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INVESTIGATING RESPIRATORY STATUS IN WORKERS EXPOSED TO BENZENE

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ABSTRACT

Purpose: Benzene is a clear, colorless, flammable liquid, accompanied by a gasoline-like odor that can evaporate and spread in air. Benzene is a by-product of incomplete combustion of many materials and due to its high utilization in the industries, it is considered as one of the 20 most important chemical products in the world. Benzene-induced industrial poisoning occurs almost entirely by inhalation of benzene vapors in the air. The main objective of this study is to investigate the effects of exposure to benzene under working environment conditions on respiratory conditions and also Spirometry results in humans.
Materials and Methods: This is a comparative and analytical cross-sectional study, in which 40 benzene-exposed workers and 40 healthy subjects with no history of being exposed to benzene as control group with the same sex and age (26-40) and with a work experience of 5 to 15 years and an exposure period of 8 hours were investigated. The concentration of benzene in air was measured using standard methods. In addition, spirometric testing was performed. For spirometry, spirolab III was used.
Results: The average concentration of benzene in the air of the studied workshops was 1.68 ppm. The results of the present study showed that the level of spirometric evaluation parameters in the exposed group with benzene has decreased. The average exposure of workers at various workshops with benzene fumes does not exceed the exposure limit values of these compounds. And it seems that in the results of the study, other factors such as alcohol consumption, smoking, non-vegetarian diet and exposure to benzene are effective.

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Introduction

Coke is a coal derivative and coal is a mixture of carbon, hydrogen, and sulfur-containing oxygen. Coke plays an important role in oxidative reactions. Workers working in coking are exposed to pneumoconiosis in the presence of coke, which is a disease of the parenchyma tissue of the lung.

This disease is caused by the inhalation of coke and coal dust [1]. Benzene is produced during the process of coal-to-coke conversion; benzene is a coke derivative and is produced by the coke's heat and the coke gas purification. Michael Faraday discovered benzene in 1825. Benzene was previously obtained by heating the coal tar and then converting it into liquid, but today benzene is extracted in high amounts from crude oil [2]. A very low amount of benzene is found in oil and coal. This is a byproduct of incomplete combustion of many materials. For commercial use, until the Second World War, benzene was obtained as a coke or lightweight coke oven product for the steel industry [3]. Benzene is a clear, colorless, flammable

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liquid, with a gasoline-like odor that can evaporate and spread in the air. Benzene is an organic compound, most of all due to the burning of coal and oil, gasoline vapors, fuel smoke, smoke, fire from wood and other sources in the air. Industry is the major cause of environmental pollution by benzene. Urban weather becomes more polluted with benzene due to transportation systems. Benzene is a pollutant that exists everywhere like the workplace and the environment. It is categorized in the first group of carcinogenic substances for humans and animals because of its carcinogenic effects [4]. The two main sources of exposure to benzene include the following: Activities related to synthesis and its construction, its use in the production of other chemicals; other businesses may also be exposed to benzene, jobs that use petroleum products or solvents. The routes of exposure to benzene in the workplace are usually breathing and absorption through the skin, and the assessment of exposure is relatively easy. Human contact with benzene does not occur only through breathing and absorption of the skin. Swallowing food or drinking water can be other ways. High levels of accumulation of benzene in groundwater can be hazardous to human health and change the diversity and structure of ecosystems [4]. Benzene is considered to be one of the 20 major chemical products of the world due to its high use in the industries. In many industries, benzene is used for the production of styrene, plastics and nylon and rubber, synthetic fibers, various resins, paints, reagents, drugs, insecticides, glues, solvents, explosives, inks, glosses and lubricants. The use of benzene in vehicles is to increase fuel recovery and octane number. The United States Environmental Protection Agency (EPA) has classified benzene in category A of Carcinogenic substances; and the International Agency for Research on Cancer (IARC) described benzene as a carcinogen for humans [5].

