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Time to Stop (TTS) Trial: a trial to investigate early antiepileptic drug withdrawal after pediatric epilepsy surgery

Submission date
28/03/2013

Recruitment status
Stopped

Registration date
08/05/2013

Overall study status
Stopped

Last Edited
08/05/2017

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
There is no consensus about timing of anti-epileptic drug (AED) withdrawal after pediatric epilepsy surgery. A previous study of 766 children suggested that early withdrawal does not affect long-term seizure outcome, unmasks incomplete surgical success sooner, and prevents unnecessary AED use in many children. The aim of this study is to demonstrate cognitive and behavioral benefits and improvement of quality of life, and confirm safety of early AED discontinuation.

Who can participate?
Patients aged younger than 16 years from participating pediatric epilepsy surgery centers in Europe.

What does the study involve?
Participants are randomly allocated to one of two groups: either an early AED withdrawal group, that starts reduction of AEDs four months after surgery and completes withdrawal within eight months after start of withdrawal, or a late AED withdrawal group, in which tapering off medication starts at 12 months after surgery and completion should be within 20 months after surgery. The primary outcome measure is attention, as measured by reaction time on CPT (Conner's Performance Test). Other neuropsychological domains are assessed by standard neuropsychological testing, as part of standard clinical care. Other outcome measures are seizure recurrences, eventual seizure freedom and cure, behavioral changes and quality of life. In both groups, the latest follow-up time point is 20 months after the start of intended withdrawal (i.e. 24 months in the early group, and 32 months in the late withdrawal group), thus the total follow-up duration of being at risk [without drugs] is identical between groups. Patients are studied in an outpatient clinical setting.

What are the possible benefits and risks of participating?
The study may be beneficial to the patients in the early withdrawal arm, as they are devoid of medication in an earlier postoperative stage. Their cognitive functions might improve and medication related side effects may be less frequent. With regard to the risk assessment, the

risk for seizure recurrences in the early withdrawal group is comparable to the late withdrawal group, as patients with known predictors of unfavorable outcome are excluded. The recurrences will only occur earlier during follow up. A recurrence rate of around 30% is expected, comparable to normal clinical practice. Most of the patients regain seizure freedom after restart of antiepileptic drugs, as shown previously and in accordance to current clinical experience.

Where is the study run from?
University Medical Center Utrecht (Netherlands)

When is the study starting and how long is it expected to run for?
January 2014 to January 2019

Who is funding the study?
Dutch National Epilepsy Fund (Netherlands)

Who is the main contact?
Prof. Kees PJ Braun

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2011-005971-18

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Time to Stop (TTS) Trial: a randomised controlled trial to investigate early antiepileptic drug withdrawal after pediatric epilepsy surgery

Acronym
TTS Trial

Study objectives
Early antiepileptic drug withdrawal is beneficial to patients with regard to cognitive outcome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics Committee of the University Medical Center Utrecht, 24/01/2014, local protocol ID: 13-617

Study design
Randomised open European multicenter clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Intractable epilepsy

Interventions
The Time to Stop trial will compare an early AED withdrawal group, that starts reduction of AEDs four months after surgery and completes withdrawal within eight months after start of withdrawal, with a late AED withdrawal group, in which tapering off medication starts at 12 months after surgery and completion should be within 20 months after surgery.

Intervention Type
Drug

Phase
Not Applicable

Primary outcome measure
The primary objective of the study is to assess whether early AED withdrawal improves cognitive function, in terms of attention, information processing- and psychomotor speed, memory,

language and IQ/DQ scores. Attention will be the main outcome measure, on which the power calculation is based.

Attention deficits (AD) are assessed using a Conner's Performance (Kiddie) test and calculate IQ /DQ scores. The other neuropsychological domains will be assessed by subtests of the intelligence tests. We will compare neuropsychological outcome between the two withdrawal groups at t1 (preoperatively), t2 (at 12 months) and t3 (at 24 months).

Secondary outcome measures
1. To confirm safety, in terms of seizure recurrences, long term seizure freedom and cure, of early AED withdrawal. In the randomized trial we determine long-term seizure outcome and cure at 20 months following intended start of AED reduction (being theoretically 'at risk' during an identical time window in both groups). Seizure freedom will be defined as complete seizure freedom for at least one year [Engel 1(3) of International League Against Epilepsy (ILAE) 1-2(4)], and cure as seizure freedom and AED freedom for at least one year. The existence of seizure recurrences will be measured every time the patient visits her/his epileptologist, and if parents call the hospital to report seizure recurrences.
2. To compare behavioural problems between the two withdrawal groups, parents of participants will, at both postoperative neuropsychological test points, complete a Child Behavior Checklist (CBCL) (12 and 24 months postoperatively)
3. To compare quality of life between the two withdrawal groups. Patients will, at both postoperative neuropsychological test points, complete a Pediatric Quality of Life InventoryTM (PedsQL™) and the The Hague Side Effects Scale (HASES) (12 and 24 months postoperatively).

Overall study start date
01/01/2014

Completion date
01/01/2019

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Younger than 16 years at surgery, with focal non-idiopathic epilepsy
2. Native speaker in the language the neuropsychological tests have to be taken
3. Be able to perform a Conner's Performance Test preoperatively (generally that means age > 4 yrs, and IQ > 60)
4. Underwent intentional curative epilepsy surgery
5. After surgery, the treating physician considers withdrawal of antiepileptic drugs (AEDs), with the intention to completely discontinue medication, at whatever point in time.
6. Both the treating physician, the patient, if capable, and the parents agree with randomization in either arm of the study
7. Postoperative seizure freedom was achieved (with the exception of so called running down seizures not outlasting longer than two weeks)

Participant type(s)
Patient

Age group
Child

Upper age limit
16 Years

Sex
Both

Target number of participants
180

Key exclusion criteria
1. A contraindication to be randomized to either of the two withdrawal arms
2. The treating physician does not want to discontinue all AEDs within a maximum time frame of eight months as prescribed in the study protocol.
3. Multifocal MRI abnormalities, incomplete resection of the anatomical or epileptogenic lesion certified before randomisation (if considered necessary by the treating physician by MRI) and, if a postoperative EEG is performed before randomisation, epileptic EEG abnormalities (these being the most important risk factors of seizure recurrence or unfavourable long-term seizure outcome).
4. Use of more than three AEDs at time of surgery. The reason to choose for a maximum of three AEDs is that clinicians would not want to wait 12 months (the late withdrawal arm) to withdraw the first AED in patients that use so many AEDs. Furthermore, withdrawing AEDs within 8 months seems reasonable and feasible for a maximum of three AEDs.
5. Patients who are on a ketogenic diet or have a vagal nerve stimulator implanted.
6. If surgery is primarily intended as tumor surgery and not as epilepsy surgery

Date of first enrolment
01/01/2014

Date of final enrolment
01/01/2019

Locations

Countries of recruitment
France

Germany

Netherlands

Switzerland

United Kingdom

Study participating centre

Heidelberglaan 100
Utrecht
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3508 AB

Sponsor information

Organisation
University Medical Center Utrecht (Netherlands)

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Sponsor type
Hospital/treatment centre

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ROR
https://ror.org/0575yy874

Funder(s)

Funder type
Charity

Funder Name
Dutch National Epilepsy Fund (Netherlands) ref: (08-10)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	26/10/2015		Yes	No