



CAN OCCUPATIONAL EXPOSURE TO FORMALDEHYDE CAUSE THYROID DYSFUNCTION? – A CROSS SECTIONAL COMPARATIVE STUDY

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Formaldehyde is a widely used chemical in Anatomy and Pathology departments in Medical Colleges.

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ABSTRACT

Abstract: Formaldehyde is a widely used chemical in Anatomy and Pathology departments in Medical Colleges.

Aim: To find out whether there is any correlation between formaldehyde and thyroid dysfunction in human beings.

Materials and Methods: Thyroid Function Test (TFT) was done by ELISA Method in 260 individuals, who were divided into two groups. Group I – Exposed to formaldehyde; Group II – Not exposed to formaldehyde.

Result: In Group I, 15.1% people had hypothyroidism whereas in Group II, only 6.4% were affected. Chi Square Test gave a P value 0.021.

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INTRODUCTION

It was observed that some of the staff of Anatomy and Pathology departments in our institution, who are exposed to formaldehyde, are on treatment for hypothyroidism. Their Thyroid Function Test (TFT) was done and necessary treatment was given from the Department of Nuclear Medicine. This fact made the authors to think about the possibility of correlation between formaldehyde and thyroid dysfunction.

Formaldehyde and Formalin.¹

Formaldehyde is a colourless gas with a pungent, irritating odour. It is commonly used and stored in solution. Formalin is the aqueous solution of formaldehyde (30%-50% formaldehyde). It typically contains up to 15% methanol as stabilizer.

Sources and Uses

Formaldehyde is synthesized by the oxidation of methanol. It is one of the 25 most abundantly produced chemicals in the world. This chemical is used in the manufacture of a number of useful materials such as plastics, resins, glass mirrors, explosives, dyes and even artificial silk. It is also used in plywood adhesives, petroleum, pharmaceuticals, germicides and fungicides. It is widely used in Medical Colleges and hospital as embalming solution, preservatives of specimens in museums and as a disinfectant.

Toxic effects of Formalin

Low doses of formalin is known to produce irritation and watering eyes, headache, rhinitis and cough; higher doses may cause bronchial asthma, bronchitis, pulmonary oedema or even pneumonia. It can lead to allergic dermatitis. A splash of formalin into the eyes may lead to corneal opacity and loss of vision if not treated immediately.

Ingestion of formalin may cause corrosive injury of mucosa of gastrointestinal tract. 30ml of formalin, if ingested, can lead to death. Formalin is also known to cause CNS depression, coma and renal failure.

Cancer risk is high among embalmers and industrial workers exposed to formaldehyde.²

Despite its toxic effects, formalin is widely used as a tissue fixative and embalming fluid because of its easy availability, low cost, effectiveness and consistent results.³

The exact mechanism of action of formaldehyde is not clear. It is known that the chemical can interact with molecules on cell membrane, can produce changes in the nuclei, vacuolation of cytoplasm, changes in proteins and DNA.¹

Even though the effect of formalin has been studied on gastrointestinal tract, liver, spleen, pancreas, lung, kidney and nasal mucosa, endocrinological effects of formalin are not much explored, especially in human beings.

The high incidence of hypothyroidism among Anatomists and Pathologists led the authors to think about the possibility of toxic effects of formalin on thyroid gland.

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The thyroid gland

The thyroid gland, a large endocrine gland, has two primary functions.⁴

1. To secrete thyroid hormones which maintain optimal tissue metabolism
2. To secrete calcitonin, which regulates calcium metabolism.

The thyroid hormones are produced by multiple acini or follicles. The follicles are lined by cuboidal epithelium. The follicles are filled with colloid, containing predominantly a glycoprotein, thyroglobulin.

The primary hormone secreted by the thyroid gland is thyroxine (T4 or Tetra-iodothyronine), along with much lesser quantities of Triiodothyronine (T3). T3 has greater biological activity than T4. It is specifically generated at its site of action in peripheral tissues. T3 and T4 are derivatives of the amino acid tyrosine.

The thyrocytes or follicular cells lining the thyroid follicles have four functions.

1. Collection and transportation of iodine
2. Synthesis of thyroglobulin and its transport into the colloid
3. To fix iodine to the thyroglobulin to produce T3 and T4.
4. Removal of T3 and T4 from thyroglobulin and secrete them into the circulation depending on the demand of various organs.

It is the free thyroid hormones in plasma that are physiologically active and produce a feed back to inhibit pituitary secretion of Thyroid Stimulating Hormone (TSH). The normal total plasma T4 level in adults is approximately 8µg/dL and the plasma T3 level is about 0.15µg/dL. Both T3 and T4 can be measured by radioimmunoassay (RIA).

Thyroid function is regulated by changes in the circulating levels of pituitary TSH. The secretion of TSH is increased by the hypothalamic hormone TRH (Thyrotropin Releasing Hormone) and inhibited in a negative feedback mechanism by circulating free T3 and T4. The normal secretion rate of TSH is about 110µg/dL.

