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Convulsive status epilepticus in children in Mozambique: Is there a treatment gap?

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Abstract

Background: Optimal care of convulsive status epilepticus (CSE) can be hampered by multiple barriers in resource-limited countries.
Objectives and methods: Since limited data of CSE management are available from South-East Africa, we performed a retrospective analysis of the electronic records of paediatric patients with CSE admitted to the Maputo Central hospital from January 2016 until April 2019.
Results: We identified 39 patients. The mean age was 5.15 ± 3.85 years (mean ± standard deviation) and demographic characteristics did not show a relationship to CSE characteristics or outcomes. However, the total stay in hospital was negatively correlated with age (p = 0.0314). Moreover, 14 patients needed to be admitted to the intensive care unit (ICU), which was correlated to having generalised motor seizures (p = 0.0253), and a relatively higher need for a second antiseizure medication (ASM) to control their CSE (p = 0.0131). Regarding ASM use, the first ASM was a IV benzodiazepine (BZD): midazolam (MDZ) or diazepam (DZP), or IV phenytoin (PHT) when BZDs were not available. There was no statistically significant difference between the efficacy of MDZ vs. DZP. Eleven patients received PHT as a second-line drug, of which only two patients needed an additional dose. None of the patients died but five patients (13.2%) showed additional morbidity after CSE.
Conclusions: Although limited ASMs were available in our study, compared to higher availability of ASMs in other developing and developed countries, we report the successful cessation of CSE in the majority of cases. We recommend strategies to improve prehospital management such as the use of non-IV BZD use, to limit the need for patients to be admitted to the ICU and thereby potentially decreasing the number of ASMs, morbidity and hospital duration. Moreover, our data underline the efficacy of PHT as second-line ASM in nearly all patients.

Keywords: Mozambique, Epilepsy, Convulsive status epilepticus, Rescue therapy.

Background

An estimated 65 million people worldwide suffer from epilepsy [1]. Sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE) remain the most severe complications in patients with known or *de novo* epilepsy [2].

Convulsive status epilepticus (CSE) has traditionally been defined as a prolonged seizure or a cluster of seizures that last for longer than 30 minutes [3]. In clinical practice, a duration of more than five minutes (time point t1, 5 min) should be considered as an imminent CSE, since these seizures are less likely to stop spontaneously and necessitate treatment to be started at time point t1 [4, 5]. Moreover, a longer duration of seizures (time point t2, 30 min) can induce neuronal damage or a self-maintaining alteration of neuronal networks, both requiring a different pharmacological approach [5, 6, 7]. It is documented that a timely conversion from benzodiazepines (BZDs) to other antiseizure medications (ASMs) may reduce treatment resistance in CSE [7]. Finally, a prompt diagnosis and treatment can significantly decrease extra comorbidities and mortality [8]. The incidence of CSE is the highest among children and the elderly [9, 10, 11]. Of importance, over 80.0% of children with epilepsy are located in resource-limited countries [12] and CSE is the second most common outpatient neuropsychiatric diagnosis in Mozambique [13]. Even though CSE is a worldwide problem, optimal care is hampered by multiple barriers in resource-limited countries. These barriers include the unavailability of ASMs, patient transportation delays, low quality health care infrastructures and the potential lack of a CSE treatment protocol [6, 14, 15]. Especially in resource-limited countries, the lack of clear treatment strategies (prehospital and hospital management) could induce unnecessary treatment delays, extra morbidities and higher mortality rates [12, 16].

Overall, there have been ample studies regarding CSE in developed parts of the world, e.g. Europe, the UK and the USA [9, 17, 18, 19, 20, 21]. Some studies have been conducted in

developing countries in Africa, such as Uganda, as reviewed by Kariuki et al. [22], and in other developing countries worldwide, such as Iran, India and Egypt [14, 23, 24, 25].

We investigated CSE in paediatric patients in Mozambique, a resource-limited country in South-East Africa, and we retrospectively examined the clinical profile, etiology, management and outcomes after CSE.

