Blood Lead Level

Among Paediatric Thalassaemia Patients

In

Kota Bharu, Kelantan

By

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List of Symbols, Abbreviations or Nomenclature

AAS	Atomic Absorption Spectrometry
BCE	Before Century Erra
BH	Berita Harian
BLL	Blood Lead Levels
CI	Confidence Interval
CDC	Centers for Disease Control
Hb	Haemoglobin
HUSM	Hospital Universiti Sains Malaysia
EPA	Environmental Protection Agency (United States of America)
NHANES	National Health and Nutrition Survey (United States of America)
RBCs	Red Blood Cells
UKM	Universiti Kebangsaan Malaysia
UPM	Universiti Pertanian Malaysia
WHO	World Health Organizations
α	Alfa
β	Beta
mg/dL	milligram per deciliter
ng/m^3	nanogram per cubic meter
μL	microliter
$\mu mol/L$	micromol per liter
$\mu g/dL$	microgram per deciliter

ABSTRAK

Latar belakang:

Keracunan plumbum telah diketahui sejak zaman dahulu lagi. Sehingga kini, keracunan plumbum masih merupakan masalah besar berkaitan kesihatan awam persekitaran di seluruh dunia. Plumbum boleh memberi kesan pada setiap peringkat umur baik pada manusia mahupun di kalangan binatang, akan tetapi keracunan plumbum boleh memberi kesan yang amat serius dikalangan kanak-kanak. Pendedahan kepada plumbum boleh berlaku melalui sistem pernafasan ataupun melalui pemakanan. Akan tetapi, menurut kajian yang diketuai oleh Bearer telah membuktikan bahawa pendedahan kepada plumbum boleh berlaku melalui proses pemindahan darah seperti yang telah beliau buktikan melalui kajian yang dijalankan terhadap sekumpulan bayi pra-matang yang memerlukan proses penambahan darah sepanjang tempoh rawatan mereka di unit rawatan rapi bayi.

Penyakit Thalasemia merupakan antara penyakit utama di negara ini di mana pesakit memerlukan proses penambahan darah sebagai rawatan utama. Sehubungan dengan itu, hipotesis telah dibuat bahawa golongan ini mudah mendapat pendedahan kepada plumbum melalui proses rawatan ini.

Objektif:

Mengkaji tahap plumbum di dalam darah pesakit Thalasemia yang bergantung kepada rawatan penambahan darah dan dibandingkan dengan golongan kontrol.

Tatacara:

Kajian ini dijalankan secara keratan rentas di Hospital Universiti Sains Malaysia, melibatkan pesakit yang dirawat di Unit Rawatan Harian Thalasemia, Wad dan Klinik Kanak-Kanak sepanjang bulan Mac 2009 hingga Ogos 2010. Sebanyak 90 sampel darah telah diambil dikalangan 45 pesakit Thalasemia dan golongan kontrol dimana golongan kontrol merupakan mereka yang memiliki umur dan jantina yang sama serta tidak pernah menerima proses rawatan penambahan darah. Sampel kajian seterusnya dianalisa menggunakan proses standard 'Atomic Absorption Spectrometer'.

Keputusan:

Hasil kajian mendapati bahawa keputusan tahap plumbum secara keseluruhannya adalah rendah (2.13 $\pm$ 1.72μg/dL) berbanding dengan tahap merbahaya yang telah ditetapkan oleh badan 'CDC'. Ia juga mendapati bahawa plumbum di kalangan pesakit Thalasemia adalah lebih rendah berbanding kontrol. Tiada hubungan secara langsung antara tahap plumbum berbanding umur pesakit dan juga tahap zat besi dikalangan pesakit Thalasemia.

Kesimpulan:

Kajian ini mendapati bahawa rawatan penambahan darah dikalangan pesakit Thalasemia tidak menyebabkan pesakit ini terdedah kepada paras plumbum yang tinggi di dalam darah mereka.

ABSTRACT

Summary:

Lead toxicity has been recognized for thousands of years. Today, lead toxicity is well documented and is recognized as a major environmental health risk throughout the world.

Lead affects humans and animals of all ages, but the effects of lead are most serious in young children. The route of lead exposure is primarily via inhalation or ingestion. However Bearer *et al* has shown that blood transfusion can be a source for lead exposure to premature infants.

