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## **Does choice of therapy save costs and improve outcomes in hyperthyroid patients?**

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### **Abstract**

**Objective:** To compare cost of treating hyperthyroidism with antithyroid medications (ATD) versus radioactive iodine (RAI). As secondary outcome we also analyzed data in terms of remission rates.

**Methods:** This was a retrospective comparative analysis of hyperthyroid patients treated with ATD or RAI from January 2000 to December 2005. Cost of ATD, TSH, FT<sub>4</sub>, doctors visits; thyroid technetium scan and RAI treatment were calculated for the duration of treatment and for one year of follow-up after remission.

**Results:** A total of 143 patients were included, with an average duration of follow-up of 32 months. Mean age was 41 ± 15.5 years and M: F' ratio was 1: 2. More expenses were incurred in treating patients with ATD (Rs. 28,900 ± 15 400 or US\$ 481.67 ± 256.67) than with RAI (Rs.18,800± 15800 or US\$313.33± 263.33). The former cost Rs.10,100 (US\$ 168.33) more, (p< 0.001; 95%). Remission rate in the RAI group were significantly higher than the ATD group (81.3% vs 49.5%, p=0.006).

**Conclusion:** Treatment of hyperthyroid patients with RAI is not only better in terms of remission of disease, but it is also a more cost effective modality, and should be considered as first line of treatment (JPMA 58:309;2008).

### **Introduction**

Hyperthyroidism was clinically recorded as a disease entity nearly two centuries ago, and means of medical treatment discovered nearly 70 years back. Currently there are two modes of medical therapy available; antithyroid medications and radioactive iodine. Debate rages over which treatment is better in terms of producing long term remission and causing fewer side effects (short and long term). For a developing country like Pakistan, an important aspect of treating any medical condition also includes the cost, not only of treatment, but also of diagnostic testing. Literature is scant about the "cost effectiveness" of various treatment modalities. Models

exist, which extrapolate costs and feasibility from hypothetical cases, but for physicians sitting in their clinics , and patients who pay out of pocket for their treatment, a realistic approach which considers the "actual" rather than the "hypothetical extrapolation" of cost needs objective evaluation.

The purpose of this study was to analyse the cost incurred in the medical treatment of patients with hyperthyroidism to see if one treatment is superior to the other. As secondary outcome we also analyzed data in terms of remission rates.

### **Methods**

This was a retrospective analysis of patient's records

from Jan 2000 to December 2005. All patients with diagnosed hyperthyroidism seen at the endocrine clinic at Aga Khan University Hospital, were recruited for consideration into this study. Those considered for the analysis, had to have a minimum follow-up of at least one year after their diagnosis and treatment. We excluded children (below 16 years of age), patients with post partum thyroiditis, sub acute thyroiditis, iatrogenic hyperthyroidism and those who had surgical treatment of hyperthyroidism. In addition to demographic variables we recorded the number and frequency of thyroid function test that they had; Thyroid Stimulating Hormone (TSH), Total or free T4 (FT4) and total or free T3. We also made note of the number of total doctors visits and average number of doctors visits. If they had had a thyroid technetium scan or treatment with radioactive iodine, this was recorded separately. We determined an arbitrary cost for the tests and doctors visits (as this may change from institution to institution and also might be revised from year to year). The cost of checking serum TSH, FT4 and T3 was considered at Rs 500 each. One doctor's visit was Rs. 650. Cost of thyroid technetium scan was Rs. 4000/- and that for I<sup>131</sup> treatment also at PKR 4000 (US\$ 66.67).

A descriptive analysis was done for demographic and clinical features and results are presented as mean  $\pm$  standard deviation for quantitative variables and number (percentage) for qualitative variables. In univariate analyses, differences in proportions for types of treatment were assessed by using the Chi-square test or Fisher exact test where appropriate. For contrasts of continuous variables, independent sample t-test was used to assess the difference of means.

