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Original Research Article

Prevalence of T3 thyrotoxicosis and it's management in new onset thyrotoxicosis patients: a prospective observational study

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ABSTRACT

Background: T3 toxicosis is a subtype of thyrotoxicosis where total triiodothyronine (TT3) level is high but total thyroxine (TT4) level is normal in presence of suppressed thyroid stimulating hormone (TSH). Accurate and rapid diagnosis is crucial in management of T3 toxicosis.
Methods: In this prospective observational study from India, newly diagnosed thyrotoxicosis patients were enrolled. T3 toxicosis patients were diagnosed based on diagnostic criteria. T3 toxicosis patients were randomized into two arms, based on dose of carbimazole (CBZ) used for treatment. All patients are following up for 12-14 weeks.
Results: Prevalence of T3 toxicosis was 8.5% in this study. 75% were diagnosed as Grave's disease (GD) and 25% were diagnosed as toxic nodular goiter (TNG). Low dose (5 mg/day) of CBZ is safer and more effective than higher dose (20 mg/day).
Conclusion: Present study suggests that a significant number of patients with thyrotoxicosis are suffering from T3 toxicosis. So, for correct diagnosis of thyrotoxicosis one should investigate for TT3, TT4 and TSH, otherwise we can misdiagnose the T3 toxicosis as subclinical thyrotoxicosis (SCT). Majority of T3 toxicosis patients are diagnosed as GD. Low dose of CBZ is very much effective and safe in these patients. We recommend low dose of CBZ in all patients with T3 toxicosis.

Keywords: T3 toxicosis, Grave's disease, Cabimazole, Thyrotoxicosis

INTRODUCTION

Thyrotoxicosis is a common thyroid disorder.[1-3] It is a clinical state due to inappropriately high circulating thyroid hormones.[4] Clinical presentation of thyrotoxicosis varies from asymptomatic to severe life-threatening thyroid storm.[4] Usual symptoms of thyrotoxicosis are weight loss, palpitation, diarrhea, sweating and heat intolerance.[4] However, it can lead to serious complications such as delirium, atrial fibrillation, heart failure, osteoporosis and altered mental status, if left untreated.[4] In patients with thyrotoxicosis usually both, TT4 (Total thyroxine) and TT3 (Total triiodothyronine) are elevated and TSH (Thyroid stimulating hormone) is suppressed. However, in some cases only TT3 is elevated, TT4 is normal and TSH is suppressed. This condition is called as T3 thyrotoxicosis.[5] Sometimes physician only advise for TT4 and TSH and they miss-diagnose this condition as subclinical thyrotoxicosis (SCT).[2] So, they do not treat the patient as American thyroid association (ATA) suggest the individualized approach for treatment of SCT and recommend treating patients when they are older than 65

years and presence of comorbidities such as osteoporosis or heart disease6. If we do not treat T3 toxicosis than patient develops various complications of thyroid hormone excess.

Prevalence and causes of T3 thyrotoxicosis vary from countries to countries. In a study from Thailand, prevalence of T3 toxicosis among thyrotoxicosis patients was 5.6%.[7] Snabboon et al, in their study from Thailand, found a higher prevalence (16.02%) of T3 thyrotoxicosis among hyperthyroid patient.[8] Higher incidence (12.9%) of T3 toxicosis was reported by Bellabarba et al from Canada.[9] Hollander et al from Chile found 56 (12.5%) cases of T3 toxicosis in 449 cases of hyperthyroidism.[10]

They also found low (4%) prevalence of T3 thyrotoxicosis from New York.[11,12] Figge et al from USA found 1 case of T3 toxicosis and 3 cases of free T3 toxicosis in 140 patients with normal T4 and suppressed TSH.[13] In early phase of Grave's disease and toxic nodular goiter (TNG), T3 toxicosis can be seen.[7] In Grave's disease (GD) and in some toxic thyroid adenoma patients, thyroid cell expresses more D2 which causes more T3 production.[14,15]

In the area of iodine deficiency frequency of T3 toxicosis is higher as thyroid gland adapt to iodine deficiency by increase in T3 production over T4.[14,15] Ideal treatment of T3 toxicosis is propylthiouracil (PTU) as it also blocks the conversion of T4 to T3. However, there is a lot of issue with usage of PTU.[16] Usage of PTU is associated with poor compliance, high risk of side effects and makes thyroid gland radio-resistance. So many prefer carbimazole (CBZ) to PTU. There is lack of study on T3 toxicosis from India. We also do not know the etiologic subtype of T3 toxicosis from India; however, we know the subtype of thyrotoxicosis from India.[17] Furthermore, Indian thyroid patients differ than western patients.[18,19] We conducted this prospective observational study with aim to know the prevalence and causes of T3 toxicosis in thyrotoxicosis patients. Further our aim was to know the appropriate dose of anti-thyroid drugs in these patients.

