Evaluation of Interleukin-4, Micro-Albumin, and Creatinine in Students Exposed to Short-Term Formalin in Nnewi, Anambra State, Nigeria

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DOI: https://doi.org/10.51244/IJRSI.2025.12020016

Received: 24 January 2025; Accepted: 29 January 2025; Published: 28 February 2025

ABSTRACT

Introduction Formaldehyde is a colorless, strong-smelling gas that is commonly used in various industries, including as a preservative in laboratories. This study evaluated interleukin-4, micro-albumin, and creatinine levels in students exposed to short-term formalin at Nnamdi Azikiwe University, Nnewi. A total of 47 students were recruited aged 18-30 comprising 47 students who were not exposed to formalin as control, and 47 students who were exposed to formalin as test subjects. Sandwich ELISA determined Interleukin-4; creatinine was determined by the Jaffe Slot Alkaline Picrate method; micro-albumin by immuno-turbidimetric assay. Data obtained were analyzed with paired t-test and Pearson correlation coefficient test. There was no significant difference in the levels of interleukin- 4 (87.54±79.38) (pg/ml), creatinine (212.54±210.38), (µmol/l), and micro-albumin (31.88±12.01), (mg/l) of students exposed to formalin compared to the control. (P>0.05). There was a correlation between interleukin-4 levels (r=0.569, p=0.000) in pre- and post-exposure. There was no correlation between creatinine, micro-albumin, and micro-albumin creatinine ratio (p>0.05). The study concluded that there were no observed abnormal changes in the levels of interleukin-4, micro-albumin, and creatinine in students exposed to short-term formalin.

Keywords: Interleukin-4, Micro-Albumin, Creatinine, Students, Formalin, Nnewi.

INTRODUCTION

Formalin is a colorless, strong-smelling, aqueous solution of formaldehyde, a highly reactive organic compound. It is widely used in many industries and settings, including healthcare, education, and research, for its preservative and disinfectant properties. However, formalin exposure is known to have potential health effects on human beings, including respiratory and skin irritation, as well as carcinogenicity. Formaldehyde increases the risk of certain types of cancer, including leukemia and brain cancer. The study found that people who are exposed to high levels of formaldehyde in their workplace have a significantly increased risk of developing this type of cancer [1]. Although formaldehyde is naturally present in the troposphere, due to its formation during the oxidation of hydrocarbons [2], the main sources determining human exposure are

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue II February 2025

anthropogenic. Among these, some are present in indoor environments such as products containing and releasing formaldehyde (insulating materials, resins, glues, chipboard, plywood, fabrics, etc.) [3]. In contrast, others are related to activities involving combustion processes, tobacco, e-cigarettes active, passive smoking, and cooking (especially frying) [4].

