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Homeopathic *Plumbum metallicum* for lead poisoning: a randomized clinical trial☆

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Introduction: **Poisoning due to lead and its compounds has short and long-term effects primarily on the nervous, hematopoietic, gastrointestinal, cardiovascular, musculoskeletal, renal and reproductive systems. It can manifest in acute or chronic symptoms. Measuring serum concentration is the primary method for diagnosing and monitoring exposed workers. Presently, elevated lead levels are treated by drugs whose effectiveness is contested on various fronts. Experimental studies suggest that homeopathic preparations may be in controlling blood lead levels in laboratory animals, creating the need for controlled studies to evaluate the effectiveness and safety of these preparations in humans.**
Objective: **To evaluate the effectiveness of the homeopathic preparation *Plumbum metallicum* in reducing the blood lead level of workers exposed to this metal.**
Design: **Double-blind randomized trial.**
Setting: **Workers' clinic in the Ajax battery plant, which employs 900 workers with varying degrees of lead exposure in Bauru, São Paulo State, Brazil.**
Subjects: **131 workers exposed to lead.**
Intervention: ***Plumbum metallicum* 15cH or *placebo*, orally for 35 days.**
Results: **The percentage of workers who demonstrated a reduction in lead counts by a percentage greater than or equal to 25% following treatment was the same for both groups: 20.3% in the homeopathic groups *versus* 21% in the control group [Relative Risk (RR) = 0.95, confidential interval (CI) 95%: 0.47–1.92)]. Analysis by intention-to-treat also did not show any difference between the groups: 18.2% in the treated group *versus* 20% in the *placebo* group (RR = 0.91, CI 95%: 0.45–1.84).**
Conclusion: **The homeopathic preparation *Plumbum metallicum* had no effect, in this study, in terms of reducing serum lead in workers exposed to lead.** *Homeopathy* (2011) **100**, 116–121.

Keywords: Lead poisoning; Controlled clinical trial; Effectiveness; *Plumbum Metallicum*; Homeopathic drug

Introduction

Lead poisoning (saturnism) from workplace or environmental exposure is common in many developing countries, in part because lead is abundant on the planet, but mostly because its physical and chemical products and compounds are useful in manufacturing a variety of products. The expansion of industrial activities in the 19th and 20th centuries, primarily the rise and growth of the automobile industry, unleashed an increase in the use of lead and the distribution of waste in the environment (approximately 300 million tons in the last 500 years) and, consequently, the exposure of individuals to various degrees.[1]

In developed countries, numerous public health campaigns have reduced the number of acute cases.

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Nevertheless, chronic lead toxicity still raises important questions concerning social and workplace healthcare. Lead-exposed workers are found in a number of industries: automobile batteries; leaded paint; ceramic glazes; munitions, PVC manufacturing; electric cables; electric- and electronic-component welding; radiator repair; non-ferrous metal smelting for metals such as bronze, tin and other alloys, in addition to secondary smelting of lead and antimony; shooting instruction; renovations and painting at construction sites, among others.

Non-occupational exposure can occur in persons exposed to environments were batteries are reconditioned, when this activity occurs at home, or with persons who reside in areas near establishments that work with lead and its derivatives (air and soil contamination).[2] There is also the possibility of contamination from a distance due to environmental contamination from compromised underground water tables and the consequent contamination of foods.[2,3] Various cases with clinical signs and symptoms of lead poisoning from an endogenous source (firearm bullets lodged in joints or contact with cerebrospinal fluid) have been reported.[2,3]

Recently, with the development in assay methods, it has been found that lead at concentrations previously considered safe may have adverse effects.[4] The family of a worker exposed to lead runs an increased risk of lead poisoning when the lead is carried home in/on the worker's body, clothing, shoes and motor vehicle. Available evidence suggests that there is no level of serum lead concentration (Pb-S) that is free from health risks for workers and their families.[5]

