Prehospital benzodiazepine use and need for respiratory support in paediatric seizures

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ABSTRACT

Background Paramedics are frequently called to attend seizures in children. High-quality evidence on second-line treatment of benzodiazepine (BZD)-refractory convulsions with parenteral long-acting antiepileptic drugs in children has become available from the ED. In order to address the potential need for an alternative agent, we set out to determine the association of BZD use prehospital and the need for respiratory support.

Methods We conducted a retrospective observational study of state-wide ambulance service data (Ambulance Victoria in Victoria, Australia, population: 6.5 million). Children aged 0–17 years assessed for seizures by paramedics were analysed for demographics, process factors, treatment and airway management. We calculated adjusted ORs (AOR) of the requirement for respiratory support in relation to the number of BZD doses administered.

Results Paramedics attended 5112 children with suspected seizures over 1 year (1 July 2018 to 30 June 2019). Overall, need for respiratory support was low (n=166; 3.2%). Before ambulance arrival, 509 (10.0%) had already received a BZD and 420 (8.2%) were treated with midazolam by paramedics. Of the 846 (16.5%) patients treated with BZD, 597 (70.6%) received 1 BZD dose, 156 (18.4%) 2 doses and 93 (11.0%) >2 doses of BZD. Patients who were administered 1, 2 and >2 doses of BZD received respiratory support in 8.9%, 32.1% (AOR 4.6 vs 1 dose, 95% CI 2.9 to 7.4) and 49.5% (AOR 10.3 vs 1 dose, 95% CI 6.0 to 17.9), respectively.

Conclusions Increasing administration of BZD doses was associated with higher use of respiratory support. Alternative prehospital antiepileptic drugs to minimise respiratory depression should be investigated in future research.

Key messages

What is already known on this subject

⇒ Recently, high-quality evidence on second-line treatment of prolonged convulsions in children has become available for the ED.

⇒ Guidance on the optimal management of prolonged seizures by ambulance staff prehospital is limited.

What this study adds

⇒ In a retrospective observational study of state-wide Australian ambulance data more than 5000 children with suspected seizures were assessed.

⇒ While prehospital antiepileptic drug use was infrequent, 1, 2 and >2 doses of benzodiazepines received respiratory support in 8.9%, 32.1% and 49.5%, respectively.

⇒ Alternative prehospital antiepileptic drugs to minise respiratory depression should be investigated in future research.

INTRODUCTION

Seizures are common paediatric emergencies encountered by paramedics and can become increasingly challenging as they get longer.[1–3] Benzodiazepines (BZD) are widely used prehospital and sometimes administered repeatedly as the only agent available.[4–6] Research in hospital suggests that administration of more than two doses of BZD can lead to respiratory depression, increased rates of intubation, intensive care unit (ICU) admission and longer hospitalisation.[7–11]

Recently, three randomised controlled trials on second-line treatment of convulsive status epilepticus (CSE) have provided high-quality evidence in hospital, suggesting levetiracetam or valproate as alternatives to fosphenytoin or phenytoin for CSE persisting after BZD administration in the ED.[12–14] This new evidence may also be relevant for prehospital seizure management. The use of non-BZD agents prehospital is currently limited by the lack of data on adverse outcomes related to multiple BZD dosing and of trials investigating treatment alternatives for this setting.

We set out to extract information from the electronic medical records of Ambulance Victoria (AV), Australia, on all suspected seizures in children to understand the association between antiepileptic drug use prehospital, and of BZD administration by paramedics in particular, and the need for respiratory support.

METHODS

Study design

This was a retrospective cohort study of all children with a seizure or who were postictal as determined by the treating AV paramedics from 1 July 2018 to 30 June 2019.

