CLINICAL RESEARCH ARTICLE

Lead: a hidden “untested” risk in neonatal blood transfusion

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BACKGROUND: Neonates may be exposed to lead (Pb) through blood transfusions from donors. Pb exposure has neurological, cardiovascular, renal, and other adverse effects. The study aimed to (i) determine the blood lead levels (BLLs) in different blood product units (whole blood, packed red blood cells (pRBCs), platelets, and plasma transfused to neonates) and (ii) estimate the proportion of units with high BLLs.

METHODS: Residual blood from blood bank bags that were used for neonatal transfusion were collected: 25 samples from each type of blood product except for whole blood (10 samples). The Pb analysis was performed using the atomic absorption method. The study was conducted at the Suez Canal University Hospital, Egypt.

RESULTS: The mean of BLL in pRBCs, platelets, plasma, and whole blood were 136, 199, 108, and 130 µg/L, respectively; 60% contained Pb above 50 µg/L. The highest BLLs were in platelet units.

CONCLUSIONS: The present study showed for the first time that platelets and plasma in addition to whole blood and pRBCs used for neonatal transfusions are sources of Pb. Re-evaluation of the guidelines is mandatory for the safety of the neonates. Long-term neurodevelopment assessment of neonates exposed to high Pb is warranted.

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INTRODUCTION

Lead (Pb) exposure is a child health concern worldwide; this problem is intensified in developing countries.¹ Preterm neonates comprise the most heavily transfused group of patients.² The critical stages of growth and cellular differentiation that occur in fetuses and neonates represent periods of greatest vulnerability to the adverse effects of environmental toxicants.³ Pb exposure in neonates has particularly been associated with long-term neurotoxic effects during the critical period of rapid brain development.⁴ Based on Canadian health risk assessment study, the maximum level of Pb in a blood donation that could safely be given to the vulnerable patients should not exceed 30 µg/L.⁵ Nevertheless, another study recommended that blood units used for young children should be screened for Pb to warrant concentrations <18.6 µg/L, and achieve the lowest possible Pb exposure.⁶

Pb is a potent irreversible neurotoxicant and exposure leads to developmental delay with effects on cognition, behavior, and intelligence quotient (IQ) with an unexpectedly great impact even at low levels.⁷ This has prompted the Centers for Disease Control and Prevention (CDC) not only to further decrease the reference cut-off value for toxic blood lead levels (BLLs) (from 100 to 50 µg/L) in children, but also to question the term “blood lead level of concern” under the assumption that there is no safe BLL.⁸ Pb neurotoxicity occurs at a cellular level on several parts of neurite growth in the developing brain. It causes direct damage to neuron synaptic development and myelin formation. The effect of Pb may be through interference in the cell to cell connectivity.^{9,10} Pb moves from the blood into soft tissues and bone with slow release over time.⁴ The amount of Pb absorbed is inversely related to chronological age.⁸ Both gastrointestinal absorption of Pb and its

accumulation in bone are higher in infants (potentially causing growth impairment and calcium deficiency) than in adults.¹¹ Moreover, children retain more Pb in soft tissues as compared to adults,³ and selective brain accumulation in the hippocampus can occur. Little to no information is available for the burden and impact of Pb exposure in preterm infants.¹²

Recently, two studies measured the BLLs in transfused whole blood and packed red blood cells (pRBCs) in USA and Canada.^{6,12} They found significant BLLs in transfusion products. As a consequence, Zubairi et al, recommended and invited the researcher to investigate BLLs in the other transfusion products (such as platelets and plasma) to obtain an accurate measurement of exposure.¹²

Up to authors' knowledge, no previous study was performed in Egypt to assess the prevalence of Pb exposure among blood product units that are prepared for neonatal transfusion. Moreover, no previous study measured Pb in blood products other than whole blood and pRBCs. Therefore, the aim of the study was to (i) determine the BLLs in various blood products (whole blood, platelets, pRBCs, and plasma) which are prepared for blood transfusion for neonates (ii) estimate the proportion of units with high BLLs, (iii) explore predictive factors of high BLLs, and, (iv) calculate the expected Pb load per transfusion.

