TELSTAR statistical analysis plan

Treatment of ELectroencephalographic STatus epilepticus After cardiopulmonary Resuscitation

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1. Aim of the study

Electroencephalographic status epilepticus is described in 9-35% of patients with postanoxic encephalopathy after cardiac arrest and is associated with case fatality rates of 90-100%. It is unclear whether (some) electroencephalographic seizure patterns in these patients represent a condition which can be treated with antiepileptic drugs to improve outcome, or have to be regarded as an expression of severe ischemic damage, in which treatment with antiepileptic would be futile. Therefore, both treatment with and treatment without antiepileptic drugs are considered standard modalities in these patients.

TELSTAR is a multicenter randomized controlled trial, with the aim to estimate the effect of medical treatment of electro-encephalographic status epilepticus on neurological outcome of patients with postanoxic encephalopathy after cardiac arrest. We hypothesize that aggressive and early treatment of electro-encephalographic status epilepticus with antiepileptic drugs improves outcome as compared to treatment without these drugs.[1]

2. Study design

TELSTAR is a multicenter clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation (PROBE design). The intervention contrast is intensive medical treatment (intervention group) vs. no treatment of electroencephalographic status epilepticus (control group), in addition to standard best medical management of comatose patients after cardiac arrest.

The study population will consist of adult patients with postanoxic encephalopathy after cardiac arrest, admitted to the intensive care unit, treated with targeted temperature management, with electroencephalographic status epilepticus on continuous EEG, who are eligible for inclusion in this trial.

Treatment of electroencephalographic status epilepticus in the intervention group will be based on international guidelines for the treatment of overt status epilepticus The objective of the treatment will be to suppress all epileptiform activity in the EEG. If the electroencephalographic status epilepticus will return after tapering sedative treatment at 24 hours, the procedure will be repeated. If the status will return after 2 x 24 hours, it may be considered refractory.

The primary outcome measure will be neurological outcome defined as the score on the Cerebral Performance Category (CPC) at 3 months dichotomized as good (CPC 1-2 = no or moderate neurological disability) or poor (CPC 3-5 = severe disability, coma, or death). Secondary outcome measures will include i) mortality; ii) the CPC scores at 6 and 12 months; iii) length of stay on the ICU; iv) duration of mechanical ventilation; v) seizure recurrence within one year; vi) quality of life as measured by the Medical Outcomes Study 36-item short-form health survey (SF36)[2] vii) depression as measured by the Montgomery and Åsberg Depression Rating Scale (MADRS)[3], and viii) cognitive functioning as measured by detailed neuropsychological examination after 12 months.

Allocation to one of the treatment groups is performed through a web-based randomization service. Treatment allocation is stratified by center. In concordance with the PROBE design, treatment allocation is open. Assessment of the primary and secondary outcome measures will be done by an investigator or research nurse that will be blinded for treatment allocation.

In the protocol, we specified an interim analysis according to O'Brien and Fleming after 86 included patients have had their primary outcome measurement. The interim analysis was performed and evaluated by an independent DSMB. If the difference in primary outcome between the treatment groups at that time would have been significant at $p<0.00557$, the trial would be stopped because of "proof beyond reasonable doubt" that treatment with anti-epileptic drugs is superior above

treatment without anti-epileptic drugs. Because of the interim analysis, we will consider a difference in the primary outcome between treatment groups with p<0.0492 statistically significant.

TELSTAR is conducted in 11 centers in the Netherlands and Belgium. Data are collected through a validated web-based database. Follow up in surviving patients is done by telephone interview by a trained investigator or research nurse three, six and twelve months after randomization. In surviving patients, additional tests for quality of life, depression and neuropsychological examination will be performed in the center where they were included.

3. Overall data and statistical analysis principals.

3.1 Handling of missing data

We will not perform imputation for data if missing for statistical summaries and analyses, unless otherwise specified.

3.2 Quality control of summary tables

Ahead of the database lock and unblinding, data for all individual subjects will be checked using consistency checks as specified in Appendix 1. Summary tables will be checked and (potential) errors checked and corrected if needed. In addition, full analyses will be run based on dummy randomization codes.

3.3 Quality control of statistical analysis

Peer review of statistical analyses will be performed of program code, log and output to ensure accuracy of the statistical analysis. Analyses will be performed in MATLAB (version R2021a).