Thalassemia is common in this country, and majority of patients are transfusion dependant, thus hypothesis been made that regular blood transfusion can represent a significant source of lead in our Thalassaemic patients.

Objectives:

To determine Blood Lead Level in Thalassaemic patients with regular blood transfusion and to compare means with non-Thalassaemic patients.

Method:

This was a cross sectional study, conducted at the Paediatric Thalassaemia Day Care Unit, General Paediatric Ward (Ward 6 Selatan) and Paediatric Clinic in Hospital Universiti Sains Malaysia (HUSM) from March 2009 until August 2010. A total of 90 patients were included, 45 were Thalassaemic transfusion dependant patients and the other 45 were control who were of same age and sex with patients group and never been transfused before. The blood lead samples were taken pre-transfusion for Thalassaemic patients group and random for control group. Samples were then analysed using standard Atomic Absorption Spectrometer analysis.

Results:

This study revealed that overall mean blood lead level (2.13 $\pm$ 1.72μg/dL) was low compared to standard CDC recommendations action plan levels. There was statistically significant difference between mean blood lead levels in Thalassaemic patients group (1.14 $\pm$ 0.85μg/dL) and control group (3.12 $\pm$ 1.81μg/dL). No correlations of age or serum ferritin level to blood lead level were found.

Conclusion:

This study shows that our Thalassaemic transfusion dependant patients do not have extra exposure to lead from their regular blood transfusion.

CHAPTER 1

INTRODUCTION

1.1 BACKGROUD

Lead is a natural compound that exists in elemental, inorganic, and organic forms. Lead is present in trace amounts in all soils, water, and foods. Lead is soft, malleable, and blue-gray in color and it is highly resistant to corrosion (Rania, 2004).

Lead toxicity has been recognized for thousands of years. In the second century BCE, the Greek physician, Discorides noted that lead makes the "mind give way." In the first century BCE, Marcus Vitruvius Pollio, the father of architecture, recommended that clay replace all of the lead-based water pipeline system in the Roman Empire because "lead destroyed the vigor of the blood," (Rania, 2004).

Today, lead toxicity is well documented and is recognized as a major environmental health risk throughout the world. Lead affects humans and animals of all ages, but the affects of lead are most serious in young children (Rania, 2004). Both occupational and environmental exposures to lead remain a serious problem in many developing and industrializing countries, as well as in some developed countries (Lee, 1999).

At high levels of human exposure, there is damage to almost all organs and organ systems, most importantly the central nervous system, kidneys and blood, culminating in death at excessive levels. At low levels, heme synthesis and other biochemical processes are affected, psychological and neurobehavioral functions are impaired, and there is a range of other effects (WHO, 1995).

The potential for adverse effects of lead exposure in children is heightened because of:

1. Intake of lead per unit body weight is higher for children than for adults.
2. Young children often place objects in their mouths, resulting in dust and soil being ingested and, possibly, an increased intake of lead.
3. Physiological uptake rates of lead in children are higher than those in adults.
4. Young children are undergoing rapid development, their systems are not fully developed, and consequently they are more vulnerable than adults to the effects of lead (WHO, 1995).

The route of lead exposure is primarily via inhalation or ingestions. It accumulates by the repeated exposures, potentially toxic to several organs and takes years to get rid of the excess lead.

Generally it is distributed among 3 main compartments; blood, soft tissues and bones. It is tightly bound in the skeleton forming 60-90% of total body burden. In blood, 90% of lead is bound to erythrocytes (Razak, 2006). Only about 10% of the ingested lead is absorbed in adult, however in children, the absorption can be as high as 50%. Lead absorption from the gut is increased by fasting as well as chronic deficiencies of any essential mineral, vitamins and proteins (Razak, 2006).

The half life of lead in our body is approximately 25-36 days in the blood, 40 days in the soft tissues and more than 40 years in the bones. Thus blood lead level may decline significantly while the body's total burden of lead remains heavy. It also appears in hair, nails, sweat, saliva and breast milk (Singh, 2007).

Furthermore, Bearer has shown that lead exposure to premature infants can occur through blood transfusion exceeding the acceptable daily intake values for lead and may result in unacceptably high post transfusion blood lead level (Bearer *et al.*, 2000).

Thalassemia is common in Malaysia, and majority of patients are transfusion dependant. From the finding in the above study done by Bearer *et al.*, there is a possibility that regular blood transfusion could represent a significant source of lead in these Thalassaemic patients.

