

Spirometric Findings in TNT Factory Workers Compared with Unexposed Controls

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Abstract

Background: Trinitrotoluene (TNT) is one of the most well-known and oldest explosive agents. In the recent decade, bioenvironmental, biochemical, and biological effects of TNT exposure have been more in the spotlight. In this study, we aimed to evaluate spirometric parameters in workers of a TNT factory exposed to TNT and other related fumes and dusts compared with the unexposed controls.

Methods: In this case-control study, spirometry was done for TNT factory workers (cases) and matched healthy controls, and their results were compared with each other. Matched controls were selected from workers who worked in the same geographic area without any history of TNT or other chemical materials exposure. Spirometric studies were done during the early hours of day.

Results: Overall, 90 subjects (47 TNT exposed cases and 43 controls) were included. The two groups showed no significant difference in demographic characteristics and smoking habits. In spirometry, it was found that the cases had significantly lower forced vital capacity ($91.4 \pm 13.7\%$ vs. $100.2 \pm 13.0\%$, $P = 0.002$), forced expiratory volume in 1 second ($98.0 \pm 14.9\%$ vs. $104.7 \pm 12.5\%$, $P = 0.024$) and peak expiratory flow ($98.4 \pm 17.3\%$ vs. $107.9 \pm 21.7\%$, $P = 0.025$) compared with controls. According to spirometric findings, 10 cases (21.3%) and no controls had restrictive pattern, which means TNT factory workers had 1.27 (CI: 1.09-1.47, $P = 0.001$) fold risk for development of restrictive patterns.

Conclusion: Chronic exposure to TNT or prolonged working in TNT factories may predispose the workers to respiratory disorders. In addition to regular screening programs, preventive measures and devices should be considered for TNT factory workers to reduce the harms.

Keywords: Lung Diseases; Occupational Exposure; Solvents; Spirometry; Trinitrotoluene

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INTRODUCTION

Trinitrotoluene (TNT) or more specifically 2,4,6-trinitrotoluene is one of the most well-known and oldest explosive agents. In the recent decade, bioenvironmental, biochemical, and biological effects of TNT exposure have been more in the spotlight (1,2). Toxicity of TNT after absorption via healthy skin was previously reported (3). TNT can make a covalent band with hemoglobin (Hb), and the resultant products named Hb adducts of 4-amino-2,6-dinitrotoluene (4ADNT) or 2-amino-4,6-dinitrotoluene (2ADNT) were reported to be responsible for its biological consequences (4).

Various disorders such as cataract (nuclear type), hematological abnormalities (such as aplastic anemia), urinary disorders, neoplasm (malignant tumors of liver), and increased liver enzymes (due to toxic hepatitis) have been reported in exposed subjects (3,5,6). The prevalence of TNT induced hepatomegaly and cataract was reported to be 41% and 79%, respectively (7). Long-term (more than one year)

exposure to TNT is a significant risk factor for malignant tumors of liver (8). It has been approved that benzene and another aromatic derivatives of TNT can induce aplastic anemia, acute leukemia and bone marrow abnormalities (9).

There is evidence of the oxidative stress role of TNT metabolites in pathophysiology of TNT toxicity. TNT leads to an imbalance between oxidative stress and antioxidants and this imbalance has an important role on pathogenesis of cataract, bone marrow abnormality, malignancy, and toxic hepatitis (10,11). After absorption and solution in water, TNT can release nitric oxide (NO) and other oxidative components which can be toxic for many cells and tissues such as lung (12).

Regarding the toxicity mechanisms of TNT via oxidative stress, affected pulmonary function in exposed cases is probable but in the literature review, there were few clinical reports about the effect of TNT toxicity on human tissues especially lung. In this study, we aimed to evaluate spirometric parameters in workers of a TNT factory exposed to TNT and other related fumes and dusts compared with unexposed controls.

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METHODS

Study Design and Participants

In this case-control study, spirometry was done for TNT factory workers (cases) and matched healthy controls, and their results were compared with each other. Workers in a TNT factory with at least one year work history were included. All cases used occupational protective devices such as gloves, glasses, masks, and uniforms. Matched controls were selected from workers who worked in the same geographic area (Tehran province) without any history of TNT or other chemical materials exposure. Cases and controls with the following criteria were excluded: clinical signs or history of asthma or chronic obstructive pulmonary disease (COPD) prior to employment in the factory, personal history of exposure to chemical substances such as detergents, inhalational anesthetic agents and chemical weapons, history of cardiopulmonary disorders, alcohol or drug abuse, chest trauma (physical or chemical), and serious or chronic medical diseases (e.g. diabetes, neoplasm or hypertension), and being under treatment of any medications influential on spirometric findings (e.g. beta-adrenergic agonists or beta blocker).