METHODS

Study design

All the thyrotoxicosis patients for this study were enrolled from single center, Endocrine Clinic and Hospital, Varanasi. A total of 153 consecutive newly diagnosed thyrotoxicosis patients were recruited between January 2021 to August 2024.

Inclusion criteria

Includes were age > 15 years and raised TT3, and /or TT4 and suppressed TSH level. Diagnosis of T3 toxicosis was done based on raised TT3, normal TT4 and suppressed TSH level.

Exclusion criteria

Subjects with history of intake of thyroid hormone, anti-thyroid drug (ATD), amiodarone, lithium and radioiodine intake were excluded from this study. Pregnant females were also excluded from present study. A total of 12 patients were excluded from study, as they do not meet the inclusion and exclusion criteria.

Diagnosis of GD was done based on clinical feature (presence of thyroid associated ophthalmopathy), TSH receptor antibody and /or positive thyroid scan. Sub-acute thyroiditis (SAT) was diagnosed on the basis of typical clinical feature (neck pain and evidence of toxicosis) and supported by suppressed thyroid scan. Diagnosis of TNG was done by typical clinical feature (nodular thyroid and biochemical evidence of thyrotoxicosis) and supported by USG and or typical thyroid scan.

All the patients were treated with CBZ and were follow up for 3 months. Clinical review and thyroid function test (TFT) were evaluated at 4-6 week and 12-14 weeks interval. We randomized the patients alternately in two groups. First group were given single daily dose of 5 mg (low dose) of CBZ. In second group patients were given 20 mg (high dose) of CBZ as single daily dose.

Treatment of CBZ was adjusted at each visit based on test results. Dose was unchanged if patients remained euthyroid or hyperthyroid. If TT4 and TT3 level had fallen below the reference range than CBZ was discontinued for 5 days and then restarted at a dose of 5 mg/day.

Immunoassay analyzer performed TT3, TT4 and TSH tests. We preferred TT3 and TT4 over FreeT3 (FT3) and FreeT4 (FT4) because thyroid binding globulin (TBG) interferes with the immunoassay of FT3 and FT4. Many patients suffering from GD have elevated TBG and many SAT patients are complicated by liver dysfunction and thus have high TBG. Besides this cost of FT3 and FT4 are higher than TT3 and TT4 and later test is also readily available.

The reference range of TT3, TT4 and TSH were 80-200 ng/dl, 5.1-14.1 µg/dl and 0.27-4.2 µIU/ml, respectively. Ethical committee of the Opal hospital approved this study. Informed oral consent was taken from all patients. This present study was performed in accordance with the Helsinki Declaration of 1964 and its latter amendments.

Statistics analysis

The data were tabulated and analyzed using SPSS version 16 software. Categorical data were expressed as numbers and percentage for their analysis. Continuous data were expressed as mean± standard deviation. Categorical variables data were compared by Chi-square while continuous data were compared by Student's t test. P value of <0.05 was considered as significant in this study.

RESULTS

Baseline demographic profile of study population

A total of 141 patients with newly diagnosed thyrotoxicosis were enrolled in this present study. 12 (8.5%) patients were diagnosed as T3 thyrotoxicosis based on diagnosed criteria. Of this 12 patients 4 were male and 8 were female and thus the male to female ratio was 1: 2. Mean± SD age (years), height (centimeter), weight (kg), body mass index (BMI), waist circumference (centimeter), TT3 (ng/dl), TT4 (µg/dl) and TSH (µIU/ml) of patients were 45±11.6, 160.4±9.2, 60±16.27, 23±4.7 90.33±11.69, 281.75±59.4, 12.73±1.16, 0.008±0.01, respectively. 9 (75%) patients were diagnosed as GD and 3 (25%) patients were diagnosed as TNG (Table 1).

Table 1: Baseline demographic profile of study population.

Parameter	Patients value
Number	12
M:F ratio	1:2
Age	45±11.6
Height	160.4±9.2
Weight	60±16.3
BMI	23±4.7
Waist circumference	90.3±11.5
TT3	281.75±59.4
TT4	12.7±1.16
TSH	0.008±0.01
Grave's disease	9 (75%)
TNG	3 (25%)

Table 2: Thyroid function status during study period.