Formalin is a well-known occupational carcinogen and a recognized sensory irritant compound, especially for sensitive individuals [5], present in many different working scenarios [6]. Indeed, Formalin is widely used in numerous production processes and sanitary applications due to its chemical-physical characteristics and broad-spectrum microbicide activity [7]. The International Agency for the Research on Cancer (IARC) has identified three main occupational scenarios where workers may be exposed to formalin at air concentrations significantly higher than the indoor and outdoor background levels: (i) the production of formaldehyde and/or its solutions; (ii) the production of products containing formaldehyde or during their use and (iii) the combustion of products generating formaldehyde [8]. Thus, workers in industrial production processes (resins, plastics, semi-finished wood products, furnishing accessories, and textiles) [9], professionals of gross anatomy and pathology laboratories, veterinarians, embalmers [10], breeders [11], carpenters, industrial launderers [12], fire-fighters, beauticians, and printing-rooms workers [13] are the categories at higher risk of exposure to formalin. In this regard, robust scientific evidence has highlighted several acute and chronic adverse health effects deriving from such exposure [14]. Moreover, after a revision of the scientific literature, IARC in 2004 classified formaldehyde as a group I carcinogen with sufficient evidence for nasopharyngeal carcinoma and ward, also for leukemia [8]. Then, given the evidence, in 2011 the listing status of formaldehyde “classified it to be a human carcinogen based on sufficient evidence of carcinogenicity” in the Twelfth Annual Report on Carcinogens of the National Toxicology Program (NTP) [15]. More recently, the European Commission (EC) has reclassified formaldehyde to carcinogenic category 1B (may cause cancer by inhalation) and mutagen category 2 (suspected of causing genetic defects) [16]. Formaldehyde is commonly used to preserve cadavers for anatomical study, research, and medical education. Cadavers are typically immersed in a solution containing formaldehyde to prevent decay and putrefaction. Fixing the tissues with formalin not only preserves the cadaver but also enhances its structural integrity, allowing more accurate anatomical study and research. The fixed cadavers can be stored for a long period without deteriorating and can be used for a wide range of purposes, including dissection, microscopy, and medical education [17]. Embalmers who handle formalin are at increased risk of exposure to this hazardous chemical, which can lead to a variety of health effects. Studies have investigated the health effects of formalin exposure among embalmers. Embalmers had higher levels of formaldehyde exposure than the general population, and exposure levels were highest during embalming procedures [18]. Another study by [19], found that the incidence of cancer among a cohort of 60,000 embalmers and funeral directors in the United States that these workers had a significantly increased risk of several types of cancer including multiple myeloma, leukaemia, and pancreatic cancer. The toxicity of formalin is thought to be related to its ability to cause DNA damage, protein modification, and lipid peroxidation, leading to oxidative stress and inflammation. Recent studies have also suggested that formalin exposure may alter the levels of certain biomarkers in human subjects, including interleukin 4, micro-albumin, and creatinine. For example, a study confirmed that formalin exposure among medical students was associated with increased levels of interleukin 4 in their serum. The study also found a positive correlation between formalin exposure and micro-albuminuria, which is a marker of kidney damage [20].

Interleukin 4 is a cytokine, a protein involved in regulating the immune response, particularly in promoting Th2 immune responses, which are associated with allergic reactions. It is produced by various immune cells, including T cells, mast cells, and basophils. Similarly, a study conducted confirmed that exposure to formalin fumes in the workplace was associated with increased levels of creatinine in the urine of exposed workers. Creatinine is a waste product excreted by the kidneys and is commonly used as a marker of kidney function. The study also found that formalin exposure was associated with increased oxidative stress markers in the blood [21].

Micro-albumin is a small amount of the protein albumin excreted in the urine. Normally albumin is not present in the urine or only small amounts are present. However, when the kidney is damaged, a small amount can leak into the urine, known as microalbuminuria [22]. A study investigated the effect of short-term exposure to formalin on creatinine levels in urine samples. The study found that exposure to formalin vapors for 10

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue II February 2025

minutes resulted in a significant increase in creatinine levels in urine samples, which persisted for up to 72 hours after exposure [23]. These findings suggest that short-term exposure to formalin can have a significant impact on the measurement of creatinine levels in urine samples, which could potentially lead to misdiagnosis or inappropriate medical treatment. Healthcare and research settings included gross anatomy, pathology, or histology laboratories [24], operating theatres [25], and other indoor environments of universities and research or training institutes [26]. In particular, some work activities performed in gross anatomy, pathology, or histology laboratories and in operating rooms involve the use of solutions containing formaldehyde for fixing and preserving biological tissues and for preparing cadavers. Thus, formaldehyde vapors can pollute the indoor air of these environments, resulting in a risk of occupational exposure in hospital settings, research laboratories, and medical schools. Besides, it also demonstrated that formaldehyde exposure can occur not only during the handling of formaldehyde and formaldehyde-treated materials but also through inappropriate storage of this substance or treated materials and an ineffective local exhaust ventilation system [27].

MATERIALS AND METHOD

The reagents and kits used for the biochemical analysis were purchased commercially, and the manufacturer's standard operating procedures were meticulously followed. This longitudinal study was carried out in Nnewi North, Anambra State, located in southeastern Nigeria.

