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ORIGINAL ARTICLE

Block & replace regime versus titration regime of antithyroid drugs for the treatment of Graves' disease: a retrospective observational study

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Summary

Context Two widely used antithyroid drug (ATD) regimes for Graves' disease (GD) include the 'block & replace' (B&R) regime (a fixed high-dose of ATD combined with levothyroxine) and the 'titration' regime (a titrating dose of ATD). Anecdotally, it is believed that B&R is less prone to fluctuating thyroid function.

Objective To study whether, in routine clinical practice, the B&R regime, compared with the titration regime, is associated with more stable thyroid function.

Methods We retrospectively analysed case-records for 450 patients treated with ATDs for GD at a secondary care hospital. Exclusion criteria included treatment with ATDs for <6 months, thyrotoxicosis due to other causes, treatment with radioiodine or thyroidectomy and pregnancy.

Results Two hundred and twenty three patients were treated with the B&R regime ('B&R group'), 149 with the titration regime ('titration group') and 78 with both regimes. The number of thyroid function tests (TFTs) performed per year (mean (SD): 3·2(1·2) *vs* 3·4(1·5); adjusted mean difference = −0·4; 95% CI: −0·7 to −0·1; and $P = 0{\cdot}008$) and the number of hospital clinic visits per year (mean (SD): 2·9 (1·0) *vs* 3·2 (1·3); adjusted mean difference = −0·4; 95% CI: −0·7 to −0·2; and $P = 0{\cdot}002$) were lower in the B&R group than the titration group. The number of abnormal TFT results per year was similar in the two groups (mean(SD): 1·8(1·3) *vs* 1·8(1·4); adjusted mean difference = 0·05; 95%CI: −0·3 to 0·4; and $P = 0{\cdot}74$).

Conclusions In this retrospective study, there was little evidence that patients under B&R have more stable thyroid function. Further data from prospective studies, however, are needed to confirm this finding.

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Introduction

Antithyroid drugs (ATDs) are widely used to treat thyrotoxicosis due to Graves' disease (GD).[1–3] The two recognized regimes of ATDs include: (a) 'block & replace' (B&R), in which a fixed high-dose of ATD is combined with levothyroxine, and (b) 'titration', in which the dose of ATD is titrated based on thyroid function tests (TFTs).[4] The use of both regimes is common in clinical practice. For example, in the UK, a third of endocrinologists use B&R, whilst the remainder favour titration.[5]

It remains controversial as to which of these regimes of ATDs is superior for treatment of GD.[6] A recent systemic review has shown similar remission rates of Graves' thyrotoxicosis with both regimes although side effects of ATDs were more frequent with B&R than titration.[7] Furthermore, titration requires patients to take fewer tablets, and many consider this to be a simpler regime. On the other hand, it is believed that B&R is associated with more stable thyroid function, and therefore, patients treated with this regime require fewer TFTs and clinic visits.[8,9] However, to our knowledge, no published studies have examined whether this view holds true in everyday clinical practice.

Therefore, we aimed to study whether, in the routine clinical setting, the B&R regime – as compared with the titration regime – is associated with more stable thyroid function.

Materials and methods

Subjects

We retrospectively examined case-records of patients with GD who were treated with ATDs in a single centre at the Thyroid Clinic, Royal Devon & Exeter Hospital between 1 January 1997 and 31 January 2012. Patients with GD were identified from the departmental electronic database. We also accessed the pathology

laboratory electronic database for the numbers and results of TFTs on each patient. This pathology database contains data on TFTs carried out by both general practitioners as well as the hospital. This work was approved by the governance unit of the Royal Devon & Exeter Hospital.

We defined GD as thyrotoxicosis with presence of a diffuse goitre, thyroid eye disease, positive TSH receptor antibodies (TSHR-Ab), thyroid peroxidase antibodies (TPO-Ab) or diffuse uptake on radionuclide uptake scan. We excluded patients with thyrotoxicosis due to causes other than GD, GD treated with ATD for <6 months, GD treated with radioactive iodine or thyroidectomy and pregnancy. For patients with relapses of Graves' thyrotoxicosis, we only included data from the first episode. For patients who were treated with ATDs for longer than 2 years, we included data for the first 2 years.

