

Intermittent Refractory Status Epilepticus

RESULTS

Characteristics of Study Subjects. One hundred ninety-seven patients (54% males) had intermittent rSE with a median (p_{25} - p_{75}) age of 3.9 (1.3 – 9.0) years. Among this population, 131 (66%) rSE episodes started out-of-hospital and 66 (34%) started in-hospital. The first BZD was administered at home in 36 (18%) patients, by EMS in 29 (15%) patients, at a non-pSERG study hospital in 41 (21%) patients, and at a pSERG study hospital in 91 (46%) patients. The main demographic and clinical features are summarized in Table 1.

Main Results

BZDs administered before first non-BZD ASMs. The median (p_{25} - p_{75}) number of BZD doses given before non-BZD ASMs was 2 (1 - 3) (Table 2). The time from seizure onset to first BZD was 16 (5 – 45) minutes. One hundred eighteen of 197 (60%) patients received at least one BZD beyond 30 minutes following seizure onset and before the first non-BZD ASM (Figure 1, Table 3), and 95 of 197 (48%) patients received at least one BZD administered after 45 minutes from seizure onset and before the first non-BZD ASM (Table 4). Patients with out-of-hospital rSE onset received similar BZD doses to patients with in-hospital rSE onset [2 (1-3) versus 2 (1-3), $p=0.66$], received their first BZD later [23 (5 – 64) minutes versus 8 (4 – 21) minutes, $p < 0.0001$], had a greater proportion of patients receiving at least one BZD after 30 minutes from seizure onset and before the first non-BZD ASM [92 of 131 (70%) versus 26 of 66 (39%); odds ratio from Fisher's exact test 0.28, 95% CI 0.14 to 0.54; $p < 0.0001$], and a greater proportion of patients receiving at least one BZD after 45 minutes from seizure onset and prior to the first non-

BZD ASM [79 of 131 (60%) versus 16 of 66 (24%); odds ratio from Fisher's exact test 0.21, 95% CI 0.10 to 0.43; $p < 0.0001$].

First non-BZD ASM. The median (p_{25} - p_{75}) time to first non-BZD ASM was 80 (35 – 170) minutes. Patients with rSE onset out of the hospital received their first non-BZD ASM later than patients with rSE onset in the hospital [109 (59 – 200) versus 40 (22 – 92) minutes, $p < 0.0001$].

Opportunities for improving time to non-BZD ASMs. Based on our analyses, we describe three treatment patterns that may potentially contribute to delays in administering the first non-BZD ASM:

1) Patients with out of hospital onset not receiving any ASM prior to hospital arrival. Among 131 patients with out-of-hospital rSE onset, 61 (51%) did not receive any medication until hospital arrival. Of these 61 patients, 27 (40%) had a prior diagnosis of epilepsy and 3 (5%) had a prior episode of SE.

2) Patients receiving more than two BZDs before the first non-BZD ASM. Sixty-five of 197 (33%) patients received more than two BZD doses, including 44 of 131 (34%) patients with out-of-hospital onset and 21 of 66 (32%) with in-hospital onset [odds ratio from Fisher's exact test 0.92, 95% CI 0.46 to 1.81; $p = 0.8731$]. The third BZD dose was administered at home in three patients. All other patients received their third BZD by EMS (10 patients), at a non-pSERG study hospital (20 patients) or at a pSERG study hospital (32 patients).

3) Repeated doses of BZDs in hospital in patients who had received at least two BZDs prior to hospital arrival. Among the 65 patients who received at least two BZDs prior to hospital arrival, 15 (23%) received at least one additional BZD at hospital arrival. Among these

15 patients, 2 BZDs (N = 8), 3 BZDs (N = 6), 5 BZDs (N = 1) were given before hospital arrival.

Despite multiple BZDs already given, all 15 patients received a BZD and not a non-BZD ASM as the first ASM in the hospital.

