytoin, GTCS = Generalized tonic–clonic seizures, N = Normal, Abn = Abnormal, AWD = Acute watery diarrhea, BP = Blood pressure, MAP = Mean arterial pressure, RR = Respiratory rate, WOB = Work of breathing, PERL = Pupils equal and reacting to light, ET = Endotracheal tube

received prehospital care, only twenty (3.2%) had received oxygen and six (0.9%) had been intubated. Prehospital diazepam and phenytoin had been administered to 123 (20.1%) and 63 (10.3%), respectively. However, route of administration had not been documented in 93 (15.2), whereas dose was not mentioned in 103 (16.8) patients.

Univariate logistic regression and penalized logistic regression analysis of five important factors that had a significant association with mortality are shown in Tables 4 and 5, respectively. Distance of >50 km was associated with 3-fold risk of mortality odds ratio (OR): 3.359 (95% confidence interval [CI]: 1.525−7.401). In addition, prehospital resuscitation was associated with 4.8-fold risk of mortality OR: 4.870 (95% CI: 2.161−10.976). Both prehospital benzodiazepines OR: 2.715 (95% CI 1.237−5.959) and phenytoin OR: 3.13 (95% CI: 1.275−7.691) were associated with a 2-3-fold risk of fatality. Penalized logistic regression showed that inappropriate prehospital care resulted in a 7-fold increased risk of mortality OR: 7.82 (95% CI: 952.10–29.06). CD was also associated with increased risk of mortality OR: 738.71 (95% CI: 97.11−999) and its resolution was associated with improved survival OR: 0.02 (95% CI: 0.003−0.17).

Discussion

The overall mortality in our cohort was 4.6%. This compares favorably with other centers in India that report mortality ranging between 30% to 31.4%.[6,7] The mean age in our study population was 37.8 months (3.1 years), whereas in other Indian studies, the reported mean age varied between 56.6 and 71.28 months.[6,7] Although our study did not demonstrate an association between age and mortality, an Indian study had found that risk was higher in age <36 months, whereas other studies have demonstrated that older ages were at greater risk.[7-9] Our study demonstrated that SE was more in boys than girls. An analysis of population-based data from Europe and United States had revealed male preponderance in most studies.[10] Mortality in our study was greater in males than females (58.1% vs. 41.9%) although no significant association was noted between mortality and gender.

The higher incidence of SSE (66%) in our cohort was probably due to a focused history that probed for failure to regain baseline sensorium and the meticulous examination for eye signs on arrival and during every step in the protocol. SE precipitated by fever, diarrhea, breathlessness, and toxin

Table 2: Baseline characteristics of children with status epilepticus presenting to pediatric emergency department

Variables	Results
Age (mean±SD), months	37.8±35.9
Gender, *n* (%)	
Male	356 (58.4)
Female	254 (41.6)
Duration of seizures before reaching hospital (mean±SD), min	171.5±410.0
Distance traveled to reach hospital (mean±SD), km	39.2±76.7
Prehospital care, *n* (%)	
Prehospital treatment	195 (31.9)
Prehospital oxygen	20 (3.2)
Prehospital intubation	6 (0.9)
Prehospital benzodiazepines	123 (20.1)
Prehospital phenytoin	63 (10.3)
Route of administration, *n* (%)	
Not mentioned	93 (15.2)
Appropriate	94 (15.4)
Inappropriate	8 (1.3)
Dose, *n* (%)	
Not mentioned	103 (16.8)
Appropriate	83 (13.6)
Inappropriate	9 (1.4)
Precipitating events before SE, *n* (%)	
Precipitating events preceding GTCS	437 (71.6)
Altered level of consciousness before seizures	524 (85.9)
Co-morbid conditions, n (%)	
Developmental delay	184 (30.2)
Past history of seizures	248 (40.5)
On anti-epileptic drugs	224 (36.7)

SD = Standard deviation, GTCS = Generalized tonic-clonic seizures, SE = Status epilepticus

Table 3: Clinical profile of children with status epilepticus on arrival into the pediatric emergency department

Variable (on arrival)	*n* (%)
Airway	
Stable	231 (37.82)
Unstable	379 (62.18)
Breathing	
Effortless tachypnea	127 (20.8)
Respiratory failure	76 (12.4)
Apnea	353 (57.8)
Circulation	
Tachycardia	501 (82)
Bradycardia	6 (0.98)
Shock	435 (71.3)
Hepatomegaly	76 (12.4)
Hypotension	143 (23.4)
Hypertension	55 (9)
Low MAP	118 (19.3)
Disability	
GTCS on arrival	204 (33.4%)
Subtle SE on arrival	406 (66.6%)
Hypoglycemia	22 (3.6)
Interventions	
BVM	358 (58.6)
CPAP	145 (23.8)
Intubated during resuscitation	167 (27.37)
Fluid bolus (<60 mL/kg)	515 (84.4)
Need for inotropes	245 (40.15)

GTCS = Generalized tonic–clonic seizures, BVM = Bag valve mask ventilation, CPAP = Continuous positive airway pressure, SE = Status epilepticus, MAP = Mean arterial pressure

exposure was predictive of mortality wherein fever and breathlessness emerged as independent risk factors. ALOC between the febrile illness or respiratory distress was noted in 86% of SE episodes.