All analyses were conducted by using the Statistical package for social science SPSS (Release I 1.5.0. standard version, copyright © SPSS: 1989-02). All p-values were two sided and considered as statistically significant if  $< 0.05$ .

## Results

A total of 143 cases were included in the study. Majority of the cases were reported to have Graves disease (42%), with 19% diagnosed with toxic nodule or toxic multinodular goiter. The remainder did not have the cause of their hyperthyroidism listed in their records, nor had a thyroid technetium scan or thyroid microsomal antibodies (also known as thyroid peroxide antibodies) checked to allow the researchers to assign the subject with a diagnosis. Average duration of follow up was 32 months. Mean age of the group was  $40.97 \pm 15.51$  years. Two thirds of the patients were women and a third were males, and 18% were single. Nearly all the patients were treated with antithyroid medications as initial choice, with 92% receiving either

**Table. Demographic and outcomes data in hyperthyroid patients.**

	<b>Antithyroid medications</b> (N = 111)	<b>Radioactive iodine</b> (N -32)	<b>P value</b>
Mean Age (years)	40.53 $\pm$ 15.6	42.50 $\pm$ 15.3	0.52
Male: female ratio	2.9 : 7.1	5.3 : 4.7	0.01
Mean duration of follow up (months)	31.34	34.77	0.45
Remission rates (%) [Number in remission/number treated]	49.5% [55/111]	81.3% [26/32]	0.006
Average cost of treatment (per patient), in rupees	28,900 $\pm$ 15,400	18,800 $\pm$ 13,400	0.001

p < 0.05 considered significant.

neomercazole or propylthiouracil as the initial treatment. Only twelve patients (8%) were treated with I<sup>131</sup> initially. An additional twenty two (15%) were given treatment with I<sup>131</sup>, once they did not go into remission with anti thyroid medications.

Table shows the demographic and outcomes data. There was a significantly higher remission rate in those treated with I<sup>131</sup> when compared to the group receiving ATD (81.3% vs 49.5%, p=0.006). Post ablative hypothyroidism was seen in 68.8% of those treated with radioactive iodine. Males were more likely to be offered treatment with radioactive iodine and received the same, as compared to female patients. There were 53.1% males and 28.8% females who received I<sup>131</sup> as opposed to 46.9% males and 71.2% females treated with antithyroid medications (p=0.01). There was no relationship of age with the preferred treatment.

Mean cost of treating patients with hyperthyroidism was PKR 21,070  $\pm$  1422 (US\$ 351  $\pm$  23.7%). The major expense to the cost was from diagnostic lab testing, with cost of thyroid function testing contributing to 48.8% of the total, followed by doctors fee from clinic visits (36.36%). Antithyroid medications contributed the least amount to the cost (about 8.13%). Radiologic investigation were requested in only 38 patients and contributed to another 6.71% of overall expenses.

There was a significant difference in the expense incurred between two modalities of treatment. Treatment with antithyroid medications was more expensive by PKR 10,100 (US\$ 168.33), as the average cost of this treatment modality was PKR 28,900  $\pm$  15,400 (US\$ 481.67  $\pm$  256.67), as opposed to I<sup>131</sup> which cost the patient PKR 18,800  $\pm$  15,800 (US\$ 313.33  $\pm$  263.33), p < 0.001; 95% CI. The

underlying cause of hyperthyroidism, age or sex of the patient, their marital status did not influence the choice of treatment.

## Discussion

Thyrotoxicosis exists in 2% of women and 0.2% of men.<sup>1</sup> Graves disease is seen most commonly between the second and the fourth decades of life and toxic multinodular goiter (toxic MNG) and toxic adenoma are seen with increasing age. Literature from Europe and North America places Graves as the most common cause of hyperthyroidism, responsible for 85% of all hyperthyroid patients.<sup>2</sup> The prevalence of toxic adenoma and TMN goiter depends on the degree of iodine sufficiency of a region and accounts for 7 -11% of all hyperthyroid patients.<sup>3</sup> Regional data regarding the etiology of hyperthyroidism is scant and derived from select patient populations (i.e. patients referred for surgery, or pediatric patients). Nonetheless this shows that prevalence of toxic MNG is much higher.<sup>4</sup> Even though Graves disease as a cause of hyperthyroidism was the most frequent, prevalence of multinodular goiter is higher than that reported from the west; 19% as opposed to 7 - 11%.