MATERIALS AND METHODS

The samples were obtained from residual blood units of different blood products in the Suez Canal University Hospital (SCUH) blood bank. The SCUH is a referral center and receives donors from different eastern regions of Egypt, mostly Ismailia and Sinai governorates. The blood units were prepared for transfusion to

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Table 1. Demographic characteristics of blood donors and blood lead levels

Variables	N (%)	Median	Mean	P value	% 50–100 µg/L	% >100–150 µg/L	% >150 µg/L
Age							
≤20	8(9.4)	40	161.2	0.401	—	—	37.5
>20–30	32(37.6)	56.7	101.1		15.6	12.5	28
>30–40	36(42.4)	93.1	178.6		18.4	10.5	36.8
>40–50	9(10.6)	70.8	94.1		33.3	22.2	11.1
Sex							
Male	70(82.4)	9	16	0.001 ^a	27	8.5	37.1
Female	15(17.6)	4	5		0	13.3	6.6
Residence							
Rural	29(34)	129.5	515.5	0.021 ^a	24	7	48.3
Urban	56(66)	60	385.7		16.1	14.2	25
Blood group type							
A	22(25.9)	120	170	0.473	13.6	13.6	54.5
B	33(38.8)	60	140		12	9	45.5
AB	9(10.6)	70	120		44	0	33
O	21(24.7)	60	110		38	9.5	14
Rh group							
+	68(80)	80	150	0.182	20.6	10	35
–	17(20)	60	90		20	5.9	24.5
Blood products							
pRBCs	25	85.7	136	0.032 ^a	18	8	36
Plasma	25	56.7	108		28	8	20
Platelets	25	140	199		8	24	48
Whole blood	10	42.5	130		10	10	20

^aStatistically significant determined by Kruskal–Wallis test ($p < 0.05$)

the neonates in the neonatal intensive care unit (NICU). The total number of collected samples was 85 which were divided into 25 samples from each type of blood product (pRBCs, platelets, and plasma), except for whole blood (10 samples). The samples were transferred into trace-mineral-free vacutainers and subsequently stored at -20°C before analysis. Routinely collected data from blood donors in SCUH blood bank were obtained by chart review, it included, age, sex, residence, blood group type, and type of blood product obtained.

The digestions of samples were done as suggested by the National Institute for Occupational Safety and Health using $\text{HNO}_3/\text{HClO}_4/\text{H}_2\text{SO}_4$, and heat. The analysis of extracted samples was performed using atomic absorption (AAS) (Thermo S4AASystem “GE711838”).^{13,14} Analysis of each sample was conducted using a replication procedure (three replicates), and the mean of the repeated measurements was taken as the result value. The replicates had good reproducibility (intra- and inter-day coefficient of variations (CVs) and bias less than 10%). The limit of detection was 20 µg/L. The AAS is routinely calibrated before any batch of samples. The mean recovery rate is 90%. To ensure the quality of results, quality control (QC) samples were blindly inserted every 20 samples. It is recommended that the BLLs in transfused units would be less than 30 µg/L,⁵ with probable risk if the donor’s BLL was more than 60 µg/L.¹¹

Data entry was performed using windows operating system, and data analysis was performed using the statistical package for social sciences (SPSS version 22). Descriptive statistics: median and mean are calculated for the detectable values of Pb concentrations to determine the distributions of blood product Pb levels (BLLs). Kruskal–Wallis (KW) test was used to compare BLLs which were not normally distributed. Multivariable linear regression and logistic regression analysis were performed to

identify the independent BLL predictors and explore the associations with these factors at BLLs of different high levels (≥ 150 , ≥ 100 , and ≥ 50 µg/L).

The quantity of transfused Pb was estimated using transfused volumes. The study was approved by the Research Ethics Committee (REC) at the Faculty of Medicine, Suez Canal University.

RESULTS

The mean of BLLs in different blood products ranged from 108 to 199 µg/L. The highest mean and median BLL recorded among platelet units were 199 and 140 µg/L, respectively. Estimated proportion of BLLs above 150 µg/L in different blood products varied from 20 to 48 % (Table 1).

The frequency distributions of BLLs in the four studied blood products are presented in Fig. 1. BLLs above 150 µg/L were found in 27 (31.8 %) of the participants. The number of participants with BLLs above 100 µg/L and 50 µg/L were 37 (43.5 %) and 51 (60 %), respectively.

