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The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus

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ABSTRACT

Purpose: This study was designed to find realistic cut-offs of the delays predicting outcome after generalized convulsive status epilepticus (GCSE) and serving protocol streamlining of GCSE patients.
Method: This retrospective study includes all consecutive adult (>16 years) patients (N = 70) diagnosed with GCSE in Helsinki University Central Hospital emergency department over 2 years. We defined ten specific delay parameters in the management of GCSE and determined functional outcome and mortality at hospital discharge. Functional outcome was assessed with Glasgow Outcome Scale (GOS1-3 for poor outcome, GOS > 3 for good outcome) and also defined as condition relative to baseline (worse-than-baseline vs. baseline). Univariate and multivariate regression models were used to analyze the relations between delays and outcome. Delay cut-offs predicting outcome were determined using ROC-Curves.
Results: In univariate analysis long onset-to-tertiary-hospital time (p = 0.034) was a significant risk factor for worse-than-baseline condition. Long delays in onset-to-diagnosis (p = 0.032), onset-to-second-stage-medication (p = 0.023), onset-to-consciousness (p = 0.027) and long total-anesthesia-time (0 = 0.043) were risk factors for low GOS score (1–3). Short delay in onset-to-initial-treatment (p = 0.047), long onset-to-anesthesia (p = 0.003) and onset-to-consciousness (p = 0.008) times were risk factors for in-hospital mortality. Multivariate analysis showed no significant factors.
Cut-offs for increased risk of poor outcome were onset-to-diagnosis 2.4 h (p = 0.011), onset-to-second-stage-medication 2.5 h (p = 0.001), onset-to-consciousness 41.5 h (p = 0.009) times and total-anesthesia-time 45.5 h (p = 0.003). The delay over 2.1 h in onset-to-tertiary-hospital time increased the risk of worse-than-baseline condition (p = 0.028).
Conclusions: GCSE treatment is a dynamic process, where every delay component needs to be optimized. We suggest that GCSE patients should be handled with high priority and transported directly to hospital ED with neurological expertise. Critical steps in the treatment, such as diagnosing GCSE and starting progressive antiepileptic medication on stages 1 through 3, if needed, should be accomplished within 2.5 h.

1. Introduction

Status epilepticus (SE) is a life-threatening neurologic emergency situation, which calls for prompt medical treatment to cease the excessive electric activity in the brain. Incidence of SE varies from 10 to 20 per 100.000[1]. Even SE treated with the best medical practices may result in substantial morbidity and mortality, the latter ranging from 1.9% to 40% in published studies [1].

SE is an extremely dynamic process and several factors during this process have been proposed to influence patients' outcome: Patient's pre-existing characteristics: age, gender, co-morbidities, pre-morbid functional status; [2–6] Factors related to the current SE episode: aetiology, SE type, refractoriness, level of consciousness at onset, duration; [4–8] Treatment and complications: Delays in the treatment, adherence to treatment protocol, anesthetic treatment, complications [3,6,9–16]. Most of the factors are pre-existing at the SE onset and cannot be affected, therefore treatment and complications should be the focus when aiming to improve SE patients' outcome.

Time is brain also in SE. Although there is no evidence-based timeframe for treatment, current guidelines strongly suggest aggressive and early treatment [17–18]. This approach is supported by the finding of GABA-A receptor trafficking and internalization after 30 min of continuous seizure resulting in pharmacoresistance

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and refractoriness [16]. Although the importance of adherence to treatment protocols has been questioned [19], the existing literature and experts' opinions strongly emphasize the significant impact of the quality of treatment on the prognosis of SE [12–13].

The number of published studies regarding delays in the treatment is relatively low [20] Nevertheless, results from the recent years show that delays in the treatment and compliance with suggested protocols are far from optimal, regarding both adults and paediatric patients [21–22].

Streamlining the treatment protocol after careful evaluation of the crucial delay components among stroke thrombolysis candidates reduced the in-hospital delay (door-to-needle-time) from median 105 min to 20 min over the years [23]. Although treatment of stroke in the early phases is more straightforward than treatment of SE, similar approaches to optimize SE treatment could be implemented. First, we should uncover the most important delay components affecting the outcome and mortality to define maximum acceptable delays.

This study was designed to find the realistic cut-offs of the significant delays predicting in-hospital mortality and functional outcome for protocol streamlining.

2. Material and methods

2.1. Study design and setting

This is a retrospective cohort study performed in Helsinki University Central Hospital (HUCH), a tertiary hospital serving a population of 1.4 million. Emergency service in the hospital district is provided by one tertiary university hospital (HUCH) with neurological emergency and seven regional hospitals with internal medicine emergency. The emergency medical service (EMS) system includes paramedic-, nurse-, and physician-based EMS units, either ambulance or helicopter. At the time of material collection second-stage medication was not dispensable by EMS. In cases of benzodiazepine-resistant SE physician- and nurse-based EMS units may induce anesthesia and intubate the patient at emergency site after consulting the physician on shift.

