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Prehospital Levetiracetam Use in Adults With Status Epilepticus: Results of a Multicenter Registry

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Background and Purpose Status epilepticus (SE) is a neurological emergency due to prolonged seizure activity or multiple seizures without full recovery in between them. Prehospital SE management is crucial since its duration is correlated with higher morbidity and mortality rates. We examined the impact of different therapeutic strategies in the prehospital setting with a focus on levetiracetam.

Methods We initiated the Project for SE in Cologne, a scientific association of all neurological departments of Cologne, the fourth-largest city in Germany with around 1,000,000 inhabitants. All patients with an SE diagnosis were evaluated over 2 years (from March 2019 to February 2021) to determine whether prehospital levetiracetam use had a significant effect on SE parameters.

Results We identified 145 patients who received initial drug therapy in the prehospital setting by professional medical staff. Various benzodiazepine (BZD) derivatives were used as first-line treatments, which were mostly used in line with the recommended guidelines. Levetiracetam was regularly used (n=42) and mostly in combination with BZDs, but no significant additional effect was observed for intravenous levetiracetam. However, it appeared that the administered doses tended to be low.

Conclusions Levetiracetam can be applied to adults with SE in prehospital settings with little effort. Nevertheless, the prehospital treatment regimen described here for the first time did not significantly improve the preclinical cessation rate of SE. Future therapy concepts should be based on this, and the effects of higher doses should in particular be reexamined.

Keywords neurological emergency; prehospital setting; anticonvulsant therapy; benzodiazepines; levetiracetam.

INTRODUCTION

Status epilepticus (SE) is a common neurological emergency with an annual incidence rate of 10–20 per 100,000 inhabitants in Germany.[1] Based on the definition of an epileptic seizure as a transient occurrence of signs and symptoms caused by excessive synchronous neuronal activity, a SE represents prolonged seizure activity. With increasing seizure duration, the risk of irreversible neuronal damage increases due to indirect or systemic factors and direct neurotoxic effects.[2]

SE is defined by a seizure duration of at least 5 minutes for generalized tonic–clonic seizures and 10–15 minutes for focal (convulsive as well as nonconvulsive) or absence seizures. In addition, a series of two or more epileptic seizures is considered to constitute an SE if consciousness or preexisting neurological findings do not recover in between them. Generalized spike-wave paroxysms are a prerequisite for diagnosing an absence seizure. This requires an electroencephalogram, making this form of SE difficult to diagnose outside of

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a hospital setting.

Patients should be treated earlier and more intensively, and no "wait and see" situations should arise without adequate therapy. Benzodiazepines (BZDs) have been established as the best first-line treatment for SE. Existing treatment recommendations therefore refer to this drug class. Studies on prehospital SE treatment have been rare, especially regarding levetiracetam use. We aimed to determine whether levetiracetam application in the prehospital setting improved the preclinical cessation rate of SE or its clinical outcome parameters, namely the need for and duration of assisted ventilation, and the durations of intensive care unit (ICU) and in-hospital stays. This retrospective, noninterventional study was performed over 2 years in the urban area of Cologne, the fourth-largest city in Germany. We took advantage of the unique opportunity of the availability of levetiracetam for prehospital treatment in Cologne since 2018.

The previous treatment recommendation for emergency physicians in SE cases was to use BZDs primarily and analgesia secondarily, for which the first choice was propofol. Since levetiracetam has become available in ambulances, the range of treatment options for emergency physicians in the field has expanded. The treatment recommendation for this includes levetiracetam as a second option after administering BZDs.

We were not aware of any comparable study that have actually collected and analyzed all cases among such a large population over such a long period of time. From our point of view, it is extremely important to perform such evaluations, because the analysis of real-world data helps to obtain a much better understanding of treatment strategies, especially when other double-blind or multicenter studies have not been conducted. If levetiracetam could be demonstrated to help in prehospital settings, this would be of great importance for the treatment options in initial SE therapy. Our results could therefore serve as a template for other specific studies and treatment recommendations.

