REVIEW ARTICLE

LEAD INTOXICATION: THE EXTENT OF PROBLEM AND ITS MANAGEMENT

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Lead is the most common heavy metal toxin and its toxic effects had been recognized for more than 2,000 years. It causes oxidative damage by disturbing the balance between prooxidants and antioxidants in favour of prooxidants. Lead is extensively used in Pakistan, because of its cost effectiveness, easy availability and resistance to corrosion. Few studies on lead intoxication have so far been conducted in Pakistan which reveal that blood lead levels of both general population as well as of the exposed groups are much above the internationally acceptable limits (10 µg/dl). The problem of lead intoxication can be fully controlled by removing it from the industry. However, like developing countries, use of lead in industry is on rise in Pakistan, causing toxicity to both general population as well as to the factory workers. Management of cases of lead intoxication relies on removing the stored lead in the body by chelation therapy. It involves oral or parenteral administration of chelating agents that form complexes with divalent cations including lead, and enhance their excretion by kidneys. The most common chelating agents used for the management of lead intoxication are Ethylene diamaine tetraacetate **(**EDTA), D-penicillamine, British anti lewisite (BAL), Dimercapto Succinic Acid (DMSA) and Dimercapto propane sulfonate (DMPS). However, chelation therapy has very high incidence of side effects inclucing death. Certain antioxidant agents, especially vitamins are being investigated to know if they can minimize the toxicity of lead by reducing the oxidative stress produced by lead. The results of vitamin C supplementation during lead exposure have revealed significant improvements and therefore need further evaluation to see if it can ameliorate the toxicity of lead in conditions of unavoidable exposure.
Keywords; Lead, blood lead levels, chelation therapy, antioxidants

INTRODUCTION

Lead is the most common heavy metal toxin for humans that has been mined and smelted, indeed, for at least 8,000 years. Egyptians used lead along with gold, silver, and copper as early as 5,000 BC. The technology of producing metallic lead by reductive melting in the presence of carbon sources slowly spreaded from China to Middle East and then to Africa during the VI and V millennia BC. During industrial revolution, lead was used widely because of its durability, malleability, low melting point, and ability to form compounds.[1]

The toxic effects of lead had been recognized for more than 2,000 years. Lead induced anaemia and colic's were known before 200 BC. Marcus Pollio, a 1st-century-BC Roman scientist, warned about the use of lead pipe for conveying water. Vitruvius referred the poor colour of workers of lead factories to the fumes of molten lead that destroyed the 'vigor of the blood'.[2]

Like other toxic metals, lead causes oxidative damage by disturbing the balance between prooxidants and antioxidants. It causes increased production of free radicals especially reactive oxygen species (hydroxyl ions, superoxide and hydrogen peroxide) and decreased availability of antioxidant reserves to respond to the resultant damage thus causing oxidative stress to the cells. The oxidative stress of lead causes damage to all components of the cell including cell membrane, proteins and nucleic acids.[3] Lead also replaces other divalent cations including calcium and zinc in the cell and inhibits various enzymes containing sulfhydral (-SH) groups, thereby interfering with the normal metabolic processes in the cell.

Lead accumulates virtually in every tissue of the body and effects almost all the body systems especially RBCs, liver, nervous system, gonads and kidneys. Blood lead level is the most reliable indicator of lead intoxication. In 1991, the Centres for Disease Control and Prevention (CDC) redefined the reference value of elevated blood lead levels (BLLs) from >25 µg/dl to >10 µg/dl[4]. Children are particularly susceptible to lead intoxication that causes various neurological and behavioural problems, ranging from raised hearing threshold to reduction in intelligence quotient (IQ) at low blood lead concentrations. Neurotoxicity and cognitive loss is a well-known side effect of lead even at low doses. The most severe sequelae of lead poisoning appears at levels of 70 µg /dl (3.4 µmol/l) and greater that includes papilledema, ataxia, afebrile seizures, apathy, loss of coordination various changes in mental status, coma and death.[1,5]

World Health Organization estimated that 120 million people had blood lead levels above the maximum acceptable limit (10 µg/dl) in 2000. Data for the children in this study showed that 99% of the children with blood lead levels above 20 µg/dl were residing in developing countries.[1] In developed countries, the use of lead had gradually been phased out during last 25 years whereas the problem of lead intoxication is on rise in the developing countries.

