Radioactive Iodine Treatment of Persistent Subclinical Hyperthyroidism Due to Nodular Goiter in Elderly Patients and its Effect on Development of Atrial Fibrillation

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A. Study Purpose and Rationale

Nodular goiter can frequently present with the biochemical abnormalities of subclinical hyperthyroidism, that is, an undetectable serum thyrotropin (TSH, thyroid stimulating hormone) concentration (<0.1 mU/L) along with normal levels of free thyroxine (T_4) and free triiodothyronine (T_3). Recommendations by a number of expert groups advocating screening for thyroid disease in asymptomatic middle-aged and elderly patients will likely bring to evaluation many more patients with subclinical hyperthyroidism and nodular goiter.

Many studies have shown deleterious effects of subclinical hyperthyroidism in patients on exogenous thyroid replacement therapy as well as those with endogenous suppression of thyrotropin. These studies indicate an increased risk of atrial fibrillation and bone loss and a poorer quality of life in patients with subclinical hyperthyroidism, many of whom are asymptomatic or minimally symptomatic.

For example, a study of patients from the Framingham Study who were 60 years of age and older showed that those with an undetectable TSH, but not a slightly low TSH, had a significantly increased risk of developing atrial fibrillation; the relative risk was 3.1 compared with those with a normal TSH (8). In addition, a 10 year cohort study of elderly patients recruited from one primary care practice in the UK showed an increase in mortality from all causes, and in particular mortality from circulatory and cardiovascular diseases, in those with a low TSH at baseline; though after year one, none of these increases were statistically significant (7). Also, a study of patients admitted to an Austrian hospital showed that among those in whom thyroid studies were done, the relative risk of atrial fibrillation was 5.8 in those with overt hyperthyroidism and 5.2 in those with subclinical hyperthyroidism as compared with euthyroid patients (9).

There is also evidence of an effect of subclinical hyperthyroidism on cardiac function and on quality of life. In a case-control study of 46 young and middle-aged patients, those with subclinical hyperthyroidism were found to have significantly greater impairment in quality of life as measured by the Short Form 36 health survey, as well as an increased heart rate, increased left ventricular mass, due to increased septal and posterior wall thickness, and impaired diastolic function as compared to age- and sex-matched controls (2).

In terms of effects of subclinical hyperthyroidism on bone, the evidence is a little less conclusive. Graves' disease patients maintained on antithyroid medication but who have persistently suppressed TSH continue to have increased bone turnover (5). In two cross-sectional studies of patients with subclinical hyperthyroidism and multinodular goiter, there was significantly lower bone density at the femoral neck and radius than in matched controls (10). However, there are no large prospective studies of patients with subclinical hyperthyroidism showing evidence of bone loss and increased fracture risk. There is, however, a small non-randomized study of 28 postmenopausal women with subclinical hyperthyroidism due to nodular goiter that showed that radioactive iodine treatment resulting in normalization of TSH prevented an estimated continued bone loss of 2% per year (4).

The optimal management of patients with subclinical hyperthyroidism, including whether treatment can reduce the risk of complications, is not known (10). To date, there is no consensus on whether these patients should be treated or how they should be treated. A recent study of the management of nontoxic nodular goiter by North American members of the American Thyroid Association indicated the lack of consensus on the treatment of an index case report of a 42 year old

woman with an irregular enlarged thyroid with no clinical suspicion of malignancy or thyroid dysfunction but with a suppressed TSH: 56% of respondents would opt to treat with radioactive iodine whereas approximately 35% chose no treatment; the remaining respondents would have opted for thyroidectomy (3).

No large randomized, controlled trials have been done with groups of patients with subclinical hyperthyroidism who have been adequately chosen to exclude those with thyroiditis or nonthyroidal illness as an explanation for an undetectable TSH and normal free T3 and T4. Also, no such studies are available to follow the results of treatment of subclinical hyperthyroidism on endpoints related to its deleterious effects. It is hypothesized here that treatment of patients with endogenous subclinical hyperthyroidism due to nodular goiter with radioactive iodine can reduce the incidence of atrial fibrillation, or fracture, reduce progression to overt hyperthyroidism, and improve overall quality of life.

