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ORIGINAL ARTICLE

Cadmium Levels in Premature Infants Exposed to Blood Transfusion

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Abstract

Background: **Cadmium is a neurotoxin, especially to developing brains. Due to their still-developing nervous systems and blood–brain barrier, very preterm newborns are particularly susceptible to the effects of neurotoxic substances.**

Aim: **To determine the relation between pre/posttransfusion erythrocyte cadmium levels in premature infants and its concentrations in the packed red blood cells donated by smokers and non-smoker blood donors.**

Patients and methods: **A case–control study included 30 premature infants from the NICU. All of the donated blood were examined for hepatitis C virus (HCV), hepatitis B surface antigen (HBs Ag), HIV and syphilis auto Ab before use. Blood samples were collected before and 6 h after blood transfusion from 15 premature infants transfused by smokers' blood and 15 premature infants transfused by nonsmokers' blood.**

Results: **The mean of cadmium percent changes before and after blood transfusion is significantly greater in group I than group II (480 % vs. 129 %) (P value = 0.000). There was a significant association amongst gestational age, neonatal weight and volume transfused with cadmium level after transfusion (P value = (0.012, 0.002 and 0.01)).**

Conclusion: **The packed red blood cell (PRBCs) donated by smokers are a source of cadmium that is probably not safe for transfusion in premature infants.**

Keywords: Blood transfusion, Cadmium, Premature infants

1. Introduction

All living things contain metals and metal complexes, which have a wide variety of important functions. Nonetheless, they can be harmful if ingested in large quantities. Cadmium, mercury and lead are all considered xenobiotics due to their extreme toxicity.[1]

Polluted air, cigarette smoke and plant roots are the primary pathways for cadmium to enter the human body.[2]

Many adverse consequences on human health have been linked to the aforementioned metal. Kidney and bone damage are the most common results of cadmium overdose. Järup suggested it might cause behavioural issues, trouble focusing and learning and lowered IQ.[3]

Metal content examination in bodily fluids and tissues (such as urine, blood, and hair) can reveal intoxication levels and potential health effects.[4]

Most metals, once in the bloodstream, attach themselves to morphotic components, particularly erythrocytes Red blood cell (RBC).[5]

Researchers discovered that infants are especially susceptible to metal poisoning.[6] Very-low-birth-weight (VLBW) newborns in the NICUs have a disproportionately high rate of anaemia (NICU). Repeated blood collection for laboratory analysis, anaemia of prematurity, infections and bone marrow suppression cause over 80 % of babies to need at least one packed red blood cell (PRBC) transfusion. Heavy metal overload via PRBC transfusions, in addition to other adverse outcomes, can be considered a hidden threat.[7]

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Early-life exposure to heavy metals (i.e. lead and mercury) has long been known to be neurotoxic, yet the placenta is a good barrier for a large variety of hazardous materials in foetal development. Due to their still-developing brains and blood–brain barrier, very preterm newborns are especially susceptible to the effects of neurotoxic chemicals.[8] We aimed in this research to determine the relation between pre/post-transfusion erythrocyte cadmium levels in premature infants and its concentrations in the packed red blood cells donated by smokers and nonsmoker blood donors.

2. Patients and methods

A case–control study included 30 premature infants from the NICU in the outpatient clinic and inpatients at Al-Azhar University Hospital and Al-Iman General Hospital from August 2020 to August 2021.

Inclusion criteria: Newborns between 32 and 36 weeks of gestation that require a blood transfusion. Also, the blood is taken from smoking and nonsmoking blood donors.

Exclusion criteria: Premature infants were excluded from this study when they had past history of blood transfusion, premature infants below 32 weeks or above 36 weeks.

Participants were randomly chosen from a group of eligible blood donors. 30 Donors were donated blood at Al-Azhar University Blood Bank and Al-Iman General Hospital Blood Bank. In total, 15 donors were cigarette smokers and the other 15 donors were non-smokers. All of the donated blood were examined for hepatitis C virus (HCV), hepatitis B surface antigen (HBs Ag), HIV and syphilis auto Ab before use.