Extent of Lead Intoxication in Pakistan

In spite of lead being one of the most prevalent toxin, only few studies have so far been conducted in Pakistan. The published data indicate that blood lead levels of both general population as well as the exposed groups are much above the internationally acceptable limits (10.00 µg/dl).

In 1990, Manser *et al*. evaluated blood lead levels of healthy Karachi population. Mean levels for males, females, soldiers and school children were 34.4, 31.8, 29.9 and 38.2 µg/dl respectively. About 93% cases of either sex had elevated lead levels. Soldiers living in relatively pollution free area had levels lower than rest of the population but 91% soldiers did have levels over 25 µg/dl. Ninety-two percent children revealed levels above 25 µg/dl with a large number having levels over 40 µg/dl. A very small percentage had normal level.[6]

In 1994, Khan *et al*. carried out screening for chronic lead poisoning of lead factory workers which revealed that 100% of the factory workers had blood lead levels higher than the maximum acceptable limits.[7]

In 1995, Khan *et al*. measured the blood lead level, haemoglobin, and urinary amino-levulinic acid (ALA) in industrial workers and individuals exposed to vehicle smoke. Both groups had comparatively higher blood lead levels than the controls ($p<0.0001$) while urinary ALA level of industrial workers was 3.82 mg/dl and of traffic exposed people was 3.68 mg/dl as compared to the controls 0.8 mg/dl ($p<0.001$).[8]

In 1996, Hafeez *et al*. investigated 92 (50 males and 42 females) preschool children residing in the urban areas of Rawalpindi. Their blood lead levels ranged from 7 µg/dl to 34 µg/dl (mean 18.8 µg/dl). The mean lead levels were higher in males (20.3 µg/dl) as compared to females (17.2 µg/dl) while more than 90% children had lead levels above the acceptable limit of 10 µg/dl.[9]

In 2002, Rahman *et al* evaluated the lead-associated deficits in stature, mental ability and behaviour of children at Karachi. A cross-sectional survey was conducted in seven primary schools of Karachi. Shed primary teeth and blood samples were collected from students of grades I to III (age range 6–10 years) and were analyzed for lead by atomic absorption spectrophotometry. Out of 138 children, over 80% had lead levels above safe limits set by the United States Centres for Disease Control and Prevention.[10]

In 2002, Rahbar *et al*. carried out a similar research in various areas of Karachi including Sadar, Malir and fishing communities. A total of 430 children between 36–60 months of age were selected through a geographically stratified design. Their blood samples were collected and analyzed for the blood lead levels. About 80% of children had blood lead concentrations above 10 µg/dl, with an overall mean of 15.6 µg/dl.[11]

In 2003, Hozhabri *et al*. conducted a cross-sectional survey of 53 young children in a fishing village on an island adjacent to Karachi. Fifty-two subjects (98%) had lead levels in whole blood above 10 µg/dl (mean 21.60 µg/dl) that was equal to the recognized threshold for potential neurotoxicity.[12]

In 2005, Agha , *et al.* evaluated the effect of environmental lead pollution on blood lead levels in 47 male traffic police constables (age 21 to 45 years) in Islamabad. They were engaged in controlling traffic for 3 months to 18 years, 8 hours/day, 6 days/week. Adolescent males (13–19 years), residing in comparatively clean and low traffic areas were included as controls. Blood lead concentration was estimated by atomic absorption spectrophotometry. The mean blood lead level in the constables (27.27 µg/dl) was significantly ($p<0.0001$) high as compared to mean blood lead level in the controls (3.22 µg/dl).[13]

Factors associated with lead intoxication in Pakistan

In developing countries like Pakistan lead paints, lead water pipes, lead-acid batteries, lead containing eye cosmetics, lead food cans, lead in petroleum as anti-knocking agent and lead oaring and mining are constant sources of lead intoxication in general population.[4]

Lead compounds are added in petrol to increase the efficiency of car engines and to prolong engine life by reducing knock. Accelerated growth in vehicle population and vehicle kilometres travelled has led to increased release of lead in the environment and lead intoxication in general population. The number of vehicles has jumped from 0.8 million to about 4.0 million within 20 years showing an overall increase of more than 400%. Projected fuel consumption for transport sector has been estimated at 40,000 tons of oil equivalent (TOE) in 2050. The high content of lead in petrol is a serious issue because its end product is the release of lead into the environment.