Nearly 15% had traveled more than 50 km to reach our PED, a feature that was associated with a greater risk of mortality. Mean duration of seizures was long in our study cohort, a finding that is corroborated with data from other centers in India.[7] A long duration of time lapse between the onset of seizures and treatment was observed in a retrospective data from developing country and a high mortality was reported in this study.[11] Delorenzo *et al*. reported a higher mortality rate when SE lasted for more than 30 minutes.[12] Referral bias and lack of transportation, causing prolonged SE, were considered contributory to increased mortality rate due to prolonged SE in another Indian study.[6] Gulati *et al*. also had identified that a delay in initiation of treatment as a risk factor for immediate mortality.[7] Nearly 40% had pre-existing seizures in our study group while 45% had been reported in a previous study.[12] Also SE was reported in 10-25% of patients with epilepsy.[13,14] Kang et al had found that nearly one-third of patients presenting with SE had pre-existing epilepsy and the risk of SE was also high in non-epileptic subjects.[15]

Silbergleit observed that the risk of respiratory depression was not different when intramuscular midazolam or intravenous lorazepam was administered in the prehospital setting..[16] In our study, however, prehospital benzodiazepines resulted in a 2-fold risk of mortality OR: 2.715 (95% CI 1.237–5.959). This, was perhaps, evidenced by the fact that <1% had received appropriate airway management. Among children who had received medications before arrival to our PED, only 83 (13.6%) had received the appropriate dose.

Prehospital use of phenytoin was associated with increased risk of mortality OR: 3.131 (95% CI 1.275–7.691). Intravenous administration of phenytoin is known to cause hypotension, decreased peripheral vascular resistance, bradycardia, complete atrioventricular block, ventricular tachycardia, ventricular fibrillation, and asystole.[17,18] Adverse cardiac events due to intravenous phenytoin have been reported in literature.[19] It could be accounted by high concentration or rapid infusion rate.[20] Profound bradycardia and severe hypotension were reported even at slower infusion rates in healthy human volunteers.[21] Most of the cardiac ill effects of phenytoin were traditionally attributed to the solvent-propylene glycol.

Table 4: Univariate logistic regression of factors associated with mortality in children presenting with status epilepticus to our pediatric emergency department

Variables	Survivors, *n* (%)	Death, *n* (%)	Unadjusted OR	*P*	95% CI
Precipitating event	412 (70.7)	25 (89.2)	3.439	0.046	1.205-11.540
Fever	357 (61.3)	24 (85.7)	3.782	0.015	1.295-11.042
Breathlessness	66 (11.3)	9 (32.1)	3.703	0.002	1.609-8.52
Distance from hospital (>50 km)	94 (16.2)	11 (39.2)	3.359	0.003	1.525-7.401
History of generalized tonic-clonic seizures	475 (86.5)	16 (57.1)	0.300	0.002	0.138-0.653
Prehospital treatment	176 (30.2)	19 (67.8)	4.870	<0.001	2.161-10.976
Prehospital benzodiazepines	112 (19.2)	11 (39.2)	2.715	0.013	1.237-5.959
Prehospital phenytoin	56 (9.6)	7 (25)	3.131	0.013	1.275-7.691
Grunt	18 (3)	3 (10.7)	3.747	0.044	1.035-13.560
Chest retraction	82 (14)	8 (28.5)	2.429	0.041	1.036-5.698
Rales	22 (3.7)	8 (28.5)	10.145	<0.001	4.027-25.560
Prolonged capillary refill time	303 (52)	22 (78.5)	3.352	0.010	1.339-8.388
Abnormal blood pressure	181 (31.1)	21 (75)	6.613	<0.001	2.762-15.837
Septic shock: Fluid bolus (>60 mL/kg)	82 (14.1)	8 (28.5)	2.439	0.040	1.040-5.721
Dopamine	202 (34.7)	21 (75)	5.599	<0.001	2.340-13.395
Norepinephrine	92 (15.8)	12 (42.8)	3.170	0.001	1.818-8.669
Epinephrine	28 (4.8)	13 (46.4)	17.055	<0.001	7.406-39.274
Dobutamine	9 (1.5)	3 (10.7)	6.828	0.005	1.768-26.363
Lorazepam	547 (93.9)	22 (78.5)	0.235	0.003	0.090-0.618
Fosphenytoin	205 (35.2)	3 (10.7)	0.219	0.014	0.065-0.734
Levetiracetam	349 (59.9)	23 (82.1)	4.101	0.010	1.404-11.974
Midazolam infusion	30 (5.2)	17 (60.7)	7.722	<0.001	2.993-19.927
Phenobarbitone	119 (20.4)	13 (46.4)	5.179	<0.001	2.378-11.278
Cardiovascular dysfunction	73 (12.5)	27 (96.4)	187.52	<0.001	25.10-1400.86
Refractory seizures	81 (13.9)	11 (39.2)	3.978	0.001	1.798-8.800
Shock corrected	436 (74.9)	7 (25)	0.110	<0.001	0.046-0.264
Resolution of cardiovascular dysfunction	184 (31.6)	3 (10.7)	0.258	0.028	0.077-0.866