This study conforms to the Finnish legislation concerning medical research and the permission was granted by the HUCH Department of Neurology.

2.2. Definition of generalized convulsive status epilepticus/GCSE

The operational definition of established SE being used at the time of material collection was continuous seizures lasting over 30 min, several recurrent seizures without returning consciousness, or occurrence of more than four seizures within any one hour irrespective of return of consciousness in between. The definition of SE has been recently revised[24]. Patients having a convulsive seizure at any point of the SE period were considered as having convulsive SE (CSE). Patients with impaired consciousness, either primarily or secondarily, were considered as having generalized SE (GSE).

2.3. Selection of participants

Consecutive adult patients (≥16 years) diagnosed with generalized convulsive status epilepticus (GCSE) and treated in the HUCH emergency department (ED) between January 2002 and December 2003 were included in the study.

The patients were identified in the HUCH electronic patient database by the ICD-10 code G41 (SE), yielding a total of 87 patients. Patients not meeting the criteria of GCSE were excluded. Altogether 70 GCSE patients were eligible for the study.

2.4. Data collection

Clinical data were collected by a trained medical doctor from the original medical records and collected on a standard form designed for this study. The electronic database was created using MS Access for data recordings and information of patient identification was removed before further analyses.

We defined ten specific delay parameters in the management of GCSE: Onset-to-initial-treatment, −diagnosis, −second-stage-treatment, −tertiary-hospital, −anesthesia, −burst-suppression, −seizure-freedom, −consciousness, total-anesthesia-time and total-ICU-time. For determining the accuracy and reliability of the collected time parameters we calculated The Weighted Accuracy Score (L_{WAS}) and the Data Availability (DA), using the method developed for evaluation of retrospective delay materials [21]. Time points that could not be estimated within the time window of 30 min were excluded from the analyses and were not scored with L_{WAS} and DA.

Outcome of the patients was defined as functional outcome and mortality at hospital discharge. Functional outcome was assessed with Glasgow Outcome Scale (GOS 1–3 for poor outcome, GOS >3 for good outcome) and condition relative to baseline condition (worse-than-baseline vs. baseline) at hospital discharge. Outcome measures at hospital discharge were collected from the medical records.

Missing events, e.g. no burst-suppression (BS), events happening during pre-status period, or events with unknown data were excluded from the final analysis. The missing data information is presented in online Table 1.

2.5. Definitions of the measures

The onset of GCSE was defined as the beginning of the first seizure fulfilling the criteria for established GCSE. Initial treatment was defined as the first antiepileptic drug (AED) given, which was

Table 1
Description of the material.

Variable		N	%
Cases		70	100
Patient Characteristics			
Age	Mean	54,3	
	Range	16–85	
Gender	Male	35	50,0
	Female	35	50,0
Medical history	Previous recorded illnesses	70	100
	Epilepsy	46	65,7
Etiologies	Epilepsy	46	65,7
	Acute brain disorder	7	10,0
	Prior brain disorder	7	10,0
	Unknown	10	14,3
STESS	2	35	50,0
	3	16	22,9
	4	10	14,3
	5	9	12,9
Refractoriness	Non-RSE	8	11,4
	RSE	30	42,9
	SRSE	32	45,7
Anesthetic treatment	No Anesthesia	8	11,4
	Propofol only	56	80
	Multiple Anesthetics	6	8,6
Outcome Parameters			
Condition at discharge	Worse-than-baseline	41	58,6
	Baseline	29	41,4
GOS at discharge	≤3	28	40
	>3	42	60
Mortality at discharge	Yes	5	7,1
	No	65	92,9

STESS status epilepticus severity score, *RSE* Refractory status epilepticus, *SRSE* Super-refratory status epilepticus, *GOS* Glasgow Outcome Scale.

not necessarily first-stage medication. The second-stage medication was defined as first given second-stage medication. Tertiary hospital exclusively refers to HUCH ED. The third-stage medication included anesthesia with propofol, thiopental or midazolam and induction was considered as the starting point of anesthesia. The cessation of GCSE was defined with three separate parameters for the treatment response: BS, clinical seizure freedom and return of consciousness. BS refers to the beginning of the first BS sequence during this SE. Clinical seizure freedom refers to the end of the last clinical convulsion, and return of consciousness refers to the time point, when the patient no longer presented altered mental status. Total time of the treatment (anesthesia/ICU) was calculated adding up the length of all individual anesthesia-/ICU- periods during the GCSE.

