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Does giving an anti-epileptic drug before surgery help prevent seizures in patients with glioma (a type of brain tumour) who have not previously had a seizure?

Submission date
10/07/2018

Recruitment status
No longer recruiting

Registration date
02/07/2019

Overall study status
Completed

Last Edited
04/07/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Gliomas are the most common type of primary brain tumour, with about 6000 new cases each year in the UK. 1 in 5 patients (20%) with a suspected glioma will present with an epileptic seizure and be treated with an anti-epileptic drug (AED). 4 in 5 patients (80%) do not present with seizures. Up to half of these patients will develop epilepsy requiring AED over their lifetime. Seizures can cause anxiety, loss of independence, affect quality of life & sometimes threaten life. AEDs prevent seizures in 50% of patients with epilepsy and reduce the frequency and severity of seizures in a further 20-30%. Currently, some doctors prescribe AEDs to patients before neurosurgery for tumours, whilst others do not. Researchers need to find out whether AEDs are effective and worthwhile to give the best advice to surgeons and patients in future. Previous studies of AEDs to prevent seizures in patients with a brain tumour have not shown clear results. However, these studies have included tumour types where the risk of seizures is low and they used older AEDs that may interfere with chemotherapy used in brain tumours and have a high risk of side effects. The newer AED, levetiracetam, has fewer side effects and does not interfere with chemotherapy drugs. There is a balance of potential advantages and disadvantages for prescribing levetiracetam. The aim of this study is to find out whether giving patients with a suspected primary brain tumour (cerebral glioma), who have never had a seizure, levetiracetam before surgery to see if it will help prevent them from developing seizures. This will help to give neurosurgeons in the UK the best advice about how to treat patients with a cerebral glioma.

Who can participate?
Patients due to have surgery who have recently been diagnosed with a possible brain tumour, and who have never had an epileptic seizure

What does the study involve?
Participants have a series of tests and examinations to confirm that they are eligible. They are then randomly allocated into two groups. The first group receive levetiracetam daily for 1 year.

The second group receive no anti-epileptic drug; this is currently normal practice. Participants are contacted by the trials research nurse monthly by phone to check about any seizures or side effects. If there is a seizure, participants are asked to contact their usual treating team. A neurologist reviews the participant to confirm whether a seizure has occurred. Participants who have a seizure are asked to complete a seizure diary card and questionnaire about the severity of their seizure. All participants are asked to complete questionnaires about their symptoms and possible side effects at entry into the study and every 3 months for a minimum of 1 year. There is no need for any additional blood tests or additional hospital visits. Participants are able to continue on levetiracetam at the end of the study or come off it if they wish.

What are the possible benefits and risks of participating?
It is not known whether there will be a direct benefit to the participants. The researchers hope to be able to find out if taking levetiracetam before surgery will have any effect on delaying, stopping or altering the severity of any seizure that happens after the surgery. Participants taking levetiracetam might expect a lower risk of developing seizures, although the size of this effect is as yet unknown. The results of the trial will hopefully allow the researchers to provide the best advice on preventing seizures in patients with suspected cerebral glioma. A disadvantage of taking part in the study is that participants could experience side effects of levetiracetam. The levetiracetam is given at a lower dose for the first two weeks before increasing to the required dose to help reduce the side effects.

Where is the study run from?
Scottish Clinical Trials Unit, Edinburgh (SCTRU) (UK)

When is the study starting and how long is it expected to run for?
February 2019 to November 2023

Who is funding the study?
The study is funded by the National Institute for Health Research (NIHR). UCB Pharma, the manufacturer of levetiracetam, have provided this drug free of charge for patients taking part in this study that are allocated to the levetiracetam group

Who is the main contact?
Mrs Tracy McEleney, Service Manager, Public Health Scotland (PHS) Research Office, Edinburgh (UK), phs.researchoffice@phs.scot

Study website
https://www.springtrial.org.uk/

Contact information

Type(s)
Public

Contact name
Mrs Tracy McEleney

Contact details
Public Health Scotland Research Office
Gyle Square
1 South Gyle Crescent

Edinburgh
United Kingdom
EH12 9EB
+44 (0)131 275 6544
phs.researchoffice@phs.scot

Additional identifiers

EudraCT/CTIS number
2018-001312-30

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
HTA 16/31/136

Study information

Scientific Title
Seizure PRophylaxis IN Glioma (SPRING): a Phase III randomised trial comparing prophylactic levetiracetam versus no prophylactic antiepileptic drug in patients with newly diagnosed presumed supratentorial glioma