FIGURE

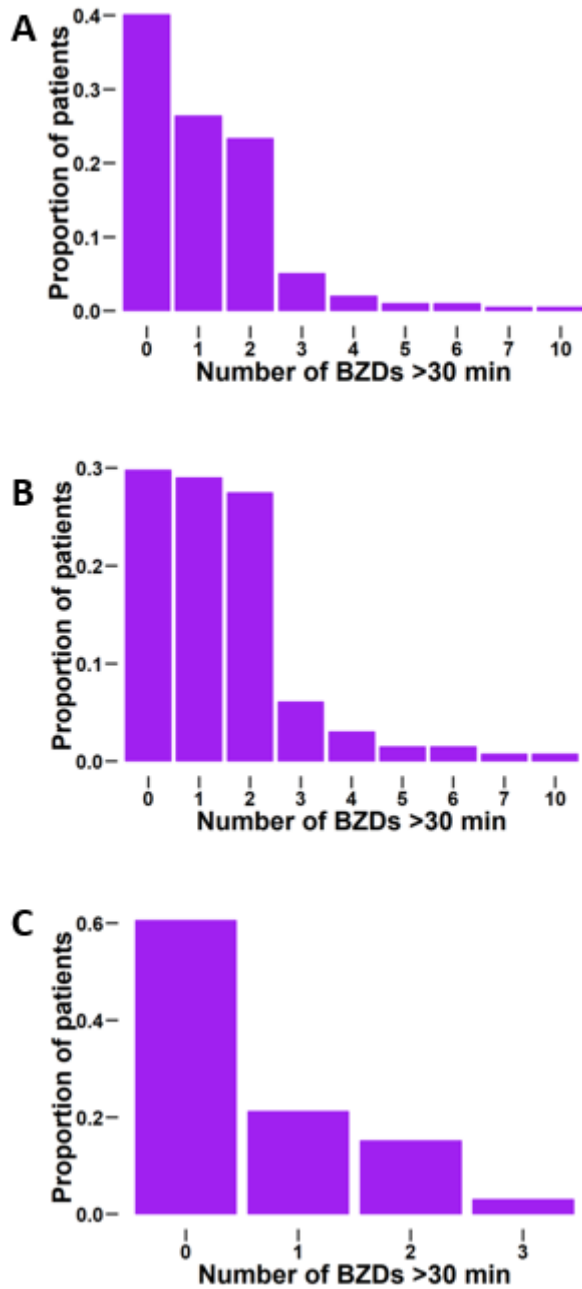


Figure 1. Number of total benzodiazepine doses administered before the first non-benzodiazepine anti-seizure medication and after 30 minutes from seizure onset. A. Entire cohort of patients with intermittent SE. B. Patients with out-of-hospital onset. C. Patients with in-hospital onset. Legend: BZD: Benzodiazepine. min: Minutes.

TABLES

Table 1. Demographic and clinical characteristics.