Our aim was to determine limitations and suggest potential improvements for better CSE management. Our findings underline the successful use of BZDs, the proper use of phenytoin (PHT) as a second-line ASM, and the need to be admitted to intensive care when first- and second-line treatments fail.

Methods

We performed a retrospective, single-centre study. After Institutional Review Board approval, we obtained the electronic records of paediatric patients admitted to Maputo Central hospital with CSE between January 2016 and April 2019. No ethical approval was necessary prior to this retrospective, database study. CSE was defined as a continuous seizure with a duration of more than five minutes and/or multiple seizures without consciousness being regained for at least 30 minutes. Children with CSE were included if they were below the age of 18 years. Exclusion criteria were an undocumented duration of seizures, non-convulsive SE, and undocumented anti-epileptic medication.

Patients were admitted to the ICU if at least one of the following criteria were fulfilled: (a) the status of the patient, (b) the severity of the seizure, (c) the level of awareness did not allow hospitalisation without intensive care, and (d) the CSE did not respond to the first ASM.' This latter criterium is also in line with the 2017 ILAE recommendations [5]. The Maputo Central hospital follows a CSE protocol where BZDs are used as first-line and repeated up to three times. In rare situations when BZDs are temporarily not available, PHT is used as first-line. The first-line approach can then be followed by PHT or phenobarbital, if seizures persist after 5-10 minutes post-administration of the first and/or second ASM.

Patient charts were reviewed for age, gender, demographics, etiology, type of seizure, new *versus* known seizure disorder, ASMs before admission, rescue ASMs, concomitant drugs, traditional medicine, length of stay at the ICU and at the hospital, and outcomes (morbidity/mortality). Etiology was divided into four classes: (a) acute symptomatic (e.g. stroke, infection, cerebrovascular disease, head trauma, toxic or metabolic derangements); (b) remote symptomatic (SE with a history of preexisting central nervous system [CNS] anomalies, more than one week before, but without an identified acute insult); (c) epilepsy-related; and (d) unclassified [26]. Morbidity was defined as a novel neurological deficit (e.g. paresis or movement disorders, visual or auditory impairments, aphasia, regression of developmental milestones or cognitive deficits). Follow-up was variable for each patient and a first checkup was usually planned within the first 15 days after discharge.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 6 software (GraphPad Software, Inc.). Numerical data were analysed by Mann-Whitney U tests (MWU) if the data did not pass the normality test (D'Agostino & Pearson omnibus normality test). Student's t-tests were used if the data were normally distributed. Categorical differences between two groups were analysed by contingency tables, followed by Fisher's exact tests. For all analyses, differences were considered statistically significant if the p-value was below 0.05 ($p < 0.05$).

Results

We retrospectively analysed paediatric patients with CSE that were admitted to the Maputo Central Hospital, Mozambique between January 2016 and April 2019. Our database documented 39 children (Table 1) of which 14 were admitted to the ICU. Patients with generalised motor seizures were more likely to be admitted to the ICU, compared to those with focal, or focal to bilateral tonic-clonic seizures ($p = 0.0253$). Moreover, patients admitted to the ICU had a significantly higher need for a second ASM (64.3%), compared to those that were not (24.0%) ($p = 0.0131$). Otherwise, there were no significant differences between the patients who were admitted to the ICU, compared to those who were not, regarding the demographic characteristics such as age, gender, provenance, residence, weight and length, current ASM use, traditional medicine use and etiology ($p > 0.05$) (Table 1). Regarding the etiology, the total number of patients with an unclassified or acute symptomatic cause of CSE was not statistically significant different in the non-IC group vs. the ICU group ($p > 0.05$). However, there were more patients with remote symptomatic epilepsy in the non-ICU group and more patients with acute symptomatic epilepsy in the ICU-group, although these differences were not statistically significant ($p = 0.09$; $p > 0.05$).