The exposure routes for inorganic lead are inhalation and ingestion. Adults absorb approximately 10% of in ingested lead through the gastrointestinal tract, while children absorb 50% in the same manner. Once absorbed, lead is found in all tissues, but 90% of the load is deposited in bone, where it accumulates over the carrier's lifetime and can act as an endogenous source of the metal.[6,7] Lead's half-life in the blood and in soft tissues is approximately 28–36 days, and the greatest part of the ingested lead is absorbed and excreted by the kidneys.[8,9] The transfer of lead to the fetus occurs easily during the gestational period.[10]

Lead poisoning, both acute and chronic, frequently requires prolonged medical care that involves specific treatment and removal from the source.[11] There is a large variation in individual susceptibility to lead poisoning, but symptoms generally appear in adults with a Pb-S concentration greater than approximately 40 μg/dL.[1] The number and severity of symptoms worsens with the increase of Pb-S concentrations.[1]

Initial symptoms are frequently subclinical and non-specific, such as general malaise, a decreased appetite, weariness, fatigue, irritability, sleep disturbance, headaches, concentration difficulties, memory disturbances, decreased libido, abdominal cramps, anorexia, nausea, constipation, diarrhea, epigastralgia, arthralgia, generalized myalgia and/or localized myalgia (in the calves).[4,5] Small increases in blood pressure are observed with Pb-S concentrations between 14 and 30 μg/dL.[12,13] Peripheral neuropathy can occur with chronic exposure and is characterized by weakness of extensor muscles, particularly in the dominant arm or leg, with a discreet loss of sensory perception and a decrease in nervous conduction observed with Pb-S concentrations in the range of 30 μg/dL.[14] A decrease in hemoglobin was found in exposed workers with Pb-S concentrations greater than 50 μg/dL.[4,15] Abnormal sperm morphology and decreased sperm counts were observed in cases with Pb-S concentrations of approximately 40 μg/dL.[16,17] Lead easily crosses the placental barrier and is present in breast milk, with impaired fetal cognitive development reported in women exposed to lead.[10,18]

To evaluate lead exposure, markers related to metal absorption and/or its absorption in tissues are used.[19] Blood is the medium in which lead is mostly frequently measured as an exposure marker. Lead poisoning shows relatively recent exposure since lead's half-life is short (28–36 days).[4,8] In Brazil, the Pb-S considered safe for workers is up to 40 μg/dL.[20] In the United States of America, in 1978, the Center for Disease Control (CDC) adopted the limit of 25 μg/dL and, in 1991, 10 μg/dL.[8] The criteria for diagnosis of inorganic lead poisoning are: (a) clinical symptoms (b) laboratory results confirming excessive exposure, like increased lead levels and/or the presence of biochemical alterations (an increase in porphyrin levels verified by determination of delta-aminolevulinic acid in the blood and urine, urinary porphobilinogen, coproporphyrin in urine, and erythrocyte protoporphyrin).[6,21]

Treatment

The first step in managing lead poisoning is to remove from exposure but, unfortunately, there are no clinical studies that point to the best evidence to guide which therapy route should be pursued.[22] Current treatment includes the use of chelating agents which link to metallic elements, forming stable complex molecules that can be excreted in urine.[11] The chelating agents used to combat lead poisoning are calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) or dimercaptopropanol (BAL or dimercaprol), dimercaptosuccinic acid (DMSA) and D-penicillamine.

The two main difficulties in treating lead poisoning are: (a) available evidence concerning the efficacy of chelating agents is based on case reports or case series[11]; (b) the diagnosis of lead poisoning is not precise in cases with moderately high Pb-S levels and when symptoms and signs are non-specific.

