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Study of two anti-thyroid drug treatment regimens in young people with thyrotoxicosis

Submission date
27/06/2011

Recruitment status
No longer recruiting

Registration date
12/10/2011

Overall study status
Completed

Last Edited
14/05/2019

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Thyrotoxicosis (an overactive thyroid) arises when there is too much thyroid hormone in the body. It is an uncommon disorder in childhood and adolescence. Most patients with thyrotoxicosis have Graves disease, where antibodies 'switch on' the thyroid gland and causes it to produce too much thyroid hormone. Many general paediatricians have experience of managing patients with thyrotoxicosis but national guidelines to assist in patient care have not been produced to date. There is no ideal therapy for thyrotoxicosis in children and adolescents. The three treatment types for thyrotoxicosis - anti-thyroid drugs, surgery and radioiodine - all have significant disadvantages. Particular considerations when managing young people include:
1. Low remission rates following a course of anti-thyroid drug therapy - when the anti-thyroid drug is stopped the condition usually returns
2. Concerns about the morbidity associated with thyroidectomy - thyroid surgery leaves a scar, can cause voice change and can leave patients dependent on Vitamin D tablets to prevent low calcium levels
3. Shortage of data on the long-term safety of radioiodine - radioiodine involves radiation which will be associated with a small increase in cancer risk

Children and adolescents with autoimmune thyrotoxicosis in the United Kingdom are usually treated with anti-thyroid drugs, from diagnosis for 1 to 4 years. Treatment is then stopped and patients whose condition deteriorates return to anti-thyroid drugs or are treated with surgery or radioiodine. Lifelong thyroid hormone replacement will be required if the thyroid gland is removed by surgery or eradicated by radioiodine. The excess thyroid hormone in thyrotoxicosis can prevent people from concentrating properly and can also affect the health of the heart and bones. Keeping thyroid hormone levels normal is therefore very important. There are two possible approaches when treating patients with anti-thyroid drug (almost always carbimazole):
1. Combined therapy - otherwise known as 'block and replace', where thyroid hormone production is prevented by anti-thyroid drug and thyroxine is then added in a replacement dose
2. Adaptive therapy - otherwise known as 'dose titration', where the dose of the anti-thyroid drug is adjusted so that hormone production is normalised

Both strategies are used in adults but it is unclear which of these approaches is the most appropriate in the young person. Potential advantages of the combined therapy include

improved stability with fewer episodes of hyper- or hypo-thyroidism, a reduced number of blood tests and visits to hospital, and improved remission rates following a larger anti-thyroid drug dose. Potential advantages of the adaptive therapy include fewer side effects with a lower anti-thyroid drug dose, and improved compliance on one rather than two medications. The aim of this study is to find out which treatment - block and replace or dose titration - is the most appropriate medical treatment during childhood and adolescence.

Who can participate?
Patients with thyrotoxicosis aged between 2 and 16 at the time of diagnosis

What does the study involve?
The study involves participants undergoing standard medical therapy for thyrotoxicosis using an anti-thyroid drug. Participants are randomly allocated to either the 'block and replace' or the 'dose titration' approach for a period of 3 years.

What are the possible benefits and risks of participating?
Risks to participants are low, as this study is looking at treatments already used in standard practice.

Where is the study run from?
Royal Victoria Infirmary (UK).

When is the study starting and how long is it expected to run for?
January 2005 to January 2013

Who is funding the study?
Newcastle upon Tyne NHS Foundation Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01436994

Clinical Trials Information System (CTIS)
2011-001238-40

Protocol serial number
2759

Study information

Scientific Title
A randomised study of two anti-thyroid drug treatment regimens in young people with thyrotoxicosis

Study objectives
Current hypothesis as of 06/10/2014:
'Block and replace' vs 'dose titration' anti-thyroid drug treatment: is there any difference between the two regimens in terms of biochemical stability.

Previous hypothesis:
Block & replace vs titration - any/no difference between efficacy, side effects or remission rates.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Thames Valley Multi-centre Research Ethics Committee (committee name changed to Berkshire Valley REC), 14/07/2004, ref: 04/12/015

Primary study design
Interventional

Study design
Two-arm randomised controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Thyrotoxicosis in children, endocrinology

Interventions
Current interventions as of 06/10/2014:
1. This is a multi-centre phase III randomised controlled trial of two standard treatments comparing outcomes for the block and replace regimen versus dose titration regimen in patients with thyrotoxicosis
2. The target recruitment is for 128 participants
3. Participants will be randomised, on a 1:1 ratio, as follows:

