Author’s response to reviews

Title: Radioiodine treatment for Graves’ Disease: a 10-year Australian cohort study

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Version: 1 Date: 11 Nov 2018

Author’s response to reviews:

12 November 2018

The Editor
BMC Endocrine Disorders

Regarding: Manuscript BEND-D-18-00304

Radioiodine treatment for Graves’ Disease: a 10-year Australian cohort study

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Thank you for the opportunity to revise this manuscript. We would like to thank the reviewers for their helpful and insightful comments to which we offer the following responses:

Reviewer 1

Zuleyha Karaca (Reviewer 1): In this paper, Fanning et al retrospectively evaluated their data on RAI treatment for 92 patients with Graves disease. They found the remission rate of hyperthyroidism as 79.3%, TSH rec ab as a predictor of response to RAI. As stated by the authors, there are important limitations of this study.

Inconsistent time point and assays for measurement of TSHR ab, lack of accurate assessment of ophthalmopathy. Unfortunately as a retrospective study the paper does not seem to be improvable in these aspects.

Response

Thank you for your comments. We agree there are a number of important limitations given the retrospective nature of the study. However, although TSH receptor antibody titres were not
consistently taken just prior to radioiodine therapy, the measurement analysed in this study was the TSH receptor antibody titre at diagnosis. The timing of this measurement therefore would have been consistent between patients.

Regarding the assessment of ophthalmopathy, this was performed by the treating clinician. This examination generally involved assessment for conjunctival inflammation, chemosis, periorbital oedema, proptosis, eye movement abnormalities or diplopia and any evidence of visual loss. While this assessment can be variable between clinicians, the likelihood that significant eye disease was missed by the treating clinician is low.

Despite the issues of the retrospective nature of the study, we feel these findings are useful to assist with counselling patients referred for I131. As mentioned in the manuscript, there have previously been no Australian data regarding outcomes of radioiodine reported. Therefore this study provides information regarding the likelihood of cure with a single dose of I131, the prevalence of adverse events and may assist to identify and counsel those patients at higher risk of treatment failure (those with high TSH receptor antibody titres) in the Australian setting. We suggest our data would also be applicable to other health care services.

Reviewer 2

Rachel Crowley (Reviewer 2): This is a report of the authors' experience with I131 for the definitive treatment of Graves' thyrotoxicosis. The subject is not original but such reports are important clinically, for counseling patients referred for I131 and for comparing the performance of I131 services between centres.

The paper is well-written and clear but I would like to see a few minor changes.

Introduction

1. Generally glucocorticoid prophylaxis is not recommended for all smokers (or high TRAb titre patients), suggest review the sentence starting on line 81.

The sentence regarding the use of glucocorticoid prophylaxis has been revised (line 82). ‘The risk can be mitigated by glucocorticoid prophylaxis in patients with mild disease or patients with multiple risk factors (14,15)’.

Methods

2. How was thyroid eye disease defined and classified?

The presence and severity of eye disease was assessed individually by the treating physician. Admittedly this assessment can be variable between clinicians but includes assessing for conjunctival inflammation, chemosis, periorbital oedema, proptosis, eye movement
abnormalities or diplopia and any evidence of visual loss. Severity was graded as mild, moderate or severe.

This has been added to the methods section line 116-120.

‘The presence and severity of eye disease was assessed individually by the treating physician. The detailed eye examination generally included assessment for conjunctival inflammation, chemosis, periorbital oedema, proptosis, eye movement abnormalities or diplopia and any evidence of visual loss. Clinical severity was graded as mild, moderate or severe.’

3. What was the fixed dose regimen? (a range is quoted in Results)

Currently the dose is 500MBq. However, this had previously been 450MBq and therefore patients in earlier years may have received a lower dose. A comment has been made in line 125-128.

A fixed dose (administered activity) of 500MBq is currently used. In earlier years of the study, this had been 450MBq and some patients received a lower dose due to the practice of an individual nuclear medicine physician.

4. What I131 preparation was used?

The preparation was sodium iodide powder in prefilled capsules supplied by +/- 10% prescribed activity.

Line 124 'I131 (sodium iodide powder in prefilled capsules) was administered orally in the Department of Nuclear Medicine at the Princess Alexandra Hospital.’