Eligible participants included all LBW babies who were admitted to the NICU and eventually went home. Each new-born received between 15 and 20 ml/kg of PRBCs, based on the patient's gestational age, current weight and transfusion volume, as recommended by our institution's guidelines. The total volume of PRBCs varied between 30 and 55 ml.

The average time between diagnosis and PRBC transfusion was 8.5 ± 6.6 days. In the first 4 weeks of life, 43 (43.3 %) babies received their first transfusion, followed by 12 (40 %) in the second week, three (10 %) in the third week and one (3.3 %) in the fourth week.

2.1. Blood specimen collection

Before and about 6 h after transfusion, about 2 cc of blood was taken from each infant. The levels of cadmium in the PRBC donations were also measured. The samples were gathered in ethylenediaminetetraacetic acid (EDTA) glass tubes for analysis. The test tubes had been labelled, numbered and protected from the elements. The samples were then frozen at 20 °C until analysis.

2.2. Assay procedure

The Assiut University Faculty of Medicine's Toxicology and Forensic Chemistry Laboratory measured the cadmium (Cd) levels in the samples (in micrograms per millilitre). After being treated with nitric acid and peroxide (5 ml of HNO_3, 2 ml of H_2O_2 to 1 ml of blood), blood samples were gently heated on a hot plate for about 30 min, during which time their volume was reduced to 1 ml. The amount of cadmium in digested blood was calculated using the AA240zeemen method of atomic absorption spectrometry (Agilent GTA 120, Australia). For the purpose of creating the elements' functional standard solution, only certified standard solutions of the elements were used.

2.3. Calculation of results

Transfusions administered during a period of less than or equal to 6 h were counted as an IV dosage of Cd for calculating neonatal exposure from PRBC transfusions based on donor PRBC concentration. The metal dose was calculated using the donor PRBC Cd (μg/L) concentration, the total volume transfused and the infant's weight. The following formula was used to determine metal exposure due to transfusion: PRBC metal level (μg/mL)/weight (kg) × volume transfused (in mL) = μg/kg/day.

The Al-Azhar University (Assiut Branch) Faculty of Medicine Research Ethics Committee reviewed and approved the updated study protocol.

2.4. Statistical analysis

SPSS version 22, a statistical tool for the social sciences developed by IBM SPSS Inc. in Chicago, was used to analyse the data. The gathered information was cleaned, coded and sorted in order to be analyzed statistically. The median and/or mean and standard deviation (SD) were used to describe the data (minimum–maximum). The P value used to determine significance was less than 0.05. The change in blood calcium level (BCL) levels before and after transfusion was graphically shown using box-and-whisker graphs for both groups.

3. Results

In this study, we enrolled 30 premature infants (18 males and 12 females) from the NICU. We divided them into two groups, group I included 15 infants: 10 males and 5 females (received PRBC transfusion from smoking donors) and group II included 8 males and 7 females (received PRBC transfusion from nonsmoking donors). The mean gestational age of the studied neonates in groups I and II had no significant differences (34.00–33.73) (P value = 0.613). The mean weight of the studied neonates in groups I and II had no significant differences (2.29–2.17) (P value = 0.245) as shown in Table 1.

The mean of In-PRBC Cd level was significantly greater in group I than group II (1.3 ± 0.34, 0.42 ± 0.07 and P = 0.000, respectively). There was no significant difference among both groups regarding neonates' pre-transfusion Cd levels. However, neonates post-transfusion Cd levels were significantly higher in group I than group II (0.70 ± 0.14, 0.32 ± 0.07 and P = 0.000, respectively). There was a significant difference in Cd levels between pre transfusion and post transfusion (P = 0.001). The mean of cadmium percent changes before and after blood transfusion is significantly higher in group I than group II (480 % vs. 129 %) (P value = 0.000) (Table 2).

