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Comparison of Therapeutic Effects of Garlic and D-Penicillamine in Patients with Chronic Occupational Lead Poisoning

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Abstract: Previous studies on animals have revealed that garlic (*Allium sativum*) is effective in reducing blood and tissue lead concentrations. The aim of this study was to investigate therapeutic effects of garlic and compare it with D-penicillamine in patients with chronic lead poisoning. After coordination and obtaining informed consent, clinical examinations and blood lead concentration (BLC) of 117 workers at a car battery industry were investigated. BLC was determined by heated graphite atomization technique of an atomic absorption spectrometer. The workers were randomly assigned into two groups of garlic (1200 μg allicin, three times daily) and D-penicillamine (250 mg, three times daily) and treated for 4 weeks. BLC was determined again 10 days post-treatment. Clinical signs and symptoms of lead poisoning were also investigated and compared with the initial findings. Clinical improvement was significant in a number of clinical manifestations including irritability ($p = 0.031$), headache ($p = 0.028$), decreased deep tendon reflex ($p = 0.019$) and mean systolic blood pressure (0.021) after treatment with garlic, but not D-penicillamine. BLCs were reduced significantly ($p = 0.002$ and $p = 0.025$) from 426.32 ± 185.128 to 347.34 ± 121.056 μg/L and from 417.47 ± 192.54 to 315.76 ± 140.00 μg/L in the garlic and D-penicillamine groups, respectively, with no significant difference ($p = 0.892$) between the two groups. The frequency of side effects was significantly ($p = 0.023$) higher in D-penicillamine than in the garlic group. Thus, garlic seems safer clinically and as effective as D-penicillamine. Therefore, garlic can be recommended for the treatment of mild-to-moderate lead poisoning.

For decades, lead (Pb) poisoning has been known as an important disorder that affects individuals through acute, subacute and chronic exposure in environmental and occupational settings. Common sources of lead poisoning are found in car battery industries, manufacturing of ceramics, plumbing, primary and secondary smelting and exposure to lead-bearing paints or contaminated food, water and fuels [1,2]. It is suggested that no threshold for lead toxicity exists, as even low-level lead exposure may result in nervous, renal, skeletal, haematopoietic and reproductive complications [3–8]. Moreover, the level in which clinical manifestations of lead poisoning appear differs extensively and is highly dependent on the acuity, age and individual variations [9]. Despite this variation and predomination of neurological and gastrointestinal manifestations [10], chronic lead poisoning may involve multiple systems [11]. Loss of short-term memory, inability to concentrate, irritability, depressive mood, paresthesia of extremities, loss of coordination, generalized abdominal pain and nausea are common symptoms of chronic lead poisoning in adults [12]. Patients may also complain of headaches, weakness and myalgia [10]. Anaemia and abnormal reaction time of deep tendon reflexes (DTR) are common signs in chronic lead poisoning [13].

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Prevention of re-exposure is critical in the treatment of lead poisoning [11,14]. Besides, chelators, such as calcium disodium EDTA (CaNa2EDTA), 2,3-dimercaptopropanol (BAL) D-penicillamine and Meso-2,3-dimercaptosuccinic acid (DMSA) named Succimer, have been widely used to treat lead poisoning over the past six decades. These agents are able to bind and facilitate the excretion of lead from the body [15–18]. However, serious side effects, high costs and some drawbacks on the use of chelators indicate that alternatives for the treatment of lead poisoning should be sought [19–21].

Previous studies on animals have demonstrated that garlic is effective in reducing blood and tissue lead concentrations through unknown mechanisms [22–27]. Besides, garlic has already been recognized to have antimicrobial, hypolipidaemic, anticancer, antioxidant and antithrombotic effects [28–33].

The aim of this study was to compare therapeutic effects of garlic and D-penicillamine on possible clinical improvements, side effects and decreasing blood lead concentrations in workers of a car battery industry with mild-to-moderate lead poisoning.

Materials and Methods

This prospective, double-blinded, randomized clinical trial was carried out in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. It was approved by the

institutional review board and ethics committee of Mashhad University of Medical Sciences.