Functional outcome was considered good, if the patient returned to the baseline condition and GOS at hospital discharge was >3.

2.6. Statistics

Results are given as mean (SD) or median (interquartile range). The Mann-Whitney test was used to find out differences in continuous variables. Logistic regression analysis was used to find out risk factors/delays for each outcome. Log transformation was used for time variables in logistic regression analysis. Bootstrap resampling (1000 samples) was used to calculate bias-corrected percentile confidence intervals for odds ratios. The receiver operating characteristics curves were created, and optimal cut-off values were calculated by maximizing the Yonden's index. Two-tailed tests were used and significance was defined as $p < 0.05$. Statistical calculations were performed with SPSS (v24, IBM Corp, New York NY).

3. Results

Patient characteristics, the outcome of the patients and the delays in the treatment are presented in Tables 1 and 2.

In 69 (98.6%) cases the initial treatment was first-stage medication, and in only one case it was propofol. For 61 cases (87,1%) initial treatment was administered pre-hospitally before or during the transportation to hospital emergency department (ED). 56 cases (80%) received diazepam as the first medication and 13 cases (18.6%) received lorazepam, average initial doses being 8.2 mg and 2.1 mg respectively. In 26 (37.1%) cases the initial treatment was administered rectally. 62 cases (88.6%) were medicated with several doses of first-stage medication before intensifying the treatment to second- or third-stages, average total dose being 29.5 mg of diazepam or 6.5 mg of lorazepam. In 35 cases (50%) first-stage treatment was followed by second-stage medication and the rest, 35 cases, received directly third-stage medication, which was propofol. 67 of all cases (95.7%) were treated with second-stage-medication, in 62 cases (92.5%) it was iv. phosphenytoin and in 5 cases (7.5%) iv. valproate. Anesthetic treatment was initiated out-of-hospital in 24 (38.7%) of the anesthetized cases. 62 cases (88.6%) were treated with iv. anesthetics in the ICU department, and all of them received propofol.

Non-survivors received initial medication median 10 min after the onset of SE, while the corresponding time for survivors was three times longer, median 30 min. All the other delays were longer among non-survivors: onset-to-alarm 4.3 times, onset-to-diagnosis 2.5 times, onset-second-stage-medication 1.4 times, onset-to-anesthesia 3.1 times and onset-to-tertiary-hospital 1.2 times that of survivors.

GCSE was diagnosed on clinical grounds in 69 (98.6%) cases and out-of-hospital in 41 cases (39.7%). Diagnostic EEG was required in one case. 51 (72.9%) of all cases were transferred straight from the scene to tertiary hospital, the rest of the cases (27.1%) were first transferred to another hospital ED and later to HUCH ED.

In the univariate logistic regression analysis (Table 3) long delay in reaching the tertiary-hospital ($p = 0.034$) was a significant risk factor for functional deterioration at hospital discharge in relation to baseline condition. Long delays in onset-to-diagnosis ($p = 0.032$), onset-to-second-stage-medication ($p = 0.023$), onset-to-consciousness ($p = 0.027$) and long anesthetic treatment ($p = 0.043$) were risk factors for low GOS score (1–3) at hospital discharge. Short delay in giving the initial AED ($p = 0.047$), long delays in starting the anesthesia ($p = 0.003$) and long delay in returning consciousness ($p = 0.008$) were related to risk of in-hospital mortality.

Onset-to-tertiary-hospital delay was significantly longer among patients not returning to baseline condition ($p = 0.027$). Long onset-to-second-stage-medication, onset-to-anesthesia, onset-to-consciousness times and total-anesthesia-time were associated with low GOS score (1–3) at discharge ($p = 0.007$, $p = 0.048$, $p = 0.032$, $p = 0.037$ respectively), and long delay in onset-to-anesthesia time was associated with in-hospital mortality ($p = 0.031$).

Cut-offs for the significant delays in the univariate analysis predicting poor/worse-than-baseline condition were determined by plotting Receiver Operating Characteristic Curves (ROC-Curve) (Fig. 1, Table 4). Diagnostic delay over 2.4 h (ODDS 3.9, 95%CI 1.4–11.0, $p = 0.011$), delay in giving the second-stage-medication over 2.5 h (ODDS 8.3, 95%CI 2.4–28.5, $p = 0.001$), altered mental status or unconsciousness prolonging over 41.5 h (ODDS 5.0, 95%CI 1.5-16.9,$p = 0.009$) and anesthetic treatment for over 45.5 h (ODDS 5.3, 95%CI 1.8–16.2, $p = 0.003$) increased the risk of poor functional recovery (GOS 1–3). Delay over 2.1 h before reaching the tertiary hospital increased the risk of worse-than-baseline condition at discharge (ODDS 3.2, 95%CI 1.2–8.8, $p = 0.023$).

