Randomised trial of block and replace vs dose titration thionamide in young people with thyrotoxicosis

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Abstract

Objective: First-line treatment of thyrotoxicosis in young people is thionamide anti-thyroid drug (ATD) in a blocking dose with levothyroxine replacement (block and replace, BR) or in a smaller dose tailored to render the patient euthyroid (dose titration, DT). Our objective was to determine which regimen provides more stable biochemical control.

Design: A multi-centre phase III, open-label randomised trial comparing BR with DT in patients aged 2–17 years with newly diagnosed thyrotoxicosis at 15 UK centres.

Methods: Patients were randomised shortly after diagnosis and treated for 3 years. The primary outcome was the percentage of serum thyroid-stimulating hormone (TSH) levels in the reference range between 6 months and 3 years. Secondary outcomes included the proportion of Free thyroxine (FT4) levels in the reference range, adverse event frequency and 4 years outcome (remission/relapse).

Results: Eighty-two patients were randomised, with details on clinical course in 81 (62 Female); 40 were allocated to BR (41 DT). Three withdrew with one ineligible. The mean percentage of serum TSH within reference range was 60.2% in BR and 63.8% in DT patients; adjusted difference 4.3%, 95% CI (−7.8 to 16.4); P = 0.48. Proportions for FT4 were 79.2% in BR and 85.7% in DT patients; adjusted difference 6.8%, (−0.2 to 15.6); P = 0.13. Three patients developed neutropenia – all on BR. 6 BR and 10 DT patients were in remission at 4y.

Conclusion: This randomised trial has shown no evidence to suggest that BR, when managing the young patient with thyrotoxicosis, is associated with improved biochemical stability when compared to DT.

Introduction

Thyrotoxicosis in young people is usually due to Graves’ disease (GD) where pathogenic antibodies stimulate the thyroid-stimulating hormone receptor (TSHR), resulting in thyroid hormone excess. The first-line treatment for most young people with hyperthyroid GD is the anti-thyroid drug (ATD) carbimazole (CBZ) or methimazole...
(MMZ). Propylthiouracil (PTU) should be used only in exceptional circumstances in the young because of the increased risk of severe liver damage when compared to CBZ and MMZ (1). ATD is usually administered in one of two ways. The first approach is to use a daily ATD dose that prevents endogenous thyroid hormone production completely. Thyroid hormone is then added in a replacement dose as serum thyroxine concentrations fall. This strategy is called block and replace or BR. The second approach is to commence an ATD dose that will render the individual euthyroid in the first weeks from diagnosis. The ATD dose is then progressively reduced as the thyroid hormone concentrations normalise and the patient is then maintained on an ATD dose that keeps them biochemically euthyroid. This strategy is referred to as dose titration or DT (2). Biochemical control is an important issue in childhood thyrotoxicosis because even subclinical hyperthyroidism can affect attention span, development and school performance (3). The short and long-term impact of more severe thyroid dysfunction can be profound (4). Excess thyroid hormone can result in rapid growth and osteopenia (5) whilst patients who are hypothyroid whilst on either regimen are at risk of slow growth and impaired quality of life. A recent study has demonstrated that prompt control of biochemical hyperthyroidism is associated with a better long-term vascular outcome than having persistently abnormal thyroid function (4, 6) which may be pertinent to the health of adolescents as they transition through into adult life.

There has been no randomised trial comparing the two approaches (DT and BR) in the young person (or indeed adults) to date. This is a concern for many clinicians because the changing thyroid requirement during rapid growth could potentially make enhanced biochemical stability particularly desirable at this time. This is also an important question because young patients may remain on ATD for a lengthy period of time (7, 8) and because they could be more susceptible to the side effects of ATD than adults (9). Understanding the potential risks and benefits of the two key ATD treatment strategies (BR and DT) is therefore important if young people and their families are to make appropriately informed decisions about their management.

