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Practice variability and efficacy of Clonazepam, Lorazepam and Midazolam in Status Epilepticus: A Multicenter Comparison

Running title: CLZ, LZP and MDZ in status epilepticus

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Portrait description:

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Abstract:

Objective: Benzodiazepines (BZD) are recommended as first line treatment for status epilepticus (SE) with lorazepam (LZP) and midazolam (MDZ) being the most widely used drugs and part of current treatment guidelines. Clonazepam (CLZ) is also utilized in many countries; however, there is no systematic comparison of these agents for treatment of SE to date.

Methods: We identified all patients treated with CLZ, LZP or MDZ as a first line agent from a prospectively collected observational cohort of adult patients treated for SE in four tertiary care centers. Relative efficacies of CLZ, LZP, and MDZ were compared by assessing the risk of developing refractory SE and the number of anti-seizure drugs (ASDs) required to control SE.

Results: Among 177 patients, 72 patients (40.62%) received CLZ, 82 patients (46.33%) LZP and 23 (12.99%) MDZ; groups were similar in demographics and SE characteristics. Loading dose was considered insufficient in the majority of cases for LZP, with a similar rate (84%, 95% and 87.5%) in the centers involved and CLZ was used as recommended in 52% of patients. After adjustment for relevant variables, LZP was associated with an increased risk of refractoriness as compared to CLZ (OR: 6.4, 95%, CI: 2.66 – 15.5) and with an increased number of ASDs needed for SE control (OR: 4.35, 95%, CI: 1.8 - 10.49).

Significance: CLZ seems to be an effective alternative to LZP and MDZ. LZP is frequently under-dosed in this setting. These findings are highly relevant, since they may impact daily practice.

Introduction:

Status epilepticus (SE) is one of the most frequent and serious neurological emergencies associated with a mortality between 7 - 33%[1,2,3,4]. Rapid and effective treatments are needed. According to current guidelines[5,6], benzodiazepines (BZD) represent the first line of treatment because of class I evidence regarding their efficacy in this setting. Intravenous (iv) lorazepam (LZP) and midazolam (MDZ) are the most widely used[7], likely due to randomized studies showing their efficacy[8,9,10] in this setting. MDZ was recently identified as the best option for out-of-hospital convulsive SE[10]. However, in many countries worldwide, mostly in Europe, such as the Czech Republic, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland, the United Kingdom, Korea, South Africa, and Turkey (iv) clonazepam (CLZ) is also registered and used widely for SE treatment[11], despite the relatively limited evidence supporting its use. In addition in some countries there has been a lack of availability of LZP intravenous formulation, leading to the use of alternative compounds.

As LZP and MDZ, CLZ has a high affinity for the $GABA_A$ receptor[12]. LZP and CLZ are both highly lipophilic, allowing rapid onset of effects in the brain[13]. In addition, CLZ has a much longer elimination half-life (between 19 and 60 hours) than LZP (7 to 26 hours) or MDZ (1 to 4 hours)[12,14]. Neither LZP, nor CLZ have any active metabolite, whereas the MDZ metabolite 1-hydroxymidazolam displays an equal activity like midazolam whereby the glucuronidated 1-OH-midazolam can critically (up to 5-10 times) prolong the sedative action in case of renal insufficiency [15].

Despite its favorable pharmacologic profile, CLZ has not been specifically assessed in SE trials, and there are no available observational studies comparing these three medications to support the current widespread use of CLZ outside North America. In order to evaluate the efficacy of intravenous CLZ as a first line drug in SE treatment compared to intravenous LZP and MDZ, we analyzed a multicenter prospective cohort of patients with SE.

Methods:

- **Primary research question:**

The primary research question is to compare practice variability in the use of BZDs and efficacy of CLZ, LZP and MDZ as a first line agent in SE management.

- **Cohort and SE definition:**

Clinical data were prospectively collected in an observational cohort of consecutive adult patients (>16 years) with SE of all etiologies (except post-anoxic SE) admitted to four university tertiary care centers, from February 1st 2013 at the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; from June 1st 2013 at the Brigham and Women's Hospital and the Massachusetts General Hospital, Boston, USA; and from November 1st 2013 at the Beth Israel Deaconess Medical Center, Boston, USA, all through March 31, 2014. Because all patients with suspected SE at each institution have electroencephalograms (EEGs) within 24 hours, subjects were screened through daily review of all EEGs ordered during that period. VA (for the centers in Boston) and AOR (at the CHUV) checked inclusion criteria for each subject and collected the data prospectively and on a daily basis. Both authors have a longstanding collaboration in SE registry[16,17,18], helping to assure uniformity in data collection. SE was defined as the occurrence of an ongoing epileptic seizure or repeated epileptic seizures, without full recovery between seizures for more than 5 min[5]. EEG diagnosis was required for non-convulsive SE in accordance to recently published criteria[19].

We identified every patient for whom iv CLZ, LZP or MDZ was administered as first line treatment. Intravenous CLZ is approved in Switzerland for the treatment of SE and is the drug of choice used in the CHUV. LZP is the first line drug most commonly used in the three hospitals in Boston, and is also available in Switzerland. MDZ is an alternative drug used in all centers.