Twenty-one out of 39 of the patients (53.8%) were known to have epilepsy. When comparing these children to the ones with no known epilepsy, there were no significant differences documented regarding demographics, the need to stay at the ICU, a hospital stay, successful treatment of CSE, and comorbidities before or after CSE. However, the total stay in the hospital was negatively correlated with age (Figure 1; Pearson correlation: $p = 0.0314$).

All patients received their in-hospital ASMs via the intravenous (IV) route. There was no use made of non-IV (rescue) medication. Overall, three different ASMs were used to treat the CSE: phenytoin (PHT), midazolam (MDZ) or diazepam (DZP) (Table 2). As per protocol, benzodiazepines (BZDs) such as MDZ and DZP were significantly more frequently used than PHT ($p < 0.0001$). MDZ seemed to be more effective than DZP since 12/15 patients treated with MDZ did not need an extra ASM (80.0%), compared to 13/24 treated with DZP (54.2%). However, this finding did not reach statistical significance ($p = 0.074$).

Table 1. Patient characteristics.

Variable	All (n = 39)	IC group (n = 14)	non-IC group (n = 25)	*p-value*
Female (%)	25.6	21.4	28	NS
African (%)	100	100	100	NS
Age (y) (range, SD)	5.15 (0.3-13.8, 3.9)	5.57 (0.3-13.5, 4.6)	4.9 (0.9-13.8, 3.4)	NS
Weight (percentile) (%)				
<3	24	27.3	20.8	NS
>3 till <25	12.9	9.1	16.7	NS
25- <50	17	9.1	2	NS
>50-97	46.1	54.5	37.5	NS
Length (percentile) (%)				
<3	20.7	15.4	26.1	NS
>3 till <25	26.3	30.8	21.7	NS
25- <50	28.4	30.8	26.1	NS
>50-97	24.6	23	26.1	NS
Etiology (%)				NS
Unclassified	48.7	57.2	44	NS
Acute symptomatic	12.8	21.4	8	NS
Remote symptomatic	38.5	21.4	48	NS
Epilepsy disorder known (%)	56.4	50	60	NS
Generalised seizures in the past (%) *	61.5	85.7	48	<0.05
Focal seizures in the past (%) *	33.3	7.7	47.8	<0.05
ASMs (%)				
First-line ASM: BZD	91.7	85.7	95.5	NS
Second ASM: as needed	35.9	64.3	20	<0.05
Hospital length of stay (range, SD)	2.0 (0-11, 3.0)	5.0 (0-11, 3.2)	0.3 (0-4, 0.9)	<0.05
Morbidity after CSE (%)	13.1	30.8	4	<0.05
Mortality after CSE (%)	0	0	0	NS

P-value between the ICU- and non-ICU group, BZD = benzodiazepine; NS = not statistically significant, SD = standard deviation; ASM, antiseizure medication

*these two parameters were analysed independently from 'epilepsy disorder known'.

PHT seemed to be the most effective, as patients who received PHT as a first ASM had a lower need for a second ASM to control the CSE (Figure 2), although no statistical significance was found for the differences in ASM use in both groups (in sub- and total group analyses; $p > 0.05$).

Only three out of 36 patients (11.5%) needed a third ASM of whom two were admitted to the ICU, one with an unknown etiology and the other with a CNS infection. The patient not admitted to the ICU had an unknown etiology. All three patients had DZP as a first ASM. The two patients with the unknown etiology were able to terminate their CSE by two doses of PHT, which was not the case for the patient with the CNS infection. None of them had other or ongoing complications.

Overall, none of the patients died and five out of 38 patients (13.2%) showed new morbidity after CSE, four of whom were admitted to the ICU (80.0%, $p = 0.0382$).

Discussion

The geographical region and setting (rural, general, tertiary, quaternary hospital or the ICU) can influence the patient's outcomes [16, 27, 28, 29]. Especially in developing countries, the quality of data and the extent of participation can reduce the validity of a study [27]. To our knowledge, this is the first retrospective study that has systematically evaluated the demographic characteristics, etiology, treatment options and outcomes by an electronic, standardised data collection form from the Maputo Central hospital in Mozambique, South-East Africa.