In Malaysian Thalassaemia Registry, there were 4,793 registered patients of Thalassaemia Major and estimated around 3-5% (around 1.35millions) of our populations are Thalassaemia carriers, majority are Malays, Chinese and Kadazan-Dusun ethnics. (BH, 4/11/2010).

Up to date, HUSM has 54 registered paediatric Thalassaemia patients under regular follow-up in Paediatric Thalassaemia Day Care Unit. Their diagnosis mainly: Hb E β- Thalassemia which are the majority of the patients, Hb β- Thalassemia Major and Intermediate and also Hb H Constant Spring.

The patients were managed with 'hypertransfusion regime' whereby aims of pre-transfusion Haemoglobin levels are 9-10gm/dL and post-transfusion levels are 13.5-15.5gm/dL respectively (Paediatric Protocols for Malaysian Hospitals, 2nd Edition, 2008).

1.1.2 BACKGROUND OF THALASSAEMIA

Thalassaemia is a heterogenous group of disorders where there is total or partial deletion of globin chain genes, resulting in reduced rate of synthesis of normal α- or β-chains. This lead to unbalanced globin chain synthesis, causing damage to erythroid precursors and thus inducing ineffective erythropoiesis or causing injury to mature erythrocytes and inducing haemolytic anaemia (Hoffman, 2005).

Several types of Thalassaemia have been described; however the common types and of clinical importance are β-Thalassaemia, Hb E β-Thalassaemia and α-Thalassaemia.

α-Thalassaemia results from the reduced or absent production of α-globin chains. These α-globin genes are duplicated and located in the telometric end of the short arm of chromosome 16. α-Thalasssaemia is most commonly caused by deletions of large DNA fragments that involve one or both α-globin alleles.

The α-Thalassaemias can be generally categorized as silent carrier (1 gene deletion), α-Thalassaemia trait (2 genes deletion), Haemoglobin H disease (3 genes deletion), Haemoglobin H-Constant Spring (elongation of α-globin chains, causes ineffective production) and α-Thalassaemia Major (4 genes deletion, Bart's Hydrop Fetalis).

The β-Thalassaemia syndromes are much more diverse than the α-Thalassaemia syndromes because of the diversity of the mutations that produce the defect in the β-globin gene. To date, more than 200 Thalassaemic mutations have been reported. These mutations occur on the chromosome 11 that affect all aspects of β-globin production: transcription, translation and the stability of the β-globin product.

Clinically β-Thalassaemia syndromes can be divided into β-Thalassaemia trait, Thalassaemia intermediate and β-Thalassaemia major. In β-Thalassaemia trait, clinically patients are asymptomatic but may have mild or minimal anaemia. Patients who were diagnosed to have β-Thalassaemia Major usually presented early during infancy period with anaemia, growth retardation, distinctive facies and hepatosplenomegaly. They will require regular blood transfusions. In β-Thalassaemia intermediate, the clinical features are less severe and the patients require less frequent blood transfusion.

Splice-site mutations also occur and are of clinical consequence, when combined with a thalassaemia mutation. Three splice-site mutations occur in exon 1 of the β-globin gene. These mutations result in three different abnormal haemoglobins: Malay, E and Knossos.

Haemoglobin E disorder is the most common structural variant with Thalassaemic properties. Hb E is characterized by substitution of lysine for glutamic acid at position 26 of the β-globin chain. This mutation results in both qualitative and quantitative β-globin gene defect. It is the most common abnormal haemoglobin in Southeast Asia, reaching a carrier frequency of 50% (Wasi, 1981). Hb E β-Thalassaemia has variable clinical manifestations, from thalassaemia intermediate to severe transfusion dependant thalassaemia major.

In HUSM's Paediatric Thalassaemia Day Care Unit, the distributions of diagnosis are as follows;

β-Thalassaemia Major	: 10 patients (18.5%)
Hb E β-Thalassaemia	: 39 patients (72.2%)
Hb H Constant Spring	: 5 patients (9.3%)

However the above patients are those who come regularly for blood transfusion in Day Care Unit. There are also patients under Paediatric Hemato-Oncology clinic follow-up with diagnosis of β-Thalassaemia carrier or intermediate and also α-Thalassaemia carrier or traits. This group of patients has either never required or have infrequent blood transfusion.