- **Local treatment protocols/recommendations:**

  The four involved centers have anti-seizure treatment protocols/recommendations based on current guidelines and recommendations [5, 20] including:

  - An emergent initial therapy of a benzodiazepine (or 1st line):

    - For the CHUV: CLZ 0.015 mg/kg or MDZ 0.15 mg/kg or LZP 0,1 mg/kg, with CLZ being preferred

    - Fort the Boston centers: LZP 0.1 mg/kg or diazepam (DZP) 0.25 mg/kg or MDZ 0.15 mg/kg, with LZP being preferred

  - An urgent seizure control therapy (or 2nd line):

    - In the four centers: phenytoin (PTH)/fosphenytoin (fPTH) 20 mg/kg or valproic acid (VPA) 20-30 mg/kg or levetiracetam (LEV) 20-30 mg/kg (or phenobarbital 10-20 mg/kg at 50-100mg/min for US centers only)

  - Refractory SE management (> 30 minutes) (or 3rd line):

    - In case of convulsive SE: Coma induction with MDZ and/or propofol or barbiturates

    - In case of focal SE without severe consciousness impairment: addition of non-sedative anti-seizures drugs: PTH/fPTH 20 mg/kg OR VPA 20-30 mg/kg OR LEV 20-30 mg/kg OR lacosamide (LCM) 200-400mg.

- **Definition of variables**

  Demographics recorded included age and gender. Worst seizure type was categorized as focal seizure with consciousness impairment, focal seizure without consciousness impairment, generalized convulsive seizures, absence seizures, myoclonic seizure[21] and non-convulsive SE in coma (NCSEC). Level of

consciousness before treatment was defined as followed: alert, confused, somnolent (arousable with clear contact), stuporous (arousable without contact) and comatose[22]. The STatus Epilepticus Severity Score (STESS) was calculated for every patient using age (< 65 years = 0 pt; ≥ 65 years = 2 pts), seizure type (simple-partial, complex-partial, absence and myoclonic in the context of idiopathic/genetic epilepsy = 0 pt; generalized-convulsive = 1 pt; non-convulsive SE in coma = 2 pts), level of consciousness (alert, somnolent or confused = 0 pt; stuporous or comatose = 1 pt), and history of previous seizures (yes = 0 pt; no = 1 pt), with a total score between 0 and 6 points[23]. The beginning of the SE was determined as precisely as possible using pre-hospital chart and emergency department summary. The last observed time of good health was considered as the beginning of the SE for episodes without clear onsets (unwitnessed, subtle non-convulsive SE). Each treatment line, including out of hospital medication was prospectively recorded using pre-medical, emergency and in-hospital patient records, including the drug used, total loading dose (repeated doses given before the introduction of the next line of treatment was considered as a total loading dose), maintenance dose (highest prescribed dose) and timing of administration.

A sufficient loading dose for the first line treatment was defined by at least 0.1 mg/kg of LZP, 0.015 mg/kg of CLZ and 0.15 mg/kg of MDZ, in accordance with the currently recommended dosages[5,24]. Second-line treatment was considered adequate if the patient received a loading dose of PHT/fPHT (at least 20 mg/kg), VPA (at least 20 mg/kg), LEV (at least 20 mg/kg), or LCM (at least 200 mg)[5]. For both first and second line agent dosages, a 25% range of deviance from current guidelines was tolerated, as previously described[18].

The end of SE episode was defined by the last observed seizure (clinical and/or electrographic) without recurrence for at least 48 hours off sedation. SE duration was defined as the time between the beginning of SE and the end of SE. Etiology was categorized as potentially fatal if not treated, or not, as previously described[22,25].

Clinical outcome at hospital discharge was categorized as return to pre-morbid clinical state, new morbidity, and death. Length of hospital stay in survivors was also recorded.

- **Primary and secondary outcomes**

  Primary outcomes for first line agent comparisons included: (1) the risk of developing refractory SE, defined as failure to respond to an initial benzodiazepine dose followed by a second recommended ASD (in other words, need for additional treatment after the first and second line treatments in order to control seizures), and (2) the number of ASDs needed to control the SE, categorized into three groups: 1 or 2 ASDs, 3 or 4 ASDs, and 5 or more ASDs. These outcomes were chosen because they are objective, and the success of first line benzodiazepine is difficult to assess in an observational study due to the common practice of rapid administration of an additional non-sedating ASD. Mortality was assessed as a secondary outcome.

- **Standard Protocol Approvals:**

  The Institutional Review Boards of each center approved this study. As this observational study involved no risk for patients and focused on acute phase of critically ill patients, consent was waived.

- **Statistical analysis**

  Data were analyzed using Stata 13.1 (StataCorp, College Station, Texas, USA). CLZ, LZP and MDZ groups were compared using χ^2, Fisher's exact, ANOVA and Kruskal-Wallis tests, as required.