4. Population for analysis

The primary analysis will be in the intention-to-treat (ITT) population, comprising all patients who have been randomized, irrespective of whether they subsequently started their allocated treatment. We will perform an additional *per protocol* analysis, in which subjects will be analyzed in the population as treated. In this analysis, we consider all patients treated with at least one anti-epileptic drug during their admission to the ICU as intervention group.

5. List of analyses to be performed

5.1 Retention

We will provide a CONSORT flow diagram, reporting the number of patients who were randomized, treated, adhered, and completed follow up by treatment group. We will summarize reasons for change in treatment and the reasons for withdrawal.

In addition, we will report per participating site the number of patients assessed for eligibility, the number of subjects randomized, the number of subjects per allocation group, and the number of subjects analyzed.

5.2 Baseline data

Baseline characteristics, raw distributions on the CPC, and scores of secondary outcome measures will be presented in a descriptive way. The following will be presented: age, sex, location of cardiac arrest (in-hospital or out-of-hospital), presumed cause of cardiac arrest (cardiac, other cause, unknown), bystander witnessed cardiac arrest (yes or no), first monitored cardiac rhythm (shockable

or non-shockable), time from cardiac arrest to start of basic life support, time from cardiac arrest to return of spontaneous circulation, motor score of Glasgow Coma Scale at time of randomization, pupillary light reflexes (bilaterally absent or present), corneal reflexes (bilaterally absent or present), APACHE-IV-scores, Target Temperature (≤33 C or > 33 C), maximum doses of propofol, midazolam, morphine, fentanyl and remifentanil before randomization, time between cardiac arrest and start of continuous EEG, time between cardiac arrest and diagnosis of status epilepticus, and presence of nystagmus or myoclonus at time of diagnosis.

In addition, we will report EEG characteristics based on central reading: type of status epilepticus (unequivocal seizures with discharge frequency ≥2,5 Hz, evolving seizures with discharge frequency <2,5 Hz, periodic discharges with frequency <2,5 Hz, or other rhythmic or periodic activity) and background continuity (continuous, discontinuous, or suppressed).

For continuous variables, we will assess the distribution of data using visual inspection of histograms. If continuous variables follow a normal distribution, they will be presented as mean (standard deviation), and otherwise as median (interquartile range). Categorical variables will be presented as numbers (percentage).

5.3 Adherence to allocated treatment

We will summarize adherence descriptively per treatment group.

5.4 Treatment details

Although we provide a guideline for treatment of status epilepticus, the exact choice of medication is left to the discretion of the treating physician. In order to describe details on treatment of status epilepticus, such as the intensity of treatment and the treatment contrast between intervention and control group, we will report the following details for both groups: proportion of subjects that were treated intensively (with the aim to suppress all epileptiform activity on the EEG) for at least 24 hours, proportion of subjects that were treated intensively for at least 2 x 24 hours, number of anti-epileptic drugs given in the first 48 hours after randomization (0,1,2, or ≥3), , and number of sedative drugs given in the first 48 hours after randomization (0,1,2, or ≥3). For relevant medication (phenytoin, valproic acid, levetiracetam, other antiepileptic drugs, midazolam, propofol, thiopental, other barbiturate) we report the proportion of subjects receiving these drugs in the first 48h after randomization, the proportion of subjects receiving a loading dose (if applicable) and the maintenance dose (if applicable). Additionally, we report the numbers of subjects with treatment restrictions during the ICU admission (do not resuscitate, withdrawal of life-sustaining treatment).

Treatment details will be reported in a descriptive way, without formal statistical testing.

5.5 Analysis of primary outcome measure

The primary analysis will be a single comparison between the treatment groups of the primary outcome measure after three months. This analysis will be performed according to the intention-to-treat principle. To assess the effect of treatment with anti-epileptic drugs, an absolute risk reduction of poor outcome and its corresponding 95% confidence interval will be calculated.

If necessary, multivariable logistic regression analysis will be used to adjust for imbalances in main prognostic variables between intervention and control group.

5.6 Analysis of secondary and tertiary outcome measures

Secondary analyses will include absolute risk reductions of poor outcome for other dichotomies of the CPC (1 vs. 2-5, 1-3 vs. 4-5, 1-4 vs. 5), as well as any shift across the CPC in the direction of a better outcome of the intervention group as analyzed by multivariable ordinal logistic regression, expressed as a common odds ratio.

