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Low Blood Lead (Pb) and Prolonged P Wave as Cardiotoxicity Indicator in 12-Lead Resting Electrocardiogram among Malaysian Adult

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Abstract: ***Background**: Cardiovascular diseases are the major causal factor of morbidity and death rate in the world. Premature death is believed to be associated with heavy metals exposure that should be identified as early at the reversible stage. In electrocardiogram, the P wave is among the suitable indicator. **Method**: This is a cross sectional study among a population in Selangor, one of the major state in Malaysia. It was carried out from January to December 2012 using purposive sampling to obtain blood samples and electrocardiogram reading. Data on sociodemography was obtained using a standardised validated questionnaire adopted for PURE study. **Results**: A total of 287 respondents was enrolled in the study, the majority of women aged between 35 to 70 years old. Nearly 52.8% of them have asymptomatic abnormal prolonged P wave. The median of blood Pb was 1.9µg/L (1.0 – 3.3µg/L). The area under curve (AUC) analysis using receiving of curve (ROC) revealed that the concentration of blood Pb of more than 2.9 µg/L associated with prolonged P wave. This point may be used as the cardiotoxicity cut off point of blood Pb among the respondents. The limit was so much lower than the standard of 100.0µg/L that have been adopted purposely to protect neurobehavioural problems. **Conclusion**: The present legislation limit of blood Pb is not protecting the population from the cardiotoxicity risk. The limit should be reviewed again in reducing premature death and CVDs problems.*

Keywords: Blood Pb, ECG, P wave, Cardiotoxicity, Indicator

1. Introduction

Cardiovascular diseases (CVDs) are identified as the main contributor to the worldwide morbidity and mortality by the World Health Organisation. It was about ten percent of the disease burden and 31% of all deaths, globally. [(1)]

Malaysia people were found to develop CVDs at the earlier age compared to the people of the United States and Australia. [(2)] More than sixty percent of them were aged less than 60-year-old, and it was presumed to be preventable. A local study revealed that for one premature death, it caused the nation to lose about RM600, 000.00. And the government had loss of RM66 billion and RM71 billion for the year 2004 and 2005 respectively, which that increasing every year. [(3)]

Conventional understanding has identified the relationship between CVDs with imbalance diet intake, lack of exercise, high blood cholesterol, and high blood pressure. However, more studies have demonstrated the smoking as one of the risk factors for CVDs. [(4-5)] There are more than 4000 chemicals like solvents and heavy metals present in the cigarette smoke. An example of the heavy metal is lead (Pb) that has found to have a significant association with the occurrence of CVDs. [(6-11)]
Lead (Pb) has multiple pathway of exposure, such as through oral ingestion, [(12-17)] and via respiratory inhalation. [(18-22)] Even though the cardiotoxicity mechanism is still not clear, but it may associate with oxidation caused by the heavy metal as an external oxidative stressor and the apoptosis mechanism. [(23-24)]

Electrocardiogram (ECG) has been used globally at all corners in screening and diagnosing CVDs. It has few wave indicators like P wave. The wave is generated during cardiac atrial node activation. In normal standard 12-lead, the height should equal or less than 0.2mV or 2mm with duration of less than 0.12 second. Prolongation of P wave indicates a delayed inter-atrial conduction which may be used as a predictor for CVDs. [(25-26)] This reversible ECG changes may be very useful as an indicator for early cardiotoxicity and for early intervention in preventing deaths due to CVDs. The determination of this relationship in the general population is important in recognising the early cardiotoxicity through a simple, non-invasive 12 lead-resting ECG.

2. Material and Method

The study adopted a cross-sectional survey design. It was conducted in a population in the state of Selangor using a purposive sampling together from January to December 2012. Verbal consent was obtained from each enrolled respondents and 12-lead resting ECG and 10mls of venous blood were taken from them.

The obtained venous blood was collected in EDTA metal free containers and keep under 4^{o}C until reaching the auxiliary laboratory that equipped with -22^{o}C freezer. The blood samples were kept frozen until further analysis using the inductively coupled plasma mass spectrometry (ICP-MS) for Pb concentration. The sociodemography data were obtained using a standardised questionnaire adapted from the Population, Urban and Rural Epidemiology (PURE) which was validated and been described elsewhere. [(27)]

The value adopted by the Agency for Toxic Substances and Disease Registry is 100.0µg/L as the normal limit for a general population. [28] The standard was based on the neurobehavioural effect of Pb on animal and human. However, knowing that Pb is non-threshold metal, the effects may be very low, even lower than the standard.