  Univariate analyses including first line medication and clinically relevant variables for prognosis (sufficient loading dose of first line agent, time to treatment (min), adequate second line treatment, STESS, and potentially fatal etiology) were conducted to assess effects on primary and secondary outcomes. Variables with a p value < 0.2 were entered into stepwise logistic or ordered logistic models. Patients without a second line treatment were excluded from the refractory SE assessment, because

this outcome was not reached in this subgroup. Results were considered statistically significant with p < 0.05.

Results:

Among 238 patients included in the study period, 177 (74.46 %) received iv LZP, MDZ or CLZ as a first line drug therapy; groups characteristics are detailed in **Table 1**. CLZ was used in 72 patients (40.62%), LZP in 82 patients (46.33%) and MDZ in 23 (12.99%). In the 61 other subjects, first line drugs included LEV in 33 (54.1%), PHT/fPHT in five (8.2%), propofol in five (8.2%), DZP in four (6.6%), clobazam in two (3.3%), VPA in two (3.3%), LCM in two (3.3%), and one each (1.3%) carbamazepine and phenobarbital. In six patients, SE ceased spontaneously prior to any treatment.

Median age, gender, SE severity evaluated with the STESS, and prevalence of a potentially fatal etiology were similar across the three groups. More than half of the episodes were generalized convulsive in all groups, with a trend towards higher incidence in the MDZ group. **Suppl. Table 1** (see in supplementary material) provides a list of the underlying etiologies of SE. The median time to treatment was similar, but the first line treatment loading dose was considered sufficient significantly more often in the CLZ group than in the LZP and MDZ groups (p<0.001). Significantly more SE became refractory in the LZP group (p<0.001). The rate of the adequacy of the second line treatment was also lower in the LZP and MDZ groups (p<0.001). While about 15% of patients needed to be treated with coma induction (without significant differences across groups), a greater number of ASDs was needed to control the SE in the LZP group (p < 0.001). Median duration of SE was significantly longer in the LZP group (p = 0.003). Length of hospital stay and mortality rates was similar among the three groups.

Demographics, STESS, worse seizure type and time to treatment among the four different centers are displayed in **Table 2**. Except for age, with patients being somewhat younger at the BWH, patient and SE characteristics and also time to treatment were similar.

Table 3 displays practice variability regarding initial dosage and relation between dosage adequacy and the three outcomes of interest. It shows that under-dosing is observed in the vast majority of cases over the three different sites using LZP, with a similar rate (84%, 95% and 87.5%). While status severity (using the STESS) seems similar overall, under-dosed patients were significantly older in the LZP group (p=0.04). In the outcome analysis, only the rate of refractory SE was significantly different in the LZP group with 60% of refractory SE in the group of patients receiving a recommended dosage and 86.11% in the under-treated patients.

Details regarding the relationship between selected variables and the refractoriness of the SE are shown in **Table 4**. After adjustment for the loading dose, LZP, as compared to CLZ, remained associated with a higher risk of refractoriness (OR: 6.4, 95% CI: 2.66 – 15.5, p<0.001), while there was no difference between CLZ and MDZ. The same results were obtained when analyzing convulsive SE only; LZP, as compared to CLZ, remained associated with a higher risk of refractoriness (OR: 13, 95% CI: 2.65 – 63.62, p=0.002), while there was no difference between CLZ and MDZ. **Table 5** shows patients stratified regarding the number of ASDs needed to control their SE. After adjustment for the loading dose and second line treatment adequacy, LZP was associated with a higher number of ASDs required to control SE as compared to CLZ (OR: 4.35, 95% CI: 1.8 - 10.49, p=0.001), while again there was no difference between CLZ and MDZ. After adjustment for first line treatment (drug choice and loading dose), an adequate dose of second line treatment was associated with a lower number of ASDs (OR: 0.47, 95% CI: 0.23 - 0.88, p=0.02). The same results were obtained when analyzing convulsive SE only; LZP was associated with a higher number of ASDs required to control convulsive SE as compared to CLZ (OR: 5.1, 95% CI: 1.47 – 17.6, p=0.01), without any difference between CLZ and MDZ. An adequate dose of second line

treatment was associated with a lower number of ASDs (OR: 0.21, 95% CI: 0.08 - 0.57, p=0.002) also for the convulsive form only. **Table 6** shows that first and second line treatments do not significantly influence mortality, as opposed to etiology and the STESS. Focusing on convulsive SE only, etiology was the only significant predictor of mortality.

Discussion:

While there is robust class I evidence for the use of LZP and MDZ as first line agents in SE treatment[8,9,10,26] this study provides class III evidence that CLZ is also effective. After correction for several major outcome predictors, LZP was associated with a higher risk of refractoriness and a greater number of ASDs to control SE as compared to the CLZ, while the efficacy of CLZ and MDZ seem comparable. Of note, these findings represent an analysis of all types of SE; subgroup analysis of generalized convulsive form only was similar.

