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# Effects of heavy metal lead on differential cell counts in occupationally-exposed subjects from Saudi Arabia

Abjal P. Shaik*[1], Abbas H. Alsaeed[1], Asma S. Shaik[1], Abdullah A. Alyousef[1], Vamsee K. Bammidi[2] and Kiranmaye Sampathirao[3]

*[1]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia*
*[2]The Unicare Group, Burton-on-Trent, Staffordshire, United Kingdom*
*[3]Alrewas Surgery, Burton-on-Trent, Staffordshire, United Kingdom*

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**Abstract.** The current observational epidemiological study analyzed blood lead levels (BLLs) in occupationally exposed workers from Riyadh region, Saudi Arabia and correlated them with the alterations in the differential cell populations of the WBC panel (lymphocytes [Lym %], mixed [Mid %] cells, and neutrophils [Neu %]). In addition, we examined the effect of confounding factors and their relation to BLLs. BLLs were estimated using the LeadCare II analyzer and hematological parameters using the ADVIA 120 analyser. An inferential analysis was conducted to detect association between the observations and the subjects' clinical characateristics. A total of 132 male subjects were included in the final analyses. Based on CDC guidelines, the subjects were categorized as Group I (BLL <10 µg/dL; n=118) or Group II (BLL >10 µg/dL; n=14) with average BLLs of 4.4 µg/dL and 18.1 µg/dL, respectively ($p < 0.0001$). The percentages of Mid cells ($p < 0.0001$) and neutrophils ($p = 0.048$), were significantly altered in subjects with High BLL. A regression analysis indicated that subjects > 50 years of age had significantly higher BLLs (53.2 µg/dL) than younger age sub-groups ($p < 0.0001$). Age, education, and profession were significant predictors for lead toxicity. Pb exposure is a major public health issue in Saudi Arabia and calls for further investigations on the cellular and molecular effects on hematological system.

**Keywords**: BLL; confounding factors; differential leucocyte counts; occupational lead exposure

## 1. Introduction

Heavy metal lead (Pb) has been used for several decades in battery manufacturing, smelting, mining, and various other occupations (ChemIDplus 2005). Therefore, lead poisoning can occur through a variety of routes including ingestion, inhalation, or transdermally (Bellinger 2004). In countries like Saudi Arabia, Pb has also been used for non-occupational purposes in traditional folk medicine (Nouioui *et al.* 2016). The Centers for Disease Control and Prevention (CDC 1991) defines a blood lead level (BLL) of >10 µg/dL as elevated and emphasizes the need for clinical intervention.

*Corresponding author, Dr., E-mail: afzalshaik@gmail.com


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Pb interferes with heme biosynthesis, most important being the inhibition of aminolevulinic acid dehydratase and heme synthetase with consequentaccumulation of aminoluvelinic acid and protoporphyrin (Ahamed *et al*. 2005, Ahamed *et al*. 2011, Dai *et al*. 2017, Deitert and Piepenbrink 2006). Pb also causes a disruption of the process of hemopoeisis impacting the ratios of other cells of the hematological system (Ahamed *et al.* 2011, Deitert and Piepenbrink 2006). Pb, affects erythropoiesis causing aplastic anemia with reduced corpuscular hemoglobin and hematocrit alterations (Dai *et al.* 2017), alters the percentages of immune cells (Dobrakowski *et al*. 2016) and reduces T cells and B cells (Fang *et al.* 2012). The mechanisms that lead to Pb-induced cellular damage may be attributed primarily to oxidative damage with ensuing free-radical generation, damage to the anti-oxidant defense mechanisms and oxidative stress caused due to lipid peroxidation, protein oxidation, and nucleic acid oxidation (Gurer-Orhan *et al.* 2004, Valko *et al.* 2005). Eventually, cell membrane damage, protein dysfunction and impaired DNA repair lead to cell death (Jomova and Valko 2011).