In Pakistan, lead free petrol was started in 1996. Efforts are being made to remove lead from the petrol on the national scale but they need to be monitored.[14]

Occupational exposure of lead factory workers is a problem for both the developed countries as well as of the developing countries. Due to the physical and chemical properties lead is continuously being used in acid batteries, packing material, food cans and beverages, lead pipes and explosive industry. The prolonged exposure of workers in these factories make them prone to lead intoxication. In Pakistan, a study was conducted in 1994 in a lead factory that revealed 100% of factory workers having blood lead levels above the maximum acceptable limits.[7]

Lead paint is a well-established cause of lead poisoning and elevated blood lead concentrations in children, often in association with pica.[15] Removal of lead from the paint industry has lowered lead levels in children, in developed countries. In New Zealand, the blood lead concentrations fell by 42% between 1978 and 1985 after lead-based paints and varnishes were abandoned and lead-soldered food and drink cans were replaced by seamless-welded containers.[16] In Pakistan, no concrete measures have so far been adopted for removing lead from paint. Lead is used extensively in locally made paints and varnishes.[17]

Traditional remedies or cosmetics can also be important sources of lead exposure. '*Surma*' and '*kohl*', which are gels or water-based fluids used for eye make-up, contain 16–80% lead.[18] A study in Faisalabad in 1988 reported that 80% of 20 samples of *surma* had a lead content >65%.[19]

Dust is a significant source of lead and can raise the blood lead levels in humans particularly in children. A study conducted at Institute of Environmental Studies, University of Karachi in 2000 evaluated the content of lead in leaves of plants in the city of Karachi and lead content in particulate deposits on them. A lead concentration of 30.00±6.6 ppm was recorded as the highest concentration in the particulate deposit, while maximum lead accumulated by the leaves was noted as 3.12±1.09 ppm. A statistically significant correlation was found between the number of passing petrol driven vehicles and lead concentration in the deposits at different designated sites.[20]

Drinking-water is also a potential source for elevated blood lead concentrations in areas where lead pipes have not been replaced with lead free pipes. Although lead levels in ground and surface water are typically low,[21] levels may increase after water from surface drainage enters the distribution system containing lead pipes. The type of utensils and containers used for storage and boiling of water or cooking food can also contribute to the elevated blood lead concentrations in children.[22]

Control of Lead Intoxication

The problem of lead intoxication can be fully controlled by removing it from the environment. As lead has no physiological role in the living organisms and it replaces other vital divalent cations including calcium and zinc in the cells, so presence of lead even in very minute quantities in the human blood causes derangements and undesired effects. Therefore minimizing the use of lead in the industry, from which it is released in the environment, is the best measure to control lead intoxication.

In certain industries, the use of lead cannot be reduced and their workers have essential lead exposure. In addition, in the developing countries because of the cost effectiveness of lead it is extensively used. Various guidelines for the management of cases of lead intoxicated are available which mostly rely on removing the stored lead in the body by chelation therapy. As removing lead from industry is a difficult challenge therefore in most of the developing countries due emphasis is required to be given to develop standard protocols to manage cases of lead intoxication.

Certain antioxidant agents, especially vitamins are being investigated to know if they can minimize the toxicity of lead by reducing the oxidative stress produced by lead. The results of vitamin C supplementation during lead exposure have revealed significant improvements and are further evaluated to see if it can ameliorate the toxicity of lead in conditions of unavoidable exposure.