Questionnaires were designed and used to obtain demographic data, past medical histories and clinical manifestations of lead poisoning in 158 workers of a car battery industry.

Clinical examinations were performed before the working hours and prior to obtaining blood samples. Clinical signs and symptoms were recorded in a nominal YES/NO scale. For example, fatigue was recorded for a worker if his tiredness did not alleviate with rest or mood irritability was considered for exaggerated responses to social stressors. At the same time, vital signs were evaluated by a clinical research assistant who was blinded to both treatment groups.

The workers who had been exposed to lead for more than a year at their work place and who revealed symptoms (e.g. fatigue, lack of memory and concentration, irritability), signs (e.g. peripheral polyneuropathy, lead line) and previous BLCs (routinely measured twice a year by the health safety authorities) between 200 and 500 μg/L were considered as patients with mild-to-moderate lead poisoning. The workers with mild–to-moderate lead poisoning who had received no pharmacological treatment for lead poisoning over the past 6 months were included. Those with a history of hypersensitivity reaction to garlic or penicillin family drugs, coagulopathy, peptic ulcer disease, taking anticoagulant, antimalarial or gold salt medications, anaemia and agranulocytosis following treatment with D-penicillamine, as well as those with a history of renal, heart and liver failure, were excluded from this study. The workers who had an appointment for elective surgery during the study (next 2 months) were also not included.

Informed consents were obtained from 117 workers with mild-to-moderate lead poisoning who had met the aforementioned criteria and had voluntarily participated in this study. Then 2 mL of heparinized venous blood (brachial) from each worker was obtained and conserved in sterile containers. Blood lead concentrations were measured by an atomic absorption spectrometer (Perkin-Elmer, Model 3030) using heated graphite atomization technique.

Treatment interventions in the workers initially consisted of eliminating the source of exposure and pharmacological treatment. But because of economic constraints and lack of employment opportunities, workers could neither abandon nor change their jobs or go on vocation for a long time. Therefore, 2 months before taking blood samples and pharmacological intervention, a meeting was convoked for all workers at the car battery plant, and we provided and distributed pamphlets about the health hazards of lead exposure and prevention of its toxicity in a direct confrontation. We taught workers how to limit lead exposure using protective devices and follow health safety rules at the work environment and at home. Then, the workers were divided into two groups based on even and odd numbers. Pharmacological intervention (either garlic or D-penicillamine) was carried out by a physician who was blinded to both treatment groups.

Garlic tablets (Garlet 400 mg; manufacturing date: 10/2007; expiry date: 10/2012; production number: 1228033537; made in Isfahan, Iran) were powdered and conserved in pink-colour size 1 capsules. According to the patient information leaflet, each garlic tablet contains 400 mg dried powder garlic that is equivalent to 1200 μg allicin or 2 g fresh garlic. On the other hand, each D-penicillamine capsule (Cupripen 250 mg; manufacturing date: 12/2009; expiry date: 12/2014; production number: 93820B; made in Barcelona, Spain) was commercially stored in size 3 capsules. To make identical capsules, the content of each D-penicillamine capsule was mixed and integrated geometrically with 150 mg of potato starch. Thereafter, the mixed product was transferred into identical pink-colour size 1 capsules.

Immediately after clinical examination and blood sampling, the workers were randomly divided into two groups based on even and odd numbers of enrolment. There were 58 and 59 patients in the D-penicillamine and garlic groups, respectively. A research assistant, who knew the identical pink-colour size 1 capsules of D-penicillamine and garlic, placed them in special containers with dates and times to achieve better compliance and provided the patients with instructions to take one capsule orally with a glass of water three times daily for 4 weeks. Also, the garlic group was treated with garlic capsules (400 mg), three times daily for the same period. During the 4-week treatment with garlic or D-penicillamine, the workers who experienced serious side effects or those who failed to receive treatment for any reason were excluded from the study. The workers could contact members of the research team to report any side effects or complications. Besides, all workers in the study were called daily and interviewed weekly by the clinical research assistant to make sure they used their drugs consistently. Any side effects noted by the workers during the study were also recorded for further analysis. Because of slow elimination phase of D-penicillamine [34], and according to the guidelines that suggest monitoring lead levels 10–14 days post-treatment owing to the re-equilibration and possible rebound of Pb [35], we rechecked BLCs 10 days after completion of the treatment. The questionnaires were used again to record the clinical data of workers who succeeded to complete the 4-week treatment period. The aforementioned methods and devices were used again to measure BLCs.

