TimeToStop (TTS) Trial, A randomized controlled trial of cognitive consequences of early versus late antiepileptic drug withdrawal after pediatric epilepsy surgery

Published: 30-12-2013
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Primary Objective: To assess whether early postoperative AED withdrawal improves cognitive function compared to late withdrawal.Secondary objectives: * To confirm safety of earlier AED withdrawal; we will assess eventual seizure freedom, seizure...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON43958

Source
ToetsingOnline

Brief title
Time To Stop (TTS) Trial

Condition

- Seizures (incl subtypes)
- Nervous system, skull and spine therapeutic procedures

Synonym
epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Nationaal Epilepsie fonds 08-10

Intervention

Keyword: antiepileptic drug, cognitive outcome, epilepsy surgery, seizure outcome

Outcome measures

Primary outcome

Primary outcome: change in neurocognitive domains (expressed as EpiTrack scores

and IQ) at one and two years after surgery, compared with presurgical

functioning. (research protocol page 22, paragraph 7.1.1.)

Secondary outcome

seizure recurrences, eventual seizure freedom and *cure* at 20 months following

start of AED reduction, quality of life and behaviour.

Study description

Background summary

Cure, is the ultimate goal for epilepsy surgery. We recently showed that early AED withdrawal seemed safe in a selected subgroup of successfully operated patients, without the identified unfavourable predictors for seizure recurrences during or after AED withdrawal or eventual seizure freedom (epileptic EEG abnormalities, multifocal MRI lesions and incomplete resection of the lesion). We question if early AED withdrawal is also beneficial for children with regard to cognition. Our hypothesis is that early withdrawal is beneficial for patients with respect to their cognition.

Study objective

Primary Objective: To assess whether early postoperative AED withdrawal improves cognitive function compared to late withdrawal.
Secondary objectives:
* To confirm safety of earlier AED withdrawal; we will assess eventual seizure

freedom, seizure recurrences and *cure* as outcome measure at latest follow up. (Engel 1 or ILAE 1-2 for at least 1 year).
* To assess whether early AED withdrawal improves quality of life after epilepsy surgery.
* To compare behavioural problems between the two withdrawal groups

Study design

randomized trial with blinded primary outcome measure, in which an early AED withdrawal group in which postoperatively seizure free patients will start tapering off AEDs 4 months after surgery, will be compared to a late AED withdrawal group in which seizure free patients will start tapering off AEDs 12 months after surgery.

Intervention

The intervention group will start tapering off medication 4 months postoperatively instead of the conventional 12 months postoperatively. The taper period may take maximally 8 months in both groups.

Study burden and risks

Early AED withdrawal has been proven safe in our recently completed European retrospective cohort study. The by us identified predictors of unfavorable outcome, have been defined as exclusion criteria for participation in the current proposed trial, in order to ensure safety (multifocal MRI abnormalities, incomplete resection of the anatomical lesion or epileptogenic lesion, epileptic abnormalities on postoperative EEC [if performed], and more than three AEDs preoperatively).

As in the protocol, and at point E9 described, we have performed a test analysis on our retrospective database, with children who would qualify for the current trial. In this group we found no relationship between the interval to AED reduction and the occurrence of relapses during or after AED withdrawal. We expect a similar rate of recurrence in both treatment arms, corresponding to the number of relapses in daily clinical practice. The DSMB will monitor safety, blinded by the number of recurrences in both arms control.

With regard to extent of the burden: the number of hospital visits will be the same as in normal clinical care. The regular neuropsychological examination for children undergoing epilepsy surgery contains IQ testing and the EpiTrack Junior. Additionally for the purpose of this trial, patients will be asked to fulfill quality of life questionnaires 12 - and 24 months after surgery (at the time of neuropsychological assessment), which will take up to 5-10 minutes, for the smaller children or infants who are mentally incapable, the questionnaire will be done by parents.

This study van only be performed in the proposed population as it is group related: medication can be withdrawn sooner and safer in children than in adults as described previously and cognitive side effects have more consequences in children as their brain is still in the process of maturation. Plus, in adults, the possibly increased relapse rate associated with early AED discontinuation has a much higher impact than in children, as it may lead to a temporary license suspension, stigmatization and obstruction of professional careers. For children, however, the possible slightly increased risk of recurrences and their impact does, not weigh against the well known neurocognitive side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Younger than 16 years at surgery, with focal non-idiopathic epilepsy, with written informed consent of parents and children when older than 12 years old.
* Native speaker in the language the neuropsychological tests have to be taken
* Be able to perform the EpiTrack Junior preoperatively
* Underwent intentional curative epilepsy surgery
* After surgery, the treating physician considers withdrawal of AEDs, with the intention to completely discontinue medication, at whatever point in time.
* Both the treating physician, the patient, if capable, and the parents agree with randomization in either arm of the study
* Postoperative seizure freedom was achieved (with the exception of so called running down seizures not outlasting longer than two weeks)

Exclusion criteria

* A contraindication to be randomized to either of the two withdrawal arms
* The treating physician does not want to discontinue all AEDs within a maximum time frame of eight months as prescribed in the study protocol.
* 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).
* Use of more than 3 AEDs at time of surgery. The reason to choose for a maximum of 3 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 3 AEDs.
* Patients who are on a ketogenic diet or have a vagal nerve stimulator implanted.
* If surgery is primarily intended as tumor surgery and not as epilepsy surgery

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Keppra
Generic name:	Levetiracetam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lamictal
Generic name:	Lamotrigine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tegretol
Generic name:	carbamazepine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-01-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-12-2014
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005971-18-NL
ISRCTN	ISRCTN88423240
CCMO	NL31045.041.13