OR = Odds ratio, CI = Confidence interval

Table 5: Penalized logistic regression analysis of various determinants associated with mortality in children with status epilepticus

Variables	OR	95% CI	*P*
Inappropriate prehospital treatment			
Yes	7.82	2.10-29.06	0.002
No	1.00		
Cardiac dysfunction			
Yes	738.71	97.11-999	<0.001
No	1.00		
Shock corrected			
Yes	1.06	0.21-5.38	0.94
No	1.00		
Cardiac dysfunction corrected			
Yes	0.02	0.003-0.17	0.0002
No	1.00		
Refractory seizures			
Yes	0.55	0.15-1.98	0.36
No	1.00		

CI = Confidence interval, OR = Odds ratio

If propylene glycol was indeed responsible for causing cardiac side effects, the propylene-free derivative, fosphenytoin is expected to be safe for the heart. Data comparing intravenous phenytoin and fosphenytoin have shown that the latter also causes cardiotoxicity, suggesting that the solvent is not the culprit.[22,23] A consensus guideline recommended that intravenous phenytoin should be avoided in patients with cardiovascular disease or when symptoms of debilitating illness, emaciation, hyponatremia, peripheral vascular disease, hemodynamic instability, or sepsis coexist.[24] The increased mortality due to prehospital phenytoin might have resulted from failure to recognize these complications in our cohort. On the contrary, our study also demonstrates that cautious use of phenytoin in our PED, however, was associated with negative risk of death. This beneficial impact was probably due to judicious usage for seizures <30 min, without precipitating events and the absence of ARF and CD.

Our study demonstrates that retractions, grunt, and adventitious sounds at arrival were associated with 2–10-fold risk of mortality. It is possible that the ARF in our cohort could have resulted from neurogenic PO. Aspiration and septic shock could also present with respiratory failure and shock. Besides, ninety children required more than 60 mL/kg for shock resolution, increasing the risk of PO.

Prolonged capillary refill time, hypotension, low MAP, and shock requiring more than 60 mL/kg or inotrope were

associated with 3–6-fold increase in mortality. Need for epinephrine, used for hypotension or bradycardia, was associated with a 17-fold risk of mortality. CD carried the highest risk of mortality.

Our data show that SE responsive to lorazepam in the PED was a negative predictor of mortality OR: 0.235 (95% CI: 0.090–0.618). Concurrent provision of bag valve mask ventilation, or CPAP, might have contributed to improved survival. SE requiring levetiracetam, midazolam, or phenobarbitone was associated with 5–7-fold increased risk of mortality. This could be explained by the longer duration of SE predisposing to greater risk of PO, hypoxia, hypotension, bradycardia, stress cardiomyopathy, acidosis, hypoglycemia, and raised intracranial pressure.

Inappropriate prehospital care and the resultant CD have emerged as important predictors of mortality. In India, suboptimally organized prehospital services substantially hinder the evaluation, management, and transport of the acutely ill and/or injured child to an appropriate facility. Furthermore, the management of the ill child at the hospital level is often provided by overburdened providers who, by virtue of their training, lack experience in the skills required to effectively manage pediatric emergencies.[25] Indeed, Chin *et al*. had reported that if pre-pediatric intensive care treatment of SE is inadequate, appropriate modifications of standard guidelines may be required.[26]

Our data lend evidence for the need for strengthening prehospital care. In addition, it emphasizes that a modified protocol may be necessary to address the critically ill child whose heart and lungs are failing due to uncorrected hypoxia, shock secondary to SE. In the retrospective study design, failure to objectively assess for PO, hemodynamic status, and intracranial pressure during resuscitation are important limitations. Our stand for modification of the SE protocol is weakened due to the lack of documented PaO_2/FiO_2 ratio. Due to the lack of EEG facility in the emergency department, continuous EEG recording was not feasible in our study. Failure to include etiological data is another limitation as the data were collected from PED database. Despite these limitations, in settings lacking effective prehospital resuscitation, perhaps a SE protocol that aimed at resolution of CD can improve survival. More importantly, improved prehospital care can reduce the risk of CD in children presenting with SE.

Conclusion

We conclude that a modified SE protocol targeting resolution of CD in settings with inappropriate prehospital care improved survival. Our study emphasizes the need for a revised protocol and strengthening of prehospital care for the management of children with SE in resource-limited settings. Prospective studies in resource-limited settings analyzing the outcome in children with a modified SE protocol are needed in the future to support our observation.

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Conflicts of interest

There are no conflicts of interest.

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