METHODS

We initiated the Project for SE in Cologne, a scientific association of all neurological departments of Cologne, which is the fourth largest city in Germany with around 1,000,000 inhabitants. There are three neurological clinics that treat adults within the city area. All three hospitals have a neurological emergency outpatient clinic and neurological ICU facilities. The accident and emergency services of Cologne can admit patients with neurological conditions directly to these clinics. Under these conditions we were able set up a multicenter registry.

The inclusion criteria for our study were as follows: patients treated between March 2019 and February 2021, patients with SE admitted directly to one of the neurology departments or by drip and ship (i.e., primarily seen in the emergency department of another hospital but being directly forwarded to another), preclinical SE onset, and age ≥18 years. Applying these criteria resulted in 328 data sets being assessed and retrieved from patient files. The protocols of the accident and emergency services were evaluated, and information on the alerting of the rescue service, the arrival on-site, and the treatments were assessed. These protocols reveal the duration and type of seizures. Only patients under protocols that allowed a clear assignment of SE were included in the study. The medication administered, including its dose, was also listed. The sequence and timing of drug administration were also evaluated, and cases were therefore only assessed if their initial drug therapy occurred in the prehospital setting and was administered by professional medical staff (i.e., paramedics or emergency physicians).

Furthermore, we evaluated the protocols of the neurological emergency departments where the patients were admitted and treated, which contain detailed information on the duration and type of seizure and drug treatment, including preexisting antiseizure medication. Finally, the subsequent inpatient stay records of the patients were assessed. The semiology and underlying etiology of SE were obtained according to the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE)[3] and the Status Epilepticus Severity Score (STESS).[4]

Finally, we evaluated whether prehospital levetiracetam use had a significant effect on SE parameters. As the primary endpoint, we determined whether levetiracetam application in the prehospital setting improved the preclinical cessation rate of SE. As secondary endpoints, the influences of levetiracetam on the other outcome parameters (need and duration of assisted ventilation, duration of ICU and in-hospital stays, modified Rankin Scale [mRS] score at discharge) were examined.

The data analysis was performed using SPSS for Windows (version 28; IBM Corp., Armonk, NY, USA). The descriptive measures of mean, standard deviation, and minimum and maximum values were calculated. Frequency differences were checked for significance using chi-square tests (and using Fisher's exact test for small groups). Differences between the two groups were tested for significance nonparametrically using the Mann-Whitney U test. A probability value of $p<0.05$ was considered significant.

The local ethics committee of the University of Cologne approved this study (No. 21-1443-retro).

RESULTS

We examined 328 data sets among 145 patients who received initial drug therapy in the prehospital setting by professional

medical staff. Baseline antiseizure medications of all patients are listed in Table 1. Intravenous levetiracetam only was provided to 5 patients, and 11 were treated using propofol infusions. Of these, 10 patients received propofol (dose=130.9±64.1 mg, mean±standard deviation) after prior treatment using midazolam (7.7±2.9 mg). Only 1 patient received propofol as an initial therapy.

Treatments with either BZDs (group A, *n*=92) or a combination of BZDs and levetiracetam (group B, *n*=37) were administered to 129 patients. These patients were further analyzed in detail.

Three different BZD derivatives were administered as monotherapies (Table 2): midazolam (*n*=78), lorazepam (*n*=8), and diazepam (*n*=6), at doses of 6.7±5.8, 2.3±1.4, and 9.2±5.8 mg, respectively. Three BZDs were also used in combination (Table 2), namely midazolam (*n*=31) at a dose of 4.3±2.1 mg and diazepam (*n*=5) at a dose of 9.0±4.2 mg. Clonazepam was also used once at a dose of 1.25 mg. The levetiracetam dose was 1,298±708 mg when combined with midazolam and 2,000±1,225 mg when combined with diazepam. Clonazepam at 1.25 mg was combined with 2,000 mg of levetiracetam (Table 2). Upon on-site arrival, initial treatment was initiated within 15 minutes in nearly 80% of the cases. In the case of levetiracetam as a secondary therapy, administration occurred predominantly within 30 minutes (Table 3).