Acronym
SPRING

Study objectives
There is no consensus regarding the need for prophylactic AEDs in newly-diagnosed suspected glioma patients who have not experienced seizures. Unfortunately, data regarding prophylactic AED use is scant and inconclusive. Most of the available evidence comes from older, small studies that enrolled patients with brain metastases and benign tumours in addition to gliomas. Furthermore, these studies universally evaluated prophylaxis with first-generation AEDs such as phenytoin, phenobarbital, carbamazepine, and valproic acid. These drugs have higher rates of early adverse effects (such as rash, haematological or liver upset) compared to levetiracetam, and they have important interactions with other drugs including corticosteroids and chemotherapeutics. Levetiracetam is an effective, safe, and well-tolerated medication. It has no known drug interactions and does not require serum level monitoring. It is however frequently associated with fatigue (15%), behavioural problems (13-38%) and problems with aggression. A definitive clinical trial is needed to determine whether the policy of prophylactic levetiracetam therapy reduces the risk of first seizures in this patient population. In addition, evaluation of the impact of levetiracetam on fatigue, behaviour and aggression is needed in this vulnerable population with already high rates of fatigue, cognitive and behavioural problems. There is some evidence that levetiracetam may worsen these symptoms. There is a need to study this area in a well-designed randomised controlled trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/02/2019, East of England – Essex REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; Tel: +44 (0)207 104 8115; Email: nrescommittee.eastofengland-essex@nhs.net); REC ref: 18/EE/0389

Study design
Two-arm multicentre phase III randomised trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Glioma

Interventions
After a patient has consented to participate in the study and after ensuring that the patient meets all eligibility criteria, sites will randomise the patient using a web-based randomisation system. This will not be a blinded study and will not have placebo control and as such will be a "real world" study of prophylactic anti-epileptic drug (AED) vs no AED. Patients will be randomised into one of two arms:
Group 1: Levetiracetam 500 mg twice daily for 2 weeks then increasing to 750 mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500 mg prior to surgery. (In those with moderate chronic kidney disease stage 3 (estimated Glomerular Filtration Rate eGFR 30-59 mL/min/1.73m2) a starting dose of 250 mg twice a day for 2 weeks, then increasing to 500 mg twice a day thereafter).
Group 2: no AED treatment (standard care)

Intervention Type
Drug

Pharmaceutical study type(s)
Comparator study

Phase
Phase III

Drug/device/biological/vaccine name(s)

Levetiracetam

Primary outcome measure
Number of patients developing seizures measured using two-sided type I error level of 5% at 1 year

Secondary outcome measures
1. Time to first seizure measured using accelerated failure time model at 1 year
2. Time to first tonic clonic seizure measured using accelerated failure time model at 1 year
3. Mood, personality, fatigue and memory measured using Mann-Whitney U test (exact method) at 1 year
4. Severity of first seizure should it occur, measured using the LAEP questionnaire at pre surgery (baseline) and 3 monthly to coincide with clinic visits
5. Quality of life, measured using the relative changes in health-related quality of life (HRQoL) resulting from the physical and psychological benefit together with any harms associated with each treatment strategy . This will be administered at pre-surgery (baseline), 3 months, 6 months, 9 months and 12 months post randomisation
6. Progression-free survival determined clinically based upon interpretation of MRI scans, clinical state of the patient and steroid dose at 1 year of randomisation
7. Overall survival measured by using by the median overall survival time for each study arm, tabulated together with the corresponding 80% confidence interval. This will be measured at 1 year of randomisation
8. Costs to the NHS and personal social services (PSS) measured using a within-trial economic analysis which will estimate the incremental cost per quality-adjusted life year (QALY) gained over a 12-month time horizon. The perspective of the analysis (i.e. whose costs and benefits are considered) will be the NHS and personal social services, but the researchers will also take a wider perspective by including costs borne by trial participants, for example out of pocket expenses on health care and the time and travel costs of accessing care. This will be measured over the 12 months trial follow-up
9. Cost-effectiveness of prophylactic levetiracetam measured as incremental cost per QALY at 12 months and modelled over estimated survival

Overall study start date
05/02/2019

Completion date
02/11/2023

Eligibility

Key inclusion criteria
Patients:
1. Patients with suspected cerebral glioma on MRI or CT
2. Capable of giving informed consent
3. Patients must be ≥16 years old
4. Patients must have a Karnofsky performance status of >60
5. Patients must be able to safely swallow pills
6. Planned surgery for presumed glioma (biopsy or resection)

Carers:
Capable of giving informed consent

Participant type(s)
Mixed

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
804

Total final enrolment
107

Key exclusion criteria
Patients:
1. Pregnant
2. History of any type of seizure for at least 10 years prior to randomisation
3. Known Severe Chronic Kidney Disease (CKD4 - eGRR <30 ml/min)
4. Concomitant methotrexate
5. Concomitant Anti-Epileptic Drug (including use for other reasons (e.g. pain))
6. Concomitant Benzodiazepines
7. Hypersensitivity to Levetiracetam