Finally, the clinical and laboratory data were collected and analysed by the Statistical Package for Social Sciences (SPSS 18, IBM Corporation, New York, USA). One-sample Kolmogorov–Smirnov test was performed to test for normality. Chi-square two-way test and ANOVA were used to analyse qualitative variables. Student's paired t-test was used to assess changes in BLCs. For non-normal distributions, non-parametric procedures, Wilcoxon signed rank-test was applied. Results were displayed as mean ±S.D. Besides, linear models were used to perform multivariate analysis. p values <0.05 were considered significant.

Results

A total of 117 workers (58 in the D-penicillamine and 59 in the garlic group) who entered the study were aged 28.78 ± 5.17 (20–48) years and weighed 69.06 ± 5.32 (56.5–78.0) kg. They had worked at the car battery factory for a period of 3.89 ± 2.40 years.

Neurological and musculoskeletal systems were most commonly affected in these workers. The most prevalent symptoms were mood irritability (40.1%), arthralgia (39.3%) and fatigue (38.4%). The most common clinical signs were dental caries (42.7%), lead line (23.7%) and abnormal deep tendon reflexes (DTRs). Increased and decreased DTRs were noted in 21.3% and 17.9% of patients, respectively (table 1).

During the pharmacological treatment, 37 patients (31.6%) experienced side effects. The frequencies of adverse

Table 1.

Demographic and clinical data of 117 workers with mild-to-moderate occupational lead poisoning.

Age (years)	28.78 ± 5.17
Weight (kg)	69.06 ± 5.32
Duration of work (years)	3.89 ± 2.40
Mood irritability	47 (40.1%)
Arthralgia	46 (39.3%)
Fatigue	45 (38.4%)
Paresthesia in feet	40 (34.1%)
Paresthesia in hands	34 (28.2%)
Metal taste in mouth	30 (25.6%)
Abdominal pain	10 (8.5%)
Dental caries	50 (42.7%)
Lead line	27/114 (23.7%)
Increased DTR	25 (21.3%)
Decreased DTR	21 (17.9%)

DTR, deep tendon reflex.

reactions were 19 and 18 in the D-penicillamine and garlic groups, respectively, as shown in table 2. The most common side effect was hypersensitivity, which affected six and five patients in the groups, respectively. Chi-square test showed that the frequency of adverse effects differed significantly ($p = 0.023$) between the two groups, because 17 workers in the D-penicillamine group were excluded from the study as a result of severe adverse reactions compared with seven individuals in the garlic group. In addition to those who were excluded from the study owing to the occurrence of complications, 33 patients failed to complete treatment because of changing of workplace, lack of taking drugs in a timely manner, going on holiday and not participating in giving blood samples after treatment.

Finally, 60 patients completed the treatment protocol for garlic (38 patients) and D-penicillamine (22 patients). The patients were aged 28.45 ± 5.13 and 27.67 ± 4.35 years in the garlic and D-penicillamine groups with no significant difference ($p = 0.558$) between them. Their weights were 66.78 ± 5.14 and 67.34 ± 4.43 kg in the garlic and D-penicillamine groups, respectively, with no significant difference ($p = 0.674$) among them. Similarly, no significant difference ($p = 0.708$) was found in duration of work between the groups. (3.75 ± 2.51 and 3.46 ± 2.26 years, respectively).

Some clinical symptoms and signs improved significantly in patients who took garlic, including irritability ($p = 0.031$), headache ($p = 0.028$), decreased DTRs ($p = 0.019$) and mean systolic blood pressure ($p = 0.021$), as described in table 3. No significant clinical improvement was observed in the D-penicillamine group.