Table 2
Delay parameters and the delays in the management of GCSE.

Variable	N	%	TIME	MIN	MAX	DA	L_{WAS}
ALL CASES	70	100	Median			%	
Delays In The Treatment							
Onset-to-initial-treatment	67	95,7	30 min	0 min	8 h 5 min	97,0	1,8
Onset-to-diagnosis	70	100	1 h 48 min	6 min	60 h 6 min	97,1	1,5
Onset-to-second-stage-medication	67	95,7	2 h 40 min	30 min	61 h 54 min	98,5	1,6
Onset-to-tertiary-hospital (HUCH)	70	100	2 h 25 min	37 min	277 h 40 min	98,6	1,5
Onset-to-anesthesia	62	88,6	2 h 38 min	0 min	66 h 20 min	98,4	1,5
Onset-to-burst-suppression	30	42,9	14 h 42 min	5 h 5 min	137 h 50 min	100,0	1,5
Onset-to-seizure-freedom	70	100	5 h 15 min	26 min	533 h 15 min	98,6	1,6
Onset-to-consciousness	61	87,1	42 h 45 min	2 h 40 min	444 h 40 min	96,7	1,4
Total-anesthesia-time	62	88,5	38 h	3 h 35 min	238 h 52 min	98,4	1,1
Total-ICU-time	63	90	58 h 40 min	7 h 45 min	520 h 25 min	100,0	1,1

Table 3
Univariate logistic regression analysis of the delays as risk factors for poor outcome at hospital discharge and summary of delay parameters.

	Median		Time		Time				95%CI		
Delays	time	IQR	(h)	IQR	(h)	IQR	p	ODDs	Min	Max	p
Condition At Discharge	**All Cases**		**Worse-than-baseline**		**Baseline**						
Onset-to-initial-treatment	0,5	0,8	0,5	0,8	0,6	0,7	0,598	0,9	0,4	1,7	0,721
Onset-to-diagnosis	1,8	2,8	2,0	4,1	1,5	1,5	0,146	2,1	0,6	11,3	0,223
Onset-to-second-stage-treatment	2,7	3,4	3,2	3,9	2,3	2,0	0,087*	2,6	0,5	41,8	0,247
Onset-to-tertiary-hospital	2,4	2,8	2,6	3,5	2,0	2,4	**0,027**	4,4	1,4	47	**0,034**
Onset-to anesthesia	2,6	4,0	2,3	4,5	3,2	2,3	0,256	2	0,67	7,7	0,233
Onset-to-Burst-Suppression	14,7	19	14,9	21,8	14,0	19,3	0,632	2,3	0,1	226,8	0,461
Onset-to-seizure-freedom	5,3	46,6	5,8	49,4	4,1	35,4	0,599	1,2	0,7	2,5	0,515
Onset-to-consciousness	42,8	51	56,3	65,3	29,0	43,8	0,082*	2,5	0,8	15,2	0,095*
Total-anesthesia-time	38,0	51,2	46,8	65,6	24,0	29,8	0,059*	3,5	0,9	30,6	0,117
Total-ICU-time	58,7	106,8	67,6	111,4	50,3	90,3	0,106	2,9	0,8	12,2	0,08*
GOS At Discharge			**GOS 1–3**		**GOS >3**						
Onset-to-initial-treatment	0,5	0,8	0,5	1	0,5	0,8	0,966	1,1	0,6	2,2	0,846
Onset-to-diagnosis	1,8	2,8	2,7	4,3	1,5	1,6	0,071*	3,4	1	20,6	**0,032**
Onset-to-second-stage-treatment	2,7	3,4	3,4	4,6	2,3	2,1	**0,007**	6,6	1,3	101,5	**0,023**
Onset-to-tertiary-hospital	2,4	2,8	2,4	4,0	2,1	2,2	0,074*	2,4	0,8	19,7	0,162
Onset-to anesthesia	2,6	4,0	4,3	4,8	2,3	2,3	**0,048**	3,1	0,92	15,2	0,059*
Onset-to-Burst-Suppression	14,7	19	16,5	33,0	13,3	17,8	0,587	2,3	0,1	44	0,444
Onset-to-seizure-freedom	5,3	46,6	7,5	55,8	4,3	31,3	0,229	1,6	0,8	3,6	0,178
Onset-to-consciousness	42,8	51	59,9	63,8	28,5	43,7	**0,032**	3,6	1,1	37,7	**0,027**
Total-anesthesia-time	38,0	51,2	57,9	57,9	26,5	39,5	**0,037**	5,1	0,9	52,5	**0,043**
Total-ICU-time	58,7	106,8	69,7	100,1	53,3	109,9	0,114	3	0,8	12,5	0,054*
In-hospital Mortality			**Dead**		**Alive**						
Onset-to-initial-treatment	0,5	0,8	0,2	0,8	0,5	0,7	0,115	0,4	0	1,7	**0,047**
Onset-to-diagnosis	1,8	2,8	4,3	6,5	1,8	2,7	0,208	2,9	0,3	35,5	0,209
Onset-to-second-stage-treatment	2,7	3,4	3,6	4,9	2,6	2,8	0,467	1,4	0	28,2	0,741
Onset-to-tertiary-hospital	2,4	2,8	2,8	49,5	2,3	2,8	0,172	2,6	0,2	7,71E + 75	0,123
Onset-to anesthesia	2,6	4,0	7,5	35,4	2,4	3,7	**0,031**	8,7	1,2	1,33E + 03	**0,003**
Onset-to-Burst-Suppression	14,7	19	22,0	18	14,0	19,1	0,22	5,1	0,6	2657,1	0,168
Onset-to-seizure-freedom	5,3	46,6	8,4	92,9	4,7	47,5	0,3	1,8	0,5	51,4	0,252
Onset-to-consciousness	42,8	51	89,3	0	40,4	50,4	0,475	6,3	3,1	30,6	**0,008**
Total-anesthesia-time	38,0	51,2	76,5	68,3	34,4	48,7	0,202	6,6	0,2	849,8	0,153
Total-ICU-time	58,7	106,8	65,9	115,2	58,6	111,4	0,613	1,8	0,3	15,5	0,463