In our study, the mean age was 5.15 ± 3.85 years (mean ± standard deviation) and the age did not show a relationship to hardly any of the SE characteristics or outcomes. However, the total stay in the hospital was negatively correlated with age (Pearson correlation: $p = 0.0314$). It has been acknowledged that younger children are more prone to CSE [11, 30] and that mortality rates are higher in this age group [31]. Nonetheless, we were not able to determine why younger children needed to stay for a longer period of time in the hospital and other researchers assume that

Table 2. Antiseizure medications (ASMs) needed to control convulsive status epilepticus (CSE). Three out of 39 patients did not need an ASM.

Patient	ASM	ASM dose	ASM successful?	ASM 2	ASM dose	ASM successful?	ASM 3	ASM dose	ASM successful?
1	DZP	0.2 mg/kg	yes						
2	DZP	0.3 mg/kg	yes						
3	DZP	0.3 mg/kg	yes						
4	DZP	0.25 mg/kg	no	PHT	15.0 mg/kg	yes			
5	DZP	0.3 mg/kg	no	PHT	15.0 mg/kg	yes			
6	DZP	0.25 mg/kg	no	DZP	0.5 mg/kg	no	PHT	20.0 mg/kg	no
7	DZP	0.15 mg/kg	no	PHT	15.0 mg/kg	yes			
8	DZP	NR	no	PHT	2.5 mg/kg	yes			
9	DZP	NR	no	PHT	NR	no	PHT	5.0 mg/kg	yes
10	DZP	0.06 mg/kg	no	PHT	15.0 mg/kg	yes			
11	DZP	0.4 mg/kg	no	PHT	9.5 mg/kg	yes			
12	DZP	0.3 mg/kg	yes						
13	DZP	0.2 mg/kg	yes						
14	DZP	0.25 mg/kg	yes						
15	DZP	0.2 mg/kg	no	PHT	2.5 mg/kg	yes			
16	DZP	0.1 mg/kg	yes						
17	DZP	0.07 mg/kg	yes						
18	DZP	0.25 mg/kg	yes						
19	DZP	0.2 mg/kg	yes						
20	DZP	0.1 mg/kg	yes						
21	DZP	0.13 mg/kg	no	MDZ	0.2 mg/kg	yes			
22	DZP	NR	no	PHT	NR	no	PHT	2.4 mg/kg	yes
23	DZP	0.2 mg/kg	yes						
24	MDZ	0.2 mg/kg	no	PHT	5.0 mg/kg	yes			
25	MDZ	0.2 mg/kg	yes						
26	MDZ	0.2 mg/kg	yes						
27	MDZ	0.2 mg/kg	no	PHT	15.0 mg/kg	yes			
28	MDZ	0.2 mg/kg	yes						
29	MDZ	0.3 mg/kg	yes						
30	MDZ	0.2 mg/kg	yes						
31	MDZ	0.2 mg/kg	no	MDZ		NR			
32	MDZ	0.16 mg/kg	yes						
33	MDZ	0.2 mg/kg	no	NR					
34	PHT	15.0 mg/kg	yes						
35	PHT	4.9 mg/kg	yes						
36	PHT	12.0 mg/kg	yes						

DZP = diazepam, MDZ = midazolam, PHT = phenytoin, NR = not reported

this age group includes a higher number of acute symptomatic cases, which can lead to a worse outcome (e.g. morbidity, mortality, hospital stay) [31].

Ample studies have shown that the most important prognostic factor of CSE is the underlying etiology [10, 14, 16], whereas our study did not unravel a significant correlation. Moreover, the etiological spectrum of CSE has been reported to be distinct in developing vs. developed countries [14, 16, 27, 32]: acute symptomatic etiologies, subtherapeutic ASM levels and cerebrovascular diseases are more prominent in developed countries; while CNS infections are predominant in developing countries. Since the etiology is mainly unknown in our study (> 50.0% of the patients), future studies should aim to better document the etiology of CSE, even in developing countries.