Study setting

AV is the single public emergency medical service for the state of Victoria, Australia (population

Table 1 Adherence to guidance for intramuscular midazolam administration by age group including weight-based dose

Age group (years)	<1 (n=27)	1–4 (n=166)	5–11 (n=111)	>11 (n=88)*
Dose advised by AV guideline[18] (mg)	1	2.5	2.5–5	5–10
Dose in accordance with guideline	23	155	107	83
% of total	85.2	93.4	96.4	94.3
Dose lower	1	9	3	5
Dose higher	3	2	1	0
Median dose/kg	0.11	0.18	0.13	0.11
Weight data available n (%)	25 (92.6)	142 (85.5)	87 (78.4)	68 (77.3)

Data are presented as n unless otherwise stated.
Data based on average dose if multiple doses were administered via the same route.
*One patient missing (no dose recorded).
AV, Ambulance Victoria.

of 6.5 million, 220 000 km^2).[15 16] Over the study period, the service responded to 940 000 cases[17] mainly using advanced life support (ALS) or mobile intensive care ambulance (MICA) paramedics. Based on published AV Clinical Practice Guidelines for seizure management,[18] intramuscular midazolam is followed in continuing convulsions by the establishment of intravenous or intraosseous access and administration of age group-related doses of midazolam (table 1 and online supplemental table 3). Administration of up to five doses of midazolam in total and intubation are treatment options for persisting convulsions.

Selection of participants

We searched the AV electronic patient care system for presentations of children aged less than 18 years matching the following criteria: final primary assessment or secondary survey of seizure, convulsion or postictal status documented by a paramedic. Seizures in the prehospital setting can be difficult to diagnose and to distinguish from other entities such as undifferentiated collapse or non-epileptic events. Therefore, in accordance with a previous adult prehospital study, we included the term 'suspected seizure' in this investigation.[19] Cases found on manual review without suspected seizures as the presenting complaint were excluded. Records of cases assessed by multiple ambulance teams during the same incident were unified as a single paramedic attendance. Interhospital transports and patients managed for cardiac arrest or head injury without active convulsions were excluded.

Data collection

Abstraction of deidentified demographic data, process factors, management and outcomes was performed in accordance with guidance for retrospective chart review.[20] Data were extracted by one researcher (CKP) using a piloted, standardised instrument with predefined inclusion and exclusion criteria. Key data including BZD administration and number of doses, hypoxaemia and type of respiratory support were also extracted by another abstractor to assess inter-rater reliability. Both abstractors had a medical background and were trained and supervised via regular meetings with a senior researcher and a statistician. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline for reporting observational studies.

Measurements and definitions

Respiratory support: We defined respiratory support as the need for manual bag-valve-mask ventilation or attempted establishment of nasopharyngeal or oropharyngeal airway, laryngeal mask airway or endotracheal intubation.

Pre-AV medication: We extracted information on antiepileptic drugs administered before AV arrival. Pre-AV medication was any antiepileptic rescue medication given for the same seizure presentation prior to the arrival of the paramedics.

Hypoglycaemia was defined as a blood sugar level below 4 mmol/L.

Hypoxaemia was defined as transcutaneous oxygen saturation (SPO_2) below 92%, in accordance with thresholds for intervention recommended by AV guidelines.[18]

Fever was defined as a temperature of 38°C or higher recorded by paramedics.

Analysis

Descriptive statistics summarised patient characteristics and study outcome measures. Non-parametric data were reported as median and IQR. Details on missing data, mostly affecting vital signs but not key variables, are included in the tables (tables 1–3 and online supplemental tables 1 and 2).

Logistic generalised estimating equation (GEE) models analysed the relationship between administered BZD doses and required respiratory support. To accommodate non-independence of observations, models were clustered at the patient level, and employed an exchangeable covariance matrix. Adjusted ORs (AOR) for BZD doses were reported, covarying for transport time, initial SPO_2, child age, sex, history of seizure, diagnosis of epilepsy, comorbidities of developmental delay, autism and cerebral palsy, and low initial GCS (dichotomised as 3–8 vs 9–15). The analysis was conducted separately for the total number of doses including pre-AV medication and midazolam doses given by paramedics only. A subgroup analysis of patients treated with intramuscular midazolam by AV, adjusting for dose per kilogram, was performed. For patients in the age bracket for possible febrile seizures (1 year to<5 years), we included a *post hoc* analysis by presence or absence of fever. Logistic GEE models were again used, with an independence covariance matrix. Cases with missing covariates and indeterminate gender (due to small group size of n=3) were excluded from the analyses.

