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ORIGINAL ARTICLE

Harmful impact of radioactive iodine (I^{131}) therapy on hematological parameters in thyroid disease patients

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ABSTRACT

Radioactive Iodine-131 is used to treat benign and malignant hyperthyroid patients. It is concentrated in thyroid tissue when taken orally. It destroys thyrocytes by omitting beta rays and also by producing reactive oxygen species (ROS). As it circulates through the blood stream, I^{131} causes direct harm to blood cells through beta radiation and indirect harm by producing free radicals. The study aims to investigate damaging effects of I^{131} on hematological parameters in patients with thyroid diseases.

Methods: A total of 100 hyperthyroid patients were recruited and split into four groups: male low-dose, female low-dose, male high-dose and female high-dose groups depending on their I^{131} dosage. Health professionals at PINUM Cancer Hospital Faisalabad administered I^{131}, provided by the Pakistan Atomic Energy Centre Islamabad, to the patients. Hematological markers were evaluated prior as well as after I^{131} therapy.

Results: Following I^{131} therapy, total leukocyte count remained stable but the absolute lymphocyte count (ALC), RBCs count and platelets counts declined significantly within two weeks. ALC decreased 41.7%, and platelets dropped by 25% whereas RBCs displayed a reduction of 10%. Gender wises the decline in ALC was same in both genders but in platelets count the decline was higher in males while the decline in RBCs count was higher in females. Neutrophils presented hyper-segmentation of chromatin while cytoplasmic vacuolation and micronuclei formation were seen in lymphocytes.

Conclusions: Radioiodine therapy has the damaging effects on blood cells and causes a significant decline in lymphocytes, RBC and platelets counts. I^{131} also exhibited genotoxic effect on neutrophils and lymphocytes.

Keywords: Beta Rays, Iodine Radioisotopes, Hematological Parameters, Reactive oxygen species

This article may be cited as: Shahid I, Mubeen H, Rakha A. Harmful impact of radioactive iodine (I131) therapy on hematological parameters in thyroid disease patients. Int J Pathol 23(4):305-14. https://doi.org/10.59736/IJP.23.04.975

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Introduction

About 30 to 40 percent of people with endocrine disorders have thyroid issues. Incidence of thyroid cancer has increased worldwide during the 1980s, although death rates have essentially remained the same (1). Margherita Pizzato et al. analyzed the

GLOBOCAN database to examine 2020 data from 185 countries in a study published in The Lancet Diabetes & Endocrinology. Among the thyroid disorders, 10.1 patients of cancer per 100,000 women and 3.1 patients per 100,000 men were recorded, while the mortality rates in these patients were 0.5 and 0.3 per 100,000 respectively (2).Thyroid disorders are more common in Pakistan's hilly regions and are more common among women (3). In the Pakistani population, the prevalence of hypothyroidism and hyperthyroidism is 4.1% and 5.1%, respectively (4). Thyroid cancer is very common in the Gujranwala Division in Central Punjab. According to the clinical epidemiology of this area, out of 236 patients of hyper thyroid diseases,48.52%were suffering from nodular goiter and 36.45% of these nodular goiter patients were malignant (5).

For over even decades, iodine-131 (I^{131}) has been the preferred medication for treating hyperthyroid conditions (6). When administered orally, it is concentrated in thyroid tissues and destroys the thyrocytes. As I^{131} circulates through the blood stream, it also directly destroys blood cells producing beta radiation and indirectly by generating free radicals like reactive oxygen species (ROS). The free radicals react with cell membranes to cause aberrant cell permeability and also react with intracellular macromolecules including DNA and cause their damage (7,8).

Additionally, I^{131} therapy causes bone marrow toxicity, which in consequence causes bone marrow dysfunction. One of the main adverse effects of radioiodine is bone marrow suppression. I^{131} therapy's radiation has an impact on bone marrow hematopoiesis (9,10). Hematological parameter alterations, however, are also related to gastrointestinal toxicity and the ensuing nutritional deficit (11). In addition, through an oxidative response, I^{131} causes RBCs to alter their shapes resulting in shortening of their lifespan (12).