		Entire cohort of patients with intermittent SE (N = 197)	Out-of-hospital onset (N = 131)	In-hospital onset (N = 66)
Age at SE in years	Median (p ₂₅ -p ₇₅)	3.9 (1.3 – 9.0)	3.7 (1.2 – 9.1)	4.7 (1.9 – 9.0)
Sex	Male	107 (54.3%)	78 (59.5%)	29 (43.9%)
	Female	90 (45.7%)	53 (40.5%)	37 (56.1%)
Race	White	129 (65.5%)	88 (67.2%)	41 (62.1%)
	African-American	37 (18.8%)	25 (19.1%)	12 (18.2%)
	American-Indian/Alaska Native	1 (0.5%)	0 (0%)	1 (1.5%)
	Asian	8 (4.1%)	3 (2.3%)	5 (7.6%)
	Arabic	3 (1.5%)	1 (0.8%)	2 (3.0%)
	Hawaiian/Pacific	2 (1.0%)	2 (1.5%)	0 (0%)
	Unknown/not reported	17 (8.6%)	12 (9.2%)	5 (7.6%)
Ethnicity	Hispanic or Latino	31 (15.7%)	24 (18.3%)	7 (10.6%)
	Not Hispanic or Latino	152 (77.2%)	98 (74.8%)	54 (81.8%)
	Unknown/not reported	14 (7.1%)	9 (6.9%)	5 (7.6%)
Medical history*	DD/ID	93 (47.2%)	67 (51.1%)	26 (39.4%)
	Cerebral palsy	23 (11.7%)	15 (11.1%)	8 (12.1%)
	SE with fever	20 (10.2%)	13 (9.9%)	7 (10.6%)
	History of epilepsy	100 (50.8%)	67 (51.1%)	33 (50.0%)
	History of SE	37 (18.8%)	20 (15.3%)	17 (25.8%)
	No past neurological history	69 (35.0%)	40 (30.5%)	29 (43.9%)
Duration of SE in minutes	Median (p ₂₅ -p ₇₅)	150 (75 - 360)	180 (93 - 405)	120 (50 - 293)
Type of SE	Continuous	152 (77.2%)	98 (74.8%)	54 (81.8%)
	Intermittent	14 (7.1%)	9 (6.9%)	5 (7.6%)
Time to first BZD in minutes from seizure onset	Median (p ₂₅ -p ₇₅)	93 (47.2%)	67 (51.1%)	26 (39.4%)
Time to first non-BZD ASM in minutes from seizure onset	Median (p ₂₅ -p ₇₅)	20 (10.2%)	13 (9.9%)	7 (10.6%)

Legend: %: Percentage. **BZD:** Benzodiazepine. **DD:** Developmental delay. **ID:** Intellectual disability. **p₂₅-p₇₅:** Percentiles 25th and 75th. **SE:** Status epilepticus. Non-BZD ASM: anti-seizure medication.

*Percentages do not add up to 100% as patients may belong into more than one category.

Table 2. Number of benzodiazepines given before the first non-ASM BZD.

Number of BZDs given before first non-BZD ASM	1	2	3	4	5	6	7	10
Entire cohort of patients with intermittent SE	56 (28.4%)	76 (38.6%)	38 (19.3%)	15 (7.6%)	5 (2.5%)	3 (1.5%)	3 (1.5%)	1 (0.5%)
Out-of-hospital onset	37 (28.2%)	50 (38.2%)	24 (18.3%)	9 (6.9%)	4 (3.1%)	3 (2.3%)	3 (2.3%)	1 (0.8%)
In-hospital onset	19 (28.8%)	26 (39.4%)	14 (21.2%)	6 (9.1%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.

Table 3. Number of benzodiazepines given before the first non-ASM BZD that were administered after 30 minutes from seizure onset.

Number of BZDs given before first non-BZD ASM that were administered after 30 minutes from seizure onset	0	1	2	3	4	5	6	7	10
Entire cohort of patients with intermittent SE	79 (49.1%)	52 (26.4%)	46 (23.4%)	10 (5.1%)	4 (2.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)	1 (0.5%)
Out-of-hospital onset	39 (29.8%)	38 (29.0%)	36 (27.5%)	8 (6.1%)	4 (3.1%)	2 (1.5%)	2 (1.5%)	1 (0.8%)	1 (0.8%)
In-hospital onset	40 (60.6%)	14 (21.2%)	10 (15.2%)	2 (3.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.

Table 4. Number of benzodiazepines given before the first non-ASM BZD that were administered after 45 minutes from seizure onset.

Number of BZDs given before first non-BZD ASM that were administered after 45 minutes from seizure onset	0	1	2	3	4	5	6	10
Entire cohort of patients with intermittent SE	102 (51.8%)	42 (21.3%)	36 (18.3%)	7 (3.6%)	6 (3.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)
Out-of-hospital onset	52 (39.7%)	32 (24.4%)	31 (23.7%)	6 (4.6%)	6 (4.6%)	1 (0.8%)	2 (1.5%)	1 (0.8%)
In-hospital onset	50 (75.8%)	10 (15.2%)	5 (7.6%)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Legend: BZD: Benzodiazepine. **non-BZD ASM:** Non-benzodiazepine anti-seizure medication.