In the garlic group, mean systolic blood pressure decreased significantly ($p = 0.021$) from 120.26 ± 13.25 to 112.27 ± 20.76 mmHg, but diastolic blood pressure did not change (from 78.16 ± 8.33 to 78.48 ± 7.95 mmHg) noticeably ($p = 0.713$) after treatment with garlic. In the D-penicillamine group, no significant changes ($p = 0.915$ and 0.714,)

Table 2.

Comparison of side effects between garlic and D-penicillamine among 117 (59 and 58, respectively) car battery workers by chi-square test.

Side effect	Garlic *N* (%)	D-Penicillamine *N* (%)	*p*-value	Garlic (excluded) *N* (%)	D-Penicillamine (excluded) *N* (%)	*p*-value
Hypersensitivity	5 (8.5)	6 (10.3)	0.762	3 (5.0)	5 (8.6)	0.490
Gastrointestinal complications	2 (3.3)	5 (8.6)	0.272	1 (1.6)	5 (8.6)	0.114
Headache	2 (3.3)	4 (6.8)	0.439	2 (3.3)	4 (6.8)	0.439
Somnolence	2 (3.3)	1 (1.7)	1.000	0	1 (1.7)	0.496
Low back pain	1 (1.6)	1 (1.7)	1.000	0	0	N/A
Chest pain	0	1 (1.7)	0.496	0	1 (1.7)	0.496
Oral ulcer	1 (1.6)	0	1.000	1 (1.6)	0	1.000
Dizziness	0	1 (1.7)	0.496	0	1 (1.7)	0.496
Increased appetite	1 (1.6)	0	1.000	0	0	N/A
Euphoria	1 (1.6)	0	1.000	0	0	N/A
Polyuria	1 (1.6)	0	1.000	0	0	N/A
Bad breath	1 (1.6)	0	1.000	0	0	N/A
Weight loss	1 (1.6)	0	1.000	0	0	N/A
Total	18	19	0.844	7	17	0.023

Table 3.

Comparison of clinical symptoms and signs of occupational chronic lead poisoning in 60 workers of a car battery industry before and after treatment with garlic (38 patients) and D-penicillamine (22 patients) using chi-square test.

	Garlic			D-penicillamine		
Symptoms/signs	Before *N* (%)	After *N* (%)	*p*-value	Before *N* (%)	After *N* (%)	*p*-value
Irritability	19 (50.0)	9 (23.6)	**0.031**	7 (31.8)	3 (13.6)	0.281
Fatigue	16 (42.1)	9 (23.6)	0.142	7 (31.8)	5 (22.7)	0.736
Paresthesia in feet	12 (31.5)	5 (13.1)	0.097	10 (45.4)	5 (22.7)	0.203
Paresthesia in hands	11 (28.9)	4 (10.5)	0.082	11 (50.0)	5 (22.7)	0.116
Arthralgia	12 (31.5)	9 (23.6)	0.609	7 (31.8)	4 (18.1)	0.488
Metal taste in mouth	10 (26.3)	4 (10.4)	0.137	8 (36.3)	5 (22.7)	0.510
Anorexia	10 (26.3)	6 (15.7)	0.399	8 (36.3)	4 (18.1)	0.310
Myalgia	9 (23.6)	4 (10.4)	0.222	3 (13.6)	2 (9.0)	1.000
Headache	8 (21.0)	1 (2.6)	**0.028**	5 (22.7)	2 (9.0)	0.412
Abdominal pain	3 (7.8)	0 (0)	0.240	3 (13.6)	1 (4.5)	0.670
Decreased DTRs	12 (31.5)	3 (7.8)	**0.019**	5 (22.7)	2 (9.0)	0.412
Increased DTRs	7 (18.4)	2 (5.2)	0.153	4 (18.1)	2 (9.0)	0.664
Mean systolic blood pressure (mmHg)	120.26 ± 13.25	112.27 ± 20.76	**0.021**	117.81 ± 10.79	117.50 ± 11.25	0.915
Mean diastolic blood pressure (mmHg)	78.16 ± 8.33	78.48 ± 7.95	0.713	78.12 ± 10.62	77.19 ± 12.10	0.714

DTR, deep tendon reflex. Bold values: statistically significant.