For logistic regression the variables were log transformed and bootstrapped confidence intervals (CI) were calculated. p values < 0.05 are bolded, p values < 0.01 are marked with *.

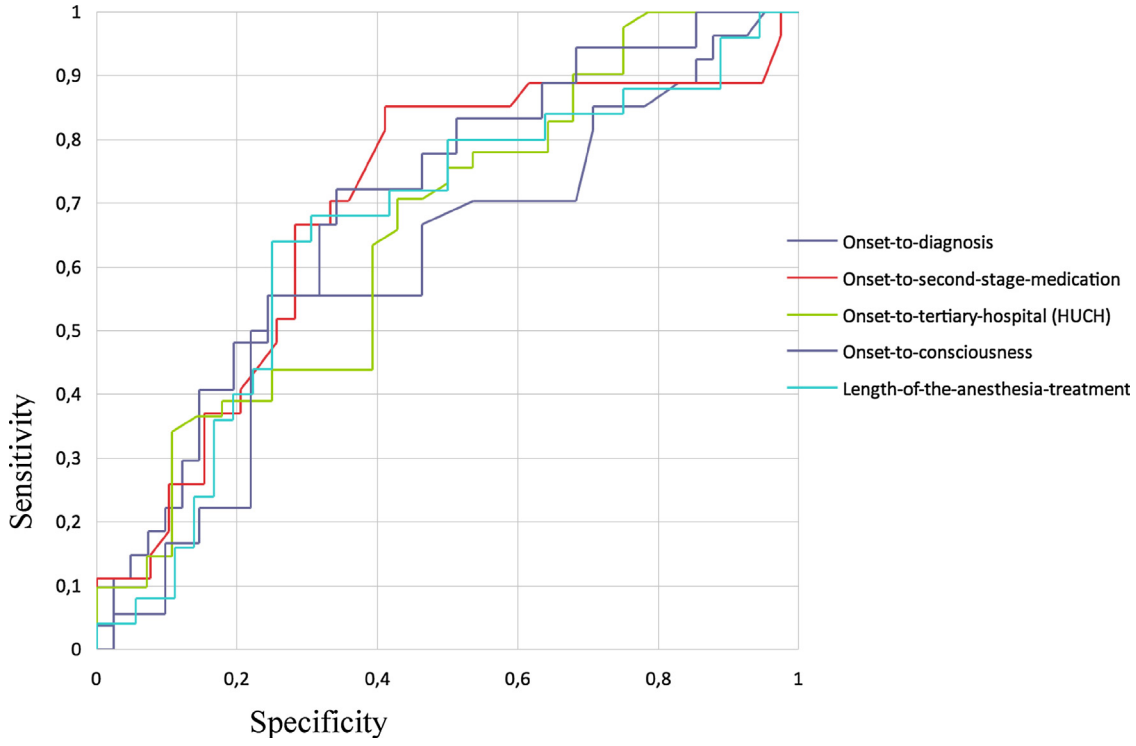

Fig. 1. Receiver operating characteristics curves (ROC-Curves) for the delays. Outcome variable for onset-to-diagnosis, onset-to-second-stage-medication, onset-to-consciousness and total-anesthesia-time is low GOS score (1–3) at hospital diacharge and for onset-to-tertiary-hospital (HUCH) is worse-than-baseline-condition.