B. Primary Question

Does radioactive iodine treatment of elderly patients with persistent endogenous subclinical hyperthyroidism due to nodular goiter reduce the incidence of atrial fibrillation?

C. Study Design

This study will be a multi-center, randomized, double blind, and placebo-controlled clinical trial. The intervention to be studied will be radioactive iodine (^{131}I) at an effective dose of 100 uCi/g of estimated thyroid weight (i.e. weight x 100 uCi/g / radioactive iodine uptake as determined from a 24 hour radioiodine uptake scan prior to treatment). For a power of 80%, testing at p=0.05, the sample size will need to be approximately 432 subjects, half in each arm of the study. Statistical analysis will include chi-square tests to determine whether the proportions of subjects meeting the various endpoints are different between the treatment vs. the placebo arm.

The primary endpoint will be the cumulative incidence of atrial fibrillation over the 5 years of planned follow-up. Secondary endpoints will include the progression to overt hyperthyroidism, cumulative incidence of hypothyroidism, cumulative incidence of new fractures, change in Short Form 36 score for overall quality of life, and all-cause mortality, all over the 5 years of planned follow-up.

D. Study Procedure

Outpatient subjects of at least 60 years of age with nodular goiter who are not on exogenous thyroid replacement therapy will be recruited via flyers, via primary care physician and endocrinologist referrals, and via patients referred to general endocrine and thyroid clinics at each center for evaluation and management of nodular goiter. Subjects will be screened at presentation and again at 6 months to verify persistent subclinical hyperthyroidism as defined by an undetectable TSH (<0.1 mU/L) and a normal free T_3 and T_4. As a result, patients with thyroiditis and non-thyroidal illness will be screened out.

Subjects with clinical evidence of central hypothyroidism as well as those who have been treated with dopamine, corticosteroids, iodinated contrast agents, or amiodarone during the 9 month period beginning 3 months prior to the first measurement of thyrotropin through the time of the second measurement will be excluded. Also excluded will be subjects with established or history of atrial fibrillation, those who have been hospitalized in the same 9 month period mentioned, elevated titers of anti-thyroid peroxidase, anti-thyroglobulin, or anti-TSH receptor antibodies at presentation, as well as those with severe compressive symptoms or large goiters for whom thyroidectomy is preferred by the subject or recommended by the subject's physician.

E. Study Drug

radioactive iodine (^{131}I)

F. Medical Devices

none

G. Confidentiality of Study Data

All subjects will be given a unique code number. A study coordinator will manage assignment to each arm of the study. Assignments will be unavailable to the subjects, investigators, or treating physicians. A placebo solution will be given in place of radioactive iodine for those who are randomized to placebo. Data will be confidential, and the study coordinators will undertake annual reviews of the cumulative patient data.

H. Conflicts of Interest

No investigator or participating center is expected to benefit financially from the results of this study.

I. Location of Study

Multiple centers including urban, suburban, and rural settings will be recruited to participate in the trial.

J. Potential Risks

Subjects undertake the risks inherent in radioactive iodine therapy, including radiation thyroiditis, radiation effects on household contacts, possible increase in risk for thyroid cancer, and eventual hypothyroidism.

K. Potential Benefits

Subjects may or may not benefit from participation in the study in that treatment of subclinical hyperthyroidism is not known to reduce the incidence of atrial fibrillation or other outcomes. Potential benefits include increased knowledge of whether there is a benefit to such treatment for future patients.

L. Alternative Therapies

Other therapies for nodular goiter exist, including no treatment, thyroidectomy, and anti-thyroid medication.

M. Compensation to Subjects

none

N. Costs to Subjects

None

O. Minors as Research Subjects

None

P. Radiation or Radioactive Substances

yes, radioactive iodine (^{131}I)

Q. References

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