Absorption and disposal of benzene and disease: Benzene-induced industrial poisoning occurs almost entirely by inhalation of benzene vapors in the air. Blood flow in the human body is quickly saturated with this substance and after half an hour, the saturation of the blood will be 70% to 80%, it will take several days for all body fluids and tissues to saturate with benzene. Benzene is almost insoluble in the blood and its balance is in mg benzene per liter of blood, divided by mg of benzene per liter of air. This means that the average concentration of benzene in the blood is 2.1 mg per 100 ppm benzene in inhaling air. Benzene in the circulating blood enters the tissues and the fat tissue stores some of it. Disposing of this substance is also done inversely, it means that this substance is transmitted by the blood and through the capillaries to the lungs and it is in equilibrium with air inside the lung cavities, and so it is repulsed. Some benzene is excreted intact by the urine and a portion of it is oxidized in the form of phenols and diphenols, which, in turn, are combined with sulfate ions in liver and excreted by the urine [6]. In acute toxicity, benzene has a sleeping and opiate effect. The inhalation of excessive benzene vapors may first create a state of expansion, resulting in confusion, drowsiness, fatigue, nausea, and headache. If the concentration is longer or the duration of contact is higher, seizure and then loss of intelligence and sensation will eventually occur, and death may eventually occur as a result of paralysis of the respiratory tract. In chronic poisoning of benzene, bone marrow testing may sometimes be normal, and in some cases it may be aplastic or hyperplastic. Symptoms and side effects include headaches, dizziness, fatigue, loss of appetite, feeling unwell, anger, nose bleeding, and other forms of bleeding [6]. Benzene has been used as a common solvent in laboratories in the past, but after scientists have taken their carcinogenic identity, its use as a solvent has been very limited and it was tried to use similar solvents such as acetone and the like. Side effects of chronic exposure to benzene include reduced blood supply, immune system impairment, as well as leukemia, respiratory distress, delay in human embryonic skeletal development, damage to the human reproductive system, infertility, production of lymph node tumors and liver damage. Several institutions, including the World Cancer Research Association, the US Environmental Protection Agency, and the US Department of Health Services have identified benzene as a cause of leukemia, which has a high degree of Carcinogenization. The secret period of leukemia usually occurs 5 to 15 years after the first contact with benzene.

The acute effects of benzene include drowsiness, dizziness, headache, anesthesia and tremors, nausea, seizure, insomnia, stomach arousal, and increased heart rate and coma [5].

Materials and Methods

This is a comparative and cross-sectional analytical study, in which 40 exposed workers with benzene and 40 healthy subjects without a history of exposure to benzene as a control group with the same gender and age (26-40), with a work experience of 5 to 15 years and 8 hours of exposure are compared. The number of people employed was about 200 people who were randomly selected on one of the days of the week and a special shift based on the lottery and satisfaction of the person. The number of people on that day was 80, and based on entry criteria (non-exposure to metals such as lead and zinc, non-consumption of alcohol, supplemental antioxidants and psychotropic drugs, lack of chronic disease and mental illness, lack of radiation history, surgery and anesthesia over the past year, the work experience and the ability to answer questions) 40 people were selected who were exposed to benzene for 8 hours and had entry criteria, and 40 who did not have entry criteria were excluded from the study. It should be noted that all 80 patients completed the questionnaire of clinical symptoms, spirometry and inclusion criteria, and all of them were interviewed by a clinical specialist; and a spirometric test was performed. Then, according to age, sex, entry criteria and place of residence, 40 healthy people from the sales office (office jobs) who had more than 50 kilometers of distance from the factory, were matched to the case group and also a spirometric test was performed. Spirolab III was used to measure Spirometry.

Spirometry method

Spirometry is a method for measuring lung volume changes during strong respiratory maneuvers. The most commonly used method of spirometric exercise is the Forced Vital Capacity (FVC) maneuver, in which the patient performs a fast and complete exhalation after a deep and maximal inhalation.

In fact, the FVC test is the most important test for spirometry. The FVC test provides us with the most and the best information about the status of pulmonary function. So it's important to know how to do this test. FVC maneuvers can be done in both open-circuit and closed-circuit modes [7].