Treatment with $CaNa_2EDTA$ or DMSA is implemented in cycles of 5 consecutive days, with intervals of 10–15 days between cycles, that continue until the levels of urinary lead excretion fall within the reference values immediately after treatment.[6,11] $CaNa_2EDTA$ forms a stable complex molecule with lead and is excreted by the kidneys, unmetabolized; nevertheless, it is nephrotoxic and depletes the body's supply of calcium and zinc.[23] When used in isolation, it can lead to a worsening of acute encephalopathy and, in such cases $CaNa_2EDTA$ should be administered in conjunction with dimercaprol or DMSA alone should be administered.[8,9] Dimercaprol (BAL) forms a stable complex molecule with lead that is eliminated in the feces and urine, and it has various reported negative side effects,

such as tachycardia, arterial hypertension, abdominal pain, nausea, vomiting, glossodynia, sialorrhea, irritability, paresthesia, muscle spasm, cephalgia and diaphoresis. It is not recommended for patients with hepatic insufficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency as it can lead to hemolysis, and its use in conjunction with iron supplements, which forms the Fe-BAL complex, can cause severe vomiting.[21,22] DMSA is less toxic than dimercaprol and more specific to lead than is $CaNa_2EDTA$; DMSA's side effects are less common that those observed with other drugs, limited to complaints of abdominal pain and discomfort and flatulence.[24] D-penicillamine is administered orally and also can cause severe adverse effects, which are similar to those caused by hypersensitivity to penicillin, varying from simple arrhythmia to Stevens–Johnson syndrome.[21]

With respect to the prognosis, removal from exposure and chelating considerably improve the majority of cases. For cases of acute lead poisoning in workers with little exposure time, the tendency is for levels to completely regress after specific treatment, with laboratory parameters reverting to normal values. When exposure has been prolonged and there are symptoms of chronic lead poisoning, there may sequelae in the central nervous system, with lasting changes to the peripheral neurology and neural behavior.[21]

For some years homeopathic preparations have been studied in experimental models as a treatment for arsenic and lead poisoning.[25,26] More recently, Moreira and colleagues reported similar results between the use of a homeopathic preparation and EDTA in terms of a reduction of lead poisoning in previously poisoned rats.[27]

The homeopathic medicines *Plumbum aceticum*, *Plumbum carbonicum* and *Plumbum metallicum* do not have the same mechanisms of action described in medical literature, there is no reference to adverse effects resulting from their use. According to the principles of homeopathy, these medications are indicated for clinical situations that involve neuro-locomotive symptoms (arthropathy, paresis or paralysis with pains and tremors) and mental symptoms (memory weakening or loss of memory, incapacity to find appropriate words to express oneself, sadness, weariness with life, despondency, anxiety, malaise characterized by sighing, aversion to conversation and work, growing apathy).[28,29]

If we consider: (a) that lead poisoning remains a serious public health problem, primarily in cases of chronic exposure to low levels of the metal; (b) that the industrial activities that expose workers to lead are, in general, not highly technological in nature but do involve a large variety of production branches and sectors; (c) that exposure to lead in the environment is increasing (d) that the possibility of non-occupational contamination affects, in large part, society's socially and economically deprived groups; (e) that recommended medical treatments produce significant adverse effects; (f) that some experimental studies with animals poisoned with lead and treated with a homeopathic preparation report results similar to those obtained with conventional treatment; and (g) that clinical research in homeopathy is still in its early stages, but necessary to better structure existing knowledge and practice; the relevance of the topic of lead toxicity to public health is indubitable, and studies with adequate design and methodologies capable of evaluating the effectiveness of new treatments for this clinical situation are vital.

Objective

To evaluate the effectiveness of the homeopathic preparation *Plumbum metallicum* in treating lead poisoning with respect to the blood lead level of workers exposed to this metal.

Methods

Double-blind, randomized clinical trial (RCT) conducted at the workers' clinic in the Ajax battery plant, which employs 900 workers with varying degrees of lead exposure in the City of Bauru, State of São Paulo. This RCT was submitted and approved by the Ethical Research Committee [(CEP) UNIFESP: 0632/02] of the Universidade Federal de São Paulo and was registered in the ClinicalTrials.gov database (NCT00931905).

Sample

This study included workers exposed to lead and who:

- had not taken a leave of absence for any reason for a period greater than 7 days in the 60 days prior to the intervention;
- where in good health, according to their medical records and physical exam;
- had an initial blood lead level less than the maximum biological concentration permitted, which is 60 μ/dL in Brazil.