There is a significant difference in the mean dose of cadmium per transfusion between groups I and II (0.26 μg/kg vs. 0.08 μg/kg) (P value = 0.000) (Table 3).

There was a significant relationship among BCL in PRBC packets and infant's BCL% change and infant's BCL after transfusions (P value = 0.000) (Table 4).

There was a significant relationship among gestational age, neonatal weight and volume transfused with cadmium level after transfusion (P value=(0.012, 0.002 and 0.01)), (Table 5).

Table 1. Comparison between both groups regarding demographic data.

Personal data	Group I (n = 15)	Group II (n = 15)	P value
Sex No (%)			
Male	10 (66.7 %)	8 (53.3 %)	0.456
Female	5 (33.3 %)	7 (46.7 %)	
Gestational age (weeks)			
Mean ± SD	34.00 ± 1.51	33.73 ± 1.33	0.613
Range	32.0–36.0	32.0–36.0	
Weight (kg)			
Mean ± SD	2.29 ± 0.33	2.17 ± 0.21	0.245
Range	1.7–2.8	1.8–2.6	

Table 2. Cadmium levels and percent change distribution of the premature infants in the studied groups.

Cadmium level	Group I (n = 15)	Group II (n = 15)	P-value*
In-PRBC Cd levels (μg/L)			
Mean ± SD	1.3 ± 0.34	0.42 ± 0.07	0.000*
Median (range)	1.32 (0.73–1.80)	0.42 (0.33–0.54)	
Neonates' pre-transfusion Cd levels (μg/L):			
Mean ± SD	0.13 ± 0.34	0.15 ± 0.05	0.456
Median (range)	0.12 (0.08–0.2)	0.17 (0.08–0.2)	
Neonates' post-transfusion Cd levels (μg/L)			
Mean ± SD	0.70 ± 0.14	0.32 ± 0.07	0.000*
Median (range)	0.75 (0.41–0.88)	0.34 (0.23–0.43)	
P-value[2]	0.001*	0.001*	
Percent of change:			
Mean ± SD	480 ± 184	129 ± 48	0.000*
Median (range)	420 (258–890)	112 (65–243)	

*: Significant P value < 0.05.

Table 3. Cadmium dose/kg/transfusion in both studied groups.

Dose of cadmium	Group I (n = 15)	Group II (n = 15)	P-value
Cadmium dose:			
Mean ± SD	0.26 ± 0.07	0.08 ± 0.02	0.000*
Median (range)	0.26 (0.14–0.38)	0.08 (0.05–0.11)	

*: Significant P value < 0.05.

Table 4. Correlation between blood cadmium levels in packets and blood cadmium levels% change and BCL after transfusion.

	BCL in PRBCs (μg/L)	
Infants' BCL% change	P-value	0.000*
	r-value	0.823
Infants' BCL after transfusion (μg/L)	P-value	0.000*
	r-value	0.94

BCL, blood calcium level.
*: Significant P value < 0.05.

4. Discussion

Cadmium is a powerful poison that can cause birth defects. Cd permeability through the placenta varies. Cd has been found in cord blood, despite research showing that it is transported less easily across the placenta. Cigarette smoke contains Cd, which also contaminates air, land and water.

Table 5. Correlation of gestational age, weight, hemoglobin level and volume transfused with cadmium level after transfusion (total cases).

	Cadmium level after transfusion (μg/L)	
Gestational age (weeks)	P-value	0.012*
	R-value	0.451
Neonatal weight (kg)	P-value	0.002*
	R-value	0.532
Hemoglobin (g/dl)	P-value	0.662
	R-value	0.083
Volume transfused	P-value	0.01*
	R-value	0.45

Cd, cadmium.
*: Significant P value < 0.05.