In closed-circuit mode, the inhalation and exhalation of the patient are done both after the mouthpiece is inserted, but in open-circuit mode, at first, the inhalation is done and then the mouthpiece is placed immediately in the mouth and then a strong exhalation is done into the mouthpiece and spirometers. In open-circuit mode, there is no risk of transmission of microbial contamination by spirometers. In most cases, the open-circuit method is sufficient to obtain the necessary spirometry parameters on the condition of being done correctly, while the risk of transmission of infections to the patient is also greatly reduced. The closed-circuit method is most often used in cases where FV-loop is required for detecting. For example, in detecting the obstruction of the upper airways, to obtain accurate and reliable results, performing the correct FVC maneuver by the patient is the most important issue in Spirometry and the main key is to guide the patient correctly to exercise. In order to properly perform this maneuver, in addition to the correct and complete explanation to patient, performing the maneuver should be shown practically to the patient. In fact, there is no substitute for a good and complete explanation and showing the correct maneuver in detail to the patient, which will result in 90%-100% of success in performing the maneuver by the patient and obtaining reliable and correct results. Observing and encouraging the patient during the maneuver, and operator's attention to the details of the maneuvers (attention to the patient and the curves drawn on the device monitor) are very important to achieve reliable results [7].

Steps of FVC maneuver performance

1. Correct guidance to the patient and full explanation of how to perform maneuvers and determine it practicality to the patient.
2. Correct state of the patient: The FVC maneuver can be done either in a sitting or standing position. When sitting, the patient should be completely flat so that the legs stick firmly to the ground. Sitting is the easiest position for spirometry. However, FVC maneuver can also be performed in standing mode. During a maneuver (sitting or standing), the patient should not bend to the front. The patient's position in performing spirometry should be recorded in the spirometric report sheet and applied in the next spirometry in the same position as the FVC in the sitting position decreases towards the standing position.
3. Attaching the nose clip to prevent the air out of the nose during strong exhalation [7].
4. Place the mouthpiece inside the mouth (so that the tongue is underneath it and the lips surround it completely)

In closed-circuit mode, mouthpiece enters inside the mouth before inhalation and in open-circuit mode, mouth piece enters inside the mouth after inhalation.

5. The patient is required to have 3-4 breaths (normal inhalation and exhalation). This is done in order to reach a fixed end-tidal point. In closed-circuit method, this is done after placing the mouthpiece in the mouth and in open-circuit mode, this is done before placing the mouthpiece in the mouth [7].
6. Doing a deep and full inhalation to the end, and at the same time fast (not with strength) and do strong exhalation without pausing as follows:

- Take a strong and quick exhale from the very beginning (without any pauses and distances from the end of inhalation) and continue until no other air leaves the lung. Exhalation must be done from the beginning with all power and continue as far as possible.

7. During work, you should carefully look at the curve drawn on the device monitor (volume-time curve and Flow-Volume loop) to make an acceptable maneuver. If the maneuver is not acceptable, the patient should be re-guided verbally and practically based on existing mistake to perform the FVC maneuver. There must be at least 3 acceptable maneuvers (according to acceptable criteria), but the maximum allowed maneuver (acceptable and unacceptable) is 8 maneuvers. When 3 acceptable maneuvers were performed and registered, then the criteria for re-production should be checked. If these criteria were present, then the best curves and parameters for interpretation would be selected. If there were no reproducibility criteria, then maneuvering should be repeated so that these criteria can be achieved (but not more than 8 maneuvers). If the best numbers in the parameters are obtained from the last maneuver, we must also repeat the maneuver to the extent that this situation is eliminated. We must not forget that even if we do not meet the above criteria, we are not allowed to do more than 8 times [7]. Any exhale maneuvers should have conditions in order to be considered acceptable in terms of the quality. These conditions are called acceptable standards. The patient must have at least 3 acceptable exhale maneuvers in order to obtain a more accurate interpretation of the spirometric results. Acceptability criteria are in a maneuver that has all of the following conditions. In fact, after performing each FVC maneuver by the patient, the operator must control all of the following criteria:

- Maneuver should have a good starting. Vital Time Curves (FV: Flow Volume), (VT: Vital time) should be without any unacceptable cases.