These findings have significant implications for clinical practice. Currently, CLZ is absent from the current American[5] and European[6] SE treatment guidelines, although it is available and used widely in many countries worldwide in its intravenous form, even while data regarding its efficacy are sparse. An older study performed in 61 institutionalized patients with refractory epilepsy presenting repeated episodes of SE showed that LZP (4 to 10 mg iv) and CLZ (1 mg iv) were comparable to control SE; LZP was more effective in treating EEG abnormalities, but CLZ was associated with better clinical responses[27]. An analysis on 17 children found that 0.25mg – 0.75mg of iv CLZ was safe and effective in treating SE[28]. More recently, a single-center retrospective assessment of 167 SE episodes found that CLZ was the most effective first line therapy, with a success rate of 50%, as compared to 29% for LZP or 18% for diazepam[29]. The favorable pharmacological profile of CLZ, including its high lipophily and $GABA_a$ affinity, and its long half-life[13,14] may account for its efficacy. It may provide a longer duration of seizure control between the CLZ and the second line drug by means of a synergistic effect on seizure cessation, and avoid seizure recurrence in the acute

setting. In this study, the LZP loading dose was found to be insufficient in more patients than those receiving other BZDs, but we adjusted for this finding in the statistical analysis. Drugs administration rates may explain in part these differences between LZP and the two others agents. CLZ and MDZ are given as rapid iv bolus (< 30 seconds) whereas LZP is administered at a slower rate (2 mg/min)[5]. Also, CLZ enters the brain more rapidly after iv administration than LZP (10 second – 1 minute vs. 2 - 3 minutes)[30]. The rapid action of CLZ was demonstrated in another uncontrolled study, with a mean time of 1.75 min between bolus injection of 1-2 mg CLZ and seizure control, without any major side effects[31]. While LZP has to be stored at 4-8°C, CLZ may be kept at ambient temperature. This represents a practical advantage.

Despite the differences in intermediate outcomes (refractoriness, and number of ASDs required to control the SE), the choice of first line BZD treatment did not influence mortality. Etiology and SE characteristics (reflected by the STESS) have major prognostic impacts, as previously described[22,32,33,34,35]. Similar findings were found previously when comparing differences in second-line ASDs[16], likely reflecting the major influence of etiology and SE characteristics, compared to the relatively limited effect of the individual anti-seizure drugs on mortality[18]. Nevertheless, a faster resolution of SE is associated with a shorter hospital stay[7], and differences in SE refractoriness or in the number of ASDs needed to stop SE may have consequences for complications, resource utilization, and cost.

Another important finding is that current treatment guidelines are relatively poorly followed. Only three quarters of the patients received one of the locally recommended BZD as first line therapy. While a small minority (6 patients) not treated according to protocol received an alternative BZD, most of them were managed with an agent usually recommended as a second line. Similar results were found in a SE management survey performed in 15 US hospitals[7] with 74.7% of patient receiving a BZD as the first treatment. Moreover, the dose of the first line drug was determined to be sufficient in only 41% of cases in our cohort similar to previous findings. One study in France found a 62% rate of non-adherence to the local

protocol for first line treatment[36]. In 75.8% of patients in an American cohort, the dose of the first ASD administered was less than recommended[37]. In another study, only 20% of SE treatments were considered adequate in a tertiary care setting and in 52% in a rural area in Italy[4]. The non-adherence to treatment protocols already observed in several countries may also explain the relative high rate of initial treatment failure as opposed to randomized trials. Effort in education of SE management and treatment protocols seems thus necessary.

The apparent under-dosage of LZP as first line treatment for SE was particularly marked in our study with a constant rate among the different involved centers. The exact protocol-mandated doses might explain much of this difference: while a CLZ dose of 0.015 mg/kg may appear more difficult to calculate than the 0.1 mg/kg required for LZP, the usually prescribed 1-1.5 mg of CLZ is equal to the required dose for an adult of average weight (65-100 kg). On the other hand, the equivalent dose of 6.5-10 mg of LZP is hardly ever achieved. Indeed, by most protocols, LZP is given in a slow infusion, up to 4 mg per dose, repeated as needed[5]. In our cohort, administrations of 4 mg were infrequently used and rarely repeated. Our findings suggest that this issue appears more marked for older patients. These considerations are important given that adequate first line treatment is strongly associated with interruption of SE[5,36].

The strengths of this study include the large number of patients and their prospectively collected data in US and European centers with large experience in SE management. There are, however, some limitations. The major limitation is that all patients receiving CLZ were treated in Switzerland, and all patients in the LZP group in the three US hospitals, so we cannot exclude the possibility of some unrecognized confounders due to a deterministic association between site and the choice of the agent. Nevertheless, the three BZD treatment groups were very similar in demographics, SE characteristics, SE severity, and etiology, rendering a major selection and information bias unlikely. Also, all four participating centers have 24/7 onsite Neurology consult teams available; in-patient Neurology and intensive care units admitting patients 24/7; and SE treatment protocols based on current guidelines.