All information was calculated and analysed using the Statistical Package for Social Science (SPSS 21.0). Sensitivity and specificity values for the prediction equations in detecting subnormal P wave duration and blood Pb were calculated using Receiver Operator Characteristic (ROC) analysis. The value of $p < 0.05$ is considered as significant.

The study has approval and budget from the Research and Etiquette Committee, UKM Medical Centre with a research code of FF-2013-313. The protocol included the study description and respondent consents were obtained before the enrolment.

3. Results

A total of 287 respondents aged from 35 to 70 years of old was involved in the study. Most of them were women and aged between 41 to 50 year-old (Table 1). And about 52.8% of those respondents were found to have a prolongation of the P wave.

Table 1: Respondents characteristic according to the age groups (n=287)

Age Group (year)	*Frequency*	*Percentage*
≤ 40	31	10.8
41 – 50	98	34.1
51 – 60	81	28.3
> 60	77	26.8

For blood Pb concentrations, their standardised skewness and kurtosis coefficients were 9.58 and 10.05 respectively. Both parameters were not distributed normally since their coefficients were more than +/- 3.00. Therefore, median for blood Pb concentration was 1.9µg/L (1.0 – 3.3µg/L).

Figure 1 shows the receiver operating characteristic (ROC) curve for the prediction of prolonged P wave due to blood Pb. The area under the curve (AUC) of prolonged P versus blood Pb was 0.579 (0.519 to 0.638) with p=0. 0202. The Youden index computed was 0.16 at the point of blood Pb of ≤ 2.9µg/L. This indicates that the blood concentration of Pb more than 2.9µg/L was significantly associated with prolongation of the P wave. The criterion was lower than the minimum concentration limit (MCL) of blood Pb of 100.0µg/L. Therefore, the current MCL is higher and inaccurate in view of the protection of cardiotoxicity due to Pb exposure.

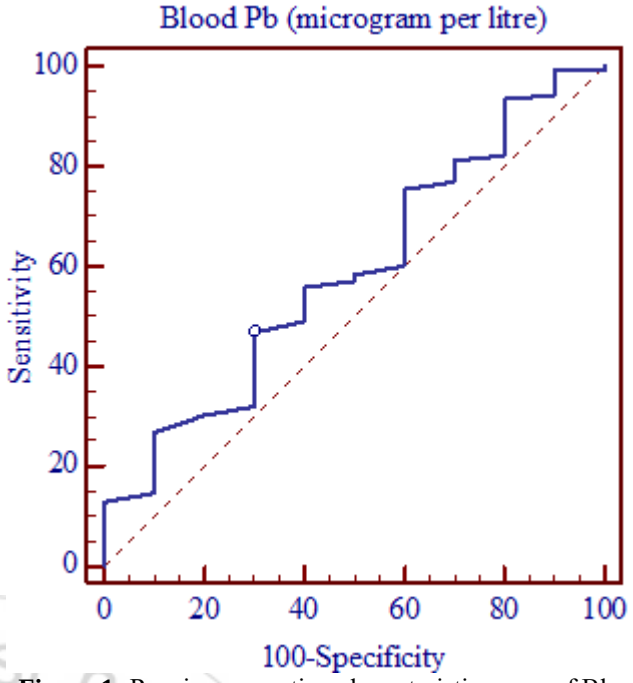

Figure 1: Receiver operating characteristic curve of Blood Pb and Prolongation of P wave

4. Discussion

Most of the data were skewed and not normally distributed. Thus, non-parametric tests were applied during the analysis using SPSS 21.0. To identify the most sensitive and significant ECG indicator for metals cardiotoxicity, MedCalc software was used to determine the area under the curve (AUC) for the receiver operating characteristic curve (ROC).

The P wave was found to be a good and sensitive biomarker for the cardiotoxicity and its level of 2.9µg/L is identified as the lowest effect concentration for ECG abnormality. This concentration was very much lower than the guideline limit of 100.0µg/L of blood Pb. Therefore, the existing limit was found not effective in protecting the study population towards abnormal P wave as one of the indicators for the cardiovascular toxicity. In addition, P wave prolongation was identified as the commonest changes seen among the subject. It is a sensitive biomarker for cardiotoxicity for metals exposure, particularly to Pb.

5. Conclusion

The present limit of 100µg/L of blood Pb is not protecting the population from cardiotoxicity. The 12-lead resting ECG should be used more frequently as it is well known to be a good screening tool for the cardiovascular diseases among the general population. Based on the result, this study recommended for the revision of the present blood Pb limit and an expansion of resting ECG uses for cardiotoxicity screening due to Pb and other heavy metals exposure. The screening should be started as early at 35-year-old for early detection of abnormal ECG to prevent premature deaths. The P wave should be a good sensitive biomarker for the cardiotoxicity due to metal effects.

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