TSH Receptors

The TSH receptor is a G protein-coupled, seven transmembrane segment receptor that activates adenyl cyclase through Gs.

Mechanism of action of T3 and T4

The thyroid hormones enter the cells and bind to thyroid receptor (TR) in the nuclei. The hormone receptor complex then binds to DNA via zinc fingers. There are two human TR genes: an α receptor gene on chromosome 17 and a β receptor gene on chromosome 3. Each forms at least two different mRNAs and two different receptor proteins. The liganded forms of thyroid receptors are nuclear transcription factors that change gene expression.⁴

An important discovery in understanding thyroid hormone action was the concept of above mentioned receptors.⁵

Aims and Objectives

To find out the following:

1. Is there any relation between exposure to formaldehyde and thyroid dysfunction?
2. Is there any correlation between number of years of exposure to formalin and its toxic effect on thyroid gland?

The authors sought methods to find out the answers to these questions. After getting permission from Institutional Ethics Committee and Research Committee, the research started.

MATERIALS AND METHODS

The study was conducted in Govt. Medical College, Kozhikode, a tertiary care teaching hospital in North-Kerala. The study was approved by the institutional review board.

Two groups were chosen for the study - Group I and Group II.

Group I: Staff and Residents exposed to formalin – Anatomy, Pathology and Forensic Medicine departments were included in this group.

Group II: Staff and Residents who are not exposed to formalin. Physiology, Pharmacology, Community Medicine, Microbiology and clerical staff of college office were included in Group II (Staff from Department of Biochemistry were deliberately avoided since they are handling lot of chemicals).

Study design and sample size

It was a cross sectional comparative study. Since references on similar studies were not available for comparison, we decided upon a sample size of 120 from each group, based on the formula: $n = \frac{(Z\alpha + Z\beta) pq \times 2/d^2}$, Where $n =$ sample size; $p = 20\%$, $q = 80\%$, $d = 15\%$. Using this formula, 'n' was equal to 114, which was rounded off to 120 (minimum number required in each group). 40 samples were collected per week after obtaining informed consent from staff and residents. We obtained whole hearted cooperation from the staff and residents and obtained 260 samples.

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Procedure

2ml of blood was collected from each person. 40-50 samples were collected in a week and transported to Department of Nuclear Medicine for doing TFT by ELISA method. The name, age, sex, occupation, department, whether the person is exposed to formalin or not, if yes, the period of exposure, whether the person is taking any medicines – all these data were recorded in the Proforma handed over to them. Each person was given a specific code number. After entering the data in the EXCEL sheet, names of persons were deleted.

Exclusion criteria

- Those who have undergone thyroidectomy
- Pregnant ladies
- Those on steroids
- Those having chronic diseases like chronic renal failure, multiple sclerosis or malignancy.

RESULTS

Table I Incidence of Hypothyroidism in Group I and II

Group	Department	Percentage of hypothyroidism
Group I	Anatomy	14.0%
	Pathology	12.5%
	Forensic Medicine	03.4%
	Community Medicine	8%
Group II	Physiology	0%
	Pharmacology	0%
	Microbiology	8%
	Office Staff	8.4%

(Prevalence of hypothyroidism in coastal cities in India is about 9%)

Table II Statistical Analysis

Sl.No	Hypothyroidism – Cross tabulation	
1	Total number of samples	260
2	Percentage of females	68.5%
3	Percentage of males	31.5%
4	Hypothyroidism in Group I	15.1%
5	Hypothyroidism in Group II	06.4%
6	p value (Chi square test)	0.021

Table III Period of Exposure to formalin and hypothyroidism - Cross tabulation

Sl.No.	Period of exposure to formalin	Number of samples	Cases of hypothyroidism	Percentage (%)
1	Nil	142	9	6.3
2	<20 years	104	14	13.5
3	>20 years	14	4	28.6
	p value	0.014 (Chi square test)		

An interesting finding

During statistical analysis, an interesting finding was observed. Values of T3 and T4 were slightly elevated, but within normal limits, in Group I when compared to Group II. The value of TSH was slightly lower in Group I and Group II. The mean values of T3, T4 and TSH are shown in Table IV.

Table IV Comparison of mean values of T3, T4 and TSH (T-Test)

Hormone	Group	Number of samples	Mean	Unit of Measurement
T3	Group I	119	1.153	ngm/ml
	Group II	141	1.139	ngm/ml
T4	Group I	119	89.96	ngm/ml
	Group II	141	78.23	ngm/ml
TSH	Group I	119	1.246	µ IU/ml
	Group II	141	1.406	µ IU/ml

(T Test- P value for T4 is 0.000)

DISCUSSION

Even though lot of studies have been carried out about the toxicity of formaldehyde / formalin, effect of formalin on the thyroid gland in human beings are few.

Dr.Izabella Wentz⁶, a thyroid pharmacist, has mentioned her doubt regarding the toxic effects of formalin on thyroid gland.