Moreover the four involved centers included similar patients regarding SE severity, seizure type and delay between SE and first treatment. The only salient difference in the management of these patients is the use of continuous EEG monitoring, performed only in selected cases in the CHUV (which favors repeated routine EEGs), while routinely applied in the US hospitals. Consequently, purely electrographic seizures may have been missed in Switzerland, and this might have influenced estimations of SE duration. For this reason, SE duration was not considered as an outcome in comparing the three drugs. The impact on refractoriness and the number of ASDs needed seems low. Because of the EEG screening process, we cannot exclude the possibility that some short SE episodes that respond rapidly to an initial first line treatment with benzodiazepines were not included. Also data collection was performed by two investigators involved in the project and not by persons blinded to the purpose of the study. Because of this we cannot exclude some bias in data collection. However, data were collected as objectively as possible and the outcomes (refractoriness, number of needed ASDs and mortality) are clear and objective measurements. The rate of success of BZDs stopping SE was lower in this study than in several trials[8,9,10,26]. This is, however, a frequent finding in observational studies[7,16,29,36] and may be explained by the common clinical practice of the rapid use of a non-sedating drug with the first line BZD[7] (which renders the first line efficacy assessment difficult and unreliable), and also by our definition of SE control as 48 hours without seizure recurrence, as opposed to convulsion cessation in the emergency department in many prospective trials. This also underscores a marked difference between the aforementioned randomized control trials, which enrolled selected patients with generalized SE, and the real world clinical practice reflected by our observational assessment, which was not limited to convulsive SE; we therefore feel that our findings may be more widely generalizable. Admittedly, the success rate of the first line agent alone could thus not be assessed as an outcome. Moreover, due to the observational nature of this study and despite treatment protocols, there is inevitable heterogeneity in treatment regimens. However, we adjusted for BZD and for second line treatment adequacy (as compared to treatment guidelines) in the multivariate analysis. Adverse effects, including

need for ventilation and hypotension, were not collected systematically, so we were unable to compare the safety of these three drugs. This would need further evaluation in future studies. Nevertheless, CLZ has been proven to be safe in this setting for several decades[28,31], as it is in our clinical experience. Finally, it is possible that tertiary care hospital settings may confer a selection bias toward the inclusion of patients with more severe SE, but we do not believe that this would affect the comparison of the three medications.

Conclusion:

Our study provides class III evidence for the efficacy of intravenous CLZ as a first line treatment for status epilepticus. Its efficacy may be similar to that of MDZ and even higher than with LZP, although other treatment factors at the different centers could also explain differences in outcome among the benzodiazepine treatment groups. While LZP is considered the first line treatment for SE in several protocols and countries, CLZ has a favorable pharmacologic profile and is used in many other countries, although to date, without strong supporting evidence. The second important finding is that LZP is frequently under dosed. Since SE requires rapid and adequate treatment to stop seizures, our data may suggest that treatment protocols may need better education. CLZ may be more effective at least in part because its simpler dosing (*vis a vis* those used for LZP and MDZ), which may improve adherence to treatment protocols. While a randomized controlled trial seems warranted to confirm our findings based on observational data, inclusion of intravenous CLZ in international SE treatment guidelines (which base their 2nd and 3rd line treatment recommendations on expert opinions and case series) seems reasonable.

Summary:

- Clonazepam seems to be an effective alternative to lorazepam and midazolam as first line treatment of status epilepticus.

- Lorazepam is under dosed in the majority of cases.

- Practice variability of initial treatment influences the risk of refractoriness and the number of anti-seizure drugs used but not outcome at hospital discharge.

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Disclosures:

Required statement:

Our work described here is consistent with the Journal's guidelines for ethical publication

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TABLES:

1: Demographic, SE characteristics, etiology, treatments and clinical outcome according to the first line treatment drug

		TOTAL		CLZ		LZP		MDZ		p	test
	n, %	177	100	72	40.68	82	46.33	23	12.99		
Demographics and SE characteristics											
Age	mean, SD	56.79	19.66	59.59	21.71	55.57	16.4	52	22.8	0.21	ANOVA
Male gender	n, %	91	51.44	42	58.33	39	47.56	10	43.48	0.29	χ^2
STESS	mean, SD	2.58	1.62	2.79	1.65	2.36	1.68	2.73	1.21	0.23	ANOVA
Potentially fatal etiology	n, %	77	43.5	30	41.67	37	45.12	10	43.38	0.91	χ^2
Started pre-hospital	n, %	138	77.97	54	75.00	62	75.61	22	95.65	0.09	χ^2
Worst seizure type	n, %										
• Absence		1	0.56	1	1.39	0	0	0	0		
• Myoclonic		1	0.56	1	1.39	0	0	0	0		
• Focal without consc. Impairment		18	10.17	8	11.1	9	10.98	1	4.35		
• Focal with consc. Impairment		49	27.68	22	30.56	23	28.05	4	17.39		
• Generalized convulsive		99	55.93	38	52.78	44	53.66	17	73.91		
• Non-convulsive in coma		9	5.08	2	2.78	7	7.32	1	4.35	0.635	Fisher
SE duration (h)	median, range	27.8	0 – 408	9.5	0.37 - 408	50	0 – 312	4	0.5 – 209	**0.003**	Kruskal-Wallis
Refractory SE	n, %	108	61.02	31	43.06	68	82.93	9	39.13	**<0.001**	χ^2
Treatment Characteristics											
Time to treatment (min)	median, range	60	5 - 7200	92.5	5 - 4320	50	5 - 7200	60	10 - 2880	0.277	Kruskal-Wallis
First line loading dose (mg)	median, range	-	-	1	0.25 - 7.5	2	1 - 12	7.5	1.5 - 30	-	-
Sufficient dose of first line drug	n, %	73	41.24	52	72.22	10	12.2	11	47.83	**<0.001**	χ^2
Adequate second line treatment (when needed)	n, %	81/156	51.92	41/59	69.49	36/76	47.37	4/21	19.05	**<0.001**	χ^2
Intubation for SE control	n, %	26	14.69	7	9.72	16	19.51	3	13.04	0.223	Fisher
Number of ASDs needed to terminate SE	mean, SD	3.21	1.48	2.69	1.38	3.73	1.41	3	1.47	**<0.001**	ANOVA
Outcomes at hospital discharge:											
Return to clinical base line	n, %	82	46.33	35	48.61	31	37.8	16	69.57		
New Morbidity		75	42.37	29	40.28	40	48.78	6	26.09		
Death		20	11.2	8	11.11	11	13.41	1	4.35	0.12	Fisher
Length of hospital stay (d) for survivors	median, range	8.21	0 - 72	8.55	0 - 72	9	1.94 - 60.03	7.23	0 - 40.29	0.913	Kruskal-Wallis