Repeat cases were presented as separate presentations in the summary statistics, but were accommodated in the inferential statistic (ie, logistic GEE modelling).

The key variables prone to review bias and error—BZD administration and respiratory support—were assessed by a second abstractor and inter-rater reliability was calculated with Cohen's κ statistic. All analyses were performed using Stata V.15.1 (Stata Statistical Software: Release 15. StataCorp. 2015 College Station, Texas, USA).

Patient and public involvement

Patients were not involved in the design of this study.

RESULTS

Characteristics of study objects

We identified 5318 cases with an assessment of seizures in the AV patient care record. Excluding incidents without seizures and duplicates, we identified 5255 cases of children with suspected seizures presenting over the 1-year study period (figure 1). This represents 8.6% of the total 60 768 paediatric cases assessed by AV within the study period. After the exclusion of 122

Table 2 Demographics and clinical characteristics of children assessed for seizures by AV

	Total (N=5112)	No BZD (n=4266)	1 BZD dose* (n=597)	2 BZD doses* (n=156)	>2 BZD doses* (n=93)
Age, years, n (%)					
<1	328 (6.4)	290 (6.8)	23 (3.9)	10 (6.4)	5 (5.4)
1–4	2183 (42.7)	1869 (43.8)	208 (34.8)	70 (38.7)	36 (38.7)
5–11	1188 (23.2)	874 (20.5)	241 (40.4)	41 (34.4)	32 (34.4)
12–17	1413 (27.6)	1233 (28.9)	125 (20.9)	35 (21.5)	20 (21.5)
Median age, years (IQR)	5 (2–12)	4 (1–13)	6 (3–11)	4 (2–10.5)	5 (3–10)
Sex, n (%)					
Male	2643 (51.7)	2226 (52.2)	294 (49.2)	73 (46.8)	50 (53.8)
Female	2466 (48.2)	2039 (47.8)	301 (50.4)	83 (53.2)	43 (46.2)
Indeterminate	3 (0.1)	1 (<0.1)	2 (0.3)	0 (0)	0 (0)
Pre-existing conditions, n (%)					
History of seizure/convulsions	2901 (56.7)	2230 (52.3)	480 (80.4)	123 (78.8)	68 (73.1)
Diagnosis of epilepsy	1353 (26.5)	917 (21.5)	318 (53.3)	77 (49.4)	41 (44.1)
History of febrile convulsions in the age group of 1–4 years	534 (24.5)	478 (25.6)	41 (19.7)	12 (17.1)	3 (8.3)
Developmental delay	406 (7.9)	258 (6.0)	110 (18.4)	22 (14.1)	16 (17.2)
Autism	442 (8.6)	355 (8.3)	59 (9.9)	17 (10.9)	11 (11.8)
Cerebral palsy	201 (3.9)	97 (2.3)	72 (12.1)	21 (13.5)	11 (11.8)
Vital signs					
Fever, n (%)†	1810 (36.7)	1620 (39.3)	104 (18.3)	50 (32.9)	36 (39.6)
Hypoglycaemia, n (%)‡	136 (4.0)	111 (4.2)	16 (3.3)	3 (2.1)	6 (6.5)
Hypoxaemia, n (%)	268 (5.6)	112 (2.8)	90 (15.4)	38 (24.5)	28 (30.1)
Initial SPO_2, median (IQR)§	98 (97–99)	98 (97–99)	98 (95–99)	98 (92–99)	96 (88–99)
Initial GCS, median (IQR)¶	14 (11–15)	14 (13–15)	9 (6–13)	4.5 (3–9)	3 (3–7)

Fever, hypoglycaemia and hypoxaemia defined in the Methods section.
See online supplemental appendix for subgroup sample sizes and other vital signs.
*Doses include BZD administered by paramedics and given before ambulance arrival.
†Temperature recorded in n=4933 cases.
‡Initial blood sugar level recorded in n=3363 cases.
§Initial oxygen saturation recorded in n=4772 cases.
¶Initial GCS recorded in n=5063 cases.
AV, Ambulance Victoria; BZD, benzodiazepine; SPO_2, oxygen saturation.

interhospital transports and 21 patients with a final diagnosis of cardiac arrest or head injury without active convulsions, a total of 5112 paediatric cases were further analysed (figure 1). These cases were recorded in 3631 individuals, of which the majority (n=2905; 80.0%) presented once during the study period, while 455 (12.5%) children were assessed twice and 271 (7.5%) three times or more.