Table 1. Baseline antiseizure medication administered among all patients (*n*=145)

	n	
Without baseline medication	41	
With monotherapy	63	
With double therapy	31	
With triple therapy	10	
Antiseizure medication	***n***	**Daily dose, mg**
Levetiracetam	59	1,957±933
Lamotrigine	28	254±154
Valproic acid	19	1,307±588
Lacosamide	14	345±105
Carbamazepine	6	200–800
Zonisamide	6	50–200
Oxcarbazepine	5	450–1,800
Perampanel	4	2–6
Brivaracetam	4	50–150
Topiramate	3	100–300
Eslicarbazepine	3	800–1,200
Gabapentin	1	1,800
Pregabalin	1	200
Phenytoin	1	300
Phenobarbital	1	200

Data are mean±standard-deviation (*n*≥10) or range (*n*<10) values.

No differences were found between groups A and B in age, sex, SE type, STESS, or mRS score before SE (Table 4), with a significant difference only found in the EMSE (43±31 vs. 53±29, $p<0.05$).

No significant differences were found between the two groups in the criteria used to assess clinical efficacy. Levetiracetam use therefore did not significantly affect the prehospital SE cessation, days in hospital, hours in ICU, mechanical ventilation, or mRS score at discharge.

Levetiracetam was used as a monotherapy in only five cases. No statistical analysis could be performed because of the small number of cases; instead, the cases are listed individually in Table 5.

DISCUSSION

This examination of a representative area of urban Germany found that levetiracetam was used as a prehospital treatment for SE in a substantial number of cases while providing no additional benefit in controlling SE in the primary care setting described herein. Based on the epidemiological data of

Table 2. Medical treatment of status epilepticus in the prehospital setting

Group A	***n***	**Dose, mg**	
Drug			
Midazolam	78	6.7±5.8	
Lorazepam	8	2.3±1.4	
Diazepam	6	9.2±5.8	
Clonazepam	0	-	
Group B	***n***	**Dose, mg**	
		BZD	**LEV**
Drug			
Midazolam+LEV	31	4.3±2.1	1,298±708
Diazepam+LEV	5	9.0±4.2	2,000±1,225
Clonazepam+LEV	1	1.25	2,000
Lorazepam+LEV	0	-	-

Group A: monotherapy BZDs (*n*=92). Group B: combination therapy of a BZD and LEV (*n*=37).
BZD, benzodiazepine; LEV, levetiracetam.

Table 3. Timing of antiseizure medication in the prehospital setting. On-site arrival of the rescue service was defined as time 0. Beginning of the treatment is indicated

	Group A (*n*)	**Group B (*n*)**	
		BDZ	**LEV**
Time, min			
<15	72	27	2
<30	20	10	22
30–60	0	0	13

BZD, benzodiazepine; LEV, levetiracetam.

an annual incidence rate of 10–20 patients with SE per 100,000 inhabitants in Germany,[1] 200–400 cases were expected in the city of Cologne for the assessed 2-year period. Our evaluation yielded 328 data sets and was thus within the predicted range. We were aware that the investigated population is very heterogeneous, which is known to be a fundamental problem for all studies on SE. This is especially true for initial treatments away from emergency departments and hospitals. However, we believe that the study cohort was representative since it included all patients with SE in the urban area of Cologne over 2 years. Baseline antiseizure medications of all patients are listed in Table 1 and represent the drugs used in Germany, with levetiracetam and lamotrigine as the first choice for monotherapy. Since levetiracetam and lacosamide are frequently used in combination therapy, they appeared more frequently in the current overview.