With this background, we undertook a randomised trial of DT vs BR in young people with thyrotoxicosis to determine which regimen provided more stable biochemical control when the interval between clinic visits was the same in the two trial arms.

### Subjects and methods

#### Study design

The trial was a multi-centre phase III, un-blinded randomised trial comparing block and replace (BR) with dose titration (DT) anti-thyroid drug treatment. The study was planned by members of the British Society for Paediatric Endocrinology and Diabetes (BSPED) and was initially managed by the Paediatric Clinical Trials Unit in Cambridge and subsequently by Newcastle Clinical Trials Unit. The trial was registered as EudraCT Number: 2011-001238-40 (DDX ref: MF8000/13328) and as NCT01436994 on Clinicaltrials.gov. A favourable ethical committee opinion was received in 2004 (Berkshire Research Ethics Committee). 15 UK paediatric units recruited patients to the trial. These units were Aberdeen, Birmingham, Cambridge, Cardiff, Coventry, Dundee, Edinburgh, Glasgow, Kilmarnock, Liverpool, London (St. George’s), Manchester, Newcastle, Norwich, Sheffield.

#### Participants

UK-based patients with thyrotoxicosis between the ages of 2.0 and <17.0 years of age were recruited between January 2004 and November 2011. Patients assented or consented to take part in the trial with parental consent in those individuals under 16 years of age. Patients were diagnosed on the basis of a suppressed serum TSH (low levels that were below the assay threshold according to the local reference range) and raised thyroid hormone concentrations (above the local reference range) as well as a typical clinical picture: tachycardia, palpitations, hyperphagia, frequent stools, altered mood and weight loss. Patients with toxic thyroid nodules, McCune Albright syndrome or previous episodes of thyrotoxicosis were excluded. Patients were recruited by tertiary trained paediatric endocrinologists (https://www.eurospe.org/education/education-training-syllabus/) who diagnosed thyrotoxicosis on the basis of the clinical and biochemical picture. Thyrotropin receptor antibody (TRAb) titres were not routinely measured in all centres when the trial started. One patient was randomised in the first months of the trial but no follow-up data were collected at this site. We report the clinical course and outcome of the remaining 81 patients.

#### Randomisation

Patients were allocated to the BR and DT treatment groups in the ratio 1:1. Randomisation was conducted
by the Paediatric Clinical Trials Unit in Cambridge using
minimisation with four stratification factors which were
age (<10 or >10 years), Free Thyroxine (FT4) level at
presentation (<50 pmol/L or >50 pmol/L), sex (male or
female) and region (Anglia, Midlands, North-East, North-
West, South East, Scotland Wales, Yorkshire). The allocation
was done using the MINIM programme which allocated to
the group minimising imbalance with probability 0.7 (10).

Procedures

Anti-thyroid drug regimen: Block and Replace regimen (BR)
or dose titration (DT)

Patients were treated with ATD from diagnosis (0.75 mg/
kg/day of carbimazole) and subsequently randomised to
either BR or DT (details of the BR and DT study regimens
are presented in the Appendix, please see section on
Supplementary materials at the end of the article). This
ATD dose was expected to abolish endogenous thyroid
hormone production in the majority of patients. Patients
in the BR arm received thyroid hormone in a replacement
dose as they became eu- or hypothyroid whilst patients
randomised to DT underwent ATD dose reduction as they
became euthyroid. Patients were managed by paediatric
endocrinologists skilled in the area of thyroid hormone
replacement in childhood but an initial dose of 75 µg/m²
of thyroxine was suggested in the BR guideline.

Patients were seen regularly for the first 6 months
(every 4 weeks up to 16 weeks) and then at 3 monthly
intervals from week 26 until the end of year 3. The protocol,
therefore, fixed the time interval between clinic visits in
the two study arms although additional, unscheduled
visits could take place between these assessments as
clinically indicated. Patients then stopped ATD at the end
of year 3 and were followed up until the end of year 4.