A commendable work was done by Kumud G Patel, H Venkatakrishna Bhatt and A Roy Choudhary⁷ at National Institute of Occupational Health, Meghani Nagar, Gujarat. They conducted the study in male albino rats. Rats exposed for longer duration and higher doses of formalin showed

decreased levels of T3 and T4 and increased levels of TSH. Microscopic study of thyroid gland showed follicular regression. Their inference is that repeated exposure to formalin might have increased thyroid activity of the follicles and rapidly deteriorated the capacity for synthesis of thyroid hormones, leading to atrophy of follicular cells.

Dr.Jayant Kumar Verma, Dr.N.N.Srivastav, Kishor Gupta and Dr.Adil Asghar⁸ have observed the changes in lungs and thyroid gland in albino rats due to inhalation exposure of formalin. Following were their observations – changes in lungs, hepatomegaly, change in colour and size of kidney, splenomegaly, weight loss in animals. They have not detected any changes in thyroid glands.

Aooelaman LM, Woutersen RA, Zwart A *et al*⁹ studied the effect of formalin for a period of one year, in male rats, on nasal mucosa.

BruzeM *et al*¹⁰ have studied the effect of formalin on skin and came to the conclusion that the chemical can cause contact dermatitis.

Checkoway H, Dell LD, Boffitta P *et al*¹¹ have conducted a cohort study of workers in Formaldehyde Industries, to correlate the exposure of formaldehyde and incidence of myeloid leukemia and other lymphohaematopoietic malignancies in the US National Cancer Institute.

Research by the Department of Medicine and Physiology at the David Geffen School of Medicine at UCLA observed that environmental agents interfere with thyroid function at multiple sites, reducing circulating thyroid hormone levels or impair the action of thyroid hormones; these agents may even be partial thyroid hormone agonists. They may trigger autoimmune thyroid disease also.¹²

Raja DS and Sultana B¹³ have highlighted the health hazards for students exposed to formaldehyde during dissection. They have recommended various methods to minimize the hazards.

The Author’s explanations for the findings obtained in the present study

T3 and T4 enter the cells and nuclei of various organs. T3 and T4 bind tightly to hormone receptors and also to DNA. Transcription and translation occurs; the amino acids, proteins or enzymes produced, control various metabolic activities in the body. This is the normal mechanism of action of thyroid hormones.

How does formalin interfere with action of thyroid hormone?

Formaldehyde is known to produce alterations in the cell membrane, cytoplasm and nuclear membrane. So, the thyroid hormones may not be able to enter the cells and nuclei. As the cells do not get enough T3 and T4, the thyroid gland produces more hormones. That is why there is an increase in T3 and T4 in the formalin exposed group. Since the circulating levels of T3 and T4 are high, a negative feedback is produced on pituitary gland; this leads to a decrease in the production of TSH by pituitary.

We have observed that, the incidence of hypothyroidism increases directly proportional to the number of years of exposure. This may be due to the damage of follicular cells of thyroid gland as was reported by Kumud G Patel, H Venkatakrishna Bhatt and A.Roy Choudhury.⁵

In three Junior Residents, who had exposure to formaldehyde for a period less than 2 years, hypothyroidism was detected. We checked the thyroid antibody in these students and it was positive. These three cases can be considered as chemical thyroiditis.

Three Pathologists, who were getting treatment for hypothyroidism, failed in consulting the Endocrinologist periodically and developed hyperthyroidism. They were referred to the Endocrinologist, necessary changes in the dose of thyroid hormone was done.

Preventive measures to be taken

1. A suitable non-toxic substitute for formalin should be used.
2. Use of mask and gloves should be made mandatory
3. Exhaust fans and good ventilation should be ensured in dissection hall, embalming rooms and Pathology labs.
4. Staff should be posted in different sections of the same department on rotation basis.
5. Formalin Test meters should be installed in labs, embalming rooms and dissection hall.
6. Pregnant ladies should avoid contact with formalin at least during the first trimester of pregnancy.
7. All departments should strictly follow the International Standards and Guidelines (USA) in the use of formalin, which are as follows:
 - OSHA* PEL (Permissible Exposure Limit) = 0.75ppm/8hrs
 - OSHA STEL (Short Term Exposure Limit) = 2ppm / 15mts
 - NIOSH** IDLH (Immediately Dangerous To Life or Health) = 20ppm

*OSHA – Organization for Safety and Health Administration
**NIOSH – National Institution for Occupational Safety and Health.

To measure the formalin level in the labs / dissection hall / embalming room, formalin meters should be used.

8. All staff members associated with formalin should be encouraged to take a break from their work for a period of two weeks to one month per year and spend their holiday in unpolluted Nature.

CONCLUSION

This study points out the toxic effects of formalin on thyroid gland. To prove the exact effect of formalin on thyroid gland and other endocrine glands in the human body, more studies will be required.

We wish our work will pave the way to more research in this field.

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