Study Participants

This study was conducted in the Department of Anatomy, Faculty of Basic Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Southeast Nigeria. It involved students aged 18–30 years who were exposed to short-term formalin for three hours. A total of 88 participants were recruited, including 47 students exposed to short-term formalin and 41 non-exposed students of similar age. Demographic information was collected using a structured questionnaire.

Sample Size

The sample size was calculated using G*Power software version 3.19.4. (Universitat Dusseldorf Germany) power analysis for the difference between two independent means (two groups), will be conducted in G*Power to determine the sufficient sample size using an alpha of 0.05, a power of 0.85, and an effect size of 0.45. Based on this, the calculated sample size is 47, which has a power of 85% power to detect the difference of 0.45 as a significant level of 0.05. A total sample size of 47 was used for this study to take care of possible attrition.

Sample Collection and Processing

Venous blood samples (5 ml) were collected aseptically through venipuncture from each subject using a plastic syringe, ensuring that the process was carried out with precision via the antecubital vein. The samples were dispensed into plain tubes and allowed to clot for one hour at room temperature. Following this, centrifugation was conducted at 4,000 rpm for five minutes using a tabletop centrifuge to effectively obtain serum for the evaluation of interleukin-4. The serum samples were then stored at controlled temperatures between 2°C and 8°C, ready for biochemical analysis. Urine samples were also collected from each subject in a universal container. An antimicrobial agent, 0.02% sodium azide, was added to the urine samples to prevent bacterial growth during the evaluation of micro-albumin and creatinine. The urine samples were similarly stored at temperatures between 2°C and 8°C.

Laboratory Methods

All the reagents were commercially obtained, and the manufacturer's standard operating procedures were strictly observed.

Serum Interleukin-4 was determined as described by Ihim et al 2024 [28]. The immunoturbidimetric method was used for the determination of micro-albumin as described by the manufacturer of the kit. Creatinine was evaluated as described by Ihim et al 2017 and 2019 [29].

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue II February 2025

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 23.0 was utilized for data analysis. Results were expressed as mean ± standard deviation (SD) and statistically evaluated using the paired Student's t-test and Pearson correlation coefficient test. A significance level of $P < 0.05$ was established, with values considered significant when $P < 0.05$.

RESULTS

Table 1: Comparison of the mean values of serum interleukin-4 (pg/ml), urine micro-albumin (mg/l), creatinine(µmol/l), micro-albumin and creatinine ratio(mg/µmol) in the participants pre- formalin exposure and post-formalin exposure samples (Mean±SD).

No significant differences were observed in the mean serum level of interleukin-4 (114.95±20.01), urine micro-albumin (86.36±80.33), creatinine (276.67±248.02), micro-albumin and creatinine ratio (1.13±0.17) of pre-formalin exposed participants compared with post-formalin exposed participants ($P>0.05$).

Table 1: The mean values of serum interleukin-4 (pg/ml), urine micro-albumin (mg/l), creatinine(µmol/l), micro-albumin and creatinine ratio(mg/µmol) of the participants; pre-formalin exposure and post-formalin exposure (Mean±SD).

Variables	**Pre-formalin Exposed (n=47)**	**Post-formalin Exposed (n=47)**	**t-value**	**p-value**
Interleukin-4 (pg/ml)	114.95±20.01	87.54±79.38	0.091	0.328
Micro-albumin (mg/l)	86.36±80.33	31.88±12.01	1.256	0.268
Creatinine (µmol/l)	276.67±248.02	212.54±210.38	1.067	0.292
Micro-albumin creatinine ratio (mg/µmol)	1.13±0.17	3.23±2.94	1.574	0.213

Table 2: Correlation between interleukin 4, micro-albumin, creatinine, and micro-albumin creatinine ratio.

A moderate positive association exists in the serum level of interleukin-4 between pre- and post-exposed formalin participants. No association was observed in urine levels of creatinine, micro-albumin, and micro-albumin- creatinine ratio between pre- and post-exposure formalin participants.

Table 2: Correlation of the level of association between interleukin 4, micro-albumin, creatinine, and micro-albumin creatinine ratio.