ATD – Caribimazole and Propylthiouracil

Participants received the ATD for 3 years, followed by a
period of ATD therapy to determine remission or need
for ongoing treatment or consideration of alternative
management. Paediatricians in the UK usually commence
children with thyrotoxicosis on carbimazole rather than
PTU. When patients were treated with PTU a similar
guideline was followed with the recommendation that
1mg of carbimazole is approximately equivalent to 10
mg of PTU. Clinicians adhered to local policy or their
usual practice in terms of blood count and liver function
monitoring.

Outcomes

Relapse and remission definition

Relapse was defined as patients with the combination of a
suppressed TSH (<0.05 mU/L) and raised thyroid hormone
level according to the local reference range up to the end
of year 4 (4 years post-presentation, 1 year following ATD
cessation).

Patients were deemed to be in remission if they did not
fit the criteria for relapse at 4 years post-diagnosis,
having been off ATD for 12 months and not receiving
definitive treatment. The patient was kept under review
by the local investigator after stopping ATD so that their
status after 12 months off ATD could be documented.

Statistical analysis

Primary outcome and power calculation

The primary outcome of the study was the proportion of
TSH measurements from each patient that were within
the normal range according to local laboratory reference
values. This variable was based on all measurements
obtained between 6 months and 3 years, including
unscheduled visits and was calculated centrally
following data collection and submission. A clinically
important difference between the treatment groups in
the mean of this variable was taken to be 0.1. In other
words, a difference of 10% in the proportion of TSH
concentrations in the reference range when the groups
were compared was deemed to be clinically important.
The standard deviation of this variable was approximately
0.2, according to preliminary data collected from patients
with thyrotoxicosis managed in Newcastle upon Tyne and
Glasgow. To obtain 80% power at the two-sided 5% level
required each group to be of size 64. The trial closed short
of the required sample size, due to initial slow recruitment
and then a subsequent funding shortfall.

A further analysis was conducted that excluded
measurements obtained from patients after they had had
definitive treatment with surgery or radioiodine (where
applicable). In addition, a sensitivity analysis of the
primary outcome variable was performed which excluded
TSH measurements that were taken more than 4 weeks
from the protocol stipulated visit date.

Secondary outcomes

Four secondary outcomes are reported:
1. The proportion of FT4 concentrations within the local laboratory reference range, collected over the same period used for the primary outcome.
2. The remission status of the patient at the end of the study period (i.e. 4 years after recruitment).
3. The number and type of adverse events reported by each patient.
4. Four additional measures of biochemical control were computed for each patient, namely the mean and standard deviation of the TSH levels and of the FT4 levels.

The difference between the treatment groups in the proportion of TSH and FT4 within the normal range was estimated using linear mixed-effects models, with 95% CIs being given for the adjusted mean treatment difference, and $P$-values quoted for the two-sided test using a null hypothesis of no adjusted mean difference. Adjustment was made for the stratification variables: age, sex, initial FT4 hormone concentration and region; the first three of these variables were entered as fixed binary covariates, with the region being treated as a random covariate. Estimation is by restricted maximum likelihood and was conducted using Stata Version 15 (11).

**Treatment following relapse**

The outcome for patients who relapsed following a course of ATD were categorised into those who subsequently returned to ATD therapy (either BR or DT) or who were treated with one of the more definitive second-line options that are associated with the ablation or removal of thyroid gland tissue (radioiodine or surgery).

Safety and adverse events were assessed according to defined criteria and all reported serious adverse events were verified against treatment notes/medical records (source data verification). Regular monitoring visits were also carried out by the Newcastle Clinical Trials Unit. The trial was overseen by a data and ethics monitoring committee. The members comprised an independent paediatrician, expert endocrinologist and statistician.