The average total Pb load per transfusion of each blood product is presented in Table 2. The highest Pb load per transfusion was associated with whole-blood exchange transfusion and platelets transfusions.

The distributions of BLLs according to age, sex, residence, blood groups (ABO & Rhesus (Rh) factor), and blood products are shown in Table 1. The mean age of donor participants was 30 years (SD, ± 8.9 years). In summary, 82.4% of the participants were males, 66% reside in an urban area, 38.8% were blood group type B, and 80% were Rh factor positive.

The results of the univariate analysis are shown in Table 1. Statistically significant differences in BLLs were found between subgroups for sex, residence, and the type of transfused blood

Fig. 1 Distribution of blood lead levels (BLL) among various blood product units; data are shown as median values (horizontal lines), interquartile ranges (the box lengths), extreme values (whiskers), outliers (o), and statistical significance (*). The difference between four blood products is statistically significant ($p = 0.032$)

Table 2. Calculated lead loading per transfusion for different blood products prepared for transfusion

Blood products	Loading Pb per transfusion (μg)	
	Median	Mean
pRBCs	51	81.6
Plasma	33.6	64.8
Platelets	84	119.4
Whole blood	51	156

(Lead (Pb) loading calculation: $\text{Pb transfused aliquot } (\mu\text{g/L}) \times \text{volume transfused (mL)} / 100 = \text{Pb load } (\mu\text{g})$)

products ($P < 0.05$). Estimated proportion of BLLs above 150 $\mu\text{g/L}$ ranged from 25 to 48.3% depending on an urban or rural residence of blood donors with higher BLLs among those who live in the rural area.

The logistic regression analysis for variables that are independently associated with BLLs above 50, 100, 150 $\mu\text{g/L}$ is presented in Table 3. The adjusted odds ratios (ORs) at $\text{BLL} \geq 100$ and 150 $\mu\text{g/L}$ ranked the highest for age but did not reach statistical significance, followed by blood group type A which was statistically significant at $\text{BLL} \geq 100$ and 150 $\mu\text{g/L}$. Results of the multiple regression analysis are presented in Table 4. All variables except for age justified 15.89% of the statistically significant variance observed.

DISCUSSION

The present study is the first to our knowledge that examined the BLLs in blood products other than whole blood and pRBCs. The results revealed that both platelets and plasma were other significant sources of Pb in blood prepared for neonatal transfusion. We also demonstrated that platelets exhibited higher Pb levels compared to other blood products. These findings are in contrast to the previously reported conclusions that most of the lead load was from the pRBCs.^{12,15}

In this study, the means of BLLs in different blood products ranged from 108 to 199 $\mu\text{g/L}$ with 43.5% and 31.8% of the samples' BLL more than 100 and 150 $\mu\text{g/L}$, respectively. A previous study of Egyptian children revealed mean BLLs of 48 $\mu\text{g/L}$, which ranged from 11 to 143 $\mu\text{g/L}$.¹⁶ The mean BLLs in the general Canadian population was 17 $\mu\text{g/L}$,⁶ which was comparable to a reported rate of 16.6 $\mu\text{g/L}$ in the United States.¹⁷ Similarly, Zubairi et al, reported the mean Pb load per transfusion was 13 μg