Diagnostic lab testing was responsible for nearly half of the incurred costs, followed by doctors visits. So even though thionamides are affordable and accessible treatment modality and preferred by many as first line in the South Asian region, yet in the long term prove to be cost ineffective, as most of those on anti thyroid medications require longer follow-up and on going medical care. A difference of PKR 10,000 (US\$ 167.67) is significant for most individuals in a region where per capita income is US\$ 847.<sup>5</sup> This coupled with the higher remission rates in those treated with radioactive iodine as opposed to those treated with anti thyroid medications, argues for the use of I<sup>131</sup> more frequently.

Qari et al have observed a significant cost benefit of treating patients with radioactive iodine, showing this modality to be the most cost effective at 1700 Saudi Riyals. Cost of medical treatment was eight times as expensive.<sup>6</sup> Clearly its use needs to be targeted to the right patient, and should take into account not only chances of remission, based on goiter size, underlying pathology, age and autoimmunity, but also the cost of long term follow-up. A group from Germany, using costing models that included follow up care for 30 years, showed radioiodine to be a cost effective first line therapy in patients with a special risk of relapse after primary conservative therapy ( large goiter, younger age, persistently elevated TSH receptor antibodies or high technetium uptake).<sup>7</sup> In their study anti thyroid drugs were considered cost effective only if they achieved a relapse rate of less than 50%, a cut in number of tests

needed and reduced number of hours absent from work. A cost utility analysis of 1000 hypothetical patients diagnosed with Graves disease at the age of 30 years, and then followed up as a cohort for 40 years quantitatively demonstrated that I<sup>131</sup> therapy was superior to ATD in both costs and utility.<sup>8</sup> Analytic models examining the cost effectiveness of different therapeutic strategies in patients with toxic adenoma found surgery to be most effective and the least costly strategy for younger patients, while radioiodine the less costly for elderly.<sup>9</sup> This model took into consideration the cost of co morbidities and expected mortality risk from surgical intervention.

The debate about which therapy has better outcome continues, and geographical differences exist based partially on epidemiological differences, patients age and preferences, local traditions and glandular size. Sixty-nine percent of thyroidologists in USA prefer I<sup>131</sup> for treating a 40 year old woman with Graves<sup>10</sup> while seventy-seven percent of their European colleagues prefer antithyroid medications<sup>11</sup>, as do the majority in Japan (eighty-eight percent).<sup>12</sup> A prospective, randomized study to objectively examine the benefits and risks of different treatment modality, conducted by Topping et al and the Thyroid Study group.<sup>13</sup> showed that the risk of relapse was highest in the medically treated young and old adults. Patient satisfaction was 90% and did not differ with respect to the treatment modality chosen.

A few limitations are inherent in this study based on its retrospective nature. In addition patients were not grouped according to disease etiology and analysed based on their cause of hyperthyroidism. The incidence of post ablative hyperthyroidism remains high in those treated with radioactive iodine, and this will need to be borne in mind.

## Conclusion

Sufficient data exists to show better remission rates of hyperthyroid patients with radioactive iodine. The additional advantage of cost savings in the long term is also an important consideration. This study has shown a significant cost benefit of radioactive iodine over anti thyroid medication. The choice of therapy should not only be guided by underlying pathology, patients age, goiter size, severity of hyperthyroidism and level of thyroid antibodies (specifically TSH receptor antibodies), but also the long term costs in economically disadvantaged regions of the world.

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