Table 4
Area under curve (AUC) and cut-offs for the significant delays.

VARIABLES		AUC	CI 95%	CI 95%	p	CUT-OFF	Sens.	Spec.
DELAY	OUTCOME		(min)	(Max)		(h)		
Onset-to-diagnosis	GOS 1–3	0,63	0,49	0,77	0,071*	2,4*	0,76	0,56
Onset-to-second-stage-medication	GOS 1–3	0,693	0,56	0,83	**0,008**	**2,5**	0,59	0,85
Onset-to-tertiary-hospital (HUCH)	Worse-than-baseline condition	0,657	0,52	0,79	**0,028**	**2,1**	0,71	0,57
Onset-to-consciousness	GOS 1–3	0,676	0,54	0,82	**0,032**	**45,4**	0,66	0,72
Total-anesthesia-time	GOS 1–3	0,658	0,52	0,80	**0,037**	**41,5**	0,75	0,64

p values < 0.05 are bolded, p values < 0.01 are marked with *.

In the multivariate regression analysis none of the delays were independent risk factors for poor functional outcome at hospital discharge or for in-hospital mortality (Data not shown).

4. Discussion

This is the first study focussing on the critical delays in the treatment chain of GCSE associated with mortality and functional outcome at hospital discharge and determining the delay cut-offs predicting poor functional outcome. We reveal several relevant associations between delays and outcome at hospital discharge, concerning most main components of the treatment chain: diagnosis, second-stage medication, third-stage medication, tertiary hospital admission and duration of SE. None of the delays were independently associated with outcome, which illustrates the dynamic nature of GCSE and elucidates that every delay component of the treatment chain should be minimized to ensure optimal outcome. Streamlining the treatment protocol calls for increased emphasis on the pre-hospital phase of the treatment.

The abundant data available for the great majority of cases and the good accuracy (Table 2) of records are the strengths of this study. Accuracy may be a benefit of concurrent systematic training of EMS personnel for acute stroke thrombolysis treatment protocol. Additional explanatory factors concerning pre-hospital setting may be high density of mobile phones and awareness of emergency actions among laymen.

This study encompasses some limitations related to its retrospective nature and limited number of patients from a single tertiary centre. Although this requires some caution in interpreting the results, retrospective setting expressly elucidates the realistic difficulties in practical treatment of SE and therefore enables plausible goal setting for protocol streamlining. Additionally, all patients in the material have GCSE, which enhances the homogeneity of the material. Although the material dates back over several years, it is still representative for present-day SE management, since during the last decade no major treatment protocol reformations have been made. Rather, fewer options for AEDs at the time of material collection and use of phosphenytoin as the primary second-stage-medication reduce bias due to heterogeneity of medication selection. The diagnosing and coding practices were bases on the operational definition and classification of SE used at the time of material collection, which likely explains the relatively high proportion of RSE cases in our material, as compared to published incidence of RSE. It is recognized that collection by G41 misses cases diagnosed as SE. The revised definition of SE [24] is expected to offer a prerequisite for improved treatment protocol of SE.

4.1. Delays related to outcome

Delayed treatment of SE has been previously associated with poor prognosis [2,9] and suboptimal or delayed response to medication [25]. Although some reports question the relation between delays and prognosis [4,26], it is indisputable that prolonged duration of SE is associated with poor outcome [7–8,27]. Since treatment delays correlate with longer duration of SE [11,22] and adherence to treatment protocol improves patients' outcome [12–13], delays should be considered as major prognostic factors of SE.

4.2. Initial treatment

Several requirements apply for effective initial treatment of acutely seizing patients. The most effective medication should be used, which according to current knowledge is intravenous benzodiazepine (lorazepam, diazepam, clonazepam) or intramuscular midazolam [28–28–29]. Adequate dosing is essential, because response to under-dosed benzodiazepines might be falsely interpreted as benzodiazepine-resistance leading to unnecessary proceeding to higher stage medication [30]. According to current treatment guidelines the medication should be administered without delay, within 5 min after seizure onset [18,31].