5. Data do not look normally distributed - quoted SEMs look odd. Suggest look at medians and 95% CI might be more useful to describe data.

Data have been changed to median and (95% CI)

Line 135 - ‘Continuous data failed parametric assumptions and therefore are presented as median and 95% confidence intervals (CI). Categorical variables are presented as simple proportions (%). A Mann Whitney U test was used to compare continuous baseline variables between groups.’

Results

6. What was the adverse reaction to anti-thyroid drugs in 29 patients?
18 patients developed complications of medical treatment. The most common adverse reaction was a rash with carbimazole in 8 patients, followed by neutropaenia in 6 patients. 3 patients developed deranged LFTs with PTU and 1 patient with carbimazole. 29 patients had an inadequate response to therapy which was defined as persistent thyrotoxicosis despite medical treatment or an inability to wean the dose of the thionamide due to a recurrence of thyrotoxicosis after 12-18 months of therapy (please refer to line number 145 of the manuscript and table 1).

Line 147-153: ‘The primary indication for definitive treatment was disease relapse following a trial withdrawal of antithyroid drug therapy in 41 patients, a poor response to medical therapy in 29 patients due and intolerance/complications of treatment in 18 patients (Table 1). The most common adverse reaction to medical therapy was a rash in 8 patients, followed by neutropaenia (neutrophils <1.0 x10^9/L) in 6 patients. LFT derangement was reported in 3 patients taking PTU and 1 patient taking carbimazole.’

7. I note a very long duration of ATD therapy in some patients, suggest comment on this and see point 5 above

The reason for the very long duration of medical therapy in a few outliers was either prior resistance to undergo definitive treatment or a previous lack of ongoing specialist input prior to referral to the endocrinology clinic at our hospital.

A comment regarding this has been made now in line 156-160.

‘The median duration of medical therapy was 24 months prior to receiving radioiodine therapy. The range was 3 weeks to 12 years. A few outliers received a very long duration of medical therapy. The reasons for this included previous lack of ongoing specialist input or prior hesitance on behalf of the patient to undergo definitive therapy.’

8. Mean TRAb and mean time to development of hypothyroidism - see point 5 above

Time to hypothyroidism (line 171) and TRAB titres (line 159) have been presented as median and (95% CI).

Line 171-172: ‘The median time from I131 administration to hypothyroidism was 4 months (3-4).’

Line 160: ‘The median TSH receptor antibody titre at diagnosis was 8 IU/L (5.4-12.8).’

9. Suggest develop the discussion on measurement of TRAb titre pre-I131 - would the authors recommend this, based on their findings? With a larger number it might be interesting to see the relative impact of TRAB titre at diagnosis and then a long course of anti-thyroid drugs - it may not be possible to get a meaningful analysis with these numbers.
This has been developed as below, line 211-229.

‘Consistent with other studies, we found a significant difference in TSH receptor antibody titre at diagnosis comparing patients who achieved remission with a single dose of I131 to those who remained hyperthyroid. Murakami et al. found that TSH receptor antibody activity immediately before radioiodine therapy was significantly higher in patients who did not achieve remission with a single dose of I131 compared to those who did (9). Chiovato et al. also found that pre-treatment TSH receptor antibody titres were significantly higher in patients who remained hyperthyroid post I131 than in those that became hypothyroid or euthyroid (10). Our study assessed the TSH receptor antibody titre at diagnosis, rather than pre-treatment as it was consistently available. Based on the above findings, the measurement of TSH receptor antibody titres at the onset of disease and prior to definitive treatment may be a useful tool to help predict patients who may be less likely to achieve remission with a single dose of radioiodine. This can assist with counselling patients prior to treatment. Nearly all patients in our study received antithyroid drugs prior to treatment as is standard management for Graves’ disease in Australia. Prolonged treatment with antithyroid drugs reduces the serum TSH receptor antibody level (17). Given that almost all patients were pre-treated with antithyroid drugs in our study it was not possible to look at the relative impact of the TSH receptor antibody titre at diagnosis and after a long period of antithyroid drug treatment on the success of radioiodine therapy, however this may be a direction for future research.’

We hope that our revisions may now render the manuscript as being acceptable for publication in BMC Endocrine Disorders.

Yours sincerely

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