We compared outcomes between patients treated solely with the B&R regime ('B&R' group) and those treated solely with the titration regime ('titration' group). Patients who were treated with both regimes during the study period were excluded when comparing outcomes. The local hospital guidelines, whilst acknowledging both regimes, preferred the use of B&R for patients with GD.[10]

Analysis of thyroid function tests and thyroid antibodies

Serum TSH, FT4 and FT3 were analysed using the electrochemiluminescent immunoassay, run on the Modular E170 Analyzer (Roche, Burgess Hill, UK). Intra-assay coefficients of variation were: TSH <5·3%, FT4 <5·3% and FT3 <5·1%. The laboratory reference ranges were: TSH 0·35–4·5 mIU/l, FT4 11–24 pmol/l and FT3 3·9–6·9 pmol/l. We classified overt hyperthyroidism (suppressed TSH with raised FT4 or FT3), overt hypothyroidism (raised TSH with low FT4) and subclinical hypothyroidism (raised TSH with normal FT4) as abnormal thyroid function. As TSH can remain suppressed for several weeks following treatment of Graves' thyrotoxicosis, we did not include subclinical hyperthyroidism (suppressed TSH with normal FT4 and FT3) as 'abnormal' thyroid function for the analysis.

Serum TPO-Ab levels were analysed using the competitive immunoassay (Roche) and a titre above 34 IU/ml was considered positive. Serum TSHR-Ab levels were measured using a second generation ELISA (Euroimmun, London, UK) and a titre above 1·8 IU/l was considered positive.

Statistical analysis

Demographic and clinical characteristics were summarized for patients under each treatment regime, using means and standard deviations (or medians and interquartile ranges) for continuous variables and percentages for categorical variables. The means for the continuous outcomes (number of TFTs per year, number of abnormal TFT results per year, number of hospital follow-up visits per year and weight change between presentation and last hospital clinic visit) were compared between the B&R and titration regimes using linear regression in crude analyses and analyses that are adjusted for age at referral, gender, relapsed thyrotoxicosis, presence of goitre, presence of thyroid eye disease, whether used carbimazole or propylthiouracil and duration of follow-up. The comparison of weight change was additionally adjusted for weight at the first hospital consultation. Logistic regression was used to compare the odds of having a TSH over 20 mIU/l and the odds of having a FT4 over 48 pmol/l between treatment regimes. In addition to the core potential confounders listed above, analysis of FT4 over 48 pmol/l was adjusted for FT4 level at diagnosis. Analysis of TSH over 20 mIU/l was only adjusted for relapsed thyrotoxicosis and whether used carbimazole or propylthiouracil due to the small number of patients with a high TSH. The chi-squared test was used to compare side effects between treatment regimes. It was not possible to use logistic regression to adjust for potential confounders as too few patients had side effects for the valid use of the method. Analyses were carried out using Stata software.

Results

Subjects

Demographic and clinical characteristics of the patients included in the study are shown in Table 1. Of the 450 patients who fulfilled the inclusion criteria, 223 were treated with the B&R regime, 149 with the titration regime and 78 with both regimes.

The age and sex distributions were similar in the three groups of patients. 64% (34/53) of patients with thyroid eye disease were solely treated with the B&R regime, whilst 71% of patients with a relapsed thyrotoxicosis (39/55) and those receiving propylthiouracil (15/21) were solely treated with the titration regime.