The median age was 5 years (IQR 2–12) and 2643 (51.7%) were male (table 2). In more than half of cases, a history of seizures (n=2901; 56.7%) was recorded, with 1353 (26.5%) incidents specifying a diagnosis of epilepsy and, in the age group from 1 to <5 years, 534/2183 (24.5%) a history of febrile convulsions. A regular antiepileptic drug was prescribed in 1426 (27.9%) cases and 916 (17.1%) attendances had at least one comorbidity.

Fever was recorded in 1820 (36.7%) of 4933 patients where temperature was assessed, and hypoglycaemia was present in 136 (4.0%) of 3363 cases assessed. The median initial GCS was 14 (IQR 11–15) and was lower in patients receiving BZD treatment (median 8; IQR 3–12) (table 2, online supplemental table 1). Paramedics responded within a median of 11 min (IQR 8–16) and attended the patient for 36 min (IQR 27–47). Patients were transported by ambulance in 89.9% (n=4594) of attendances, increasing to 97.8% (91/93) in patients treated with >2 doses of BZD (online supplemental table 2). MICA paramedics attended in 12.5% (n=637) of all cases increasing to 90.3% (84/93) in patients receiving >2 doses of BZD.

Main results

Caregivers administered pre-AV medication in 506 (9.9%) cases (table 3). The majority received midazolam (n=468; 92.5%). Paramedics treated patients with midazolam in 420 (8.2%) cases; 265 (63.1%) received 1 dose, 91 (21.7%) 2 doses and 64 (15.2%) >2 doses of midazolam. Median doses were 0.15 mg/kg (IQR 0.11–0.19) for intramuscular administration (dose per kilogram available for n=322); for intravenous and intraosseous median dose was 0.07 mg/kg (IQR 0.05–0.08; dose per kilogram available for n=64) (tables 1 and 3 and online supplemental table 3). Average doses were in accordance with the AV guideline in 368 (93.9%) patients with intramuscular and 64 (87.7%) with intravenous midazolam. Eighty-three patients (1.6%) received BZD both as pre-AV medication and by paramedics. The median number of doses in this group was 2 (IQR 2–3) with 35 (42.2%) receiving >2 doses of BZD. In 116 (2.3%) cases, medical control consultation with a clinician regarding the administration of midazolam was documented and in 41 (35.3%) incidents, no midazolam was given by paramedics after consultation.

Respiratory support beyond oxygen therapy and airway suctioning was required in 166 (3.2%) patients, involving manual ventilation, oropharyngeal or nasopharyngeal airway,

Table 3 Antiepileptic drug treatment of prehospital seizures

	n/median	%/IQR
Antiepileptic drug administration by caregivers	506	
Drug		
Midazolam	457	90.3
Clonazepam	19	3.8
Diazepam	10	2.0
Midazolam+other BZD	11	2.2
Other*	6	1.2
Unknown	3	0.6
Routes of midazolam	468	
Intranasal	205	43.8
Buccal	117	25.0
Oral	83	17.7
Other†	20	4.3
Unknown	43	9.2
Median total midazolam dose (mg)‡	5	2.5–5
Most frequent doses		
2.5	51	13.1
5	190	48.7
10	39	10.0
Midazolam administration by paramedic	420	
Median number of doses	1	1-2
1	265	63.1
2	91	21.7
3	34	8.1
4	8	1.9
5	12	2.9
>5	10	2.4
Median total dose by paramedic (mg)§	5	2.5–5.5
Most frequent doses		
2.5	146	34.8
5	111	26.5
10	42	10.0
Routes		
Intramuscular	393	93.6
Intravenous	60	14.3
Intraosseous	15	3.6
BZD administration preambulance and by paramedic		
BZD both preambulance and by paramedic	83	
Median total number of doses	2	2–3
>2 doses	35	42.2
Median dose (mg)¶	7.5	6.3–10