Minimizing the use of lead

As minimizing the use of lead is the best measure to control lead intoxication therefore there is a dire need to develop and implement policies that facilitate the lead phase out at the earliest. Strong measures have been taken to control the use of lead in gasoline successfully in most of the developed countries during last 25 years[23] and use of lead has been minimized in certain industries. However, stringent measures have not yet been taken in most of the developing countries for minimizing the use of lead from industries.[24]

In developed countries, with the best possible measures to minimize the use of lead in the industry, many of the industries still depend on lead. At present out of five million tons of lead that is mined and used annually, about 75% is consumed in lead-acid batteries. This industry is constantly expanding with automobile industry and

therefore use of lead is on its rise.[25] In addition, lead is also used in explosives, food cans, glass industry, ceramics, and in plastic manufacture throughout the developed world.

Measures for minimizing the use of lead in industry in developing countries were started late. In Pakistan, phase out plan of leaded gasoline was started in 1996 and now all the four oil refineries of Pakistan are producing lead free petrol. However, phasing out lead from gasoline needs continuous monitoring.[26]

Like other developing countries, in Pakistan use of lead in manufacturing batteries, food cans, explosive, pipes, cosmetics and utensils is going unmonitored. Eventually it leads to adding up more and more lead as a pollutant in the environment. This stresses the need for continuous up gradation of the standard management protocols of lead intoxication and exploring other viable means to minimize toxicity of lead in the exposed population.

Guidelines for the Management of Lead Intoxication

The management of lead intoxication depends upon the blood lead levels and age of the intoxicated population. Since children are more prone to develop lead toxicity and are affected more severely therefore medical management is primarily designed for the treatment of lead intoxicated children.[27] Timely diagnosis and treatment of the lead intoxicated children produce significant improvement in their clinical manifestations and prevent cognitive and neuropsychological impairment in them.

The guidelines for the management of children with elevated blood lead levels recommended by the Centres for Disease Control and Prevention in USA have been summarized in the Table-1.[1]

Table-1: Management of Lead Intoxication Based on Blood Lead Levels (BLLs)

Blood Lead Level (µg/dl)	Recommended Action
<10 µg/dl Risk Level: I	● Obtain a careful environmental history
	● Provide risk reduction and nutrition education
	● If risk assessment indicates exposure to lead is likely, consider retesting within 3 months
10–14 µg/dl Risk Level: II (Moderate)	● Report BLL to local Department of Health (refer to local laws)
	● Obtain a careful environmental history
	● Provide risk reduction and nutrition education
	●Repeat all capillary samples, confirming with a venous sample within 1 month for new cases and 1–3 months for known cases
15–19 µg/dl Risk Level: II (Moderate)	● Follow steps from BLL 10 through 14 µg/dl
	● If BLL remains 15 through 19 µg/dl for 3 months, proceed with actions for BLL 20 through 44 µg/dl
	● Collaborate with lead poisoning prevention programs (LPPP), which will provide home inspection and other services
	● If initial sample was capillary, repeat with a venous sample in 1 week to 1 month. The higher the BLL, the more urgent.
20–44 µg/dl Risk Level: III	● Follow steps for child who has BLL of 10 through 14 µg/dl
	● Provide complete medical evaluation, including detailed environmental history, High developmental assessment and physical examination. If particulate ingestion is suspected, obtain abdominal radiograph and order bowel decontamination if indicated
	● Consider chelation therapy (not currently recommended for BBL <45 µg/dl in consultation with a clinician experienced in lead toxicity treatment
	● Collaborate with LPPP, which will provide home inspection and other services
45–69 µg/dl Risk Level: IV (Urgent)	● Confirm BLL with venous sample within 24 to 48 hours before initiating chelation
	● Provide or refer for chelation therapy within 48 hours. Child must be in a lead safe environment during chelation
	● Follow all steps for BLL of 20 through 44 µg/dl
	● Perform complete neurologic examination and consider free erythrocyte protoporphyrin (FEP) or zinc protoporphyrin (ZPP) testing to assist in evaluating child's response to management
>70 µg/dl Risk Level: V (Emergency)	● Arrange immediate hospitalization and chelation at a facility that has expertise in treating lead-poisoned children. Assistance can be obtained from Poison Control Centres.
	● Confirm BLL immediately with venous sample processed as an emergency laboratory test
	● Follow all steps for BLL 20 through 44 µg/dl
	● Perform complete neurologic examination and consider FEP or ZPP testing to assist in evaluating child's response to management.