During the recent years the knowledge of effective initial medication has grown and after the RAMPART study [28] the usage of intramuscular midazolam has increased [32]. Development of various administration routes (buccal, intranasal, intramuscular) has enabled more rapid and socially more acceptable administration of medications [29]. Pre-filled medication dispensers might be influential in adequate dosing. In spite of progress, median treatment delays are still far from optimal and range from 28 min to several hours [2,9,13,21,22] in public onset SE cases. This might relate to the fact that delays due to the patient (i.e. onset-to-alarm delay) are still long and are possibly difficult to reduce as seen in studies on layman education campaigns [33]. In addition, only the minority of patients are treated out-of-hospital [22], which is suboptimal, since pre-hospital treatment is associated with shorter duration of SE [13]. Although clinical common sense suggests that treatment delay is essential to SE prognosis [2,9], there are also opposite results [4,26,34] including the current study, where short delay in giving the initial medication was associated with increased in-hospital mortality. This unexpected result could be explained by the finding that although non-survivors received the initial treatment significantly quicker than survivors, all the other delays of non-survivors were multiple, possibly due to greater severity of non-survivors' SE and/or their burden of complication [35]. This might reflect problems in recognition of SE after medication or erroneous interpretation of medication response, as proposed in a pre-hospital study [10]. Because patients in this study received effective initial medication with adequate doses in a reasonable time frame, the finding strengthens the idea that all the other above-mentioned requirements for effective initial treatment should be met to ensure optimal treatment for SE patients.

4.3. Second-stage treatment

Current optional medications of SE include intravenous phosphenytoin, valproate, levetiracetam and lacosamide. The latter two drugs were not available at the time of our material collection. This does not influence the conclusions of our study, since no evidence of any agents' superiority has been published. The situation should be reconsidered once the results of the ongoing randomized ESETT trial comparing phosphenytoin, valproate and levetiracetam in the treatment of established SE [36] become available. It is worth noting that in ESETT, patients are randomized according to the drug, but the delay in drug application remains uncontrolled.

Only a few studies report the onset-to-second-stage medication delay. In those studies median delay ranges from 69 min to 3 h [21–22] and is clearly longer than the guidelines' suggestion to start second-stage medication of persisting seizures within 20–40 min after first-stage treatment [18,31]. Onset-to-second-stage medication delay is correlated with delay in return of consciousness in GCSE patients and prolonged time between initial treatment and second-stage treatment predicts a delayed clinical seizure freedom and return of consciousness [11]. In the present study, delayed second-stage treatment, which in most cases was phosphenytoin, was associated with the risk of poor outcome at hospital discharge. The predictive cut-off for poor outcome due to delayed second-stage medication was 2.5 h, which directs the focus of streamlining the treatment protocol toward pre-hospital phase. These observations suggest that second-stage medication given already by EMS and use of newer medications with less storage, monitoring and safety problems should be considered. However, further studies are needed, since evidence has been reported that use of newer AEDs may lower the chance of return to baseline condition at discharge and result in higher rate of refractoriness [37]. Delays were not controlled in that study and therefore it is possible that any second-stage agent given in adequate doses during the first 2.5 h might improve the outcome. Naturally, an adequate physician's evaluation is needed to ensure correct diagnosis and patient safety during the medication. This could be obtained by recruiting physician-staffed EMS units with high priority for acute SE cases.

4.4. Diagnosis

As long as SE remains undiagnosed, effective and properly targeted symptomatic treatment is not started. Consequently, delay in diagnosis is associated with a higher likelihood of poor response to treatment and worse outcome [38]. Median diagnostic delay was over 2 h in a study including all SE types [21], and 45 min in a study including only GCSE cases [13]. In the current study including only GCSE patients the diagnostic delay remained under 2 h, mainly due to the fact, that almost all cases could be diagnosed on clinical grounds. Focal SE is associated with longer diagnostic delays [10], as is also electrographic SE, whereby availability of EEG is essential for diagnosis. In a paediatric material, delay of cEEG in electrographic SE was associated with increased mortality [39]. Our results agree with earlier knowledge by showing that long diagnostic delay is associated with low GOS score at discharge.

To improve diagnostics of SE, common awareness of the risk of SE among acutely seizing patients should be increased among laymen, ambulance dispatchers and paramedics in EMS and hospital personnel. Even the risk of SE, preferably recognized by adequate SE detection algorithm, should be handled with highest priority equal to that used in stroke emergencies. This might imply sending a physician-staffed unit to the scene not only for diagnostics, but most importantly for starting adequate treatment before hospital admission. In order to catch those cases of SE not evident on clinical grounds, attempts should be made to enable EEG and/or video recordings already at the scene and telemedical consultation of an epileptologist. Electronic seizure prediction and detection devices carried by epilepsy patients and connected to closed-loop warning systems may be useful in selected cases [40], although it is recognized that in the majority of cases SE occurs in patients without premorbid epilepsy. Diagnostic improvements depicted should enhance detection of non-epileptic seizures and thus prevent potentially harmful overtreatment.