Tertiary analyses will include between-group differences in mortality, CPC scores at 6 and 12 months, length of stay on the ICU, duration of mechanical ventilation and seizure recurrence within one year, analyzed by means of independent samples t-tests, Mann-Whitney tests, Chi-Squared tests, or Fisher exact tests, as appropriate. Because of the expected high mortality in both treatment groups, the analysis of long-term outcomes at 6 and 12 months will be descriptive.

In addition we will report the treatment effect based on central reading of EEG, for subjects in both the intervention and treatment groups: degree of suppression of epileptiform activity from 0 to 24h after randomization (no suppression, partial suppression, complete suppression), whether the electrographic status epilepticus was returning / ongoing at 24h after randomization or not. degree of suppression of epileptiform activity from 24 to 48h after randomization, and whether the electrographic status epilepticus was returning / ongoing at 48h after randomization or not.

5.7 Subgroup analysis

Although the study lacks statistical power for precise estimates of treatment effects in subgroups, we will assess heterogeneity of treatment effects in pre-specified subgroups defined by EEG patterns at inclusion (unequivocal seizures, evolving seizures, generalized periodic discharges, other rhythmic or periodic activity), EEG background continuity at inclusion (continuous, discontinuous, or suppressed), and time of onset of status epilepticus (≤24h, 24-48h, ≥48h after resuscitation). The statistical significance of possible differences between subgroups with regard to treatment effect will be tested with interaction terms. No adjustments for multiple tests will be made.

5.8 Serious adverse events

We will report serious adverse events (SAEs) other than outcome events grouped by body system, tabulated per treatment group.

6. References

1. Ruijter BJ, van Putten MJ, Horn J, et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials 2014;15(1):433.

2. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 1992;30(6):473–483.

3. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 1979;134:382–389.

Appendix 1

Ahead of the database lock and unblinding, data for all individual subjects will be checked using the following consistency checks (programmed in MATLAB with automatically generated errors or warnings):

Baseline variables
- Age below 18 (error)
- Age above 100 (warning)
- A negative time between cardiac arrest and resuscitation (error)
- A negative duration of resuscitation (error)
- Delay between cardiac arrest and resuscitation > 15 minutes (warning)
- Duration of resuscitation of > 30 minutes (warning)
- Dose of propofol before randomization > 8mg/kg/h (warning)
- Dose of midazolam before randomization > 200 µg/kg/h (warning)
- Dose of morphine before randomization > 50 µg/kg/h (warning)
- Dose of fentanyl before randomization > 3 µg/kg/h (warning)
- Dose of remifentanil before randomization > 10 µg/kg/h (warning)

Treatment details
- dose of midazolam <30 µg/kg/h or > 200 µg/kg/h (warning)
- loading dose of phenytoin < 10 mg/kg or > 20 mg/kg (warning)
- maintenance dose of phenytoin < 1mg/kg/day or > 5mg/kg/day (warning)
- loading dose of valproic acid < 10 mg/kg or > 25 mg/kg (warning)
- maintenance dose of valproic acid < 10mg/kg/day or > 20g/kg/day (warning)
- loading dose of levetiracetam < 10 mg/kg or > 25 mg/kg (warning)
- maintenance dose of levetiracetam < 10mg/kg/day or > 25mg/kg/day (warning)
- dose of propofol < 1mg/kg/h or > 8 mg/kg/h (warning)
- dose of thiopental < 1 mg/kg/h or > 15 mg/kg/h (warning)
- dose of pentobarbital < 1 mg/kg/h or > 15 mg/kg/h (warning)

Treatment restrictions
- Patient died from withdrawal of life-sustaining treatment (WLST) but WLST was not recorded as treatment restriction (error)

Inconsistencies in timing of study events
- start time of treatment does not match start time of first medication used to treat status epilepticus (error)
- admission time to ICU before start time of resuscitation (error)
- admission time to ICU > 12 hours after time of resuscitation (warning)
- EEG start time before time of resuscitation, before admission to ICU or > 24 hours after resuscitation (error)
- time of diagnosis before time of start EEG recording (error)
- time of diagnosis more than 100 hours after resuscitation (warning)
- time of randomization before time of diagnosis or > 3 hours after diagnosis (error)
- time of start of treatment before time of randomization (error)
- start of second 24h of treatment less than 24h after start of first 24h of treatment (error)
- start of second 24h of treatment > 48h after start of first 24h of treatment (warning)
- stop of mechanical ventilation after time of ICU discharge (error)