Table 4.
Blood lead concentrations (μg/L) before (B) and after (A) treatment in 60 patients treated with garlic (38 patients) and D-penicillamine (22 patients). Data are compared by Student's paired t-test.

	Total	Penicillamine	Garlic	*p*-value
B	419.70 ± 186.55	417.47 ± 192.54	426.32 ± 185.128	0.895
A	338.47 ± 128.05	315.76 ± 140.00	347.34 ± 121.056	0.485
p-value	<0.001	0.002	0.025	

in the systolic and diastolic (p value = 0.714) blood pressures were observed.

Student's paired t-test showed that there was no significant difference in pre-treatment BLCs between the two groups ($p = 0.895$). BLCs decreased significantly (p value <0.001) after treatment from 419.70 μg/L ± 186.55 to 338.47 μg/L ± 128.05 in all 60 patients. BLCs were reduced significantly ($p = 0.002$) from 426.32 ± 185.128 to 347.34 ± 121.056 μg/L in the garlic group. As expected, BLCs also decreased significantly ($p = 0.025$) from 417.47 ± 192.54 to 315.76 ± 140.00 μg/L in the D-penicillamine group. Further analysis by an independent Student's t-test demonstrated that there was no significant difference between the garlic and D-penicillamine groups in the amount of reducing BLCs ($p = 0.892$).

However, increases in BLCs were noticed in eight patients (36.4%) who took D-penicillamine, while it occurred in nine cases (23.7%) in the garlic group. Chi-square test showed that there was no significant difference in the frequency of increased BLCs between the two groups ($p = 0.376$).

Discussion

In this study, the most common symptoms and signs of patients with chronic mild-to-moderate lead poisoning were neuropsychiatric and neuromuscular complaints, which improved in a number of patients after treatment with garlic, but not with D-penicillamine. Naarala *et al.* [36] suggested that lead may cause neurotoxicity by producing reactive oxygen species and decreasing cellular glutathione. Wang *et al.* [37] suggested that oxidative stress, resulting from significant accumulation of aminolevulinic acid, plays an important role in lead-induced neurotoxicity in mice. They also showed that low-concentration lead exposure induces apoptosis of renal tubular cells, which was mainly mediated by oxidative stress [37,38]. Besides, there are studies which indicate that lead induces oxidative damage to liver [39,40]. However, we did not investigate the lead renal and liver toxicities in this study, but the previous investigations on these car battery workers with mild-to-severe occupational lead poisoning revealed no evidence of such organ complications [41,42].

Allicin (diallyl thiosulfinate) is the main biologically active compound of garlic which is produced from alliin by aliinase enzyme after garlic is chopped, crushed or chewed. It is responsible for the intense odour of fresh garlic [43].

Chung [44] assessed antioxidant activities of garlic compounds against free radical damage in the body and showed that allicin and alliin acted against superoxide. In addition, alliin could scavenge hydroxyl radicals. Furthermore, Prasad *et al.* [45] suggested that allicin is able to scavenge hydroxyl radicals as it blocked lipid peroxidation in liver. Therefore, because of the antioxidative effects of garlic compounds, we believe that its antioxidant activity may have a role in the alleviation of neuropsychiatric manifestations of lead toxicity in patients with chronic lead poisoning.