Thyroid function tests and other outcomes in patients treated with the block & replace regime versus the titration regime

There was evidence that the mean number of TFTs performed per year is lower in the B&R group than the titration group (adjusted mean difference = −0·4; 95% CI: −0·7 to −0·1; and $P = 0·008$) although the difference is not marked (Table 2). The number of abnormal TFT results per year was similar in the B&R and the titration groups (adjusted $P = 0·74$). There was little evidence that the percentage of patients with at least one TFT result showing overt biochemical hypothyroidism (defined by TSH above 20 mIU/l) and severe hyperthyroidism (arbitrarily defined by FT4 above 48 pmol/l, which is double the upper limit of the reference range) during follow-up differs between the two groups (adjusted $P = 0·67$ and 0·45, respectively, Table 2). The mean number of hospital follow-up visits per year was lower in the B&R group than in the titration group (adjusted mean difference −0·4; 95% CI: −0·7 to −0·2; and $P = 0·002$).

The percentage of patients reporting skin rash was lower in the B&R group (1·3% *vs* 6% in the titration group, $P = 0·01$). The percentages of patients who developed neutropenia (B&R *vs* titration: 1·3% *vs* 0·7%, $P = 0·54$) and liver dysfunction (B&R *vs* titration: 0% *vs* 0·7%, $P = 0·22$) were similar in the two groups. In both groups, patients gained weight between at presentation

Table 1. Demographic and clinical characteristics of patients at baseline

Characteristics N*	B&R only 223	Titration only 149	Both titration and B&R 78
Age at referral in years, mean (SD); range	49 (15); 16–91	49 (18); 21–93	48 (15); 16–74
Female,%	79·8	86·6	82·1
Current smokers,%	19·9	23·9	26·0
Positive family history of thyrotoxicosis,%	27·3	22·2	36·6
Positive family history of hypothyroidism,%	12·1	15·7	8·5
Duration of follow-up in months, median (IQR)	20·0 (17·9–22·5)	19·0 (13·4–28·1)	20·9 (17·9–25·9)
TSH mIU/l at diagnosis, median (IQR)	0·01 (0·01–0·03)	0·03 (0·01–0·03)	0·02 (0·01–0·03)
FT4 pmol/l at diagnosis, median (IQR)	46·1 (33·9–68·9)	41 (28·1–65·4)	53·5 (39·3–68·4)
FT3 pmol/l at diagnosis, median (IQR)	13·4 (9·6–24·2)	13·8 (8·4–22·4)	18·5 (7–28·1)
Relapsed thyrotoxicosis at referral,%	4·6	26·7	8
Presence of goitre,%	58·4	63·9	70·5
Presence of thyroid eye disease,%	15·5	6·3	13·0
Presence of dermopathy,%	2·8	1·4	5·2
Body weight at first hospital consultation, median (IQR)	66·6 (58·7–78·2)	65·2 (56·4–74·9)	67·1 (59·2–74)
Positive TPO antibodies,%	65·5	71·9	53·8
Positive TSHR antibodies,%	58·4	67·5	67·4
Drug use			
Carbimazole only,%	95·5	72·5	76·9
Propylthiouracil only,%	2·2	10·1	1·3
Both carbimazole and propylthiouracil,%	2·2	17·5	21·8

B&R, block & replace; IQR, interquartile range; TPO, thyroid peroxidase; TSHR, TSH receptor; SD, standard deviation.
*The lowest sample size was for the FT3 variable: 68 for the B&R group, 72 for the titration group and 24 for the mixed group. Otherwise sample sizes were in the range 198–223 for the B&R group, 115–149 for the titration group and 71–78 for the mixed group.

Table 2. Outcomes of patients by treatment regime

Outcomes	B&R (n = 223) mean (SD)/%	Titration (n = 149) mean (SD)/%	Mean difference/ odds ratio estimate	Adjusted mean difference/odds ratio		
				Estimate	95% CI	P value
Number of TFTs per year	3·2 (1·2)	3·4 (1·5)	−0·2	−0·4	−0·7–−0·1	0·008
Number of abnormal TFTs per year	1·8 (1·3)	1·8 (1·4)	0·05	0·05	−0·3–0·4	0·74
Patients with at least one abnormal TFT in first 3 months (%)	77·1	67·1	1·65	1·40	0·81–2·42	0·23
Patients with TSH>20 mIU/l at any time during follow-up (%)	9·9	6·0	1·70	1·20	0·51–2·83	0·67
Patients with FT4 >48 pmol/l at any time during follow-up (%)	43·9	36·2	1·38	1·34	0·63–2·87	0·45
Number of follow-up visits per year	2·9 (1·0)	3·2 (1·3)	−0·3	−0·4	−0·7–−0·2	0·002

