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Sustained Effort Network for treatment of Status Epilepticus (SENSE) – A multicenter prospective observational registry

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ABSTRACT

Status epilepticus (SE) is an important neurological emergency lacking adequate evidence for efficacy and safety of treatment beyond the application of benzodiazepines as first treatment step.
To bridge the gap between the few pivotal trials and retrospective uncontrolled case series, we established a prospective multicenter registry recruiting patients in experienced centers in German-speaking countries. We could document 1179 episodes of 1049 patients over a period of 5 years. First data analysis showed that in the majority of the episodes, established treatment guidelines were not followed. Latency between status onset and different treatment steps were longer, and bolus doses lower than recommended. Moreover, a relevant proportion of the patients did not receive a benzodiazepine but levetiracetam as first treatment step. Although SE could be controlled in more than 90% of the episodes, lower bolus dose and longer treatment latency were associated with refractoriness of the SE in multivariate analysis.
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Although status epilepticus (SE) is a frequent neurological emergency, evidence regarding treatment strategies from large controlled trials that fulfill the criteria of Class-1 evidence is scarce. Two large trials have assessed the efficacy and safety of benzodiazepines in a prehospital setting [1,2]; one large trial compares different substances in established SE in an inpatient setting [3]; and a fourth trial investigates the additional effect of immediate administration of levetiracetam after clonazepam in a prehospital setting [4]. All studies were restricted to generalized convulsive SE (GCSE) forms. Further evidence can be obtained from several smaller controlled and uncontrolled studies, but owing to the small patient numbers and other methodical problems, validity, reliability, and generalizability of their results is limited.

Several major obstacles have impeded the initiation of further large controlled trials in the setting of established, refractory, or super-refractory SE, among them the lack of evidence for equipoise for different treatment options, the problem to obtain informed consent in sedated or comatose patients, and the tremendous effort necessary to organize and coordinate a multicenter, transnational controlled study for an emergency situation such as SE [5].

To bridge the gap between small series and the necessary large randomized trial, an informal working group of experts in SE from German-speaking countries (Germany, Austria, Switzerland) developed a prospective multicenter registry for patients treated for SE with the

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acronym SENSE (for Sustained Effort Network for treatment of Status Epilepticus).

Its methods and design have been published elsewhere [5]. In brief, eight high-volume centers with special expertise in SE treatment in German-speaking countries participated and recruited patients: Germany: Epilepsy Center University Marburg, University Hospital Schleswig-Holstein Campus Kiel, Klinikum Osnabrück, Krankenhaus Barmherzige Brüder Regensburg; Austria: Christian-Doppler-Klinik, Universitätsklinikum der Paracelsus Medizinischen Universität Salzburg, Department of Neurology, Innsbruck Medical University; and Switzerland: University Hospital Basel, University Hospital Lausanne. The study was approved by the appropriate local ethics committees and registered at the German Clinical Trials Register (DRKS00000725).

Status epilepticus was defined as seizure duration of 5 min or longer, or consecutive seizures without returning to baseline for more than 5 min, or in comatose patients who fulfilled the electroencephalogram (EEG) criteria for nonconvulsive SE as defined by Beniczky et al. [6]. Patients with status-like phenomena owing to hypoxic brain injury and patients under the age of 16 years were excluded. We prospectively documented the following variables: demographics, health-related parameters, including SE etiology and comorbidities unrelated to it, SE onset, SE semiology, treatment, and outcome. The modified Rankin scale (mRS) [7,8] was used for global assessment of health before SE onset and at hospital discharge, and the Status epilepticus severity score (STESS) was applied.

1. Results

Between January 2011 and June 2015, 1049 patients with 1179 episodes of SE were enrolled.

As of yet, parts of the results have been published in two manuscripts in peer-reviewed journals [9,10].

The first manuscript [9] gives an overview of the characteristics of the whole cohort of patients, using only the first episode of each patient for analysis. Most patients are elderly (median age: 70 years), approximately half of them are women. Forty-four percent of the patients have generalized convulsive semiology during the course of the SE, 27% have focal motor semiology. Acute etiologies are found in 41% of the patients, progressive etiologies in 15%. Status epilepticus treatment started within 30 min in 32% of the patients and consisted in one or several benzodiazepines in the majority of patients. However, 15% of the patient received levetiracetam as first drug. Success rate of the first treatment step was overall low (15%). Correspondingly, the bolus dose used was significantly lower than recommended in more than 75% of the patients. The second and all other treatment steps were successful in approximately 40%, irregardless of the substances used.