Date of first enrolment
15/07/2019

Date of final enrolment
31/08/2022

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Western General Hospital
Crewe Road South

Edinburgh
United Kingdom
EH4 2XU

Study participating centre
The Walton Centre
Department of Neurosurgery
The Walton Centre
Lower Lane
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Kings College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2WB

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
University Hospital Southampton
Southampton University Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre

Salford Royal Hospital
Stott Lane
Eccles
Salford
United Kingdom
M6 8HD

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
United Kingdom
PR2 9HT

Sponsor information

Organisation
Public Health Scotland

Sponsor details
Gyle Square
1 South Gyle Crescent
Edinburgh
Scotland
United Kingdom
EH12 9EB
+44 (0)131 275 6114
nss.spring@nhs.net

Sponsor type
Government

Website
https://www.publichealthscotland.scot/

ROR
https://ror.org/023wh8b50

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The research output of the study will be to inform patients and funders what the benefits and risks are to taking prophylactic AED (levetiracetam) over a one- year period and whether this significantly reduces the chance of having a seizure. It is also likely to give information on the short-term benefits and harms in the first post-operative week (“early seizures”). It will inform the research community what the additional side effects of Levetiracetam are over and above symptoms associated with surgery and radiotherapy. Lastly, although not specifically designed to look at any anti-tumoural effect of levetiracetam, it will give information about whether Levetiracetam improves time to progression or overall survival. As this is the first ever prophylactic AED study in a group of patients at high risk of developing seizures, the result will inform the international research community and may lead to a change in national and international neurosurgical or neuro-oncological guidelines. Exploratory analyses may identify particularly high-risk groups, e.g. cortex or temporal lobe based gliomas, or large mass lesions. The study will be able to determine the cost and cost-effectiveness of prophylactic AED.

Study clinicians will be involved in developing recommendations for practice and policy, based on the results of the SPRING trial. Health service provision/requirements may change. The results will impact on how future clinical trials are designed to ensure acceptability to patients and clinicians. If conclusive the research will change activity by resulting in the routine use, or

discontinuation of use of prophylactic AEDs prior to tumour surgery in future, in neurosurgical centres in the UK and possibly beyond. The results may change the attitudes, awareness and behaviour of neurosurgeons in prescribing prophylactic AEDs and increase awareness of potential benefit in less high-risk preoperative patients or potential futility where there has been no benefit in this high-risk group, thereby clarifying the decision making process and standardising practice throughout the NHS. The study is important even if negative, as it will influence practice and provide guidance NOT to give prophylactic levetiracetam.

Beneficiaries will be patients, neurosurgeons, neurologists and oncologists. They will benefit when the study is analysed and ready for presentation at scientific conferences, ideally as late-breaking platform presentations at relevant international meetings. The results will be fully available after the publication of full articles in a journal.

Research will be reported via publication in the NIHR HTA Journal to ensure the research is published fully, with the abstract/full report freely available via the NIHR Journals Library website via Europe PubMed Central. The researchers will prepare for a research Open Access publication in a peer-reviewed journal e.g. Lancet or New England Journal of Medicine.

The research will be disseminated to the wider public as well as research participants by actively involving patients, participating centres, their staff and via presentation at professional UK /international bodies involved in management of patients with brain tumours (Society of British Neuro-Surgery (SBNS); Association of British Neurologists (ABN); Royal College of Radiologists; British Neuro-Onc Society (BNOS). The researchers will use networks of relevant UK charities through regular research updates and annual publications, including the IBTA magazine (13,000 copies sent to recipients in 113 countries and widely distributed at international neuro-onc and cancer conferences).

The PPI panel will develop a dissemination plan so that patients/caregivers understand the findings and can engage confidently with clinicians about the prophylactic use of AEDs. They will write lay summary of findings, create materials for media forms e.g. press releases, blogs, be a voice for the researcher/consumer community, and contribute to the final paper. Presentations with key patient messages will be planned with professional organisations, local health systems. Dissemination methods include podcasts, available through journals (NEJM) and through the SPRING website, linked to NOCTURN (Neuro-Onc Clinical Trials UK Research Network) and SBNS, ABN, BNOS sites.

Intention to publish date
01/09/2025

Individual participant data (IPD) sharing plan
All presentations and publications relating to the trial must be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial Management Group, representatives from SCTRU and high accruing clinicians. The trials offices and all participating centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version V5.1	04/02/2019	11/07/2019	No	No
HRA research summary			28/06/2023	No	No