Pre and Post Formalin Exposure	**R-value**	**P-value**
Interleukin-4 (pg/ml)	0.569	0.001
Creatinine (µmol/l)	0.025	0.879
Micro-albumin (mg/l)	0.052	0.948
Micro-albumin creatinine ratio (mg/µmol)	0.304	0.696

DISCUSSION

Formalin exposure has been linked with serious histopathological and biochemical derangements in renal tissue and increased risk of developing certain types of cancers including nasopharyngeal cancer and leukemia [29]. Formaldehyde exerts toxic effects on multiple bodily systems, and both experimental and clinical studies have explored its impact on the urinary system [30]. Exposure to formalin in daily life is unavoidable due to its presence in home environments, food, exhaust fumes, smoke, pollution from natural gas usage, wood and coal burning, and air inhalation. Additionally, significant formalin exposure occurs during embalming and dissection in histology, pathology, anatomy laboratories, and dialysis units. This study's results indicate no significant difference in the mean serum levels of interleukin-4, urine microalbumin, creatinine, and the microalbumin-to-creatinine ratio between participants before and after formalin exposure. Urinary microalbumin and creatinine are well-established renal biomarkers and early indicators of kidney disease

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue II February 2025

progression in individuals with polycystic kidney disease, offering greater predictive value than traditional serum biomarkers [31]. Previous studies have shown that formalin exposure leads to a decline in kidney function [32], and a decrease in immune cell count [33]. Elevated creatinine levels serve as key markers of nephrotoxicity following formalin exposure [34,35]. In their study on the effects of formalin inhalation on the physical characteristics and renal profile of Albino Wistar rats, Egwurugwu et al. [35] reported a significant increase in serum sodium, potassium after 8 hours of exposure while, serum urea, and creatinine levels significantly increased after longer duration of exposure (2 weeks), indicating a decline in kidney function with prolonged formalin exposure. Ihim et al. [32] investigated the effects of short-term (3-hour) formalin exposure on kidney function in students in Nnewi and found no significant changes in creatinine levels before and after exposure, suggesting that brief formalin exposure may not result in immediate renal dysfunction. Similarly, Kum et al. [36] exposed rats to formalin for 8 hours daily over 15 days and observed no significant differences in creatinine and microalbumin levels between the exposed rats and the control group. These findings imply that creatinine and microalbumin may not be sensitive markers for detecting kidney damage after short-term formalin exposure. Longer exposure durations or the use of more specific biomarkers may be required to assess renal impairment more accurately. A study by Jia et al. demonstrated an increase in the expression of IL-10 and IL-4, and the low expression of IFN-γ, which promotes the Th2-skewed immune responses. Elevated IL-4 levels following formalin exposure could indicate an increased risk of allergic reactions or an exaggerated immune response, especially in individuals with pre-existing sensitivities. A study by Jia et al. [37] showed an increase in the expression of IL-10 and IL-4, alongside a decrease in IFN-γ expression, promoting Th2-skewed immune responses. The study by Camila et al. [38] also indicates that formaldehyde exposure triggers inflammation, which in turn impacts the levels of interleukin-4. This elevation may suggest a higher risk of allergic reactions or an exaggerated immune response, particularly in individuals with pre-existing sensitivities.

CONCLUSION

In conclusion, this study observed that short-term exposure did not make significant changes in the kidney function of the participants it could be due to the participants being only exposed for 3 hours.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Contributors

ACI, NJ, and PCO conceived and designed the research proposal. OIJ, ROO, ITA, and ACI performed sample collection, experiments, and data analysis. CUO, ACI, ROO, and OIJ contributed to the final version of the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors would like to pay their most profound gratitude to the management and staff of Nnamdi Azikiwe University Teaching Hospital Nnewi, and Reene Medical Diagnostic Laboratory, Awada, Anambra State, for all laboratory analyses of all biochemical parameters

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Funding:

No funding sources.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue II February 2025

Conflict of interest:

None declared.

Ethical approval:

The study sought and obtained ethical approval from the Ethics Committee of the Faculty of Health Sciences and Technology College of Health Sciences Nnamdi Azikiwe University with reference no. FHST/REC/023/00214

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