After receiving radioactive iodine therapy (RAIT), organ damage and the activation of several inflammatory factors cause changes in TLCs. Furthermore, alterations to TLC count and changes in their functions may result from radiation-induced modifications to growth factors and supportive stroma. Induction of cellular apoptosis and aberration of genetic material by radioiodine also affects WBCs (13). Platelet (PLTs) count fluctuations are caused by RAIT-associated essential organ damage, including apoptosis and genetic abnormalities in these organs. Furthermore, PLTs quantity and function are altered when radioisotopes directly harm megakaryocytes and their progenitors (14,15).

The effects of I^{131} on blood cells are not well studied, particularly in the effects of I^{131} on various blood cell types and in future such damage if present can be mitigated by substitution of some radioprotectives and antioxidants.

Methods

After the approval of ethical review committee at Faisalabad Medical University, Faisalabad (Registration No. 702/2016), the study was conducted over a period of one year at the Punjab Institute of Nuclear Medicine (PINUM) Cancer Hospital, Faisalabad in 2016. The study was conducted in two main groups High RAIT (malignant patients) and Low RAIT (benign patients) and treatments were randomly assigned in each group. The sample size for 5.1 % hyperthyroid population with 95% confidence level and 5% margin of error was calculated to be 75.

A total of 100 patients suffering from benign hyperthyroid diseases (n=72) and malignant hyperthyroid diseases (n=28) of 18 to 60 years of age were included while the patients having acute and chronic inflammatory diseases, renal

and heart failure and allergy to the I^{131} were excluded in the study. The written informed consent of volunteer patients was taken. The low therapeutic dose of I^{131} i.e. 15-29 milli Curie (mCi) was given to benign hyperthyroid patients and called as low radioactive iodine therapy (Low RAIT) group while high dose of I^{131} i.e. 100-250 mCi was given to the differentiated thyroid cancer patients, at least four weeks after thyroidectomy and labelled as high radioactive iodine therapy (High RAIT) group (16). Both Low RAIT and High RAIT groups were subdivided gender wise as male Low RAIT (n=32) and female Low RAIT (n=40) groups, male High RAIT (n=12) and female High RAIT (n=16) groups.

Blood samples from volunteers were collected through venipuncture at three different occasions. First sample was taken before the administration of I^{131}; second sample was collected 3 hours after the dose of radioiodine while third one was obtained 2 weeks after RAIT because half-life of I^{131} is 7.6 days and after 2 weeks the radioactivity in blood is equal to background radiation (17). A 3 mL blood sample was drawn from the forearm vein under aseptic conditions for complete blood count (CBC) and peripheral smear. CBC including counts of RBCs, WBCs, DLC and platelets, were determined by using CBC analyzer "Hemalyzer-203D Plus-Bolton". Morphological changes in the blood cells were studied in the peripheral blood films after staining with Giemsa stain, under the light microscope (Olympus SH-2). The photographs were recorded by mounting the mobile phone camera "Samsung C5" on the eye piece. The data was presented as Mean ± SD and percentage change in the means. The comparison of different means was presented in graphs by using Microsoft Excel 2010.The statistically significant difference in means was calculated by two-way ANOVA followed by Tukey's multiple comparison tests by Graph Pad Prizm 7 and $p<0.05$ was considered as statistically significant.

Results

In cancer patients receiving high-dose of RAIT, there was non-significant increase in WBC count ($p=0.0647$) in both genders. Conversely, in benign thyroid patients treated with low-dose of I^{131}, WBC count decreased in both genders, more in males (19.6%) than that in females (15%) at 2 weeks of RAIT (Table 1).