Exclusion criteria: Workers who, in the last 6 months, had used medication that interfere with the level of lead in the blood, such as EDTA, BAL, penicillamine and DMSA;
workers who had the right to vacation during the study period;
workers who did not give their consent to participate in the study.

Initially, a series of lectures were given to educate workers on the objective of the study, and the workers were subsequently requested to provide written consent that they intended to participate in said research. One thirty one workers who satisfied the inclusion criteria attended the first consultation and signed the consent form.

Intervention

Because this study did not individualize homeopathic treatment, it is considered a tautotherapy-based. The homeopathic medication *Plumbum metallicum* 15CH was used, (the same used by Moreira *et al.*[27]). Powdered metallic lead was ground up with lactose until 3CH and the 4CH was suspended in 30% ethanol then diluted using the Hahnemann centesimal method. The 4CH preparation was obtained from the Schraiber laboratory, the preparations from

5CH to 15CH were made by a manufacturing pharmacy (Flora Farma) according to the Brazilian Homeopathic Pharmacopoeia.[30] The *placebo* consisted of hydroalcoholic solution prepared in 30% ethanol and was sucussed. The medication and *placebo* had the same color appearance and packaging. Treatment was administered orally (10 drops) twice daily – at the beginning and the end of the shift and under supervision for 30 days. The patients were instructed not to take other medication without medical guidance during the time they were participating in the research.

Randomization, blinding and allocation concealment

For randomization, we used a table of random numbers between 0 and 200, which corresponded to A or B. The vials containing the medication were, thus, numbered sequentially from 0 to 200 and were given directly to the researcher in charge of medication administration. Treatments were administered, consecutively, to the patients in the clinic. The person responsible for the randomization, the evaluator, the person responsible for administering the drug, and the patients were not aware of the whether the drug or the *placebo* was administered to each patient.

Measured outcome

The primary measured outcome was the reduction in the Pb-S by 25% relative to the concentration measured prior to intervention. The decision to establish an average reduction of 25% of lead counts in the blood was based on the percentage that would benefit the greatest number of workers involved in the research taking into account the Pb-S levels they initially demonstrated and the value of 25 μg/dL, the maximum level that is currently recommended internationally.[8] Therefore, a 25% reduction of the Pb-S level was used as the desired outcome to evaluate the effectiveness of the homeopathic preparation.

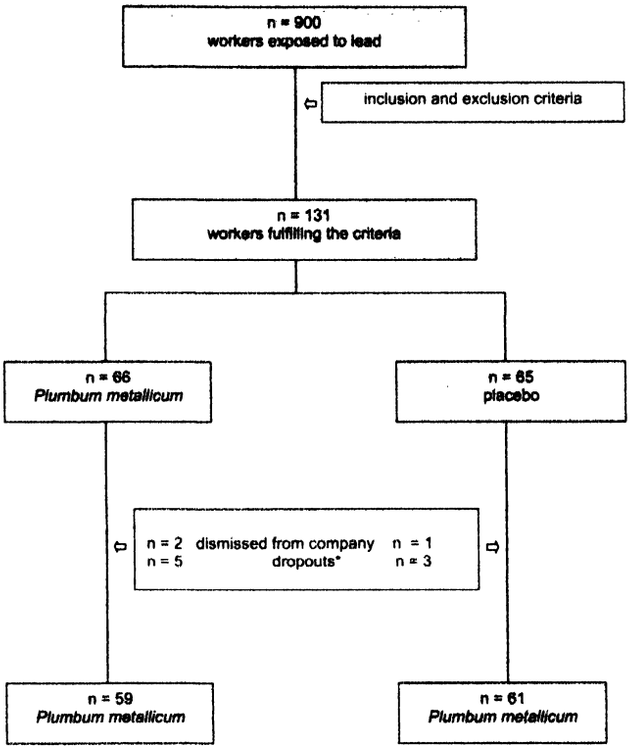
The Pb-S was determined by atomic absorption spectrophotometry. The blood samples used in processing the toxicological analyses were collected between 6:30 a.m. and 7:30 a.m. at the company where the workers were employed, away from the production line. The workers wore their own clothes from their homes and did not come in contact with the production line prior to taking blood samples. After washing the region, a polyethylene syringe with a polyethylene plunger was used to puncture the vein.