Before starting our study, intravenous levetiracetam administration had already been introduced as an emergency therapy of SE in emergency ambulances within the city of Cologne since 2018. We thus examined whether levetiracetam administration had become established in initial prehospital therapy for SE. Of the 145 patients who received prehospital initial drug treatment, levetiracetam was used in 42 patients (29%), mostly in combination with a BZD (n=37, 25%). The first result of our study was that levetiracetam use occurred regularly but was not part of the standard initial therapy. Nevertheless, the use of BZDs was the unchallenged standard for prehospital therapy, and our study found that midazolam was by far the most commonly used BZD in the prehospital setting (Table 2), at a rate of 85%. Only intravenous BZDs were used and intranasal or intramuscular application of BZDs did not play any role. This is probably because only patients older than 18 years were examined in this retrospective study.

Levetiracetam was used as monotherapy in only five cases (Table 5), and so no statistical analysis could be performed; instead, the cases are listed individually. All five cases had focal SE with impaired consciousness, which led to the assumption that the type of SE impacted the decision about the prehospital medication selected as the initial therapy. One explanation for this finding might be that in SE with impaired consciousness, the use of additional medication that could potentially further impair consciousness was intentionally omitted.[5] Further, if levetiracetam was already present in the medication history of the patient, its subsequent use might have

Table 4. Characteristics of patients, course of inpatient treatment, and outcomes

	Group A	Group B	*p*
Age, years	58±18	63±17	n.s.
Sex, female/male	47/45	18/19	n.s.
Generalized convulsive SE	52	18	n.s.
Focal SE with impaired consciousness	21	13	n.s.
Focal SE without impaired consciousness	19	6	n.s.
Prehospital SE control	31 (33.7)	12 (32.4)	n.s.
<30 minutes	24	9	
<60 minutes	7	3	
mRS score before SE	2.43±1.99	2.84±1.89	n.s.
mRS score at discharge	2.64±2.09	3.19±1.91	n.s.
STESS	2.45±1.46	2.73±1.41	n.s.
EMSE	43±31	53±29	<0.05
Hospital stay, days	6.1±8.7	8.1±10.9	n.s.
ICU stay, h	61.3±136.7	88.9±194.8	n.s.
Mechanical ventilation	11	7	n.s.
Mechanical ventilation duration, h	9.1	10.1	n.s.
Death	5	2	n.s.

Data are mean±standard-deviation or *n* (%) or *n* values.
EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; ICU, intensive care unit; mRS, modified Rankin Scale; n.s., not significant; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

Table 6. Benzodiazepine therapy relative to the reference dose of 10 mg of diazepam (equivalent doses: 7.5 mg of midazolam, 2 mg of lorazepam, and 2 mg of clonazepam[10])

	Group A	Group B
Diazepam, mg		
0–10	73	33
11–20	15	3
21–30	2	1
31–40	2	-
>30	-	0
>40	0	-

Table 5. Prehospital treatment of SE: LEV monotherapy

Case	Age, years	Sex	SE	LEV dose, mg	Preexisting LEV therapy
1	40	Female	Focal, impaired consciousness	2,000	Yes
2	72	Male	Focal, impaired consciousness	2,000	No
3	62	Male	Focal, impaired consciousness	1,500	Yes
4	87	Male	Focal, impaired consciousness	500	Yes
5	74	Male	Focal, impaired consciousness	3,000	No

LEV, levetiracetam; SE, status epilepticus.

been more likely. Since nonadherence to the prior medication constitutes a significant risk factor for SE, supplementing levetiracetam in the prehospital phase would be a plausible strategy.