The main treatment of Thalassaemia is blood transfusion and it is dependent on the type: β-Thalassaemia major; interval between transfusions varies from two to six weeks, β-Thalassaemia intermediate; late onset and milder form, symptomatic treatment and α-Thlassaemia; transfuse if symptomatic (James Green, 2000).

1.2 INCIDENCE AND CURRENT TRENDS OF LEAD POISONING

Incidences of lead poisoning in United States of America shows decreasing trends pattern according to increasing awareness in eliminating lead exposure to children (Figure 1.1).

The first NHANES survey (1975–1980) had indicated that of the 14 million children in the United States between 6 months and 5 years of age, 4% (or approximately 650,000 children) had a blood lead level above 30 μg/dL, a level that is associated with very clear toxicity.

The second NHANES survey (1991–1994) indicated that the situation had improved dramatically. In 1994, 7% (or approximately 900,000 children) had blood lead levels above 10 μg/dL (a level at which toxicity, if present, is mild and questionable), and only 0.1% (or 13,000 children) had blood lead levels above 20 μg/dL (the level at which the child should be brought to medical attention, according to the recommendations of the Centers for Disease Control (CDC) (Sergio, 2002).

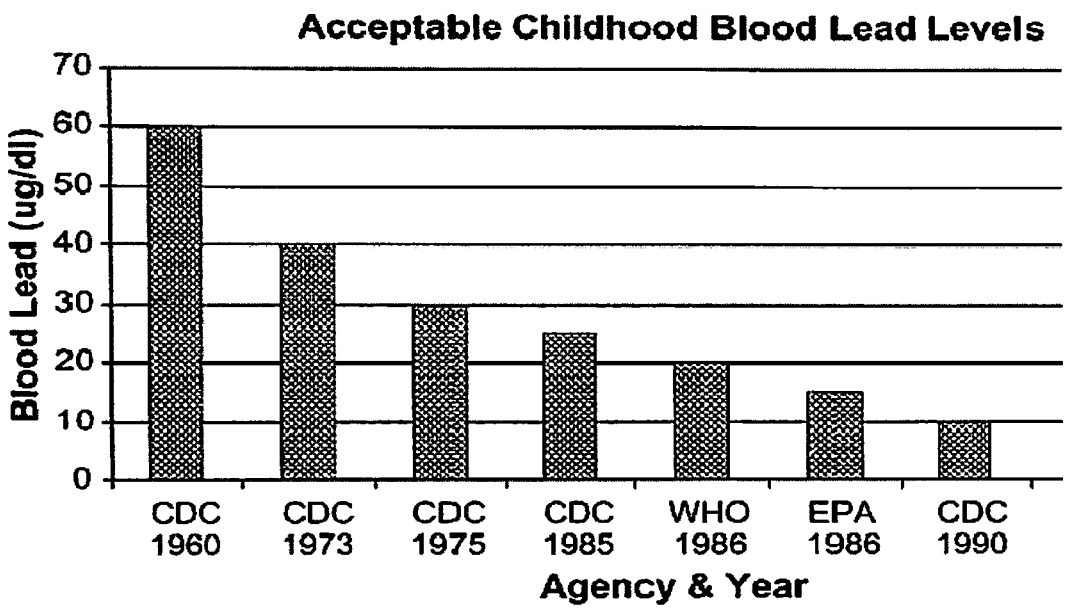

Figure 1.1 Acceptable childhood blood lead levels trend

Figure 1.1 showing the decreasing acceptable value of blood lead levels in children, based on survey and studies done by CDC, EPA and WHO.

Currently CDC recommends that the safe blood lead level in children is below 10μg/dL (CDC, 2002). Even though few researchers still argue this value and urge for further low safe value, this is the standard value accepted worldwide (Bernard, 2003).