Table 1: Comparison of WBC count before, 3 hours and 2 weeks after I^{131} therapy, in malignant and benign thyroid patients, in both genders

Groups		WBC count (/µL)			Decrease/increase (%) in WBC count	
		Before RAIT	3 hours after RAIT	2 weeks after RAIT	3 hours after RAIT	2 weeks after RAIT
Male (High RAIT)	Mean	6270	7073	6360	−12.8†	−1.4†
	SD	1465	1757	1615		
Female (High RAIT)	Mean	7162	7977	7000	−11.4†	2.3
	SD	1176	2867	2188		
Male (Low RAIT)	Mean	6890	6646	5541	3.5	19.6
	SD	2831	2010	1078		
Female (Low RAIT)	Mean	6300	5893	5353	6.5	15.0

	SD	1324	1476	1590		

†Negative (−) values indicate (%) increase in WBC count

Table 1a: Two-way ANOVA of WBC count, in both genders

SOV	SS	DF	MS	F (DFn, DFd)	P value
Interaction	5566678	6	927780	F (6, 114) = 0.322	P=0.9243
Gender and Dose	21426133	3	7142044	F (3, 114) = 2.479	P=0.0647
Before vs. after RAIT	8642426	2	4321213	F (2, 114) = 1.5	P=0.2275
Residual	328424813	114	2880919		

Gender wise difference and Before RAIT vs. 2 weeks after RAIT differences in WBC count when analyzed by ANOVA was found non-significant showing p=0.0647 for gender and p=0.2275 for comparison of WBC count before RAIT vs. 2 weeks after RAIT (Table 1a).

There was continuous reduction in the absolute lymphocyte count (ALC), in both genders, from 3 hours after radioiodine therapy to 2 weeks after RAIT. There was 41.7% reduction in lymphocyte count in males while the reduction in its count was 37.6% in females at 2 weeks after RAIT. There was greater reduction in lymphocyte count in low RAIT groups as compared to that in high RAIT groups. The low or high activity of I^{131} provides the almost similar destructive effects to the lymphocytes. There was significant decline (p=0.0019) in ALC in all the four groups but higher reduction was in low dose groups. It was also observed that the decline in ALC was more in males than that in females but the p=0.4217 indicates that this difference was non-significant. The destructive outcome of RAIT on the lymphocyte count is presented in Figure 1.

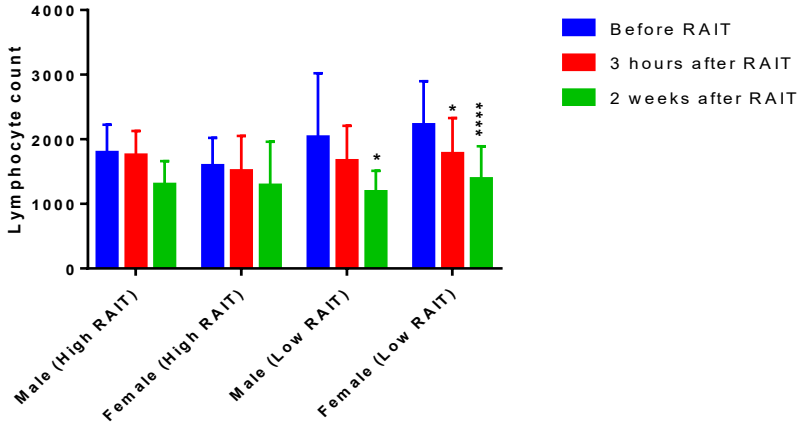

Figure 1: Comparison of absolute lymphocyte count before, 3 hours and 2 weeks after I131 therapy, in malignant and benign thyroid patients, in both genders. Symbols *, ** represent degree of significant differences in ascending order, from base line**

The platelets count was declined within 3 hours of radioiodine therapy and this decrease in platelets count continued up to 2 weeks (Table 2). Again, the decline was more in benign thyroid patients being treated with low activity of I^{131} than those in neoplastic, thyroidectomized individuals being treated with high dose of RAIT. The depression in

platelets count after RAIT was 22% in benign thyroid patients while in malignant thyroid patients the decline in platelets count was only 7%. The decline in platelets count within 3 hours after RAIT was more prominent in females (16%) than that in males (3%). After 2 weeks of RAIT the situation was reversed, where there was lesser reduction in platelets count in females as compared to that in males. The decline in platelets count in males and females, at 2 weeks after RAIT was in the following order Male (Low RAIT) (22%) > Female (Low RAIT) (13%) > Male (High RAIT) (7%) > Female (High RAIT) (1.2%).