In this study, garlic reduced BLCs. Therefore, it is presumable that garlic ingredients (allicin or alliin) through their biologically active agents, such as thiosulfinate or amino functional groups, act through similar mechanisms as those of chelators like DMSA, penicillamine, dimercaprol and calcium edetate (Ca-EDTA) to facilitate the excretion of lead from the body. Aslani *et al.* [46] showed that blood and tissue lead concentrations in mice are reduced when they are treated simultaneously with oral allicin and DMSA. They proposed that allicin acts as a chelating agent in the treatment of lead poisoning. In another study by Najar-Nezhad *et al.*, [27] treatment of subacute lead toxicity with oral administration of allicin led to significant reduction of blood, kidney, bone and ovary lead concentrations in sheep. These therapeutic effects of allicin were attributable to the chelation and elimination of lead from the body. Hanafy *et al.* [25] also investigated therapeutic effects of garlic on lead poisoning in chicken and claimed that garlic contains chelating compounds that are able to reduce lead contents from tissues of chicken In addition, oral administration of garlic extract in three different doses (100, 200 and 400 mg/kg body weight) for 6 weeks has been effective in lowering liver, kidneys, brain and bone lead concentrations in rats [24]. Pourjafar *et al.* [23] indicated that garlic extract has almost the same effect on lowering blood and tissue lead concentrations as garlic tablets. Lead burden was efficiently reduced when garlic tablets were administered with doses 100, 50 and 25 mg/kg body weight for 8 weeks. In our study, 4-week treatment with an average of 17.9 mg/kg body weight powdered garlic resulted in significant (P value <0.001) reduction of BLCs. We postulate that garlic compounds may bind to Pb and facilitate its excretion from the body. It is also suggested that S-allyl cysteine and S-allyl mercaptocysteine, which are found in garlic extract, inhibit lead absorption from gastrointestinal tract [19,24,47]; thus, they are effective in both treating and preventing lead poisoning.

Elimination of the source of exposure should be the first step in the treatment of lead poisoning. Then, chelators are used to facilitate the excretion of lead from the body. We had already admitted that because of economic and social constraints and high level of unemployment, the workers could not abandon their work. Therefore, as an alternative, counselling was performed for 'all' workers 2 months before the study to limit lead exposure. Our clinical research assistant was in regular contact with the workers and the management of the factory to ensure the wearing of protective devices, taking the medications in a timely manner, side

effects and safety measures. Therefore, all workers had equal access to the information provided by the research team.

The standard antidotal treatments of lead poisoning have side effects [19–21], are expensive or require hospitalization. Shannon *et al.* [48] demonstrated that although low-dose D-penicillamine efficiently reduced BLCs in children, side effects were inevitable. They administered D-penicillamine with a dose of 15 mg/kg body weight. In fact, WHO has recently removed D-penicillamine from the list of lead antidote because of its serious side effects for children, but not for adults (http://www.who.int/entity/ceh/capacity/Lead.pdf).

Although the exact mechanism of garlic lowering BLCs remains unknown, it may prevent lead-induced oxidative stress, chelating lead in the body and inhibiting its absorption from the gastrointestinal tract. Patients who received garlic revealed better clinical improvement (significant reduction in irritability, headache and decreased DTR; table 3) and less side effects as judged by the total withdrawal from the study (seven in the garlic and 17 in the D-penicillamine group; table 2). Therefore, garlic can be considered as a safer medication than D-penicillamine for the treatment of mild–to-moderate lead poisoning. As garlic is an antioxidant with few side effects, we also recommend it for the prevention of lead poisoning in workers with occupational exposure, particularly in developing countries where complete prevention of lead exposure in the work environment is almost impossible.

We initially aimed to treat patients four times a day with D-penicillamine and garlic. However, because of the reported serious side effects of D-penicillamine [48–50], which concerned the Medical Ethics Committee, and possible poor compliance of taking these drugs in a timely manner, we preferred to reduce the treatment dose to three times daily for both groups. We are now pleased that even lower doses of both drugs were effective in lowering BLCs. However, we admit that limitations in our study such as lack of elimination of lead exposure sources and 24-hr urinary lead concentrations prevent us from making a general conclusion.

According to the authors' knowledge, this double-blinded clinical trial was the first study in which therapeutic effects of garlic was investigated in human individuals and compared with D-penicillamine as the old-established well-known antidote for the treatment of lead poisoning. However, more studies on the efficacy of allicin alone or in combination with the other standard treatment of lead poisoning are suggested. As we assessed the effect of garlic only in male patients, studies on women and children with lead poisoning in larger populations are recommended.

Conclusion

Based on the results of this study, garlic was as effective as D-penicillamine in significant reduction of BLCs. In addition, garlic revealed less side effects and more clinical improvement than D-penicillamine. Thus, garlic may be considered as an alternative to D-penicillamine in the treatment of mild-to-moderate occupational lead poisoning. However, more studies are required in larger groups of patients including women and children to make a general conclusion.

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