with a range from 0 to 86 μg .¹² However, in a metropolitan population in the United States; 2 and 0.5% of blood bags contained BLL of more than 50 and 100 $\mu\text{g/L}$, respectively.¹⁸ Another study including Pb levels in pRBC units transfused to extremely low birth weight neonates, reported concentrations that exceeded the estimated upper limit of acceptable concentration (ETC) in 26% pRBC units; which comprised 84% of units with at least one heavy metal above the ETC (aluminum, arsenic, beryllium, cadmium, manganese, mercury, nickel, lead, and polonium).¹⁹ Lead exposure had been an environmental problem in the Southern regions of China secondary to the high e-waste disposal and occupational exposure.^{2,20,21} A study in China revealed that the average BLLs in children was more than 60 $\mu\text{g/L}$, with 7–10 % of children having BLLs above 100 $\mu\text{g/L}$.¹ Higher BLL mostly related to high environmental exposure were reported in developing countries. A regional study in Morocco reported a mean BLLs of 87 $\mu\text{g/L}$.²² A Brazilian survey among blood donors demonstrated 5% of tested BLLs contained 100 $\mu\text{g/L}$.²³ However, BLL as low as 4 $\mu\text{g/L}$ were reported from a small sample study of blood donors in Poland.²⁴ In comparison to the reported BLL in the literature, the present study demonstrated a higher mean Pb load per transfusion that ranged from 64.8 to 156 μg within different blood products. This observation strongly suggests an alarmingly high Pb exposure in this study population. It is noteworthy to mention that 82.4% of blood donors were males in the present study which is in line with previously reported gender rates for blood donation in Egypt.²⁵ Males are more likely than females to donate blood as most females in the age interval 20–40 years—the most common donation age interval in the present study—are childbearing or lactating. Besides, females are deferred if they were found to be anemic in the blood donation screening process.²⁵

The high BLL in plasma in the present study could be due to a high level of exposure which corresponds to a relatively more substantial change in plasma Pb concentration, with a small change in whole-blood Pb concentration. This is due to the non-linear relation between whole-blood lead and plasma Pb at a high level of exposure.²⁶ Moreover, it is important to mention that the increase in the Pb plasma level could be due to potential Pb contamination from hemolyzed RBCs.²⁷ It is essential to be cognizant when deciding on plasma transfusion, as plasma Pb is the main biologically active compartment with greater bio-availability (diffusible form). Thus, it is available to cross cell membranes and influence other tissues' concentrations more directly, which in turn burdens the newborn body. Pb is bound in a slow-diffusible form with RBCs.^{28,29}

Previous studies reported that BLL in plasma comprises about 0.06–0.5%,³⁰ 0.1 to 0.4%,²⁹ and 0.2–0.8 % of whole BLLs.²⁷ The Pb concentration in RBCs is 2–3.5 times that in the blood.¹⁵ Moreover, the estimated RBCs-to-plasma lead ratio was 26.4:0.66 (about 40:1).²⁸ Those ratios were not estimated in the present study as not all four blood products' units were prepared from the same donor, unlike other studies that used corresponding donors with blood products.^{15,26–30} It is also notable to state that plasma-to-blood Pb ratio can vary quite widely within and among individuals.³¹ This may be owing to differences in toxicokinetics with respect to δ -aminolaevulinic acid dehydratase (ALAD) gene polymorphisms.³² In addition, BLLs in plasma and RBCs of different samples could vary according to the storage capacity of their RBCs, and/or to the binding capacity of some ligands in plasma.²⁸ The wide range of variance was also noticed regarding the ratio between Pb concentrations in RBCs and blood.¹⁵ By the estimation of Pb loading per transfusion, the whole blood and platelets could be of higher risk compared to other blood products due to the high volume required per transfusion in case of whole blood transfusion.

A unique finding of the present study is the significant higher BLLs reported from platelet units in comparison to other transfused

Table 3. Logistic regression analysis of BLLs among different blood product prepared for transfusion

Characteristics	<i>n</i>	≥150 µg/L			≥100 µg/L			≥50 µg/L		
		ORs	95%CI	<i>P</i>	ORs	95%CI	<i>P</i>	ORs	95%CI	<i>P</i>
Age										
≤20	8	8.39	0.57–123.72	N.S.	3.44	0.34–34.87	N.S.	0.38	0.05–2.96	N.S.
>20–30	32	4.92	0.44–55.14	N.S.	4.22	0.58–30.89	N.S.	1.10	0.19–6.33	N.S.
>30–40	36	7.80	0.746–81.59	N.S.	4.96	0.72–34.13	N.S.	1.44	0.26–7.90	N.S.
>40–50	9	—	—	—	—	—	—	—	—	—
Sex										
Male	70	0.114	0.014–0.92	0.041 ^a	0.250	0.07–0.964	0.044 ^a	0.115	0.02–0.37	0.001 ^a
Female	15	—	—	—	—	—	—	—	—	—
Residence										
Rural	29	2.73	0.95–7.84	N.S.	2.43	0.88–6.65	N.S.	2.84	0.95–8.46	N.S.
Urban	56	—	—	—	—	—	—	—	—	—
Blood group type										
A	22	6.5	1.29–33.07	0.02 ^a	6.216	1.43–27.08	0.015 ^a	1.58	0.39–6.25	N.S.
B	33	3.98	0.90–17.65	N.S.	2.89	0.79–10.51	N.S.	0.80	0.25–2.64	N.S.
AB	9	3.92	0.54–28.53	N.S.	1.92	0.30–12.12	N.S.	2.48	0.36–17.24	N.S.
O	21	—	—	—	—	—	—	—	—	—
Rh group										
+	68	0.42	0.09–1.79	N.S.	0.34	0.09–1.29	N.S.	0.60	0.19–1.93	N.S.
–	17	—	—	—	—	—	—	—	—	—
N.S. Non-significant										
^a Statistically significant (<i>p</i> < 0.05)										