Table 2: Comparison of platelets count before, 3 hours and 2 weeks after I^{131} therapy, in malignant and benign thyroid patients, in both genders

Groups		Platelets count (/μL)			Decrease/increase (%) in Platelets count	
		Before RAIT	3 hours after RAIT	2 weeks after RAIT	3 hours after RAIT	2 weeks after RAIT
Male (High RAIT)	Mean	253333	246000	235333	3	7
	SD	16743	25515	33531		
Female (High RAIT)	Mean	292000	243833	288500	16	1.2
	SD	70849	45490	66744		
Male (Low RAIT)	Mean	234857	235286	183000	−0.18†	22
	SD	65976	43342	46257		
Female (Low RAIT)	Mean	298833	263583	261250	12	13
	SD	78430	65869	80566		

†Negative (−) value indicates (%) increase in platelets count. The value −0.18 may be considered as experimental error.

Table 2a: Two-way ANOVA of platelets count, in both genders

SOV	SS	DF	MS	F (DFn, DFd)	P value
Interaction	15029631762	6	2504938627	F (6, 114) = 0.5322	P=0.7828
Gender and Dose	39624983705	3	13208327902	F (3, 114) = 2.806	P=0.0429
Before vs. after RAIT	10220723613	2	5110361806	F (2, 114) = 1.086	P=0.3411
Residual	536577944614	114	4706824076		

Two-way ANOVA revealed a statistically significant interaction between gender and RAIT dose (low dose vs. high dose) on platelet count, indicating a differential effect (p = 0.0429) (Table 2a). In pair wise comparison of the platelets counts after low and high RAIT, in both genders, there was significantly lesser decline (p=0.0056) in its count in females than that in males.

Regarding the red blood cell (RBC) count, overall, there was a decline of 11% in absolute number of RBCs. The deterioration in RBC count was dose dependent i.e. higher in those patients receiving higher activity of I^{131}. The RBCs in females were more prone to radioiodine damage. There was 11% decline in RBC count in females as compared to 8%

decline in RBC count in males in high RAIT group. In the benign thyroid patients receiving low dose of RAIT again the decrease in absolute count of RBCs was more marked in females. There was a decline of 7.6% in RBC count in females while in males it was only 4% (Table 3).

Table 3: Comparison of RBC count before, 3 hours and 2 weeks after I^{131} therapy, in malignant and benign thyroid patients, in both genders

Groups		RBC count ($\times 10^{12}$/L)			Decrease (%) in RBC count	
		Before RAIT	3 hours after RAIT	2 weeks after RAIT	3 hours after RAIT	2 weeks after RAIT
Male (High RAIT)	Mean	4.76	4.69	4.38	1.5	8
	SD	0.65	0.64	0.96		
Female (High RAIT)	Mean	4.03	3.68	3.58	8.8	11
	SD	0.96	1.24	1.57		
Male (Low RAIT)	Mean	5.07	5.01	4.87	1.3	4
	SD	0.76	0.55	0.60		
Female (Low RAIT)	Mean	4.40	4.30	4.06	2.2	7.6
	SD	0.69	0.90	0.84		

Table 3a: Two-way ANOVA of RBC count, in both genders

SOV	SS	DF	MS	F (DFn, DFd)	P value
Interaction	0.2298	6	0.03831	F (6, 114) = 0.05116	P=0.9994
Gender and Dose of RAIT	14.29	3	4.763	F (3, 114) = 6.36	P=0.0005
Before vs. after RAIT	1.388	2	0.6941	F (2, 114) = 0.927	P=0.3987
Residual	85.36	114	0.7488		

A significant P value (0.0005) for gender and dose showed differential effect of I^{131} on RBC count in both genders (Table 3a). In Tukey's test it was found that in Low RAIT group the RBC count remained more stable in males as compared to that in females (p=0.0046). Overall, males resist better to radioiodine therapy.