No substance has been successfully established alongside BZDs as the initial treatment option for SE. A multicenter, double-blind, randomized study tested the additive effect of levetiracetam in combination with clonazepam as a baseline therapy, but an interim evaluation indicated no additive effect, and so the study was discontinued.[6] The question of whether there is therapeutic relevance in levetiracetam adjunctive to a BZD as the initial treatment for SE has therefore not yet been definitively answered. This topic has become even more critical since the use of levetiracetam has become established in SE treatment. A recent review article by Webb et al.[7] concluded that the available evidence suggests that levetiracetam is as effective as valproic acid or phenytoin for terminating SE in adults. Moreover, in a nationwide questionnaire among neurointensive care departments in Germany about treatment preferences in SE, levetiracetam was named as the first-line antiseizure medication after BZD by 91% of the responding physicians despite the lack of authorization for its use in that condition.[8] Levetiracetam has three significant advantages: 1) it is easy to store and administer, 2) it can be rapidly administered intravenously at high doses, and 3) it has no unmanageable adverse effects in the prehospital setting.[9]

We evaluated 42 cases in which levetiracetam was applied in the prehospital setting: the 5 cases in which levetiracetam was administered as a monotherapy are discussed above, while it was administered alongside BZDs in the other 37 patients (Table 2). Among them, midazolam combined with levetiracetam was most frequently used (n=31, 84%), followed by diazepam plus levetiracetam (n=5, 13%). Only one patient received clonazepam and levetiracetam. While lorazepam was administered several times as a monotherapy in the prehospital setting, it was not used in combination with levetiracetam. On the other hand, clonazepam was not administered as a monotherapy, while in one case it was combined with levetiracetam.

One limitation of our study was that the prehospital care protocols were not sufficiently detailed to allow determination of the milligrams of medication administered per minute. It was possible to divide the time sequences into sections and to summarize them. Time 0 was chosen as when the ambulance service arrived on the scene, and time windows for drug treatment were defined as <15, <30, and 30−60 minutes, which reflected the on-site situation well. Comparison of treatment timings did not reveal any abnormalities (Table 3). Initial treatment with BZDs was generally successful within 15 minutes, and levetiracetam was predominantly administered as a secondary therapy within 30 minutes. These findings were consistent with the standard treatment recommendations. We concluded that levetiracetam was mostly given as a secondary therapy because the SE had not yet ceased.

We next evaluated whether levetiracetam use was correlated with fewer BZDs being administered overall by observing the equivalent doses in combination therapies (Table 6). Treatment with a diazepam-equivalent dose of 0−10 mg was provided to 33 of 37 cases, and only 4 received higher doses (3 at 11−20 mg and 1 at 21−30 mg). This finding most likely reflects that levetiracetam might have replaced a second BZD bolus. The application of levetiracetam tended to result in a slightly lower dose of BZDs. On the other hand, the application of BZDs did not lead to a higher rate of intensive-care treatment or prolonged ventilation, which contrasts with the findings of Spatola et al.[5] However, this did not impact the clinical outcome parameters.

Of particular importance is that the rate of prehospital SE control appears low for both groups. Looking at the clinical patient data and treatment timing, this cannot be adequately explained, and thus medication doses are a major issue. Our data indicate that a low initial dose of BZD administration tended to be chosen in both groups, which may have crucially influenced the rate of prehospital SE control but might have also been responsible for secondary therapy with levetiracetam being less effective. Last but not least, the therapeutic levetiracetam dose plays an important role, and again our data indicate that increasing this could be effective.

In summary, we found that levetiracetam was quite regularly administered as an initial prehospital treatment and that its use is possible and feasible without great effort. Nonetheless, a significant positive outcome effect of levetiracetam use was not detected when it was combined with BZDs compared with applying BZD as a monotherapy. Based on our data, levetiracetam use in prehospital SE therapy warrants critical evaluation, in which the therapy regime described here appears to require improvement due to the tendency of selecting low doses. Notwithstanding this, the combined application of a BZD and levetiracetam −each at a high dose and right at the start of SE treatment (i.e., hit early and hard)− could have a positive effect on early prehospital SE therapy. Our data have therefore provided the first important perspective for improving prehospital SE treatment, since the logistical requirements for such combination therapy are readily available. Future studies of this strategy are warranted.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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