N.S. Non-significant

^aStatistically significant ($p < 0.05$)**Table 4.** Association of BLL with risk factors based on a multiple regression analysis

Variables	F value	P value	R ² (%)
Sex	6.2	0.02 ^a	6.9
Age	0.201	0.655	0.24
Address	3.440	0.067	3.98
ABO group	2.119	0.149	2.49
Rh group	2.150	0.146	2.52
Total	3.35	0.01 ^a	15.89

^aStatistically significant ($p < 0.05$)

blood products. This sheds light on transfused platelet units which may carry an equivalent or higher risk of Pb exposure compared to pRBCs and other blood products. The elevation in cytosolic calcium (Ca^{2+}) concentrations is essential for platelet activation in thrombosis and hemostasis. It occurs through Ca^{2+} release from intracellular stores and Ca^{2+} entry through the plasma membrane. Lead mimics Ca^{2+} and enters the platelets, thus impairing calcium regulation.³³ The entry of Pb in the platelets could follow a similar mechanism, contributing to the high Pb levels in the platelet units. However, the exact means whereby Pb is high in platelets is unclear. Elevated BLL also can cause activation of protein kinase and reduction of nitric oxide. This lead to endothelial injury and impaired coagulation,³⁴ which poses a potential risk of transfusing Pb-laden platelets to thrombocytopenic neonates. Several studies have demonstrated that Pb caused alteration of platelet counts and indices in Pb-exposed workers^{35,36} and pre-school children living in Guiyu; one of the highest electronic waste and recycling areas in the world.^{20,21}

The results of this study are presented with several caveats. First, the small sample size of the different blood product units. Second, the four studied blood products were not consistently

obtained from the same donor; thus, we were unable to calculate plasma and platelets to whole-blood ratios. Third, there is a possibility of contamination of plasma and platelets units with red blood cells. Nevertheless, the RBCs are strictly checked in the centrifuged plasma and platelets units. Besides visual assessment,³⁷ the blood bank at the SCUH³⁸ routinely measure RBCs on a cell counter to ensure RBC counts <2 ml, adopting the guidelines of American Association of Blood Banks (AABB).³⁹ Overall, it is unlikely that minute volume contamination with RBC would cause the high reported Pb levels in the plasma and platelet units. Another factor to consider is, the limit of detection of our analytical method was 20 ug/L. This limit may underestimate the burden of lower BLL that could pose a potential threat to the transfused neonates.

In conclusion platelets and plasma in addition to pRBCs and whole blood used for neonatal transfusions are significant sources of Pb. Sixty percent of blood units had BLLs higher than the CDC defined toxic cut-off levels. The highest BLLs were in the platelet units. This could be reflective of the magnitude of this potential health problem in developing countries. Screening blood donors and the analysis of Pb in blood are recommended. Future long-term neurodevelopment assessment of neonates exposed to lead is warranted to determine the actual impact and health burden of this toxic heavy metal.

AUTHORS CONTRIBUTIONS

J.G.: revised the article critically for important intellectual content and final approval of the version to be published. S.A.: study design, acquisition of data, data analysis & interpretation, drafting the article and final approval of the version to be published. AO: conception, design, acquisition of data, drafting the article, and final approval of the version to be published. M.O.A.: collection and analysis of samples, final approval of the version to be published. D.M. data interpretation, editing and final approval of the version to be published.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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