Spirometry

All spirometric studies were done during the early hours of day. All graphs of spirometry were interpreted by a pulmonologist (MG). Spirometric parameters were measured with a Vmax 20 Spirometer (Chest Co., Italy). The best of three maneuvers was selected and expressed as a percentage of the predicted value and as an absolute value. Spirometry was carried out by an experienced technician. The parameters of spirometry that were compared between the two groups included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, forced expiratory flow (FEF), peak expiratory flow (PEF), maximum midexpiratory flow (MMEF), FEF50% and FEF75%. These measurements of spirometry were subsequently interpreted to normal, obstructive or restrictive patterns. In obstructive pattern, FVC is often normal or only mildly reduced (near normal), FEV1 is reduced and so the ratio of FEV1/FVC is lower than normal. In restrictive pattern; however, FVC is less than the predicted value for age, gender and size, FEV1 is also reduced but in proportion to the reduced FVC and so the FEV1/FVC ratio is normal (13).

Ethical considerations

All issues of Helsinki protocol were considered. There was no intervention on the patients in this study. Spirometric

studies were done after informed consent form was signed by the subjects. The study was approved by ethics and scientific review committee of Baqiyatallah University of Medical Sciences, Tehran, Iran.

Statistical Analysis

The data was analyzed using SPSS (version 16.0, SPSS Inc., Chicago, IL). The results are shown with mean and standard deviation (SD) for quantitative variables and frequency and percentage for qualitative variables. Independent samples t-test and chi square test were used for further analysis. P values less than 0.05 were considered statistically significant.

RESULTS

Overall, 90 subjects (47 TNT exposed cases and 43 controls) were included. The two groups showed no significant difference in demographic characteristics and smoking habits (Table 1). All cases and controls were men.

In spirometry, it was found that the cases had significantly lower FVC ($91.4 \pm 13.7\%$ vs. $100.2 \pm 13.0\%$, $P = 0.002$), FEV1 ($98.0 \pm 14.9\%$ vs. $104.7 \pm 12.5\%$, $P = 0.024$) and PEF ($98.4 \pm 17.3\%$ vs. $107.9 \pm 21.7\%$, $P = 0.025$) compared with controls. However, there were no significant differences in FEV1/FVC ratio ($P = 0.586$), MMEF ($P = 0.990$), FEF50% ($P = 0.661$), FEF75% ($P = 0.256$) between the two groups (Table 2).

According to spirometric findings, 10 cases (21.3%) had restrictive pattern, while no controls were involved with such pattern that meant a statistically significant difference between the groups ($P = 0.001$, Odds ratio = 1.27 (CI: 1.09-1.47)). On the other hand, obstructive pattern was observed in no cases (0.0%) but in two controls (4.7%) which was not significantly different between the groups ($P = 0.225$) (Table 3).

DISCUSSION

In this study, we found significant decreases in some spirometric parameters including FVC, FEV1, and PEF following chronic exposure to TNT and related dusts. We also found that TNT exposed workers had 1.27 fold risk for development of restrictive patterns in spirometry. Restrictive ventilatory pattern is caused by conditions that affect the pulmonary tissue itself (not airways in early phase). Conditions that cause fibrosis or scarring of the lungs give restrictive patterns on spirometry. The possible etiology of development of this pattern in cases with exposure to TNT and other toluene-based compounds would be gradual pulmonary

Table 1. Demographic characteristics of the study subjects

Variables	Cases	Controls	P value*
Age (year); mean \pm SD	43.8 \pm 3.9	42.1 \pm 5.9	0.114
Weight (kg); mean \pm SD	77.6 \pm 11.8	74.4 \pm 10.8	0.183
Exposure duration (year); mean \pm SD	11.4 \pm 1.1	0	---
Smoking (pack year); mean \pm SD	5.2 \pm 8.8	3.6 \pm 8.6	0.369

SD: standard deviation

*Calculated by independent samples t-test

Table 2. Spirometric findings in cases and controls

Spirometric parameters	Study groups		P value*
	Case	Control	
FVC (%); mean ± SD	91.4 ± 13.7	100.2 ± 13.0	0.002
FEV1 (%); mean ± SD	98.0 ± 14.9	104.7 ± 12.5	0.024
FEV1/FVC; mean ± SD	82.0 ± 4.9	81.4 ± 5.7	0.586
MMEF (%); mean ± SD	100.7 ± 26.5	100.8 ± 25.4	0.990
FEF50% (%); mean ± SD	102.5 ± 29.0	105.1 ± 26.3	0.661
FEF75% (%); mean ± SD	86.4 ± 28.1	94.1 ± 35.5	0.256
PEF (%); mean ± SD	98.4 ± 17.3	107.9 ± 21.7	0.025

SD: standard deviation

*Calculated by independent samples t-test

Table 3. Spirometric patterns in cases and controls

		Case (no. = 47)	Control (no. = 43)	P value	Odds ratio (95% CI)
Restrictive pattern; no. (%)	Yes	10 (21.3)	0.0 (0.0)	0.001*	1.27 (1.09-1.47)
	No	37 (78.7)	43 (100.0)		
Obstructive pattern; no. (%)	Yes	0 (0.0)	2 (4.7)	0.225**	-
	No	47 (100.0)	41 (95.3)		

CI: confidence interval

* Calculated by chi square test

** Calculated by Fisher's exact test

parenchyma injuries, incomplete healing, persistent mild inflammation, and pulmonary fibrosis (14,15). On the other hand, obstructive ventilatory pattern denotes narrowing of airways that is mostly seen in asthma and COPD, though in TNT exposed cases this pattern was not seen.