Research has linked prenatal exposure to mental retardation, dyslexia and anxiety.[9]

VLBW new-borns may be exposed to Cd through packed red blood cell infusions. At this formative period of brain growth and neurodevelopment, the preterm infant is especially vulnerable to the effects of this neurotoxicant. Although population-based reference dosages and means have been developed for older children and adults, it is unclear what doses are safe for the very-low-birth-weight new-born. Due to immature and developing metabolic mechanisms, premature new-borns have a reduced capacity to digest and eliminate toxicants. Thus, the risks of neurotoxicity in this population are probably underestimated using reference levels determined to be safe for older children and adults.[10]

Our study revealed that PRBC transfusions are potentially a significant source of heavy metal (cadmium). This was evidenced by the increase in blood Cd levels proportionally to the metal amounts in the PRBC-transfused units most specially in PRBCs of smoking donors.

Cigarette smoking is widely recognized to raise the Cd level in blood donors.[11] According to research by Averina et al.,[12] vulnerable patient populations, such as premature new-borns, face an increased risk of exposure to Cd because of transfusions. Just 4 % of donors had cadmium levels below the minimum of 16 nmol/L.

Our study showed a positive correlation between increased Cd level postblood transfusion in relation to premature infant's age but not with gender. Liu et al.[13] say that no gender-related differences were found for Cd concentrations and that blood Cd concentrations were positively correlated with age.

In our study, we found that the mean of BCLs in premature infants was 0.17 (0.08–0.2) μg/l. As shown in Laamech et al.[14] study, the mean of BCLs in kids was 0.221 μg/L. The mean of our study is lower than Laamech study due to lower age of our infants than his children aged 6–12 years.

According to the results of this research, there was a statistically significant relationship among cigarette smoking and elevated cadmium levels in blood samples. Smokers have two to three times the amount of cadmium in their blood than non-smokers. Blood cadmium concentrations were observed to be higher in smokers compared with non-smokers by both Erzen and Kregelj.[15]

As this study showed that cadmium levels were strongly associated with smoking with a mean 1.32 μg/L than in nonsmokers with a mean 0.42 μg/L. Cadmium levels were strongly associated with smoking, cadmium levels were significantly higher in current smokers relative to never-smokers (1.64, 0.21 (μg/L), respectively). Garner et al.[16] study confirmed higher blood levels of cadmium in the blood of smokers (1.5 times higher than in non-smokers), statistically significant differences were observed between Cd blood levels in smokers and non-smokers in studies done by.[17–19]

Donor Cd levels were compared with national averages using data from the National Health and Nutrition Examination Survey (NHANES) 2013–2014, which was conducted to evaluate the health of the general US population. Donor blood had a mean Cd content of ±0.46 μg/L, which is greater than the 0.30 μg/L threshold used in the assay.

Our study showed that blood Cd dose in infants transfused blood from smokers was 0.26 (0.14–0.38) μg/kg/day that is higher from the estimated intravenous reference doses (IVRfDs) 0.1 μg/kg/day for Cd. Falck et al.[10] found that Cd levels in premature infants after receiving PRBCs were not greater than the estimated IVRfD 0.1 μg/kg/day for Cd, because their research was not conducted on smoking donors and Cd levels are not as high in Egypt, they conclude that PRBC transfusion may not constitute a substantial source of exposure to Cd.

The hazard quotient (HQ) has risen to 52.5 due to the added exposure through smoking, as shown in a recent study by Wu et al.[20] The HQ is 2.56, and the percentage of noncancer risk attributable to food consumption is 16.4 %. The dramatic increase in HQ from 2.96 to 52.5 indicates that cigarette smoking is a greater risk to human health than ingesting Cd through food or any other method.

4.1. Conclusion

The PRBCs donated by smokers are a source of cadmium that is probably not safe for transfusion in premature infants.

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Nil.

Authors' contribution

D A G: idea formulation, data collection, analysis and writing. W E A: data collection and writing. A M M H: supervision, writing and revision. M M A: supervision, writing and revision.

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Nil.

Conflicts of interest

Nil.

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