Finally, SE could be controlled in 93% of the patients. Fifteen percent of the patients died during the hospital stay.

The second manuscript [10] focusses on prognostic factors for the cessation of the SE before becoming refractory. When analyzing the dataset, it became clear that the criteria for refractory SE, i.e., ongoing SE after an adequate dose of a benzodiazepine followed by an adequate dose of another intravenous anticonvulsant, are difficult to apply outside controlled studies. In clinical practice, SE treatment frequently does not follow guidelines, but consists of the administration of multiple relatively low doses of one or more anticonvulsants [11,12]. Frequently, two or more agents are administered at the same time, or after a very brief interval. This results in underestimation of the effect of the later substance, and conversely in overestimation of the effect of the earlier substance. Therefore, we defined refractoriness as ongoing SE 60 min after treatment onset for GCSE, and as ongoing SE 12 h after treatment for non-GCSE.

Patients with GCSE were treated earlier and more aggressive than patients without GCSE, as expected, and received the first treatment in the prehospital setting significantly more frequent.

Factors contributing to early cessation of the SE are summarized in Table 1.

Multivariate analysis using Cox regression demonstrated that in patients with GCSE, younger age, lower mRS before SE onset, lower STESS, the application of a benzodiazepine as initial drug, a higher cumulative dose of anticonvulsant agents given within the first 30 min of treatment, and shorter latency from SE onset to treatment initiation independently predicted a shorter time to cessation of SE within the first hour of treatment. In patients without GCSE, significant factors associated with a shorter time to SE cessation within the first 12 h were lower STESS, lower number of comorbidities, use of a benzodiazepine as first drug, and higher cumulative standardized drug dose within the first 60 min.

2. Discussion and conclusion

First analysis of data from the SENSE registry shows that in clinical practice, most patients are initially treated with benzodiazepines as recommended, but a substantial portion receives levetiracetam or other agents as first treatment step. This is associated with a higher risk of refractoriness in both patients with and without GCSE. In addition, many patients receive bolus doses significantly lower than recommended. Lorazepam and midazolam tend to be significantly underdosed, in contrast to diazepam and clonazepam. Even levetiracetam and valproate are frequently underdosed, in spite of the evidence that rapid application of high doses of these drugs is not associated with respiratory or cardiovascular problems [13,14]. However, the total amount of drug applied within the first treatment phase is strongly correlated with treatment success.

Table 1
Prognostic factors for noncessation of SE in patients with GCSE and patients without GCSE.

		Patients with GCSE, cessation < 60 min (n = 138)	Patients with GCSE, noncessation < 60 min (n = 319)	Patients without GCSE, cessation < 12 h (n = 250)	Patients without GCSE, noncessation < 12 h (n = 342)
Country	D/A/CH	57/32/49	142/66/111	80/70/100	278/116/198
Age	Median	**58 years**	**67 years****	68.5 (20–100)	74 (18–94)
Gender	Male/female	85/53	169/150	133/117	201/141
mRS >2		**70**	**115***	125	142
Comorbidity	Number of diagnoses	2	2	**2**	**3****
Etiology	Acute or acute on remote	58	145	98	129
Latency SE onset to treatment	Minutes (median/IQR)	**20 (15–60)**	**25 (20–120)*****	120 (30–127)	180 (60–420)
Cumulative standardized bolus dose[a] <30 min	Median/IQR	**86.5 (41.7–133.3) n = 133**	**54.5 (31.3–97.8)***** **n = 308**	**62.9 (30.8–104.1) n = 245**	**41.7 (27.7–67)***** **n = 326**
BZD as first step	Yes/no	**134**	**278****	**214**	**223*****

SE = status epilepticus; GCSE = generalized convulsive SE; D = Germany; A = Austria; CH = Switzerland; mRS = modified Rankin scale; BZD = benzodiazepine; IQR = 25/75 interquartile range; results in bold print were significant in multivariate analysis using Cox regression, backward stepwise analysis, p = 0.1 for inclusion and exclusion.
* = p < 0.05; ** = p < 0.01; *** = p < 0.001
[a] Actual bolus dose/recommended bolus dose * 100.