*Other medication: clobazam n=4, lorazepam n=1, phenobarbital n=1.
†Other routes: intramuscular n=10, sublingual n=7, buccal and intranasal n=2, rectal n=1.
‡n=390.
§n=419.
¶n=71.
AV, Ambulance Victoria; BZD, benzodiazepine.;

laryngeal mask airway and intubation (table 4, figure 2). No patients received home ventilator support. The proportion of cases requiring respiratory support increased with the number of BZD doses administered. AORs of receiving respiratory support increased with BZD doses, with 2 BZD doses having an AOR of 4.6 (95% CI 2.9 to 7.4) and >2 BZD doses having an AOR of 10.3 (95% CI 6.0 to 17.9) compared with 1 BZD dose given either pre-AV or by AV. When including initial GCS (3–8 vs 9–15) in the logistic GEE model (pre-AV and AV doses), AOR estimates decreased slightly from the original model. Results show those with 2 BZD doses had 3.7 (95% CI 2.3 to 6.1) times, and those with >2 BZD doses having 7.5 (95% CI 4.3 to 13.2) times the odds of respiratory support when compared with those with 1 BZD dose. When examining midazolam administration by paramedics alone (n=417), AORs of 3.5 (95% CI 2.0 to 6.1) and 6.1 (95% CI 3.2 to 11.6) were found for 2 and >2 BZD doses, respectively, compared with 1 BZD dose. Subgroup analysis of patients treated with intramuscular midazolam, additionally adjusting for average dose per kilogram (n=319), resulted in similar AORs of 3.8 (95% CI 2.0 to 7.0) for two doses and 6.4 (95% CI 3.1 to 13.0) for more than two doses, respectively.

In the subgroup analysis of children aged 1 to <5 years with fever (n=106), the AOR for 2 BZD doses was 4.0 (95% CI 1.2 to 13.3), and the AOR for >2 BZD doses was 15.4 (95% CI 3.4 to 71.0) when compared with those with 1 BZD dose. In the subgroup analysis of patients without fever (n=202), those with 2 BZD doses had 7.5 (95% CI 2.7 to 20.9) times, and those with >2 BZD doses had 14.4 (95% CI 4.5 to 46.2) times the odds of respiratory support when compared with those with 1 BZD dose.

Inter-rater agreement analysis found that Cohen's κ was 0.988 for administration of any BZD, 0.974 for pre-AV BZD, 0.995 for AV midazolam and 0.961 for the groups of 0, 1, 2 or >2 BZD. Inter-rater reliability for hypoxaemia (κ=1) and any respiratory support (κ=0.985) was strong. Results of the κ analysis for distinct airway procedures were: oxygen therapy 0.999, airway clearance 1, manual ventilation 0.969, nasopharyngeal airway 1, oropharyngeal airway 0.980, laryngeal mask airway 1 and intubation 0.952.

DISCUSSION

In this large prehospital study, we assessed the relationship between the number of BZD doses administered for paediatric seizures and the need for respiratory support by paramedics. Our data indicate that when BZDs are used prehospital, multiple doses are not uncommon. Respiratory support was required in a small number of patients (3.2%) overall, yet increased with increasing administration of BZD and was needed in half of patients with >2 doses of BZD. Our regression analysis showed that these patients were significantly more likely to require manual ventilation, nasopharyngeal/oropharyngeal airways or intubation.

Our data are in line with previously published hospital-based studies, which found that use of >2 doses of BZD for CSE was associated with poor outcome[7–9] and prehospital data indicating an increased risk of intubation and ICU admission.[21] It is unclear if the increase in the need for respiratory support in our data was related to the BZD itself, the prolonged CSE or both. BZDs appear to become less effective with increasing duration of a convulsion.[22 23] Local prehospital guidelines allowing for >2 BZD doses may need to be re-evaluated.

In contrast to previous prehospital studies,[19 24 25] we described prehospital BZD management by both paramedics and caregivers. Administration of home medication was common and in the majority of cases, no paramedic treatment was required afterwards. This stresses the necessity for paramedics to consider home medication in their decision-making.

