

HEMATOLOGICAL DISORDERS OF PROPYLTHIOURACIL IN THYROID PATIENTS AT TERTIARY CARE HOSPITAL OF HYDERABAD

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ABSTRACT

Objective: To find out the frequency of anemia, agranulocytosis and thrombocytopenia in hyperthyroid patients after the use of propylthiouracil.

Study Design: Cross sectional study.

Place and Duration of Study: Out Door Patients Department and Pathology Laboratory in Liaquat University Medical & Health Sciences, Hospital Hyderabad/Jamshoro, from May 2016 to Apr 2017.

Methodology: Two hundred cases, comprising of adult patients were categorized into five groups, age group 15-30 years 79 (39.5%) patients presenting the highest out of total, age group 31-45 years 68 (34%) patients, age group 46-60 years 36 (18%), age group 61-75 years 14 (7%) patients, age group >75 years 3 (1.5) patients. Complete blood count was analyzed on Sysmex Kx21 and thyroid profiles were analyzed on Elecysis 2010 from the Pathology Department. SPSS version 22 was used for data analysis.

Result: Out of total patients, 32 (16%) were males and 168 (84%) were females with mean age of 37.44 ± 14.82 years. Majority of patients 68 (34%) were anemic, while 4 (2%) had agranulocytosis and 11 (5.5%) had thrombocytopenia. Headache was reported in 111 (55.5%), exophthalmos in 106 (53%), sore throat in 172 (86%), fever in 136 (68%) and weight loss in 95 (47.5%) patients.

Conclusion: Propylthiouracil causes defective hematopoiesis in hyperthyroid patients because propylthiouracil has adverse suppressive effects on bone marrow.

Keywords: Agranulocytosis, Anemia, Hyperthyroid, Propylthiouracil, Thrombocytopenia.

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INTRODUCTION

Hyperthyroidism can be defined as a clinical syndrome that results from a high level of thyroid hormones usually due to the overactivity of the thyroid gland.¹ After Grave's disease toxic multinodular goiter and solitary toxic adenoma are common, although in iodine-sufficient regions almost 80% hyperthyroid patients have Grave's disease while 50% of hyperthyroid patients possess toxic multinodular goiter and toxic adenoma.² Graves' orbitopathy develops in 25% of Graves' disease.³ Propylthiouracil (PTU) (Thionamide) is an antithyroid medicine. PTU is commonly used for hyperthyroidism and also used as an alternative therapy for the patients with Grave's disease and toxic multinodular goiter when the methimazole and Radioactive Iodine (RAI) treatment is contraindicated.⁴ It is used prior to thyroid surgery or Radio Active Iodine ablation to cure hyperthyroidism. PTU also used to treat thyrotoxicosis crisis and thyroid storm in hyperthyroid patients.⁵ Pro-pylthiouracil inhibits the

function of thyroid peroxidase enzyme, which generally converts iodide to iodine molecule and joins the iodine into tyrosine (amino acid). Therefore, monoiodotyrosine and diiodotyrosine are not produced, which are the basic components for the synthesis of thyroxine (T₄) and triiodothyronine (T₃).⁶ It also inhibits the peripheral conversion of thyroxine to triiodothyronine.⁷ PTU possess anti-inflammatory as well as immunosuppressive effect⁸. Major adverse effects of anti-thyroid drugs (ATD) include agranulocytosis, which is rare but potentially fatal in which absolute granulocyte count becomes <500 cell/mm.³ Aplastic anemia is in frequently and extremely rare adverse effect of propylthiouracil. PTU inhibited myelopoiesis which produces agranulocytosis, anemia and thrombocytopenia. Whilst PTU bounded more tightly to the albumin than the carbimazole or methimazole, hence may pass less through the placenta and recommend in the trimester of pregnancy.⁹

Rationale of this study was to investigate the frequency of hematological disorders of propylthioracil in hyperthyroid patients and to identify the potential of adverse effects in local population.

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METHODOLOGY

A cross-sectional study was conducted and data of 200 patients were collected by non-probability consecutive sampling technique who were diagnosed by hematological disorders at OPD and Pathology Laboratory in Liaquat University Medical & Health Sciences, Hospital Hyderabad/Jamshoro Pakistan from May 2016 to April 2017 and their thyroid profiles and complete blood count were evaluated after medication of propylthiouracil. Ref no. DRUGS/1011 was taken from the institution’s ethical board. Verbal consents were taken from all patients before collected data.

Inclusion Criteria: All the adults with hyperthyroidism who were taking (Propylthiouracil) were included.

Exclusion Criteria: Patients of other endocrine disorder, autoimmune disease and all other diseases were excluded.