**Role of the funding source**

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

We report the clinical course and outcome of the 81 patients who were recruited and have follow-up data. The characteristics of the two study groups (BR and DT) are shown in Table 1. Patients were recruited between 2004 and 2011. As anticipated there were more females than males and a greater proportion were over the age of 10 years at diagnosis. Mean (S.D.) TSH concentrations at the baseline visit were 0.043mU/L (0.052) and 0.028mU/L (0.024) with some patients taking ATD at the time of this assessment. The recruitment flow diagram for the clinical trial is shown in Fig. 1. Forty-eight patients (23 BR, 25 DT) had thyrotropin receptor antibodies (TRAb) measured during the study period with 44 found to be positive (20 BR, 24 DT).

Attendance varied considerably between participants but the median number of scheduled visits during the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient baseline characteristics of the two groups (BR and DT).</th>
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<tbody>
<tr>
<td>Variables</td>
<td>BR</td>
</tr>
<tr>
<td>Sex</td>
<td>BR</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>34</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>12.9 (2.6)</td>
</tr>
<tr>
<td>Free T4 level, pmol/L</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>19</td>
</tr>
<tr>
<td>&gt;50</td>
<td>20</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>57.5 (27.1)</td>
</tr>
</tbody>
</table>

*Refers to patients in the primary analysis; **Refers to patients randomised with follow-up data.
period of analysis (between 6 months and three years) was the same in the two groups with a median of 10 visits out of the expected 11 in the BR group (range: 3–11) and a median of 10 out of the expected 11 in the DT group (range: 5–11). There were a total of 24 additional unscheduled visits over the same period in the BR group and 16 in DT.

The mean CBZ dose between 6 months and 3 years was 0.61 mg/kg in the BR group and 0.30 mg/kg in DT. At the start of the period of biochemical analysis at 6 months, 11 patients in the BR group and 11 in DT still had a suppressed TSH concentration with 5 patients in the BR group yet to commence thyroxine replacement. The mean percentage of TSH measurements within the reference range was 63.8% in participants allocated to DT compared to 60.2% on BR. The absolute adjusted difference was 4.3% in favour of DT (95% CI: −7.8% to +16.4%; P = 0.48) after adjustment for stratification factors. Omitting values obtained following definitive treatment gave very similar results: mean difference of 4.3% in favour of DT (95% CI: −8.1% to +16.6%; P = 0.50).

Figure 2A shows the distribution of the proportions of TSH values on a patient that are within the reference range. Similarly, there was no evidence of a difference in the proportion of FT4 concentrations within the reference range between the two groups, with an adjusted mean difference of 6.8% in favour of DT (95% CI: −2.0 to +15.6; P = 0.13, Fig. 2B). The sensitivity analysis suggested that 11.6% more FT4 values were within the reference range for those patients on DT (95% CI: −0.1% to +23.4%; P = 0.05). The analyses of all four additional measures of control were consistent with the above results, with none providing evidence of a difference between BR and DT.

Of the 81 patients recruited, 4 withdrew from the trial or were ineligible (three patients withdrew in the first year because of a reluctance to attend study visits and to take medication; one patient was diagnosed with thyroid hormone resistance and was excluded). Of the remaining 77 patients, 6 (15%) in the BR group and 10 (26%) in the DT group were known to be in remission at the end of year 4: difference 11%, 95% CI (−7% to 29%) (Fig. 3) 41 patients had relapsed and 13 patients remained on ATD in breach of the trial protocol because of reluctance to stop treatment or because of issues such as failure of biochemical control on lower ATD doses, concurrent or impending key life events. Seven patients were lost to follow-up prior to
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Table 2  Summary of adverse event data.