- Expiratory maneuvering time should be appropriate [7].

The appropriate starting of a maneuver is when both of the following criteria are present:

- BEV (Back Extrapolation Volume) would be less than 150 cc or less than 5% of the FVC value.
- Time-to-PEF would be less than 120 thousandths of a second [7].

The most important indicator of the suitability of starting a maneuver is the index of Beverly Expiratory Volume (BEV), which indicates the amount of air drawn out from the lung before exhalation maneuver (distance between the inhalation and exhalation), and the main reason for this is the pause and excessive reflection between the end of deep inhalation and start of a strong exhalation. Most new spirometric devices compute and display this indicator through flow type. If BEV is more than 150 cc or more than 50% FVC, it indicates the inappropriate start of the test. That is, the patient did not initiate a rapid exhalation maneuver. Based on the NIOSH spirometric guide when the FVC is greater than 3lit [7].

Using the 5% benchmark and when the FVC is equal to or less than 3 liters, the use of the cc150 benchmark is more appropriate for the BEV test.

A BEV more than 5% FVC or more than 150 cc will result in wrong FFV1 evaluation.

Another indicator for examining the suitability of the start of exhale maneuver is Peak Expiratory Flow (PEF), which represents the amount of time needed to increase expiratory flow from 10% to 90% of Peak Flow.

If this time is more than 120 milliseconds, exhale maneuver is unacceptable (it does not start well), meaning all of the following criteria are available:

- Coughing or glucose closure doesn’t exist in the first few seconds.
- Exhalation doesn’t have cut off.
- Maneuvers are done uniformly, not with variable forces
- There is no leakage around the mouth
- During the maneuver, mouthpiece should not be blocked by tongue
- Curves FV, VT should be without dent and perfectly flat

Exhalation should be suitable and good in terms of time, meaning each of the following criteria: End-of-test-Criteria, exhalation should continue at least for 6 seconds, In the VT curve, a smooth mode is created for at least 1 second, or the patient is not able to continue to exhale for any reason, or if the expiratory time is reasonable, for example, in asthmatics it may not reach a smooth state for up to 20 seconds [7]. It should be noted that in normal young people, FVC maneuvers might end before 6 seconds. This is not due to the fact that these people are taking out the entire air volume of their lungs in a short time and no other air is left in the lung to escape [7]. In contrast, people with small and medium-sized obstructive airways diseases (such as asthmatics) and the elderly may have a very long exhalation period (even 15 seconds or more) due to stenosis of the airway, but usually a strong exhalation of more than 15 seconds does not give any further information. When 3 acceptable maneuvers are performed and recorded with the above criteria, repeatability criteria should be checked. To test these criteria, numerical differences between the two larger FVCs and the two larger FEVs should be considered. If any of these differences is greater than or equal to 200 cc or more than 50%, exhale maneuvers should be repeated until the difference reaches less than 200 cc or 5% (but at the same time a maximum of 8 maneuvers can be done).

Note: The percentage of re-production should be calculated separately for both the FVC and for the FEV, and in each case, more than 5%, exhale maneuvers should be repeated [7]. If the acceptable percentage is more than 5% in the FEV, it indicates that one maneuver has not been performed with maximum effort. Also, Poor Reproducibility reduces the confidence in the interpretation of changes in serial and periodic spirometry. (For example, in examining changes in indices during a work shift or annual variations in spirometric parameters), in the following graphs, the right chart shows repeatable maneuvers and the left chart is related to unrepeatable maneuvers.

How to choose the best results and curve for interpretation?

After making three acceptable maneuvers along with good criteria, it is time to choose the best results and curve to be interpreted.

From among the three maneuvers with the above conditions, one should be selected for interpretation. Selection should be done as following:

1. Best curve: is chosen from the maneuver that has the largest FEV + FVC set.
2. The largest FVC and the largest FEV should be chosen even if they are not from a single maneuver.
3. Forced Expiratory Flow (FEF25-75%) is selected from the maneuver that has the largest FEV + FVC set.
4. PEF (Peak Expiratory Flow): is selected from a maneuver that has the largest FEV + FVC set.