4.5. Tertiary hospital delay

Organization of EMS systems and treatment protocols of SE in hospital districts vary tremendously throughout the world and even within countries. There are very few studies comparing different systems and their effect on patient outcomes. An Italian study compared patients with SE onset and treatment in urban versus rural area hospitals and reported significantly higher mortality in urban areas. The quality of drug treatment significantly differed in disfavor of urban area, although the availability of neurological consultation and EEG were equal [12]. In a small prospective cohort comparing the outcome of SE patients treated in tertiary hospital versus regional hospitals, a trend towards worse outcome in tertiary hospitals was found, although the groups were equal in age and SE severity (STESS) [41]. In the current study, a long delay in reaching the tertiary hospital was associated with worse-than-baseline condition at discharge. This finding is most likely related to an earlier finding reporting that transportation directly to tertiary hospital led to quicker diagnosis and earlier administration of second- and third-stage medications [10]. We believe that treating SE patients in EDs providing neurological consultations round-the-clock, as in HUCH ED, and where EEG is readily available, leads to better prognosis.

The predictive cut-off of little over 2 h in onset-to-tertiary hospital time calls for prompt recognition of SE and direct transportation of even suspected SE cases to tertiary hospital.

4.6. Duration of anesthesia and ICU treatments

Initiation of third-stage treatment i.e. intravenous anesthetic drug treatment (IVAD) is recommended after 30–70 min of continuous seizure activity, especially in GCSE cases [18,31]. Although some reports propose that IVAD treatment itself might be harmful for the patients [14], poor prognosis of IVAD treated patients has mainly been associated with more severe aetiology of SE, refractoriness and increased number of complications [27]. So far there are no studies showing the superiority of any particular IVAD. In a previous report, the delay in starting the IVAD treatment after the SE onset was median 2 h 55 min [21], whereas in another study only 37% of the patients were anesthetized within 2 h and the rest within 24 h [42]. Generalized, convulsive, public-onset SE cases transported directly to tertiary hospital are more likely to have short delays in starting anesthesia [10]. Krishnamurthy et al. suggested that long delay in starting anesthesia does not necessarily mean poor outcome [5]. We showed otherwise in the present study, since long delays were associated with higher in-hospital mortality. Therefore, in cases needing third-stage treatment, IVADs should be initiated as early as possible after first-, and second-stage treatments fail, possibly already out-of-hospital.

Reported total anesthesia times vary from median 21.5 h to several days, depending on the severity and refractoriness of the SE [15,21,42]. We confirm the previous finding that long anesthesia time is associated with poor outcome [15] and our study is in line with the recent report on high mortality of SRSE [43]. IVAD treatment predisposes to complications, the risk increasing with time. A trend-like association of total-ICU-time with poor

functional outcome reflects most likely the same phenomenon. Although IVAD treatment exceeding ca. two days predicts poor functional outcome at hospital discharge, it does not mean that the IVAD treatment should be limited to two days in all patients. In all aetiologies other than anoxia continuation of the IVAD treatment seems reasonable, since even in prolonged refractory SE cases meaningful functional and cognitive recovery is possible [7]. Targeting IVADs quickly, albeit with strict criteria should prevent or minimize complications and seems to be essential for improved prognosis of IVAD treated patients.

4.7. Return of consciousness

Long duration of SE has been associated with poor prognosis after SE, and the predictive timeframe varies from 1 h to 10 days [2–3,27]. Since exact endpoint of SE is conceptually problematic and varies even in the few previous studies that have clearly defined the endpoint [7,34], we used stepwise definition for the end of SE, as described in Material and methods section. Still, the return of consciousness is the only clinically reliable marker for the end of GCSE. Even the definition regarding the onset of SE seems to vary in previous studies. This makes comparison with the previously published results problematic. In the present study the delay in return of consciousness was related to poor functional outcome and in-hospital mortality, which is concordant with a previous study defining the end of SE based on clinical recovery [7]. Little less than two days of unconsciousness seems to be critical for the prognosis after SE. Burst-suppression delay and onset-to-seizure freedom delay did not have significant relation to outcome. The fact that they both are correlated to onset-to-consciousness delay confirms their position as significant components of the continuum leading to cessation of SE [11].

5. Conclusions and protocol streamlining suggestions

Streamlining the whole treatment chain of GCSE is necessary. Every delay component of the treatment should be optimized, especially in the pre-hospital phase of the treatment. We suggest that even patients with suspected GCSE should be handled with high priority by physician-staffed EMS units and transported directly to hospital EDs with neurological expertise. Critical steps in the treatment, such as diagnosing GCSE and stepwise initiation of all stages of antiepileptic medication should be made possible to accomplish within 2,5 h.

Conflicts of interest

None.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2017.12.007.

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