Statistical analysis

To analyze the characteristics of data distribution (Gaussian or otherwise), the Kolmogorov–Smirnov and Shapiro–Wilk tests were applied. Analysis of variance (ANOVA) was used for continuous data analysis, and the chi-square test was conducted when outcomes were dichotomous. Both intention-to-treat (efficacy) and an effectiveness analysis were performed.

Results

Of the 131 randomized workers, 11 did not complete the treatment: three of the 11 (two from the group receiving the drug and one from the *placebo* group) withdrew just after treatment commenced; and eight quit during treatment (five from the group receiving the drug and three from the *placebo* group). The loss totaled 8.4%, 10.6% of the active group and 6.1% of the control group. Thus, 120 workers completed the study: 59 from the group receiving medication and 61 from the *placebo* group (Figure 1).



** Reasons for dropouts: sick leave (2), personal reasons (2), excessive absence from work(1), vacation (2), change in shift schedule (1).*

Figure 1 Flow chart of the subjects through the study.

The groups were homogenous in terms of age, duration of exposure and blood lead levels (Figure 2).

When the treated workers were stratified by the concentration of lead in the blood, homogeneity was maintained (Table 1).

Figure 3 and Table 2 show the results, and statistical analyses.

Accounting strictly for the patients who finished the study (efficacy analysis), the rate of positive results, that is to say a reduction of lead concentration in the blood of 25% or greater after treatment, was practically the same in both groups: 20.3% (CI 95% 10.0–30.6) in the group that

Characteristics		Drug	Placebo	Total
Number of workers		66	65	131
Average age (years)		34.0	32.1	33.0
Sex	Female	3	1	4
	Male	63	64	127
Average exposure time to lead (years)		5.8	5.5	5.6
Pb-S_1 (μg/dl)		32.6	33.1	32.9

Pb-s_1 – measure of lead count in blood in initial sample *p> 0.05

Figure 2 Baseline characteristics of the randomized workers.

Table 1 Distribution of randomized workers by initial Pb-S

Pb-S$_T$ (μ/dL)	Plumbum metallicum	Placebo	*Total*	
			N	%
10–24	17	12	29	22%
25–39	31	35	66	50%
40–49	15	14	29	22%
50–59	3	4	7	6%
Total	66	65	131	100%

received the medication, and 21.3% (CI 95% 11–31.6) in the *placebo* group. Thus, after follow-up, there was no statistically significant difference between the two groups.

The efficacy analysis (intention-to-treat) of Table 2, which includes all the randomized workers (whether or not they finished treatment), also did not reveal a difference between the groups in terms of positive outcomes, which were 18.2% (CI 95% 8.9%–27.5%) and 20% (CI 95% 10.3%–27.5%) respectively for the treated and control group. The reductions of Pb-S levels were similar in the two groups (RR = 0.91 CI 95% 0.45–1.84).

Table 2 Statistical analysis of results (intention-to-treat analysis)

Proportion of workers with a decrease of Pb-S ≥ 25%	*Valor*	*IC 95%*		*Result*
		LI	*LS*	
Rate of events in the treated group	18.2%	8.9%	27.5%	
Rate of events in the control group	20.0%	10.3%	29.7%	
RR	0.91	0.45	1.84	NS*
Relative Risk Reduction (RRR) = [1 − RR]	0.09	−0.84	0.55	NS
Absolute Risk Reduction (ARR)	1.8%	−11.7%	15.3	NS
Number Needed to Treat (NNT) = 1/ARR	–	–	–	–
χ^2	0.002	$p = 0.97$		

Pb-S: level of serum lead concentration; LL: Lower Limit; UL: Upper Limit; NS: Not Significant; χ^2: chi-squared test.
* Result is statistically insignificant with the 5% probability level ($p > 0.05$).