Fourteen out of 39 patients needed to be admitted to the ICU. There were no significant patient characteristics for these children; however, the ones with generalised seizures were significantly more likely to be admitted to the ICU. This finding can underline that patients with generalised seizures have more severe epilepsy. About 53.8% of the children had a known seizure disorder, which did not influence the ASM use, the stay at the ICU or hospital, the morbidity or the mortality rate. This is in line with the study of Chegondi et al. in a developed country (Miami, USA) [21].

Three different ASMs were used to treat the CSE of which BZDs (MDZ and DZP) were significantly more frequently used than PHT as first line agents. This in line with recently published studies, protocols and a Cochrane review [6, 15, 31]. First

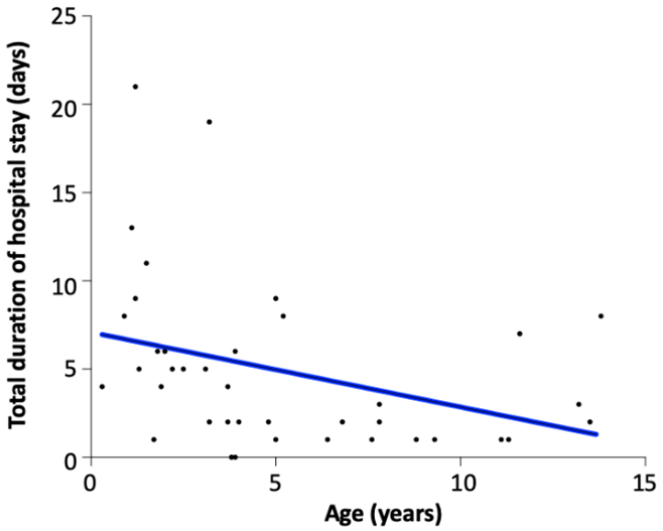

Figure 1. Linear regression of the total hospital stay (days) as a function of age (years).

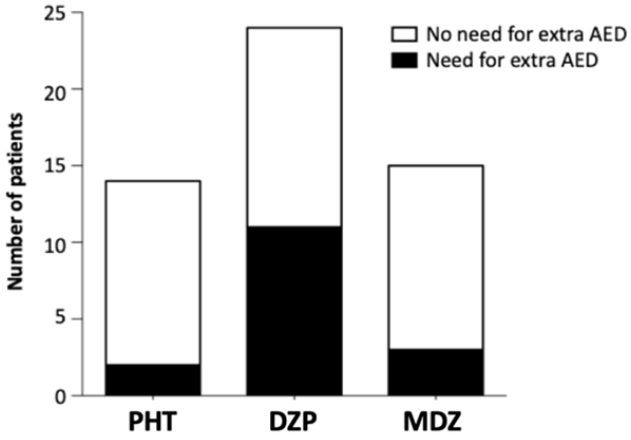

Figure 2. Need for an extra antiseizure medication (ASM). *Black bars refer to the number of patients who need an additional antiseizure medication (ASM): phenytoin (PHT), diazepam (DZP) or midazolam (MDZ). White bars refer to the number of patients in whom CSE was terminated after the administration of one ASM.*

line treatment with BZDs seems to resolve CSE in 70.0% of the patients [33]. In our study, MDZ seemed to be more effective than DZP as 80.0% of the patients with MDZ did not need a second ASM to terminate CSE, compared to 54.2% with DZP. Even though this finding did not reach statistical significance, buccal MDZ has been suggested to treat CSE in developing countries [14]. PHT seemed to be the most effective first line ASM in our study as CSE was stopped in nearly all patients after PHT was initiated. Additionally, PHT was the most common second-line agent in 78.6% of the patients, comparable to Reddy et al., reporting PHT as secondary agent in 84.0% of the patients [12]. This treatment approach is in line with the paediatric protocol of Stredney et al. [6], which describes the initial use of a BZD (intranasal MDZ within the first five minutes), followed by IV BZD and PHT after 10-15 minutes. The authors state that delays in treatment can induce morbidities. Moreover, a recent study underlined the need for a timely transition from BZDs to other ASMs like PHT to decrease treatment resistance in patients with CSE [7]. According to current knowledge, PHT seems to be an adequate second-line ASM, and other drugs such as levetiracetam, were not superior [33, 34]. In our study only 7.7% needed a third ASM to stop CSE, compared to 72.0% in the study by Reddy et al. [12].