Note: Spirometry devices themselves will select the best outcomes and curves above and will show the best results on the monitor or print, But at the same time, Spirometric performer should be aware of the best result [7].

Results

Due to the non-normalization of data (FVC, Fev1, FEF25-75%, PEF), the Mann-Whitney test was used to compare the study parameters. In our study, 80 patients (40 in experimental group and 40 in control group) participated.

Table 1. Frequency table

Groups	Frequency	Frequency percentage
Experimental (Benzene)	40	40%
Control	40	40%

Table 2. Age of experimental and control groups

Variable (age)	N	Minimum	Maximum	Mean	Standard deviation
Experimental (Benzene)	40	26	40	31.55	4.662
Control	40	26	40	32.40	4.447

Table 3. Average rating of spirometric variables of workers exposed to benzene and control group

	FVC (Lit)	Fev_1 (Lit)	PEF (Lit/s)	$FEF_{25-75\%}$ (Lit/s)
Group 1 Experimental (Benzene)	58.32	59.71	60.61	61.32
Groups 2 Control	42.68	41.29	40.39	39.68

Table 4. Mann-Whitney Test

	FVC (Lit)	Fev_1 (Lit)	PEF (Lit/s)	$FEF_{25-75\%}$ (Lit/s)
Mann-Whitney	859	789.5	744.4	709
Wilcoxon	2134	2064.5	2019.5	1984
Z	-2.696	-3.175	-3.485	-3.73
Significant level p-value	0.007	0.001	0.001	0.001

According to the results of the data analysis, there is a significant difference between the spirometric parameters FVC, Fev1, FEF25-75%, PEF ($P < 0.05$). According to the mean scores of both groups, the spirometric evaluation parameters have decreased in the second group. It seems that both groups are in the mixed pattern for the interpretation of spirometry.

Discussion

According to the results of the data analysis, there is a significant difference between Spirometric parameters of Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV1), Forced Expiratory Flow (FEF25-75%), Peak Expiratory Flow (PEF). Studies in this field are consistent with some studies and are inconsistent with some other studies.

In his article, "The Types of Cancer Caused by Benzene Occupational Exposure: a Review of Recent Observations in Turkey," Akswy (1980) stated that a small amount of evidence suggests that lung cancer may be the result of exposure to benzene [8].