Abbreviations:
ASD: anti-seizure drugs, CLZ: clonazepam, consc: consciousness, LZP: lorazepam, MDZ: midazolam, min: minutes, mg: milligram, SD: standard deviation, SE: status epilepticus, STESS: STatus

Table 2: Demographics, status epilepticus characteristics and time to treatment among the four involved centers

		CHUV		BWH		MGH		BIDMC		p	test
	n, %	91	51.41	52	29.4	14	14.12	9	5.1		
Demographics and SE characteristics											
Age	mean, SD	57.9	22.5	50.1	14.6	62.7	15.9	64.8	14	**0.03**	ANOVA
Male gender	n, %	51	56.04	20	38.5	14	56	6	66.7	0.15	χ^2
STESS	mean, SD	2.79	1.57	2.11	1.55	2.84	1.59	2.77	2.2	0.1	ANOVA
Potentially fatal etiology	n, %	37	40.6	21	40.38	16	64	3	33.4	0.16	χ^2
Started pre-hospital	n, %	70.3	80.22	39	75	19	76	7	77.8	0.89	χ^2
Worst seizure type	n, %										
Absence		1	1.1	0	0	0	0	0	0		
Myoclonic		1	1.11	0	0	0	0	0	0		
Focal without consc. Impairment		9	9.9	7	13.5	2	8	0	0		
Focal with consc. Impairment		26	28.6	10	19.2	10	40	3	33.3		
Generalized convulsive		52	57.14	31	59.52	12	48	4	44.4		
Non-convulsive in coma		2	2.2	4	7.7	1	4	2	22.2	0.49	χ^2
Treatment Characteristics											
Time to treatment (min)	median, range	90	5 - 4320	50	5 – 7200	55	5 – 2340	75	5 – 2820	0.45	Kruskal-Wallis

Abbreviations:
BIDMC: Beth Israel Deaconess Medical Center, BWH: Brigham and Women's Hospital, CHUV: Centre Hospitalier Universitaire Vaudois, consc: consciousness, MGH: Massachusetts General Hospital, min: minutes, SD: standard deviation, STESS: STatus Epilepticus Severity Score. In Bold: statistically significant

Table 3: Analysis of practice variability, age, status epilepticus severity and outcome association regarding first line treatment dosage adequacy for clonazepam, lorazepam and midazolam

		CLZ		p (test)	LZP		p (test)	MDZ		p (test)
		Adequate dose	Insufficient dose		Adequate dose	Insufficient dose		Adequate dose	Insufficient dose	
N		52	20		10	72		11	12	
Center	n (%)									
CHUV		52 (72.22)*	20 (27.78)*		0 (0)*	0 (0)*		11 (57.89)*	8 (42.11)*	
BWH		0 (0)	0 (0)		8 (16)	42 (84)		0 (0)	2 (100)	
MGH		0 (0)	0 (0)		1 (4.17)	23 (95.83)		0 (0)	1 (100)	
BIDMC		0 (0)	0 (0)	n/a	1 (12.5)	7 (87.5)	0.34 (Fisher)	0 (0)	1 (100)	0.205 (Fisher)
Age	mean (SD)	57.6 (21.7)	64.9 (21.3)	0.2 (t-test)	46.1 (11.9)	57 (16.6)	**0.04 (t-test)**	46.5 (27.7)	57 (17.1)	0.28 (t-test)
STESS	mean (SD)	2.86 (1.53)	2.6 (1.95)	0.54 (t-test)	2.2 (0.42)	2.38 (1.78)	0.74 (t-test)	2.36 (1.2)	3 (1.16)	0.16 (t-test)
Refractory SE	n (%)	25 (48.8)**	6 (30)**	0.165 (χ2)	6 (60)**	62 (86.1)**	**0.04** (χ2)	4 (36.36)**	5 (41.67)**	0.795 (χ2)
Number of ASD	n (%)									
0-2		23 (44.23)**	13 (65)**		3 (30)**	10 (13.9)**		5 (45.45)**	6 (50)**	
3-4		23 (44.23)	6 (30)		5 (50)	42 (58.33)		6 (54.44)	2 (16.67)	
≥5		6 (11.54)	1 (5)	0.362 (Fisher)	2 (20)	20 (27.78)	0.47 (Fisher)	0 (0)	4 (33.33)	0.07 (Fisher)
Mortality		4 (7.69)**	4 (20)**	0.137 (χ2)	1 (10)**	10 (13.89)**	1 (Fisher)	0 (0)**	1 (8.33)**	1 (Fisher)