3.1. Block and replace regimen: [carbimazole (or propylthiouracil) plus thyroxine]
3.2. Titration regimen: carbimazole (or propylthiouracil)
4. Block and replace regimen:
4.1. The objective of treatment is to maintain free thyroxine concentrations in the normal laboratory range (mean -2SD < FreeT4 > mean + 2SD) with a TSH that is also within the normal laboratory range (neither elevated nor suppressed)
4.2. Carbimazole is commenced in a dose of 0.75 mg/kg/day The intention is to completely prevent endogenous thyroxine production
4.3. Thyroxine is then added in a low replacement dose as the thyroid hormone levels fall into the lower half of the laboratory normal range
5. Dose titration regimen:
5.1. The objective of treatment is to maintain free thyroxine concentrations in the normal laboratory range (mean -2SD < FreeT4 > mean + 2SD) with a TSH that is also within the normal laboratory range (neither elevated or suppressed)
5.2. Carbimazole is commenced in a dose of 0.75 mg/kg/day until thyroid hormone levels fall into the local laboratory normal range
5.3. The dose is then reduced to 0.25 mg/kg/day with the intention of maintaining a euthyroid state as reflected by a free thyroxine and TSH within the normal range

Previous interventions:
1. This is a multi-centre phase III randomised controlled trial of two standard treatments comparing outcomes for the block and replace regimen versus dose titration regimen in patients with thyrotoxicosis
2. The target recruitment is for 160 participants
3. Participants will be randomised, on a 1:1 ratio, as follows:
3.1. Block and replace regimen: [carbimazole (or propylthiouracil) plus thyroxine]
3.2. Titration regimen: carbimazole (or propylthiouracil)
4. Block and replace regimen:
4.1. The primary objective of treatment is to maintain free thyroxine concentrations in the normal laboratory range (mean -2SD < FreeT4 > mean + 2SD) with a TSH that is also within the normal laboratory range (neither elevated nor suppressed)
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5.3. The dose is then reduced to 0.25 mg/kg/day with the intention of maintaining a euthyroid state as reflected by a free thyroxine and TSH within the normal range

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Carbimazole, propylthiouracil, thyroxine

Primary outcome(s)
Current primary outcome measures as of 06/10/2014:
Biochemical control as reflected by blood thyroid stimulating hormone (TSH) levels. The standard deviation of the proportion of TSH measurements above or below the laboratory normal range on block and replace and dose titration regimens (n=12) is approximately 0.2. A clinically important difference in means between the two study groups is 0.1. 128 patients (two groups of 64 patients) required to detect a mean difference in control of 0.1 with 80% power at the 5% level. This primary outcome measure will be assessed at year 3 when subjects will have received anti-thyroid drug for 3 years.

Previous primary outcome measures:
We have undertaken a power estimation based on the assumption that a 20% absolute improvement in remission by 4 years would establish an indisputable clinically significant benefit of one regimen over the other. To gain 80% power with an assumption of 5% loss to follow up, we calculate that we would have to allocate 80 subjects to each treatment group

Key secondary outcome(s)
Current secondary outcome measures as of 06/10/2014:
Additional measures of biochemical control:
1. A comparison of the mean and variability (SD) of TSH and thyroid hormone concentrations in the two treatment groups
2. Remission rates as defined by patients who are biochemically euthyroid at the end of the 4-year study period
3. The frequency of adverse events on the two treatment regimens

Previous secondary outcome measures:
We have also undertaken a power calculation so that we can be confident that a key secondary outcome measure (measure 2) will also be addressed. The standard deviation of the proportion of TSH measurements above or below the laboratory normal range on block and replace and dose titration regimens (n=12) is approximately 0.2 (unpublished data from Newcastle-upon-Tyne and Glasgow). These outcome measures will be assessed at year 3, year 4 and year 6 using biochemistry results to show the stability of the patients thyroid function

Completion date
01/11/2015

Eligibility

Key inclusion criteria
1. All patients with thyrotoxicosis aged between 2 and 16 years at the time of diagnosis
2. Thyrotoxicosis will be diagnosed by the paediatrician on the basis of the clinical picture and the biochemistry [suppressed thyroid stimulating hormone (TSH) with high thyroid hormone levels]
3. Child must consent/assent or consent via parent/guardian must be gained prior to any study-specific procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 Years

Upper age limit
16 Years

Sex
All

Key exclusion criteria
1. Known toxic adenoma/toxic hyperplasia [germline activating thyroid-stimulating hormone receptor (TSHR) mutation]
2. McCune Albright Syndrome
3. Previous episodes of thyrotoxicosis
4. Known allergic response to any of the study medication or ingredients as per Summary of Product Characteristics (SmPC)
5. Previous participation in this study

Date of first enrolment
12/01/2005

Date of final enrolment
29/11/2011

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Victoria Infirmary
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
The Newcastle upon Tyne NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Newcastle upon Tyne NHS Foundation Trust (UK)

Funder Name
British Thyroid Foundation

Alternative Name(s)
The British Thyroid Foundation, BTF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Child Growth Foundation (UK)

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date