Thyroid status	Low dose group		High dose group	
	4-6 weeks	12-14 weeks	4-6 weeks	12-14 weeks
Euthyroid	6	6	3	2
Hypothyroid	0	0	3	4
Hyperthyroid	0	0	0	0

Thyroid function test during study period

Patients were alternately randomized in to high dose (20 mg/day) group and low dose (5 mg/day) group. 6 patients were given high dose and remaining 6 were given low dose. In high dose group 3 patients developed hypothyroidism at 4-6 weeks and one patient developed hypothyroid at 12-14 weeks thus leading to reduction of dosage.

In low dose group all patients become euthyroid and non-developed hypothyroid during study period (Table 2). This shows that in high dose group more patients develop more hypothyroidism as compared to low dose group which is statistically significant ($p<0.01$).

Effect of side effect of ATD

All patients tolerated the drug well. Discontinuation of drug was not done in any patients because of side effects. One patient develops pruritus but was treated effectively by antihistaminic. None of the patients develops arthralgia, hepatitis, agranulocytosis, headache and asthma. Hematological test did not show any significant alternations.

DISCUSSION

Present study suggests that prevalence of T3 toxicosis is higher in Indian thyrotoxic patients. Prevalence of T3 toxicosis is higher than USA (8.5% vs 4%) because average iodine intake in USA is higher than India20. Other reason could be different study population. High prevalence T3 toxicosis is also seen in Thailand and Chile thyrotoxic patients.[8,10] In these countries prevalence of iodine deficiency is high as compared to USA. Prevalence of T3 toxicosis in many countries remains to be established. Reason for more T3 production in T3 toxicosis patients is due to preferential production of T3 over T4. It is usually seen in early phase of disease or relapsing phase of thyrotoxicosis.[21] Higher expression of D2 in Grave's thyroid tissue and in some cases of toxic nodular thyroid tissue causes more conversion of T4 to T3 and thus T3 toxicosis.[14] In area of iodine deficiency higher frequency of T3 toxicosis is due fact that body tries to conserve iodine and thus more T3 production.[10] Follicular cells of thyroid gland are structurally and functionally heterogeneous. In area of iodine deficiency those follicular cells are more selected who have more D2 and thus more T3 production.

Accurate sub-classification of T3 toxicosis is important as outcome of treatment and prognosis varies with subtype of thyrotoxicosis4. Treatment of choice for GD is ATD but for TNG, surgery is the treatment of choice6. In this study 75% and 25%% of patients were sub-classified as GD and TNG, respectively. Higher prevalence GD is seen in present study (75%) which is similar to study from Thailand (88.3%).[7] In USA majority of T3 toxicosis patients were subclassified as TNG13. However, Hollander et al in their study from USA found higher prevalence of GD (72.5%) while prevalence of autonomous adenoma and TNG were 20% and 7.5%, respectively.[12]

We do not know the reason for this discrepancy but iodine status and ethnicity of that area may determine the cause. This present study shows that low dose of CBZ is highly effective in controlling T3 toxicosis. Higher dose is associated with more risk of development of hypothyroidism. We know that follicular cells preferentially take up CBZ and thus they are accumulated inside the cells leading to more response than

anticipated.[22,23] This is the first study in T3 thyrotoxicosis, which compares the low dose vs high dose of CBZ. In this present study when patients were put on 5 mg/day of CBZ, all became euthyroid within 4-6 weeks of therapy and with same dose all remains euthyroid at 12-14 weeks. When patients were put on higher dose, 50% of patients became hypothyroid at 4-6 weeks and 66.67% of patients become hypothyroid at 12-14 weeks of therapy leading to reduction in dosage.

Limitations of present study are single center study and shorter duration of follow up. However, this study has much strength also. This is the first study from India on T3 toxicosis. Also, there is adequate number of thyrotoxicosis patients in this study as prevalence of thyrotoxicosis in population is low. Other strength of this study is that diagnoses of all patients were made by through investigations such as thyroid scan, TSHR Ab and/or USG.

CONCLUSION

In conclusion, present study suggests that a significant number of patients with thyrotoxicosis are suffering from T3 toxicosis. So, for correct diagnosis of thyrotoxicosis one should investigate for TT3, TT4 and TSH, otherwise we can misdiagnose the T3 toxicosis as SCT. Majority of T3 toxicosis patients are diagnosed as GD. Low dose of CBZ is very much effective and safe in these patients. We recommend low dose of CBZ in all patients with T3 toxicosis.

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