*: Raw percentage
**: Column percentage
Abbreviations:
ASD: anti-seizure drug, BIDMC: Beth Israel Deaconess Medical Center, BWH: Brigham and Women's Hospital, CHUV: Centre Hospalier Universitaire Vaudois, MGH: Massachusetts General Hospital, SD: standard deviation, STESS: STatus Epilepticus Severity Score. In Bold: statistically significant

Table 4: Clinically relevant variables and their association with refractory SE (univariate analysis and after logistic regression), excluding patients with no administration of a second line ASD. Analyses were performed for the whole cohort and for convulsive status epilepticus only.

			Univariate Analysis:			Multivariate Analysis:		
		Total	No Refractory SE	Refractory SE	p (test)	OR	95% CI	p
Total	n (%)	156	49 (31.34)	107 (68.59)				
First line								
CLZ	n (%)	57	29 (49.15)	30 (50.85)		Ref.		
LZP	n (%)	76	8 (10.53)	68 (89.47)		6.4	2.66 – 15.5	**<0.001**
MDZ	n (%)	21	12 (57.14)	9 (42.86)	<0.001* (χ2)	0.85	0.31 – 2.26	0.995
Time to treatment (min)	median (range)	60 (5 – 7200)	60 (5 - 4320)	60 (5 - 7200)	0.498 (Wilcoxon)			
Sufficient dose of first line drug	n (%)	60	26 (43.33)	34 (56.67)	0.011* (χ2)	1	0.45 – 2.2	0.995
Adequate second line	n (%)	81	27 (33.33)	54 (66.67)	0.591 (χ2)			
STESS	mean (SD)	2.69 (1.62)	2.87(1.57)	2.61 (1.64)	0.35 (t-test)			
Potentially fatal etiology	n (%)	70	23 (32.86)	47 (67.14)	0.725 (χ2)			
Convulsive SE only	n (%)	85	28 (32.94)	57 (67.06)				
First line								
CLZ	n (%)	38	17 (54.84)	14 (45.16)		Ref.		
LZP	n (%)	44	3 (7.69)	36 (92.31)		13	2.65 – 63.62	**0.002**
MDZ	n (%)	17	8 (53.33)	7 (46.67)	<0.001* (χ2)	1.01	0.26 – 3.9	0.982
Time to treatment (min)	median (range)	45 (5 – 2880)	65 (5 – 2880)	40 (5 – 2820)	0.09* (Wilcoxon)	0.99	0.99 – 1	0.199
Sufficient dose of first line drug	n (%)	38	18 (47.37)	20 (52.63)	0.011* (χ2)	0.69	0.19 – 2.43	0.367
Adequate second line	n (%)	38	15 (39.47)	23 (60.53)	0.24 (χ2)			
STESS	mean (SD)	3.16 (1.29)	3.21 (1.25)	3.14 (1.32)	0.8 (t-test)			
Potentially fatal etiology	n (%)	34	11 (39.29)	23 (40.35(	0.925 (χ2)			

*: Used in regression model because p<0.2
Abbreviation:
CI: confidence intervals, CLZ: clonazepam, LZP: lorazepam, MDZ: midazolam, mulitvar: multivariate, OR: odds ratio, ref: reference, SE: status epilepticus, STESS: STatus Epilepticus Severity Score
In Bold: statistically significant

Table 5: Clinically relevant variables and their association with the number of ASDs needed to control the SE (univariate analysis and after ordered logistic regression). Analyses were performed for the whole cohort and for convulsive status epilepticus only.