A sample size of 200 patients was calculated by using Sloven's formula ($n=N/1 \pm Ne2$), where the total population (N) was 400 patients per year admission in hospital and margin of error (e) was 0.05. Slovin’s Formula is used when the number of people are easily accessible to sample because it is inexpensive and reducing sampling error¹⁰. All data was evaluated by using the Statistical Package for the Social Sciences (SPSS) software version 22. Percentage and frequency were calculated for the qualitative variables; while mean and standard deviation were calculated for the quantitative variables. Independent sample t-test was used to compare Thyroid profile and blood disorders between males and females. The difference was considered significant if *p*-value was found <0.05.

RESULTS

Out of 200 patients, 168 (84%) were females and 32 (16%) were males. The overall mean age was 37.44 ± 14.82 years. Patients were categorized into five groups, age group 15-30 years 79 (39.5%) patients presenting the highest out of total, age group 31-45 years 68 (34%) patients, age group 46-60 years 36 (18%), age group 61-75 years 14 (7%) patients, age group >75 years 3 (1.5) patients and majority of the patients 79 (39.5%) were observed in age group 15-30 years shown in Figure-1.

Most common presenting symptoms were headache 111 (55.5%), blurred vision 106 (53%), sore throat 172 (86%), fever 136 (68%) and weight loss 95 (47.5%) (shown in figure-2).

Out of 200 patients, 16 (8%) were hypothyroid and 43 (21.5%) were hyperthyroid. Thyroid profile

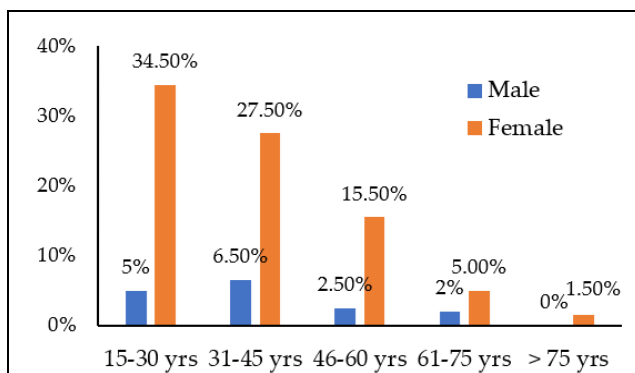


Figure-1: Gender wise distribution of age groups in hyperthyroid patients.

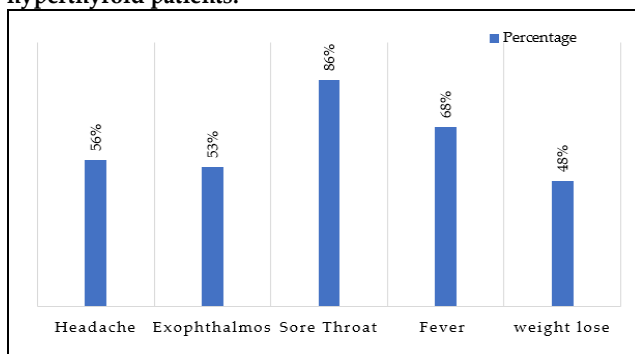


Figure-2: Adverse drug reactions after the use of propylthiouracil.

results after PTU medication, showed that TSH was normal in 166 (83%), low in 21 (10.5%) and high in 13 (6.5%) patients. T3 value was normal in 158 (79%), low in 1 (0.5%) and high in 41 (20.5%) patients whereas T4 level normal in 171 (85.5%) low in 3 (1.5%) and high in 26 (13%) (shown in Table-1). The overall mean of TSH (uU/ml) was (2.4 ± 0.34) , T3 (ng/ml) was (1.41 ± 0.13) , and T4 (ug/dl) was (8.94 ± 0.42) .

Table-I: Comparison of thyroid profile (TSH,T3 &T4) in males and females after the use of Propylthiouracil.

Thyroid Profile	Males (n=32) [mean ± SD]	Females (n=168) [mean ± SD]	<i>p</i> -value
TSH (uU/ml)	1.58 ± 0.18	3.19 ± 0.5	0.003
T3 (ng/ml)	1.45 ± 0.17	1.36 ± 0.09	0.661
T4 (ug/dl)	9.19 ± 0.65	8.70 ± 0.19	0.480

PTU related alteration was observed in RBCs (hemoglobin), WBCs (leucocytes) and platelet (thrombocytes), there was marked reduction in hemoglobin having mean 13.62 ± 0.36 gm/dl in males and having mean value 11.90 ± 0.13 gm/dl in females, decreased WBCs was also observed being 2 (1%) in males with mean value 7.52 ± 0.35 10^3 /ul and 2 (1%) in females with mean value 8.06 ± 0.20 10^3 /ul, reduction in thrombocytes was also reported 2 (1%) in males with mean value 268 ± 13 10^3 /ul and 9 (4.4%) in females

with mean value 323 ± 88 10^3 /ul as shown in Table-II. Twenty nine (14.5%) anemic patients were observed in age group of 15-30 years, 18 (9%) anemic patients in age group of 31-45 year, 16 (8%) anemic patients in age group of 46-60 years, 4 (2%) anemic patients in age group of 61-75 years and 1 (0.5%) anemic patient in age group of >75 years. Three (1.5%) patients with agranulocytosis were observed in 3 (1.5%) patients in age group of 46-60 years and 1 (0.5%) patient in age group >75 years.