Since studies on hematological aspects play an important role in understanding the cellular aspects of Pb toxicity including absorption, an understanding of the effects of Pb on cells of the various populations of white blood cells (WBCs) was deemed necessary. Moreover, there is dearth of literature in the Saudi Arabian population that is endowed with unique heterogeneity, ethnicity and socio-demographic features. The aim of this study was to analyze BLLs in occupationally exposed Pb workers and correlate them with the alterations in the various cell populations of the WBC panel viz percentages of lymphocytes (Lym %), mixed (Mid %) cells (monocytes, basophils, eosinophils, blasts, and large unstained cells [immature/precursor cells of certain size range]), and neutrophils (Neu %). In addition, we examined the effect of confounding factors and their relation to BLLs.

## 2. Materials and methods

An observational epidemiological study was conducted (Feb 2015–Feb 2017) on subjects from Riyadh, Saudi Arabia working in battery manufacturing, painting and plumbing for at least 1 year. Information pertaining to their health status, job, income, education, use of vitamins, and smoking were collected in a detailed proforma. This study was approved by the Institutional Ethics Review Board (15/0163/IRB, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, KSA). Written and signed informed consent in accordance with the Declaration of Helsinki was obtained from all subjects. Blood samples (5 mL) were collected from each subject.

BLLs were estimated using the LeadCare II analyzer according to the manufacturer's instructions (Magellan Diagnostics, Meridian Bioscience, OH, United States). Subjects were categorized as Group I or Group II based on BLLs – Low BLL (Group I, <10 µg/dL) and high BLL (Group II, >10 µg/dL) as per the guidelines defined by the Centers for Disease Control and Prevention (CDC).

Hematological parameters were assessed using the differential ADVIA 120 haematology analyzer (Siemens Healthcare Pte. Ltd, Singapore). Assessments of white blood corpuscles (WBC), red blood corpuscles (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), percentage of lymphocytes (Lym%); mixed cells (Mid %, combined estimates of

Table 1 Comparison between both groups in terms of different blood parameters

| Clinical Parameter | Group 1 (BLL <10 µg/dL) N: 118 | Group 2 (BLL >10 µg/dL) N: 14 | p value |
|---|---|---|---|
| WBC | 6.7 (1.9) | 7.6 (5.3) | 0.517 |
| RBC | 5.3 (0.7) | 5.4 (0.6) | 0.713 |
| HGB | 13.7 (1.1) | 14.7 (1.8) | 0.006* |
| HCT | 43.6 (5.1) | 44.8 (4.5) | 0.423 |
| MCV | 81.5 (8.1) | 82.9 (3.2) | 0.514 |
| MCH | 26.2 (2.4) | 26.8 (1.9) | 0.347 |
| MCHC | 31.9 (1.7) | 32.9 (1.2) | 0.037* |
| PLT | 287.9 (378.3) | 239.3 (66.2) | 0.634 |
| Lym % | 41.0 (8.4) | 38.9 (11.2) | 0.422 |
| Mid % | 6.4 (3.7) | 3.2 (1.3) | <0.0001* |
| Neu % | 51.4 (8.7) [n=116] | 58.6 (10.1) [n=13] | 0.048* |

*: significant; Lym %: percentage of lymphocytes; Mid %: monocytes, basophils, eosinophils, blasts, and large unstained cells (immature/precursor cells [cells in a particular size range]); Neu %: neutrophils

monocytes, basophils, eosinophils, blasts, and large unstained cells [immature/precursor cells of a particular size range]), and neutrophils (Neu %) were performed.

### *2.1 Statistical analyses*

Data analyses was performed using SPSS version 22 (IBM Inc., Chicago, Illinois, USA). Descriptive analyses for categorical variables was presented as frequencies and percentages while continuous variables were presented as mean (SD). Inferential analysis was conducted using Chi2 test to detect any association between different characteristics and the subjects' clinical indices. Comparison of means across both study groups was done using Student's t test. Linear regression analysis was conducted to detect potential associations between the available confounding factors and the study groups. Confidence interval level was set to 95%, the corresponding p value threshold was identified as 0.05 where any output p below 0.05 would be interpreted significant. Logistic regression analyses was tested but was not eligible.

## 3. Results

A total of 150 male subjects aged 19–65 years were recruited. Subjects who did not provide signed informed consent were excluded (N=18). Subjects meeting the inclusion criteria (N=132) were included in the final analyses. Based on CDC guidelines, the subjects were categorized as Group I (BLL <10 µg/dL; n=118) or Group II (BLL >10 µg/dL; n=14). Patients across a broad age range were included in this study. The average BLL in Group I was 4.4 µg/dL while in Group II it was 18.1 µg/dL (p<0.0001).