The changes in blood cells morphology were determined by the light microscope. There was reduction in the number of all the blood cells including granular and agranular leukocytes, RBCs and platelets. The RBC population presented increased ratio of target cell within 3 hours and 2 weeks after RAIT. There was reduction in the ratio of lymphocytes among the white blood cells and even the reduction in the sizes of existing lymphocytes. The polymorphonuclear leukocytes (neutrophils) showed hyper segmentation of their chromatin material after administration of I^{131}.Before RAIT there were 3-4 lobes of chromatin material in neutrophils while after administration of I^{131} the number of lobes in the chromatin

material increased upto 5-6. There was also appearance of toxic granules/vacuoles in neutrophils and lymphocytes after the RAIT (Figure 2).

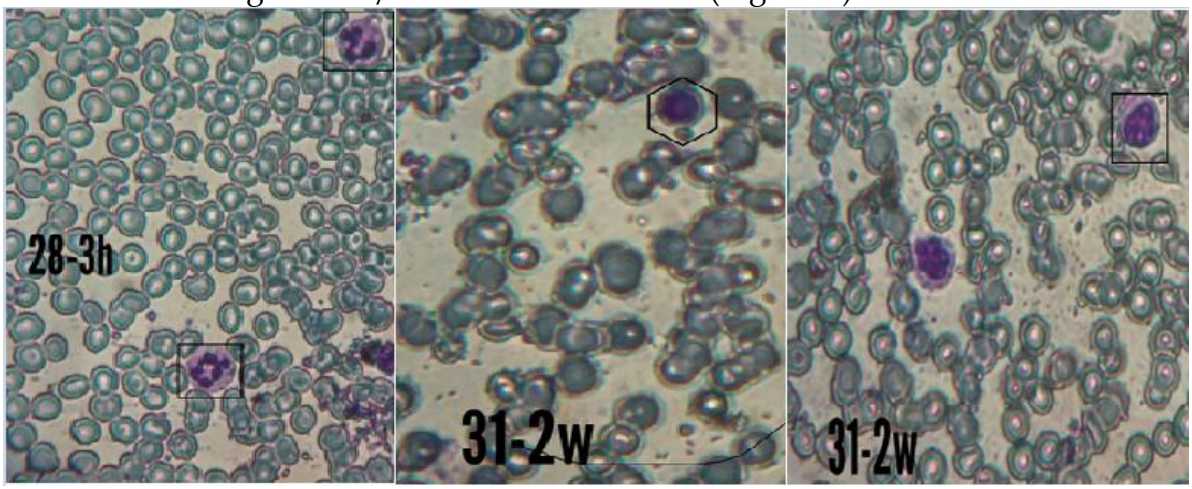

Figure 2: Photomicrographs showing hyper segmentation in neutrophil in slide tagged with 28−3h (1600X) and micronucleus formation in slide tagged with 31−2w (2000X) and vacuolation in lymphocytes in slide tagged with 31-2 (1600X), after RAIT

In figure 2, the peripheral blood slide marked with 28−3h presented two hyper segmented neutrophils with 5-lobes in each. This hyper segmentation in neutrophils was found just 3 hours after RAIT in blood of 56 years old male suffering from malignant thyroid diseases treated with a dose of 200 mCi. The slide tagged with 31−2w presented micronucleus in lymphocyte encircled with hexagonal ring, after 2 weeks of a dose of 200 mCi of I^{131}. It was a female patient of 34 years old suffering from malignant thyroid disease. The blood slide labelled with 31−2w presented two lymphocytes each having multiple vacuoles.

Discussion

In this study the hematological consequences of RAIT in patients suffering from benign and malignant thyroid diseases were assessed in both genders and in low and high doses of I^{131}. Our findings confirm that I^{131} have a major impact on hematopoietic cells when employed in any dose for the treatment of thyroid diseases. In accordance with previous studies, the decrease in RBCs, WBCs and platelets seen after treatment may be due to oxidative stress, direct bone marrow suppression and hematopoietic progenitor death. When the antioxidant system of the body becomes dumpy due to excessive production of ROS, the DNA counteracts with the ROS and becomes damaged resulting in formation of another small nucleus called "micro nucleus". Micro nuclei formation in the peripheral blood lymphocytes after RAIT is an indicator and cytogenetic biomarker of radiation toxicity of I^{131} therapy(18).