Another important aspect of prehospital CSE management, especially in paediatric populations, is dosing. The correct weight-based dose of intramuscular midazolam has been subject to discussion ranging from 0.1 to 0.2 mg/kg[4 5 26] and fixed doses of 5 mg for patients weighing from 13 to 40 kg and 10 mg above

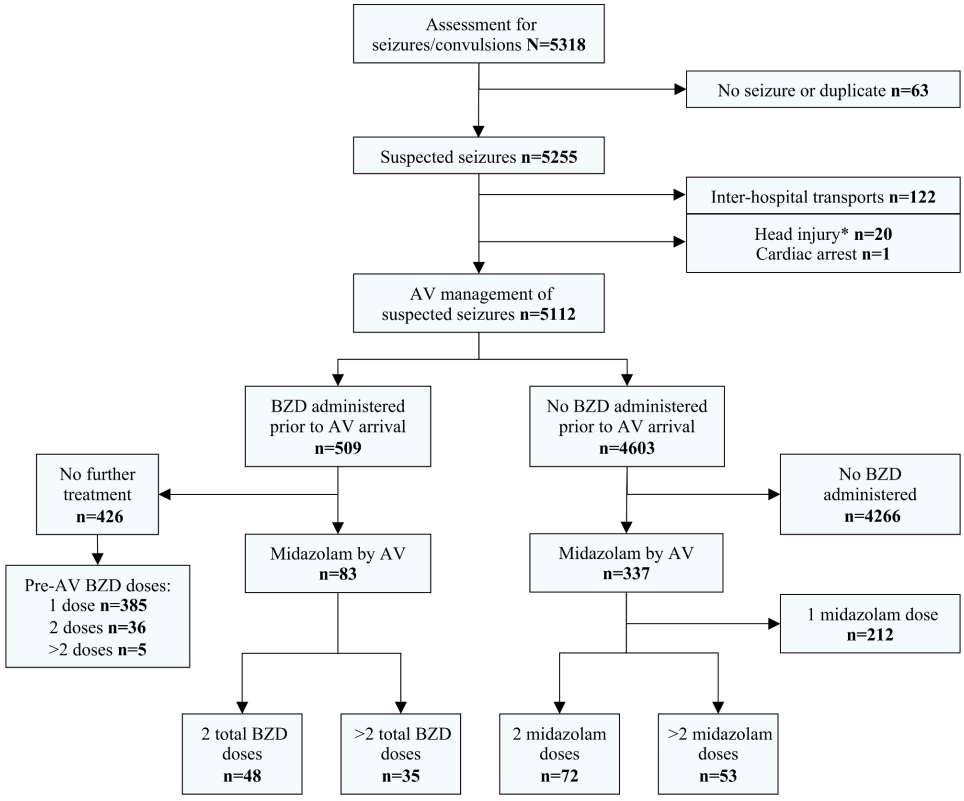

Figure 1 Flow chart—management of paediatric seizures in the prehospital setting. Pre-AV medication as defined in the Methods section. *Head injury without active convulsion with AV. AED, antiepileptic drug; AV, Ambulance Victoria; BZD, benzodiazepine.

40 kg.[11 27 28] Incorrect weight-based dosing in the prehospital setting has been an important issue of concern for paramedics[29] and in a recent study, a third of treated patients received an incorrect dose.[30] In our study, on the other hand, 94% of doses were in accordance with the local guideline and the median dose resulting from the age-based regimen was 0.15 mg/kg. In an additional subgroup analysis of patients receiving intramuscular midazolam, adjusting for the weight-based dose, the correlation

Table 4 Procedures performed or attempted by ambulance paramedics in children with suspected seizures by total number of BZD administered