While the total WBC counts in both groups did not differ significantly (Table 1), the percentages of Mid cells and neutrophils were significantly altered in subjects with High BLL (Group II). There were no significant changes in RBC counts, Hb levels, HCT, MCV, MCH,

Table 2 Differences across age groups based on blood lead levels (BLL)

| Age groups | Group 1 (BLL <10 µg/dL) N: 118 | Group 2 (BLL >10 µg/dL) N: 14 |
|---|---|---|
| [18 – 35] | 4.3 (1.8) | 14.1 (4.5) |
| [35 – 50] | 4.6 (1.7) | 17.5 (7.2) |
| > 50 | 4.3 (1.1) | 53.2 (0.0) |
| p value | 0.747 | <0.0001* |

*: significant

Table 3 Linear regression analysis for the entire study population

| | Unstandardized Coefficients[a] | | Standardized Coefficients[a] | | |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | t | Sig. |
| (Constant) | 1.791 | 3.249 | | 0.551 | 0.583 |
| Profession | 1.107 | 0.526 | 0.225 | 2.104 | 0.038* |
| Age | 0.091 | 0.064 | 0.151 | 1.412 | 0.162 |
| Education | 0.162 | 1.133 | 0.015 | 0.143 | 0.887 |

[a]Dependent Variable: Pb_level (mechanics had significantly high BLLs); *: significant

Table 4 Linear regression analysis for subjects of Group I (subjects with BLL <10 µg/dL)

| | Unstandardized Coefficients[a,b] | | Standardized Coefficients[a,b] | | |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | t | Sig. |
| (Constant) | 3.428 | 0.922 | | 3.717 | 0.000 |
| Profession | 0.166 | 0.152 | 0.125 | 1.090 | 0.279 |
| Age | 0.002 | 0.019 | 0.015 | 0.129 | 0.898 |
| Education | 0.883 | 0.330 | 0.306 | 2.678 | 0.009* |

[a]BLL <10 µg/dL; [b]Dependent Variable: Pb_level (mechanics had significantly high BLLs); *: significant

Table 5 Linear regression analysis for Group II (subjects with BLL >10 µg/dL)

| | Unstandardized Coefficients[a,b] | | Standardized Coefficients[a,b] | | |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | t | Sig. |
| (Constant) | -9.038 | 16.831 | | -0.537 | 0.603 |
| Profession | 1.332 | 2.960 | 0.118 | 0.450 | 0.662 |
| Age | 0.647 | 0.300 | 0.591 | 2.157 | 0.05* |
| Education | 0.973 | 5.081 | 0.054 | 0.191 | 0.852 |

[a]BLL <10 µg/dL; [b]Dependent Variable: Pb_level (mechanics had significantly high BLLs); *: significant

MCHC, and platelet counts. Surprisingly, the levels of hemoglobin, although within the clinical normal range, were significantly increased in High BLL group (p=0.006).

A regression analysis performed to understand the association of cofounders and BLLs indicated that subjects (>50 years) of age had significantly higher BLLs (53.2 µg/dL) than younger age sub-groups (Table 2; p<0.0001).

In the other age groups, BLLs of 14.1–17.5 µg/dL were observed. Age, thus had a direct association with BLLs and was therefore a significant predictor for lead toxicity (Table 3).

A regression analyses for the variables, profession, age, and education for the entire population versus the dependent variable BLL, indicated that profession was a significant (p=0.038) and strong predictor for lead poisoning (Table 4).

Similarly, a regression analyses for Group I subjects indicated education to be a strong predictor (Table 4, p=0.009) while age was a significant predictor for Group II subjects (Table 5, p=0.05).

## 4. Discussion

Although, the physiological role of lead is not yet known, it can easily mimic divalent cations and disrupt the normal functioning of cell enzymes (Ballatori 2002, Jan *et al*. 2015). Therefore, Pb exposure and BLLs could be critical to human health (Vorvolakos *et al*. 2016). Almost 99% of absorbed Pb binds to erythrocytes, while the remaining diffuses into soft tissues and equilibrates with blood Pb (Goyer 2001, Nombela-Arrieta *et al*. 2013). Owing to the potential of Pb to interrupt heme biosynthesis and hematopoiesis, we investigated the variations in the cell population of the hematological system (immune cells) and their association with BLLs.