Table 1.1 Current CDC management recommendations (CDC, 2002):

Blood lead level (μg/dL)	Actions	Time frame for beginning intervention
< 10	None	
10 – 14	Provide caregiver lead education. Provide follow-up testing Refer the child for social service if necessary	Within 30 days
15 – 19	Above action, plus: if BLLs persist (i.e 2 venous BLLs in this range at least 3 months apart) or increase, proceed according to actions for BLLs 20-44	Within 2 weeks
20 – 44	Above action, plus: provide coordination of care (Case management). Provide clinical evaluation and care. Provide environmental investigation and control current lead hazards.	Within 1 week
45 – 70	Above actions	Within 48 hours
> 70	Above action, plus hospitalize child for chelation therapy immediately	Within 24 hours

Studies on blood lead level in Malaysia are still very limited. The earliest study on blood lead level was done in 1982 by Lim *et al.*, among Malay pregnant women. It showed a statistically significant difference between the blood lead levels of urban women (17.3μg/dL) and rural women (15.5μg/dL) (Lim *et al.*, 1985). Subsequent study among Malay women in 1995 found a blood lead level of 4.5μg/dL (Moon *et al.*, 1996). This trend of decreased in blood lead level pattern were similar worldwide.

Studies in blood lead levels in Malaysian children are very limited. From extensive literature search there were only 3 studies found. The topics and results are summarized in Table 1.2 below.

Table 1.2 Studies on childhood blood lead levels in Malaysia

Years	Authors	Topics	Mean Blood Lead Levels (μg/dL)
2000	Jamal *et al.*,	Blood Lead Levels of Urban and Rural Malaysian Primary School Children	Kuala Lumpur (Urban): 5.26 Kemaman (Semi-urban): 2.81 Setiu (Rural): 2.49
2007	Elias *et al.*,	Relationship Between Blood Lead Concentration and Nutritional Status among Malay Primary School Children in Kuala Lumpur, Malaysia	3.4 ± 1.91 (standard deviation)
2008	Zailina *et al.*,	The Influence of Low Blood Lead Concentrations on the Cognitive and Physical Development of Primary School Children in Malaysia	Industrial area: 3.75 Urban area: 3.56

In the first study, Jamal *et al* from UKM (Universiti Kebangsaan Malaysia) examined respirable lead and blood lead of 346 school children from Kuala Lumpur (urban), Kemaman (semi-urban) and Setiu (rural). The objective was to study the influence of exposure and socio-economic variables on the blood lead level of Malaysian school children. The findings were: respirable lead and blood lead were highest for Kuala Lumpur ($95ng/m^3$ and $5.26\mu g/dL$) followed by Kemaman ($27ng/m^3$ and $2.81\mu g/dL$) and Setiu ($15ng/m^3$ and $2.49\mu g/dL$), and the differences were statistically significant. They also found that the percentage of school children with excessive blood lead of $10\mu g/dL$ or greater was 6.36% overall and highest for Kuala Lumpur (11.73%).

While in the second study by Elias *et al.,* from UPM (Universiti Pertanian Malaysia), they have done a cross sectional study to identify the relationship between blood lead concentration and nutritional status among primary school children in Kuala Lumpur. A total of 225 Malay students, 113 boys and 112 girls, aged 6.3 to 9.8 were selected. The mean blood lead concentration was low ($3.4 \pm 1.91\mu g/dL$) and was significantly different between gender. They also concluded that nutritional status might affect the children's absorption of lead.

In the last study, Zailina *et al.,* from UPM (Universiti Pertanian Malaysia) have done a study to determine the relationship between blood lead concentration and cognitive and physical development in school children. This study involved 169 urban children and 100 industrial children of Malay ethnicity, in the age range of 6.5 to 8.5 years old. The mean cognitive score (102.55) of the children from the industrial area was significantly higher than that of the urban children (95.09; $P<0.001$). However they found that there were no significant differences in the blood lead levels between these 2 groups (industrial 3.75μg/dL; urban 3.56μg/dL). They also found that there was significant inverse correlation between blood lead levels and cognitive scores for all children ($P<0.5$).

Overall, from the above three studies, we can concluded that the blood lead levels among children in Malaysia are less than standard value of 10μg/dL and are generally higher in the urban area.

Most of the studies also found that the blood lead levels are significantly decreasing in trend mainly due to more awareness and also due to introduction of the unleaded gasoline in the late 1990s (Zailina *et al*, 2008).

There is no study done yet regarding blood lead levels in children in Kota Bharu or Kelantan area. However there was one study done by Mohamad *et al.*,in adult age group with topic of 'Effects of very low Blood Lead level on neurobehavioral performances of Male Policemen in Kota Bharu, Kelantan which showed a mean blood lead concentration of 2.5 ± 1 μg/dL with no significant neurobehavioral performance (Mohamad *et al.*, 2004).