Discussion

At initial testing 28% of the workers had Pb-S levels greater than 40 μg/dL (Table 2). Scientific evidence holds that such concentrations may result in subclinical effects.[20] Seventy eight percent of the workers had lead counts greater than 25 μg/dL, a concentration currently considered a 'flag' level, pointing to the need for more frequent monitoring.[31,32]

The results obtained in this study diverged from those obtained in the experimental study conducted by Moreira, who reported a reduction of nearly 100% in the lead concentrations in rats intoxicated with lead and treated with a homeopathic preparation (*Plumbum metallicum*).[27]

Randomization made for comparable groups; treatment was administered under supervision, and efforts were made to avoid follow-up loss. The loss of 10.6% in the treated group and 6.1% in the control group was entirely accounted for (three were excluded and eight withdrew).

The proportional differences of workers with a 25% (or greater) reduction in blood lead counts, were considered the greatest interest in deciding to treat. The estimates of these outcomes in the two groups (analysis by intention-to-treat) were 18.2% in the treated group and 20% in the control group. Nevertheless, there is the possibility of the existence of a small effect for which the sample used does not provide sufficient statistical power. Assuming a ratio of positive outcomes of 20% in the control group and 25% in the treated group, to obtain 90% statistical power and to detect said difference with a CI of 95%, it would be necessary to include 1,543 cases in each group. Given that removing a worker from exposure for a month greatly reduces blood lead levels, it is unlikely that human and financial resources could be justified. To remove the worker from his duties also implies high social and economic costs. In a more conservative scenario, assuming a positive outcome ratio of 20% in the *placebo* group and 50% in the treated group, with $p = 5\%$ (CI of 95%) and 90% statistical power, 48 patients in each group would have to be studied.

This is the first clinical trial of the use of the homeopathic medication *Plumbum metallicum* in workers with workplace exposure to inorganic lead. The lack of other studies means that comparisons cannot be made, but this may be the best evidence on the subject to date. This study, however, does not close the matter and opens the possibilities that other similar investigations should be implemented, with the results submitted to a meta-analysis when appropriate.

It should also be underscored that there are no studies in the scientific literature which sufficiently strong evidence to offer recommendation in terms of the use of chelating

Groups	Decrease (↓) of Pb-S		Total
	↓ Pb-S ≥ 25%	↓ Pb-S < 25%	
Plumbum metallicum	12	54	66
Placebo	13	52	65
Total	25	106	131

Pb-S: level of serum lead concentration

Figure 3 Distribution of workers by treatment response (analysis by intention-to-treat).

agents to reduce lead levels in exposed individuals. The bibliography used for this study in the Medline, Cochrane, Lilacs and Embase databases did not show any systematic review of the use of chelating agents. We found only one randomized control trial measuring the effect of a chelation with DMSA in children with moderately elevated Pb-S levels, although concentration was reduced after 1 month of treatment, there was no significantly statistical difference with respect to *placebo*.[33]

Taking into consideration this study's conclusions and the practical absence of research on the effect of chelation therapy, knowledge and evidence to date concerning the treatment of lead poisoning puts doctors and workers in a rather delicate situation. There is a need for deeper studies that compare intervention to the mere removal of the worker from the source of the contamination. Indeed, distancing a worker from the source is the only method that is supported by scientific literature for workers with high lead concentrations. In addition, preventive health measures are the only effective protection against the effects of lead exposure.

Conclusions

Considering the reduction in the lead counts by 25% as the measure of success, the results of the groups treated with *Plumbum metallicum* and with the *placebo* were similar. The homeopathic preparation had no effect, in this study, in terms of its effectiveness to reducing lead toxicity in workers exposed to inorganic lead.

Conflict of interest

To the author's knowledge, no conflict of interest, financial or other, exists.

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