Further analysis of our database will include the subgroup of refractory and super-refractory patients. In addition, SE semiology and its prognostic value for treatment success could be analyzed in more detail. Data from Salzburg suggest that SE semiology may have significant impact on treatment prognosis [15]. Moreover, the use of single substances such as lacosamide, or the use of enterally applied drugs such as topiramate could be analyzed regarding effect and tolerance.

The database has several limitations, such as different recruitment rates in individual centers, lack of independent monitoring, underascertainment of adverse events, lack of randomization, or fixed treatment protocols. However, its standardized documentation of more than 1000 patients with SE may help to detect differences between the world of guidelines and everyday practice, and can be an important tool for generating hypotheses for randomized controlled trials.

Declaration of competing interest

CK received speaker honoraria from UCB Pharma nd Eisai. He served on advisory boards for Eisai and UCB Pharma.

ET has acted as a paid consultant to Eisai, Bial, GW Pharma, and UCB Pharma and has received speaker honoraria from Bial, Eisai, GW Pharma, Newbridge, Viropharma, and UCB Pharma in the past three years. He has received research funding from UCB Pharma and Eisai.

FR received personal fees from Eisai, UCB Pharma, Desitin, Hexal, Novartis, GW-Pharma, Shire, as well as research grants from UCB Pharma.

IU received speaker honoraria from UCB Pharma and Eisai. She served on advisory boards for UCB Pharma and Eisai.

NL received a research grant from UCB Pharma, travel grants from UCB Pharma and Eisai, speaker honoraria from UCB Pharma, Eisai, Desitin and Janssen-Cilag and has served as a paid consultant for UCB Pharma and Eisai.

SR received unconditional research grants from UCB, honoraria from serving on the scientific advisory boards of Desitin, Eisai, and UCB, travel grants from Janssen-Cilag, and UCB, speaker fees from UCB, and from serving as a consultant for Eisai, Janssen-Cilag, and UCB.

AS reports personal fees and grants from Desitin, Eisai, and UCB Pharma.

CT received honoraria from Eisai, Desitin and UCB Pharma. He served on the scientific advisory boards of Eisai.

TWM received financial support from Desitin for visiting scientific meetings and received honoraria for speaking engagements from Eisai and Desitin.

AOR and ZU have nothing to disclose.

References

[1] Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345(9):631–7.
[2] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366(7):591–600.
[3] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339(12):792–8.
[4] Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol. 2016;15(1):47–55.
[5] Kellinghaus C, Lang N, Rossetti AO, Ruegg S, Tilz C, Trinka E, et al. Making SENSE–Sustained Effort Network for treatment of Status Epilepticus as a multicenter prospective registry. BMC Neurol. 2015;15:230.
[6] Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013;54 (Suppl. 6):28–9.
[7] Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2(5):200–15.
[8] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604–7.
[9] Kellinghaus C, Rossetti AO, Trinka E, Lang N, Unterberger I, Ruegg S, et al. SENSE registry for status epilepticus. Epilepsia. 2018;59 Suppl 2:150–4.
[10] Kellinghaus C, Rossetti AO, Trinka E, Lang N, May TW, Unterberger I, et al. Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). Ann Neurol. 2019;85(3):421–32.
[11] Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia. 2015;56(8):1275–85.
[12] Rossetti AO, Alvarez V, Januel JM, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol. 2013; 260(2):421–8.
[13] Limdi NA, Knowlton RK, Cofield SS, Ver Hoef LW, Paige AL, Dutta S, et al. Safety of rapid intravenous loading of valproate. Epilepsia. 2007;48(3): 478–83.
[14] Wheless JW, Clarke D, Hovinga CA, Ellis M, Durmeier M, McGregor A, et al. Rapid infusion of a loading dose of intravenous levetiracetam with minimal dilution: a safety study. J Child Neurol. 2009;24(8):946–51.
[15] Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea C, Rohracher A, et al. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia. 2019;60(1):53–62.