	Total (N=5112)	No BZD (n=4266)	1 BZD dose* (n=597)	2 BZD doses* (n=156)	>2 BZD doses* (n=93)
	n (%)	n (%)	n (%)	n (%)	n (%)
Access					
Intravenous access†	295 (5.8)	76 (1.8)	75 (12.6)	72 (46.2)	72 (77.4)
Successful	215 (72.9)				
Intraosseous access†	26 (0.5)	0 (0)	3 (0.5)	5 (3.2)	18 (19.4)
Successful	24 (92.3)				
Airway and breathing					
Oxygen therapy	849 (16.6)	365 (8.6)	279 (46.7)	117 (75.0)	88 (94.6)
Airway clearance with suction	247 (4.8)	41 (1.0)	97 (16.2)	52 (33.3)	57 (61.3)
Manual ventilation	149 (2.9)	13 (0.3)	48 (8.0)	44 (28.2)	44 (47.3)
Nasopharyngeal airway†	11 (0.2)	1 (<0.1)	3 (0.5)	3 (1.9)	4 (4.3)
Successful	6 (54.5)				
Oropharyngeal airway†	50 (1.0)	4 (0.1)	15 (2.5)	16 (10.3)	15 (16.1)
Successful	33 (66.0)				
Laryngeal mask/supraglottic airway†	2 (<0.1)	0 (0)	0 (0)	1 (0.6)	1 (1.1)
Successful	1 (50.0)				
Intubation†	11 (0.2)	0 (0)	1 (0.2)	3 (1.9)	7 (7.5)
Successful	11 (100.0)				
Respiratory support‡	166 (3.2)	17 (0.4)	53 (8.9)	50 (32.1)	46 (49.5)

Procedures were classified as successful unless otherwise stated.
*Doses include medication administered by paramedics and given before ambulance arrival.
†Attempt of procedure.
‡Respiratory support as defined in the Methods section=need for manual ventilation or attempted establishment of nasopharyngeal or oropharyngeal airway, laryngeal mask airway or endotracheal airway.
BZD, benzodiazepine.

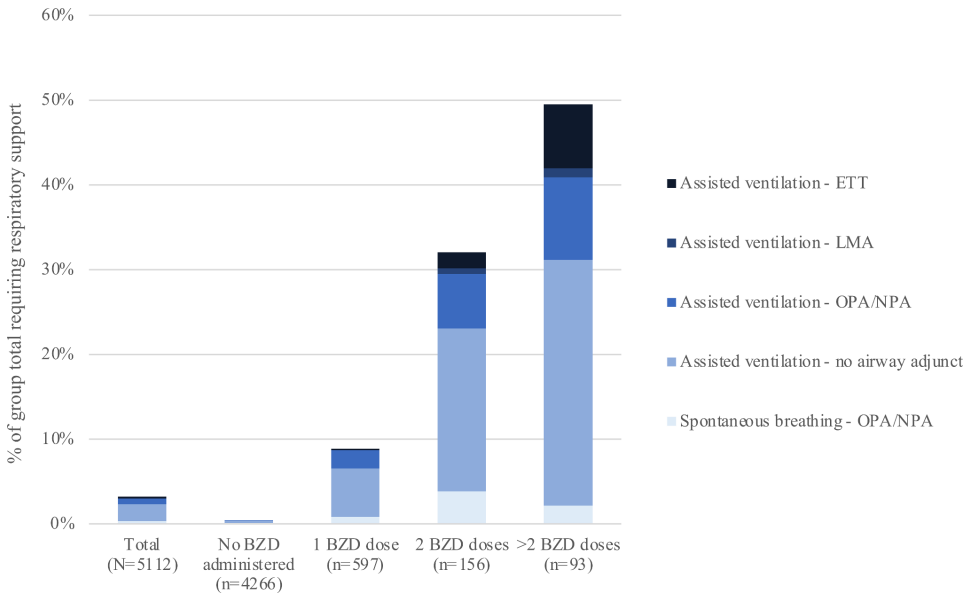

Figure 2 Need for respiratory support in the management of paediatric seizures presenting to Ambulance Victoria by total number of benzodiazepine doses administered (% of group total). Doses include all BZD doses given per seizure presentation by paramedics or caregivers. For patients receiving multiple airway interventions only the most invasive procedure is listed. BZD, benzodiazepine; ETT, endotracheal tube; LMA, laryngeal mask airway; NPA, nasopharyngeal airway; OPA, oropharyngeal airway.

between number of doses and respiratory depression remained strong.