Saudi subjects were categorized into two sub-groups (Group I [<10 µg/dL] or Group II [>10 µg/dL]. This categorization was performed in accordance with CDC guidelines (CDC, 1991). Most subjects had BLLs <10 µg/dL (n=118; 4.4 µg/dL) while a significant proportion had BLLs >10 µg/dL (n=14; 4.4 µg/dL) (p<0.0001).

Pb has been often reported to alter the physiological processes pertaining to hematological and nervous systems (Tuakuila *et al.* 2013, Li *et al*. 2017). The hematological system is a tightly regulated process of producing all blood cells and can therefore be disrupted in the presence of xenobiotics (Wang and Wagers 2011, Baldridge *et al*. 2011). Studies have shown that Pb reduced corpuscular hemoglobin and HCT (Ahamed *et al*. 2011, Dai *et al*. 2017), increased the numbers of leukocytes and lymphocytes (Dobrakowski *et al*. 2016), and altered the mechanisms of myelopoiesis (Li *et al.* 2017). However, there is scarcity of literature with respect to the understanding of which specific WBC population is altered by occupational Pb exposure especially in Saudi Arabia. A comprehensive assessment of these alterations may help in better evaluation of Pb toxicity. To understand the influence of Pb on the cells of the leucocyte population, the percentages of Lym, Mid and Neu cells were measured in the blood samples of all subjects.

Alterations in the various cells of the leucocyte population could be attributed to oxidative tissue damage (Ni *et al.* 2004) and ensuing oxidative stress due to increased free radical generation with effects ranging from mitochondria lyses, protein damage and lipid peroxidation (Ahamed *et al.* 2005). Moreover, Pb has been reported to alter the expression of various cytokines that have a role in the development of hematopoietic cells (Fang *et al*. 2012, Li *et al*. 2013, Zhang *et al*. 2013).

The involvement of Pb in causing anemia and hematocrit alterations, and reducing corpuscular hemoglobin has been well documented (Ahamed *et al*. 2011, Dai *et al.* 2017). Although, the hemoglobin levels in this study were strangely higher in the sub-group with high BLLs, this could be a chance event owing to the small sample size of this population. The total WBC count was similar for both groups, however, the percentages of Mid cells and Neu cells, were significantly elevated in Group II.

The alterations in the numbers of immune cells found in this study is consistent with the findings of Dobrakowski *et al*. (2016) who reported decreased levels of lymphocytes and leucocytes following occupational Pb exposure. Pb has been shown to interfere with clearance of reactive oxygen species within the cells due to its high affinity to glutathione (Jaishankar *et al*. 2014), a process that could cause an increase in monocytes and neutrophils at early stages of exposure followed by reduced numbers of the same cells at later stages (Li *et al.* 2017). In the current study, we have reported that high BLLs act by decreasing the numbers of Mid % cells and increasing the numbers of Neu % cells, indicating that Pb impacts hematopoiesis and alters the functions of the immune system. A study by Metryka *et al*. (2020) that evaluated the in vitro effect of Pb on monocytes and macrophages indicated that both these cell types demonstrated dose- and time-dependent decrease in cell viability with a corresponding increase in apoptosis. These results further corroborate our findings in the current in vivo set up. It is obvious that Pb may not decrease the numbers of cells of the immune system (as indicated in the CBP assessments), however, it can alter the functioning/regulation of these cells – although further studies are needed for confirmation. It must be emphasized that Pb is a pro-inflammatory mediator (Dietert and Piepenbrink 2006, Metryka *et al*. 2018).

We also assessed the role of confounding factors and BLLs. Subjects aged >50 years had significantly higher BLLs (53.2 µg/dL). Age, profession (mechanics had higher BLLs) and education were strong predictors for lead toxicity. Taken together, this research findings indicate that Pb exposure is a major public health issue and calls for further detailed investigations with regards to understanding the cellular and molecular mechanisms of Pb-induced effects on the hematological system.

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