Cinder et al. (1988), in a paper titled "Cancer due to discontinuous exposure to benzene in CD-1 and C57B1/6 mice, inferring the tumor response in mice, showed that the discontinuous, but long-term exposure to a low amount of Benzene has a much greater impact than short-term but intense exposure. Also, the metabolism of benzene in the lungs is important for several reasons. The lungs are the target organs for Benzene poisoning in animals, and benzene is received by the lung after the amount of cardiac output. After breathing, the lung is the first contact area [9]. Faris et al. (1993), in a paper entitled "Benzene-induced cancers in CBA mice," showed that studies on respiration through the lungs indicated an increase in the types of tumors, such as the tumor of the lung zymbolotomers in mice [10]. Weaver et al. (2007), in a paper titled "The Effect of Benzene Exposure on Apoptosis in Lung Capillary Cells", show that chronic exposure to benzene poisons the respiratory tract. Weaver et al. reported that in mice that breathed seven days of benzene (4.958 mg/m3) auto-death of cells (apoptosis) occurred, especially in the lungs' original tissue [11]. Parsley et al. (2009), in an article titled "The Effect of Toluene and Benzene in air on Human Lung Cells (A549)," stated that both benzene and Toluene are used in the industry and are steamable organic compounds. Their toxic effect depends on their tendency to lipids, when they are exposed to lipids, in the long run, fall into fat deposits and accumulate in Molecular lipid membranes. It is said that benzene has a toxic effect on the gene, and it can cause cancer, but its major role on the lungs cannot be neglected. By breathing benzene, the lung cells undergo chemical change and become reactive metabolites [12]. In his doctoral dissertation, "Investigating Pulmonary Diseases Related to Selection," Harbinison (2013) states that there are many industries in Florida that expose workers to air pollution by gases, vapors, particles and dust. When the air in the environment is a nerve disturbing or involves blistering or fibrinogen inducing, lung function may be impaired, especially if acute (short-term) exposure to high benzene or chronic exposure (long-term exposure) is not well controlled. Also About testing lung function in a care standard: 1. The broker must ensure that the test subjects (if they are not licensed doctors) have passed at least one advanced spirometric trial period at one of the valid educational centers. 2. At the examination of workers who have had to use masks for at least thirty days a year, special attention has to be paid to the functioning of the cardiovascular system and we should absolutely ensure that the lung function test is performed on them. 3. People who use masks at least thirty days a year must perform lung function test every three years. The function of heart and lungs can also be measured at the same time [13]. Server et al. (2013), in a paper titled "The Protective Effect of Vitamin C Against Benzene-Induced Lung Damage", show that benzene, as an organic solvent, damages lung cells and this is associated with the formation of free radicals. [14]. In an article entitled "Assessing and comparing pulmonary function tests In workers of gas station exposed to fuel", Anoja et al. (2014) stated that periodic examinations and pulmonary function tests should be carried out regularly among workers, and the development of appropriate equipment for environmental monitoring and testing in the community will also be very helpful. Petroleum products cause significant respiratory symptoms such as chronic cough and shortness of breath. At high concentrations, it also causes inflammatory reactions in the lungs. Compared with the larger particles in the air, these particles fall into the lungs and in the deeper parts of the lungs for longer periods of time. Met Hemoglobin (MetHb) is a product of the metabolism of benzene in the body that is effective in the development of anemia. When methemoglobin levels increase, symptoms such as shortness of breath, palpitations, anxiety, and confusion are evident. Exposure to benzene with a concentration of 1 ppm for 8 hours in fuel distribution centers and exposure to 2 and 3 ppm concentrations for a shorter time can cause symptoms. In a study by Anoja et al in 2014, the comparison of pulmonary function of 50 gas station workers exposed to benzene with 51 people with unrelated job was done and evaluated. There was no statistical significant difference between the two groups. FEV in the first second and PEFR in the exposed group of benzene fumes were significantly reduced compared to the control group [15]. Solanchi et al. (2015) conduced a study entitled "Spirometry survey of 227 gas station workers in Ahmedabad in India who did not use any protective equipment such as masks, compared to 227 office workers, they observed a Significant decrease in lung function in the mean values of FEF25-75%, FEV1, FVC, PEFR. Rahul et al. (2016), in their study entitled "Assessment of Pulmonary Spirometry in Gas Station Workers in Jaipur, Rajasthan, India", evaluated the spirometry of 40 gas station workers in Jaipur, Rajasthan, India, who worked there for 3 years and 40 people Control group, there was a significant decrease in FVC, FEV1, FEF25-75% and PEFR in the exposed group with benzene fumes. However, the mean values (FEV1 / FVC%) were not statistically significant between the two groups. All of the studied traits were decreased from the pulmonary function test in the intervention group compared to the control group, except for the FEV1 / FVC ratio (%), it was significant in all of the parameters of the pulmonary function test. Side effects of benzene vapors in the lungs may occur in a variety of ways. In some laboratory animals, Petroleum hydrocarbons increase Malondialdehyde (MDA), an indicator of lipid peroxidation. These Petroleum hydrocarbons reduce the glutathione and decrease the activity of superoxide dismutase (SOD), which is the main line of defense in destroying free radicals. Hence, the stimulation of oxidative stress leads to loss of tissue and lung cells [17]. Zafar (2016), in his article entitled "Relationship between respiratory symptoms and the pattern of lung spirometry among Karachi gas station workers in Pakistan," investigated the relationship between respiratory symptoms and the pattern of lung spirometry among Karachi gas station workers in Pakistan (a study of 150 workers exposed to Benzene, and 150 controls), as a conclusion, respiratory symptoms have been reported as an important cause of lung function disorder among gas station workers, and these studies show also a decrease in FEV1, FVC and FEV1 / FVC. [18].

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