			Univariate Analysis:				Multivariate Analysis:		
		Total	1-2 ASDs needed	3-4 ASDs needed	≥5 ASDs needed	p (test)	OR	95% CI	p
Total	n (%)	177	60 (33.9)	84 (47.46)	33 (18.64)				
First line									
CLZ	n (%)	72	36 (50)	29 (40.28)	7 (9.72)		Ref.		
LZP	n (%)	82	13 (15.85)	47 (57.32)	22 (26.83)		4.35	1.8 - 10.49	**0.001**
MDZ	n (%)	23	11 (47.83)	8 (34.78)	4 (17.39)	<0.001* (χ2)	0.73	0.25 - 2.16	0.577
Time to treatment (min)	median (range)	60 (5 – 7200)	80 (5-4320)	66 (5-7200)	50 (5-2340)	0.389 (Kruskal-Wallis)			
Sufficient dose of first line drug	n (%)	74	31 (42.47)	34 (46.58)	8 (10.96)	0.036* (χ2)	1.39	0.63 - 3.05	0.409
Adequate second line	n (%)	81	25 (30.86)	45 (55.56)	11 (13.58)	0.031* (χ2)	0.45	0.23 - 0.88	**0.02**
STESS	mean (SD)	2.58 (1.62)	2.53 (1.69)	2.59 (1.58)	2.66 (1.63)	0.934 (ANOVA)			
Potentially fatal etiology	n (%)	77	26 (33.77)	40 (51.95)	11 (14.29)	0.374 (χ2)			
Convulsive SE only	n (%)	99	34 (34.34)	46 (46.46)	19 (19.19)				
First line									
CLZ	n (%)	38	19 (50)	17 (44.74)	2 (5.26)		Ref.		
LZP	n (%)	44	7 (15.91)	23 (52.27)	14 (31.82)		5.1	1.47 – 17.6	**0.01**
MDZ	n (%)	17	8 (47.06)	6 (35.29)	3 (17.65)	0.003* (χ2)	0.56	0.13 – 2.38	0.439
Time to treatment (min)	median (range)	45 (5 – 2880)	50 (5 – 2880)	42.5 (5 – 2820)	30 (5 – 390)	0.89 (Kruskal-Wallis)			
Sufficient dose of first line drug	n (%)	47	21 (44.68)	22 (46.81)	4 (8.51)	0.017* (χ2)	0.77	0.27 – 2.2	0.63
Adequate second line	n (%)	38	13 (34.21)	22 (57.89)	3 (7.89)	0.007* (χ2)	0.21	0.08 – 0.57	**0.002**
STESS	mean (SD)	3.03 (1.31)	3 (1.37)	3.13 (1.24)	2.84 (1.42)	0.813 (ANOVA)			
Potentially fatal etiology	n (%)	37	11 (29.73)	20 (54.05)	6 (16.22)	0.5 (χ2)			

*: Used in regression model because p<0.2
Abbreviation:
CI: confidence intervals, CLZ: clonazepam, LZP: lorazepam, MDZ: midazolam, mulitvar: multivariate, OR: odds ratio, ref: reference, SE: status epilepticus, STESS: STatus Epilepticus Severity Score
In Bold: statistically significant

Table 6: Clinically relevant variables and their association with mortality (univariate analysis and after logistic regression). Analyses were performed for the whole cohort and for convulsive status epilepticus only.

			Univariate Analysis:			Multivariate Analysis:		
			Deceased	Alive at discharge	p (test)	OR	95% CI	p
Total	n (%)	177	20 (11.3)	157 (88.7)				
First line								
CLZ	n (%)	72	8 (11.11)	64 (88.89)				
LZP	n (%)	82	11 (13.41)	71 (86.59)				
MDZ	n (%)	23	1 (4.35)	22 (95.65)	0.478 (χ2)			
Time to treatment (min)	median (range)	60 (5 – 7200)	60 (5 - 4320)	60 (5 - 7200)	0.88 (Wilcoxon)			
Sufficient dose of first line drug	n (%)	73	5 (6.85)	68 (93.15)	0.117* (χ2)	0.59	0.18 - 1.86	0.371
Adequate second line	n (%)	81	10 (12.35)	71 (87.65)	0.854 (χ2)			
STESS	mean (SD)	2.58 (1.62)	3.8 (1.47)	2.43 (1.57)	<0.001* (t-test)	1.64	1.19 - 2.25	**0.002**
Potentially fatal etiology	n (%)	77	15 (19.48)	62 (80.52)	0.003* (χ2)	3.59	1.16 - 11.1	**0.026**
Convulsive SE Only	n (%)	99	10 (10.1)	89 (89.9)				
First line								
CLZ	n (%)	38	3 (7.9)	35 (92.1)				
LZP	n (%)	44	6 (13.64)	38 (86.36)				
MDZ	n (%)	17	1 (5.88)	16 (94.2)	0.565 (χ2)			
Time to treatment (min)	median (range)	45 (5 – 2880)	42.5 (15 – 360)	45 (5 – 2880)	0.75 (Wilcoxon)			
Sufficient dose of first line drug	n (%)	47	4 (8.51)	43 (91.49)	0.618 (χ2)			
Adequate second line	n (%)	38	5 (13.16)	33 (86.44)	0.72 (χ2)			
STESS	mean (SD)	3.03 (1.31)	3.8 (1.15)	2.94 (1.3)	0.05* (t-test)	1.45	0.84 – 2.5	0.173
Potentially fatal etiology	n (%)	37	8 (21.62)	29 (78.78)	0.003* (χ2)	6.92	1.34 – 35	**0.02**

*: Used in regression model because p<0.2

Abbreviation:
CI: confidence intervals, CLZ: clonazepam, LZP: lorazepam, MDZ: midazolam, mulitvar: multivariate, OR: odds ratio, ref: reference, SE: status epilepticus, STESS: STatus Epilepticus Severity Score
In Bold: statistically significant.