<table>
<thead>
<tr>
<th>Anti-thyroid drug regimen</th>
<th>BR</th>
<th>DT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-serious AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs related/possibly related to treatment</td>
<td>200</td>
<td>226</td>
</tr>
<tr>
<td>Patients experiencing non-serious AEs, n</td>
<td>78</td>
<td>57</td>
</tr>
<tr>
<td>Patients with expected AEs commonly linked to thionamide therapy, n</td>
<td>34/40</td>
<td>36/41</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Joint related</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Serious AEs related/possibly related to treatment</td>
<td>3 with neutropenia (&lt;1000/µL)</td>
<td>1 with fever and sore throat, hoarse voice, mild cough, difficulty swallowing, admitted with excessive vomiting and then with frontal headache, vomiting, blurred vision and palpitations</td>
</tr>
</tbody>
</table>

year 4 but had biochemical data that could be analysed whilst they were treated with ATD. Of the 41 patients who relapsed, 22 (7 BR) returned to ATD therapy, 11 (6 BR) underwent surgery (total thyroidectomy) and 8 (5BR) received radioiodine therapy.

Adverse events in the two trial arms are presented in Table 2. Five patients in the BR group and 2 in DT changed from CBZ to PTU during the trial. There were 426 non-serious AEs recorded from 71 of 81 patients with 200 in the BR group and 226 in the DT group. The number of adverse events deemed to be related or possibly related to treatment with ATD was 78 in the BR group compared to 57 in the DT group. A total of 35 (of 40) in the BR group and 36 (of 41) in the DT group experienced at least one non-serious AE.

There were five serious adverse events (SAEs) from five patients in the BR group with three related or possibly related to trial medication. All 3 SAEs considered to be related to ATD involved the development of neutropenia (neutrophil count less than 1000 per µL) in the BR group. The three patients were taking 15, 30 and 40 mg of CBZ once daily. One of these patients (on 30 mg CBZ daily) remained on ATD with the neutrophil count recovering spontaneously. There were four SAEs from three patients in the DT group with three considered to be related or possibly related to trial medication. One involved the development of a sore throat but the patient was not neutropenic and classified as unrelated. The remaining two serious AEs (same patient) involved vomiting and an associated admission to hospital and in the second instance vomiting and headache. The development of a rash did not result in permanent discontinuation of ATD in any patient.

Discussion

Children and adolescents with thyrotoxicosis are often treated with ATD for a lengthy period of time because the remission rate after a 2- to 3-year course of ATD treatment is typically only between 20 and 30%. The likelihood of remission appears to increase with the duration of therapy (7, 8). Knowing how best to administer ATD in young people is therefore important. This trial is the largest prospective study comparing the two ATD regimens (BR and DT) that has ever been conducted in young people and is the first to provide level-1 evidence. The trial has shown no evidence to suggest that there is an important difference in biochemical control in young people with thyrotoxicosis treated with BR when compared to DT. The trial, which was designed to detect a difference between the BR and DT regimens of at least 10% in the proportion of time in control, has shown that the difference in favour of BR is no greater than 8% and that in favour of DT could be as large as 16%. In the case of both TSH and FT4 concentrations, the CI indicates that any difference in favour of BR is less than the minimum clinically important difference specified when planning the study. While there could be a difference in favour of BR, its size would not be clinically important, whereas the difference in favour of DT could be much more substantial.