B&R, block & replace; TFT, thyroid function test; SD, standard deviation; CI, confidence interval.

and the last clinic visit. There was weak evidence that weight gain was greater in the B&R group (B&R *vs* titration: mean (SD) 5·2(7·1) *vs* 2·9(8·4) kg; adjusted mean difference 1·6 kg (95% CI: −0·3 to 3·5); and P = 0·09).

Discussion

In this study of routine clinical practice, we found evidence that GD patients treated with ATDs on the B&R regime have fewer TFTs and follow-up visits. The mean difference between the groups, however, was not marked. The number of abnormal TFTs was similar in the two groups. These results provide little support to the common belief that the B&R regime is less prone to fluctuating episodes of hypo- and hyperthyroidism.[8,9] As this is a nonrandomized observational study, the results may have been influenced by selection bias and unmeasured confounding factors, for example, patients' concordance of medications, clinicians' experience (consultants versus trainees working under supervision of consultants) and clinicians' selection of the ATD regimes for different types of patients. We do not have data on patients' concordance, and as many patients were seen by several clinicians in the clinic during the study period, we were unable to analyse the data based on individual clinicians and explore whether the results are influenced by the experience of the clinicians (consultant endocrinologists versus trainee endocrinologists). We collected data retrospectively from case-notes; therefore, we will have missed the clinical data that were not recorded in the case-notes during consultations. However, as we

used the electronic central pathology database, it is likely that we have captured all the data on the number and results of TFTs. Furthermore, 17% of the patients in this study were treated with both regimes. It is possible that several of these patients had to change the regime because of problems, and therefore, their exclusion may have influenced our results. However, it is also possible that, as the B&R regime is more complex than the titration regime, it is more susceptible to errors, which may explain why we did not observe more stable thyroid function with this regime as expected. Finally, this study was carried out in a secondary care specialist thyroid clinic, and the results may not be generalizable to other settings.

We found that patients on the B&R regime are seen slightly less often (on average by just under half a clinic appointment per year) in the hospital than those on the titration regime (Table 2). The frequency of hospital clinical visits may be affected by several factors other than types of the ATD regimes and the clinical need, including clinicians' behaviour, patients' choice and the availability of clinic appointments. Furthermore, although it was usual practice in the district during the study period for patients with GD to be followed up face-to-face in the hospital clinics, we do not have data on additional telephone or email advice, which may have influenced the frequency of hospital clinic visits. In addition, we do not have information on the patients' extra visits to their general practitioners for the condition.

There was a higher incidence of reported skin adverse effects in the titration group. This is in contrast to the findings of a systemic review of randomized controlled trials, which showed an increased incidence of side effects of ATDs when used in the B&R regime compared with the titration regime.[7] Furthermore, recent observational studies have also shown an association between a higher-dose of ATDs and adverse effects.[11,12] A possible explanation for the apparently contradictory finding of our study is the clinicians' preference to use the titration regime in patients reporting the mild skin side effects. In addition, it is well documented that side effects of ATDs tend to manifest within 3 months of starting the drug.[13,14] Most patients with severe side effects will have stopped the ADT, and as we have excluded patients who were not on ATDs for more than 6 months, it is very likely that we have not captured all adverse events relating to the two regimes of ATDs. It is also possible that not all adverse events are documented in the clinical case-records.

In summary, there was little evidence to support the hypothesis that, in the routine clinical practice, patients with Graves' disease on the block & replace regime of antithyroid drugs have more a stable thyroid function compared with the titration regime. Despite our attempt to adjust for key confounding factors, further prospective studies (ideally randomized controlled trials) are needed to ascertain whether the block & replace regime is superior to the titration regime.

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Conflict of interest

Nothing to declare.

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