Table-II: Comparison of hematological abnormalities in males and females after the use of propylthiouracil.

Complete Blood Count	Males (32) [mean \pm SD]	Females (168) [mean \pm SD]	p-value
Hemoglobin (gm/dl)	13.62 \pm 0.36	11.90 \pm 0.13	0.0001
Total leucocyte count (10^3 /ul)	7.52 \pm 0.35	8.06 \pm 0.20	0.190
Platelets (10^3 /ul)	268.2 \pm 13	323 \pm 88	0.001

Thrombocytopenia was observed in 5 (2.5%) patients with age group of 15-30 years, 2 (1%) patients with age group of 31-45 years, 3 (1.5%) patients with age group of 46-60 years and 1(0.5%) patient with age group of >75 years. A total of 68 anemic patients (51 patients with headache and 17 patients without headache), (39 anemic patients with blurred vision and 29 without blurred vision), (62 anemic patients with sore throat and 6 patients without sore throat), (51 patients with fever and 17 patients without fever), (38 patients lost their weight and 30 patients without weight loss). Agranulocytosis was observed in 4 patients, (all 4 patients had headache), (3 patients with blurred vision and 1 patient without blurred vision), (all 4 patients with sore throat), (3 patients with fever and 1 patient without fever), (2 patients with weight loss and 2 patients without weight loss). Thrombocytopenia was observed in 11 patients, (8 patients with headache and 3 without headache), (4 patients with blurred vision and 7 without blurred vision), (9 patients with sore throat and 2 patients without sore throat), (6 patients with fever and 5 without fever), (8 patients with weight loss and 3 patients without weight loss).

DISCUSSION

Hyperthyroidism is a clinical manifestation characterized by increased production of thyroid hormones, most commonly observed in females than males (5:1 ratio). Propylthiouracil is used as a first line drug therapy in the management of hyperthyroid patients and it inhibits the production of thyroid hormones by

blocking the oxidation of iodine in the thyroid.¹¹ In this the ratio of females and males suffering from hyperthyroidism was 5.25:1. According to American Thyroid Association females are 5-8 time more prone to thyroid disorders.¹²

Agranulocytosis is a rare but potentially fatal complication of the anti-thyroid drugs which is associated with life threatening infection in hyperthyroid patients. In present studies, agranulocytosis was observed only in 2% patients. The ratio of anti-thyroid drug induce agranulocytosis in female to male ratio was 1:1 and the overall mean age was 37.44 ± 14.82 years. The most commonly observed adverse effects included sore throat (86%), fever 68(%) and headache (55.5%). Similar study conducted in Taiwan showed only 13 (0.23%) patients developed agranulocytosis.¹³ In another similar study the ratio of females and males with agranulocytosis was 10.4:1. The other most common sign and symptoms were fever (92%), sore throat (85%) and headache (8%),¹³ and in another study sore throat (72.8%) and fever (78.9%) were the common manifestation of agranulocytosis.¹⁴

In this study, hematological disorders were observed in 83 out of 200 patients suffered from hematopoietic damage, 4 patients had agranulocytosis, 79 patients had pancytopenia (68 patients had anemia and 11 patients had thrombocytopenia). A study conducted in Japan included 50385 patients with Graves' disease showed that 55 patients suffered from hematopoietic damage. Patients with agranulocytosis were 50 while, 5 patients had pancytopenia, either anemia or thrombocytopenia was also observed.¹⁵ Hyperthyroidism can cause weight loss in majority of hyperthyroid patients, less than half of the patients reduced their weight during the treatment with propylthiouracil (47.5%). However, a study in 2019 reported the weight gain by the patients with hypothyroidism using PTU and propylthiouracil reduced the weight of the hypothyroidism patients along with the fever and myalgia.¹⁶

Ophthalmopathy is considered as a disorder of immune system in hyperthyroid patients, almost 53% patients reported eye disorders and ophthalmopathy was observed in 106 patients which worsened after the treatment with propylthiouracil. Similarly, in 2003, a study reported 30% cases of ophthalmopathy due to immune system disorders in hyperthyroidism patients.¹⁷ It is postulated that Graves' orbitopathy is an ocular manifestation of the auto-immune process commonly and reflects excessive thyroid hormone, eye signs are seen in approximately 25-63% of adolescents.¹⁸

CONCLUSION

Propylthiouracil causes defective hematopoiesis in hyperthyroid patients because Propylthiouracil has adverse suppressive effects on bone marrow.

Conflict of Interest: None.

Authors' Contribution

UNS: Research designing, data collection, data processing & analyzing, manuscript writing, MAG: Literacy design, proforma design, AD: Data analysis, data interpretation, MIA: Study design, manuscript writing, RP: Proof reading, data collection, JK: Guidance of research paper.

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