At two weeks after treatment, benign patients treated with low-dose of I^{131} had a decrease in WBCs, which was greater in males than that in females. Similar investigations show the susceptibility of WBCs to radiation and indicate the drop in WBC count is mostly due to the decrease in neutrophil numbers. These results highlight the necessity of monitoring the hematological parameters during RAIT that is particular to gender and dose (13).

There was a greater reduction in lymphocyte and platelets count in low RAIT group as compared to that in higher RAIT group. It

may be due to no thyroid tissue (thyroidectomized) in malignant patients and lesser retention of radioiodine in the body. The higher reduction in lymphocyte and platelets count in males may be due to the hormonal differences in genders. Similarly, a different study highlighted cumulative hematopoietic toxicity by reporting substantial leukopenia, thrombocytopenia, and lymphopenia with RAIT dosages exceeding 175 mCi, especially after several administrations(19).

Both genders in our study showed a consistent decline in absolute lymphocyte counts (ALC) starting three hours after radioiodine therapy and continuing for up to two weeks after RAIT. These results are in accordance with another research that shown that leukocyte, neutrophil, and lymphocyte counts significantly decreased in the first year following RAIT. By the third year, leukocyte and neutrophil counts had stabilized, but lymphocyte numbers continued to be suppressed until the fifth year. These findings are in consistent with a 2023 retrospective analysis of patients with differentiated thyroid carcinoma (DTC) who received RAIT, which found that leukocyte, neutrophil, and lymphocyte count sharply dropped in the first year following RAI. Male gender, advanced disease stage, advanced age and greater I^{131} dosages were found to be risk factors for blood cell abnormalities, including moderate lymphopenia. Furthermore, compared to other cell lines, lymphocyte suppression lasted longer, suggesting persistent lymphopenia even when other counts improved(20).

According to our research, the decline in RBC count is dose dependent that is higher decline in malignant patients treated with high activity of I^{131} and a larger decrease in females as compared to that in males in low as well as in high activity of I^{131}.However, in another study higher reduction in RBC and hemoglobin levels were found in all dosing groups, indicating that different people's hematologic parameters react differently to RAIT and can vary(21).

A single moderate dosage of I^{131} (100 mCi or 150 mCi) was linked to bone marrow suppression one week following RAIT. Hb levels and the WBC count, primarily lymphocytes decreased significantly within one week, but the platelets count decreased between one and six months. Within a year, every component of the blood was recovered(22).

Significant morphological alterations in peripheral blood cells were noted after I^{131} treatment. The hyper segmentation of chromatin in neutrophils and micronucleus formation in lymphocytes is frequently linked to nuclear damage, while cytoplasmic vacuolation in lymphocytes is sign of genotoxic stress and early apoptosis. These changes are a result of radioiodine's cytotoxic and radiobiological effects on circulating immune cells.

Despite their clinical importance, these morphological changes especially in our local population have received little attention in the literature so far. As a result, our findings add to a comparatively unexplored field of post-therapeutic hematological examination and provide insightful information about the cellular-level effects of RAIT.

Conclusions

Although I^{131} is drug of choice in the management of benign and malignant hyperthyroid diseases but it takes its toll in the form of destruction and deterioration of hematological cells including WBCs, RBCs and platelets. Among the WBCs lymphocytes are more radiosensitive. These effects vary in genders and in different doses of radioiodine

and appear soon after therapy. In the light of these findings, regular hematological monitoring should be considered in patients undergoing radioiodine therapy. These potential side effects may be minimized by administration of potent antioxidants prior to and in conjunction with radioiodine therapy.

Source of Fundings: None

Conflict of Interest: None

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HISTORY	
Date received:	17-08-2025
Date sent for review:	20-09-2025
Date received reviewer's comments:	20-09-2025
Date received revised manuscript:	09-10-2025
Date accepted:	20-10-2025

CONTRIBUTION OF AUTHORS	
AUTHOR	**CONTRIBUTION**
Conception/Design	IS, HM
Data acquisition, analysis and interpretation	IS, HM, AR
Manuscript writing and approval	AS, HM, AR
All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.	