Ophthalmologic, hematologic, hepatic, and cutaneous toxicity of TNT exposure have been reported in several studies (4-6,10,14-18). However, this is the first study that pulmonary sequels of TNT in human subjects measured by spirometry was reported and analyzed. A reason of lack of research about pulmonary effects of TNT on human could be the security considerations.

Nevertheless, the TNT toxicity on the lungs was previously ascertained in some experimental studies (19,20). Paden et al. in 2008 evaluated the pulmonary system of the adult bullfrog after acute and short-term exposure to TNT. They found the lungs cyanotic but they did not carry out pathologic assessments (19). In another study, Johnson et al. concluded that TNT can induce oxidative-antioxidant system imbalance in the lung tissue of tiger salamanders (20).

Sabbioni et al. showed that the activity of GSTP1, GSTT1, NAT1, SULT1A2, and SULT1A1 genes were significantly increased in normal cells exposed to TNT or other nitrate derivatives (21). In this regard, Zhang et al. proved the prominent role of these genes especially SULT1A1 in neutralizing the toxic effects of chemical

toxins in pulmonary tissue (22). Therefore, mutation in these genes can predispose a person to lung cancer (17). But in this study, we did not assess TNT exposed cases for the mutation of the mentioned genes, and so, we suggest genomic, proteomic and metabolomics investigation for this kind of chemical exposure.

Workers in TNT factories or other units in explosives and propellants production industry are also exposed to chemical dusts, particulate contaminants and solvents. In this respect, Cakmak et al. showed higher prevalence of asthma-related symptoms in chronic exposure to solvents including toluene, acetone, butanol, xylene, benzene, and trichloroethylene in a gun factory (23). They found that restrictive pattern was more common in these cases, which were in agreement with our findings; however, they did not segregate TNT exposed and unexposed workers in their study, a different point from our study. In addition, their findings were weakened as smoking was not controlled in that study. They finally concluded that smoking and exposure to solvents can predispose gun factory workers for asthma-related symptoms (23). In another study, Saygun et al. indicated that the chronic exposure to low doses of solvents may not adversely affect the pulmonary functions, whereas it increases the asthma prevalence from 1.1% to 3.6% in a five-year follow-up (24). They also demonstrated that annual level of FEV1 in the workers exposed to solvents in gun factory did not significantly

decrease compared with that of the unexposed workers (24).

Prolonged parenchyma injuries in exposure to toluene-derived materials can lead to asthma-related symptoms and activation of the fibrotic process which induces restrictive patterns in spirometric assessment (25,26). In this regard, Sahri and Widajati found shortness of breath, cough and rhinorrhea in Indonesian workers exposed to toluene, the main component of TNT (27). Therefore, conducting basic and animal studies are necessary to evaluate the cellular and molecular effects of toluene-based compounds on the lung parenchyma by focusing on the role of oxidant-antioxidant imbalance, free radicals (e.g. NO) release, airway epithelium damage, and inflammatory and pro-fibrotic cytokines release (25-28).

Altogether, the pulmonary disorders in workers of explosives and propellants production industry, such as TNT factories, might be caused by the main products of these factories (e.g. TNT in the present study), though the effect of solvents, fumes and chemical dusts in the working space should not be overlooked.

LIMITATIONS

One of the limitations of this study was that the environmental and air dose of TNT was not measured. In the air of TNT factories, in addition to TNT, other related fumes and dust are diffused and this means that the patients' manifestations can be caused by other materials rather than TNT. One other limitation is that the clinical presentations of the cases including cough, dyspnea, wheeze, rale, etc. are not reported in our results which could be helpful for more effective conclusion.

Moreover, all exposed cases had used protective devices and we could not confirm exposure with a sufficient dose of TNT. Therefore, a study that is conducted on cases exposed to TNT without protection for long-term (such as workers in illegal manufactories) might produce more convincing results. Furthermore, the possible effect of the existent air pollution in the city of Tehran was not considered. Although spirometry is the simplest method for evaluation of the lungs, we suggest other advanced methods such as high-resolution computed tomography or pathologic assessments to be performed in future studies to better clarify the pulmonary effects of TNT.

Chronic exposure to TNT or prolonged working in TNT factories may predispose the workers to respiratory disorders. In addition to regular screening programs, preventive measures and devices should be considered for TNT factory workers to reduce the harms.

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Conflict of interest: The results presented in this paper were part of a screening study on TNT factory workers in Tehran, Iran. Hepatic, hematologic, and ophthalmologic

results of this study were previously published (15), by the scientific team same as the authors of the current paper, and some limited data about respiratory assessment of the cases were also reported in that paper. However, the findings of the current paper are more comprehensive and include all the spirometric findings. All parts of the current paper were written again rather than the mentioned article, and a different draft was used.

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