Recently, three high-quality multicentre trials on second-line treatment of CSE in the ED setting have become available.[12–14] In two paediatric-only trials, levetiracetam and phenytoin were compared,[12 13] and in one adult and paediatric trial, levetiracetam, fosphenytoin and valproate[14] showed similar outcomes in terms of seizure cessation. This has led to a change in clinical practice guidelines.[31 32] While many prehospital providers, including Australian emergency medical service systems,[26] are still limited to first-line BZD treatment only, levetiracetam and valproate are attractive alternatives to repeated BZD. Levetiracetam requires a 5 min intravenous infusion but has a favourable adverse event profile, while valproate can be given as an intravenous bolus but has some hypothetical concerns regarding use in young infants.[33] In comparison, phenytoin requires a prolonged infusion and is associated with serious adverse events.[34] So far, only one randomised trial on the prehospital use of second-line treatment in adults has been conducted. No difference was found between levetiracetam and placebo after clonazepam in terms of seizure cessation, although long-term outcomes suggested a potential neuroprotective effect of levetiracetam.[35] Ideally, a future prehospital study in children would compare an adequate dose of BZD followed by either a second dose of BZD or a second-line antiepileptic agent.

Limitations

The diagnosis of epileptic seizures prehospital was based on the clinical judgement of the paramedics without neurological consultation or electroencephalograms. However, in the majority of cases, a history of seizures was recorded, and a diagnosis of epilepsy or prescription of antiepileptic drugs was common, especially among treated patients. Consultation with a medical control clinician was encouraged by AV guidelines for unclear cases and was performed in a fifth of patients receiving midazolam in our cohort.

It was not possible to determine the exact aetiology of the seizures or the onset and duration of seizures from this retrospective data set. We were unable to track patients beyond the prehospital setting. Further research using prospective and hospital-linked data may clarify this aspect.

Another shortcoming is that it was not possible to distinguish whether respiratory support was necessary because of the seizure activity itself, or due to administered antiepileptic medication. However, we adjusted for initial SPO_2 in our regression analysis for both total BZD doses and treatment by paramedics only, with the association between BZD doses and respiratory intervention remaining strong. This result suggests that respiratory depression requiring support is not explained by the pre-BZD condition of the patients alone, making it plausible that it may be related to the BZD treatment. Multiple BZD doses may cause respiratory problems, and persisting CSE can become refractory to BZD.[22 23] Therefore, the high rate of almost 50% of patients with >2 BZD doses needing respiratory support may be a result of both direct respiratory depression by the drug and ineffective treatment of a seizure impacting airway and breathing. Availability of second-line agents in the prehospital setting may be a solution to both of these problems.

In terms of generalisability of the findings, our overall numbers of seizure presentations among paediatric patients are similar to EMS data from other jurisdictions, where seizures accounted for 8%–12% of attended cases.[1 2] Another study on paediatric prehospital seizure management reported a higher rate of BZD use (19%). However, only patients transported to a tertiary hospital were included and therefore may represent a different population.[24] In our state-wide study, the majority of patients were transported to non-tertiary destinations and around 10% were not transported at all. While the state of Victoria, Australia, is similar in size to the whole of the UK, the majority of our population and ambulance service provision were concentrated in one large city, Melbourne. This may limit the generalisability of the findings.

Our data were based on a retrospective record review of a comprehensive electronic database. We followed guidance to optimise retrospective data extraction by using trained abstractors, predefined inclusion and exclusion criteria and variables extraction with a piloted data instrument.[20] However, abstractors were not blinded to the purpose of the project. Missing data were found mostly among vital signs and its proportion was at a low level of missingness. Inter-rater analysis for key variables demonstrated that agreement for all tested variables was high.

CONCLUSIONS

Children with prehospital seizures who require pharmacological intervention frequently receive multiple doses of BZDs. Increased use of BZD was associated with an increased need for respiratory interventions. An alternative prehospital pharmacological approach with earlier use of second-line agents to minimise respiratory depression should be investigated in future research.

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Correction notice Since this article was first published online, figures 1 and 2 have been replaced to include updated abbreviations.

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