Overall, the Cochrane Database of systematic reviews in 2018 did not show evidence for intranasal MDZ and showed that buccal MDZ and rectal DZP are first line anticonvulsants in the absence of IV access [15]. In addition, a study in Ugandan children showed that buccal MDZ was safe and more effective for treating seizures [35]. MDZ could also be superior, especially when there are difficulties to gain IV access [16, 36, 37], which is more likely to be the case in resource-limited countries.

Even though only three ASMs were available in Mozambique (our study), compared to, for instance, eight ASMs in Durban, South Africa [12], we report a lower need for ASMs, and lower mortality and morbidity rates. Moreover, no deaths have been reported in our study, which is consistent with a low mortality rate (1.2-7.0%) reported by other studies in the USA, UK, Italy and New Zealand [9, 17, 21, 38, 39]. Nonetheless, mortality rates due to CSE vary worldwide from 5.0 to 56.0% [16]. A separate study from South Africa (Durban) reported a relatively high mortality: 21.0% of the 76 children with CSE admitted to intensive care [12].

Overall, patients with generalised seizures and the need for a second ASM were statistically more likely to be admitted to the ICU. In addition, 13.2% of the patients had an extra comorbidity after CSE, of which 80.0% had been admitted to the ICU. Hence, these findings underline that more critically ill patients with poorly controlled seizures are more likely to be admitted to the ICU, rather than pointing out a causal relationship between the types of seizures, the need for more ASMs, and inducing comorbidities. However, the abovementioned data need to be interpreted with caution since it is plausible that the most severe cases in our study were not able to reach the hospital in time.

Limitations

Our study has several limitations. For 16 out of the 39 patients (41%), it was difficult to ascertain whether they really suffered seizures for at least ten minutes (duration of the CSE). In addition, we only had access to a small number of CSE patients, as well as scarcely any diagnostical information (neuroimaging, EEG), limited bloodwork (ASM levels), no longterm data (limited follow-up), and no data regarding a potential admission to another hospital. With the current results, it was also impossible to define the exact timing and administration of ASMs. Even though we have performed several analyses to determine any superiority or inferiority of the ASMs, our findings did not reach any statistical significance. Furthermore, our data do not allow us to determine the delay in treatment, which is an important limitation regarding CSE studies in general [40, 41]. Nonetheless, more studies have acknowledged many of the aforemen-

tioned limitations [9, 14, 21, 42], and observational studies, like ours, remain necessary to elucidate the etiology, demographics and treatment modalities of CSE in a resource-limited country.

Conclusion

Overall, our study in a developing country documented that the use of BZD and changing to a second-line ASM, such as PHT, are in line with data and protocols from developed countries. Consistently, a global audit of 50 countries, a systematic review, and several studies regarding CSE have shown that CSE characteristics and outcomes are predominantly similar [10, 14, 27, 32]. In conclusion, the overall prognosis in our study is not considerably worse than that from developed countries. However, we emphasise the need to educate patients, families and healthcare workers about CSE and the need for timely prehospital management as epilepsy is related to significantly more admissions to hospital, higher morbidity as well as mortality rates [22]. Thus, our study could be a first step in developing a framework for strategies that could reduce the requirement for ICU admissions.

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Competing interests

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Author contributions

All authors were involved in the outlines of the manuscript. J.S. and L.L. were mainly involved in the manuscript preparation and statistical analyses. D.I.S. was responsible for the data collection. All authors approved the final manuscript version.

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