Furthermore, there is no evidence that either adverse events or remission rates are superior in BR patients compared to DT patients. The patients who developed neutropaenia were in the BR group with a larger number of adverse events deemed to be related or possibly related to treatment with ATD in the BR group as well.
A sensitivity analysis suggested that the proportion of time that FT4 was within the normal range could be higher on DT, with an advantage in favour of BR being very small. This potential outcome was anticipated when designing the trial and was one reason why TSH concentrations were chosen as the primary endpoint. Replacing thyroid hormone when there is no endogenous thyroid hormone release may require relatively high FT4 levels to normalise TSH (12). This is because endogenous thyroid hormone release includes both T4 and tri-iodothyronine (T3). We do not, therefore, feel that this is evidence in favour of the DT strategy. The two different approaches (BR and DT) have been the subject of a systematic review in adults which led to the recommendation that the DT approach be used because it was associated with fewer side-effects (13, 14). This may be because the DT approach is associated with a smaller dose of ATD (15, 16) although clinicians have highlighted the fact that some studies incorporated in the systematic review that formed the basis for the American Thyroid Association (ATA) recommendation administered higher doses of ATD (such as CBZ 100 mg daily) than normally used during routine clinical practice (17, 18). The DT approach is also recommended by the European Thyroid Association (19) and American Thyroid Association (ATA) in young people for the same reason (18), although the studies analysed as part of the systematic review were conducted primarily in adults and it has been argued that BR may be associated with improved biochemical stability with the potential for fewer hospital appointments and blood tests as a result (17, 20). There are retrospective paediatric (20) and adult (21) studies showing fewer clinic visits in patients managed with a BR regimen although it is unclear to what extent differences were clinically meaningful (21). A recent audit suggested improved biochemical control in paediatric patients managed with BR but patient numbers were small and individuals managed with BR had been on ATD for longer (22). Paediatric endocrinologists in the UK still use the BR strategy (23) which may indicate that some clinicians feel that BR is a useful strategy in selected patients where DT does not result in biochemical stability.

The trial that we report here provides the first level 1 evidence to support the recommendation of the ATA guideline to use a DT regimen on the basis that the risk of adverse events is greater with BR. In the present study, three patients in the BR arm developed neutropenia in comparison to none in the DT group although the overall number of AEs was similar in the two groups.

Childhood Graves’ disease has a worse outlook than the equivalent condition in older people, with several studies showing a remission rate of 25% or less after 2 years’ ATD therapy (7, 8, 24) compared to figures around 50% in adults. The reasons for this are unclear but it could reflect the fact that younger people tend to have more severe thyrotoxicosis at presentation than adults, that the recognition is frequently delayed or that the compliance with disease-modifying ATD medication may be suboptimal, particularly during teenage years. There was no evidence of a difference in the proportion of patients in remission in the two groups that we studied: but CIs are large such that the remission rate could be up to 7% greater on BR or up to 29% greater on DT. This is in keeping with earlier data from adult studies (14). It is interesting to note that the proportion in remission (20%) is of a similar order of magnitude to those reported in the paediatric literature.

We found that young people with thyrotoxicosis are a challenging group of patients to study. Therapeutic changes may be delayed by school examinations, moving into higher education or travelling, and many appeared to struggle to attend out-patient appointments as scheduled. Monitoring patient progress for a period of 4 years was not always straightforward in these young people. We suspect that the fact that 13 patients opted to stay on ATD at the end of the initial 3-year period was linked to the desire to maintain biochemical stability at an important stage of the young person’s life. This trial has a number of weaknesses that we have alluded to above. First, whilst the trial did not recruit as many subjects as hoped this is still the largest ever randomised trial of the two key treatment approaches conducted in young people. Secondly, whilst patients were diagnosed with thyrotoxicosis, not all had thyroid receptor antibodies measured and so it is possible that some young people had self-limiting thyroiditis (25). Not all laboratories could access a thyroid receptor antibody assay when the trial commenced but it is of note that patients were recruited by paediatric endocrinologists who will be familiar with the spectrum of thyroid disease in the young and when TRAb were measured they were raised or positive in 92% of participants. Finally, thyrotoxicosis in young people due to Graves’ Disease is characterised by elevated serum FT3 concentrations and we would ideally have measured FT3 levels and used this as one of the secondary outcome measures. When the trial commenced many laboratories did not measure FT3 concentrations.

This study has not shown any evidence to refute the current guidelines that recommend DT in most growing people with thyrotoxicosis. There is no evidence from this trial to suggest that BR is associated with important improvements in biochemical stability compared with DT.

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Declaration of interest
T C and S P were members of the NICE Thyroid guideline committee 2019. No competing financial interests exist.

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References
23 Lawrence N, Cheetham T & Elder C. How do paediatricians use and monitor antithyroid drugs in the UK? A clinician survey.

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