The mainstay of treatment is chelation therapy. It involves oral or parenteral administration of chelating agents which form complexes with divalent cations including lead, zinc, magnesium and calcium and enhance their excretion by kidneys.[28] Ethylene diamaine tetraacetate **(**EDTA), D-penicillamine, British anti lewisite [2,3-dimercaptopropanol (BAL)] Dimercapto Succinic Acid (DMSA) and Sodium 2,3-dimercapto-1-propanesulfonate (DMPS) are the most common chelating agents used in the medical management of lead intoxication. EDTA, D-penicillamine, and BAL came into clinical use after World War II to treat lead and mercury intoxication. During 1950s, DMSA and DMPS came into use in China and Soviet Union.[29,30] Since

1970s, these drugs have been available in western countries. DMSA and DMPS are efficient antidotes for intoxications with several divalent metals besides lead and mercury as well as some organo-metal or metalloid compounds.[31]

Chelation therapy has very high incidence of side effects and a considerable fraction of individuals experience nausea, vomiting, sweating, high fever, hypertension, and tachycardia. BAL is significantly more toxic than DMPS, which is slightly more toxic than DMSA. BAL administration increased the deposition of arsenite and organic mercury compounds in brain and increased the toxicity of cadmium and lead in animal experiments.[32] Adverse reactions during treatment with DMSA or DMPS include gastrointestinal discomfort, skin reactions, mild neutropenia, and elevated liver enzymes. DMPS seems to be better tolerated than is DMSA with respect to gastrointestinal symptoms but may cause hypotension, especially after rapid intravenous infusion. Some patients, especially those with allergic asthma symptoms, may develop hypersensitivity to DMPS.[33] In addition to having very high incidence of side effects during the chelation therapy deaths due to hypocalcaemia have occurred during the chelation therapy because of excessive removal of calcium ions from the body along with other divalent cations.[34]

Research has been carried out for exploring other means to minimize the toxicity of lead by interfering with the generation of ROS, caused by lead. Research has shown that antioxidant supplements have a role in minimizing the toxicity of lead and other heavy metals which cause oxidative stress in the body. Effect of dietary supplementation with vitamin C, vitamin E, methionine, N- acetylcyteine, alpha lipoic acid, selenium, pyridoxine (vitamin B_6) and taurine is being evaluated by different researchers on different parameters of lead intoxication.[35–38] Among these antioxidant supplements, vitamin C appears to be more effective in minimizing the toxicity of lead.[39] Shalan *et al* have shown that ascorbic acid and silymarin supplementation ameliorates hepatotoxicity of lead in rats.[40] Role of antioxidants, especially of asocorbic acid in minimizing the toxicity of lead is very promising for the developing countries because of its cost effectiveness and easy availability. However, quantitative impact of antioxidant vitamin supplementation on toxic effects of lead intoxication and their role in the management of lead intoxication alone or in combination with the chelating agents is yet to be established.

CONCLUSION

Extensive and unmonitored use of lead in paints, lead-batteries, plumbing, water supply pipes, cans, ceramics and gasoline products in developing countries is posing a serious threat to the general population. World Health Organization estimated that 120 million people had blood lead levels above the maximum acceptable limit (10 µg /dl) in 2000. 99% of the children with blood lead levels above 20 µg/dl, in this study, were residing in developing countries. At present the measures taken by the developing countries, including Pakistan, for the control of this problem are inadequate. Stringent measures to minimize the use of lead in industry and to develop standard management protocols for lead intoxication should be adopted by the developing countries as are being practiced by the developed world. In addition, therapeutic use of antioxidant vitamins alone or in combination with chelation therapy should also be evaluated for being cost effective and readily available.

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