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Original Article

Comparison of Garlic therapeutic effects and standard therapy with De Penicillamine in patients with Lead poisoning

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ABSTRACT

Objectives: According to the studies done by the scientists on animals, garlic (Allium sativum) is effective in reducing blood and tissue lead concentrations. Investigation of therapeutic effects of garlic and compare it with D-penicillamine in patients with lead poisoning is the main goal of this study. Methods: The present study is a double-blind controlled clinical trial that was performed on 160 lead poisoning patients referred to the Razi Hospital in Ahvaz in 1397. Patients were randomly divided into two groups of penicillamine and placebo, and garlic (6 cubes of garlic and penicillamine tablets containing the usual dose of this drug) and they were treated for 4 weeks and taken medication three times a day. Blood lead levels (BLL) and Hb were measured before and after treatment. Also, clinical signs and symptoms of lead poisoning were compared with early finding. Results: In this study, BLL levels decreased significantly in both garlic and placebo groups (P = 0.0001 and P = 0.001), and in the garlic group from 103.75 ± 14.49 µg to 83.63 ± 13.3 and in the placebo group decreased from 96.71 ± 12.99 µg / ml to 85.16 ± 14.13. The mean difference of BLL before and after treatment in garlic and placebo groups was 20.20 ± 6.75 µg / ml and 11.56 ± 5.76 µg / ml, respectively, and the difference between the two groups were significant (P=0.0001). Conclusion: In result, clinically garlic was safer and as effective as D-penicillamine.

Keywords: Therapeutic Effects of Garlic, D-Penicillamine, Lead Poisoning

Introduction

For many years, lead (Pb) poisoning has been a much known important sickness, individuals are affected by it through acute, subacute and chronic exposure in environmental and occupational settings. Most commonly causes of it 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] As it is advised threshold for lead toxicity exists, as even low-level lead exposure may cause nervous, renal, skeletal, haematopoietic and reproductive elaborations. [3-8] Moreover, the level of clinical manifestations of lead poisoning appear differs extensively and depends highly on the acuity, age and individual variations. [9] Even though neurological and gastrointestinal manifestations is variated, [10] chronic lead poisoning may engage multiple systems. [11] Loss of short-term memory, inability to concentrate, irritability, depressive mood, paresthesia of extremities, and loss of coordination, generalized abdominal pain and nausea are the main symptoms that would occur in adults by chronic lead poisoning. [12] Clients may also complain about headaches, weakness and myalgia. [10] Anaemia and abnormal reaction time of deep tendon reflexes (DTR) are other common signs found in adults suffering chronic lead poisoning. [13] Preventing the redisposal is critical in patient's treatment suffering lead poisoning. [11, 14] Besides, chelators, such as calcium disodium EDTA (CaNa2EDTA), 2,3-dimercaptopropanol (BAL) d-penicillamine and Meso-2,3-

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dimercaptosuccinic acid (DMSA) named Succimer, have been very common to use treating 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, there are some problem with these treatments such as side effects, high costs and some drawbacks on the use of chelators. This indicates scientists should find alternatives for lead poisoning treatments. [19-21] Previous studies done on different types of animals have suggested that garlic has a significant effect in reducing blood and tissue lead concentrations through unknown mechanisms. [22, 23] In addition, garlic has already been known to have antimicrobial, hypolipidaemic, anticancer, antioxidant and antithrombotic effects. [24, 25] Investigation of therapeutic effects of garlic and compare it with D-penicillamine in patients with chronic lead poisoning is the main goal of this study.

Material and Methods

Participants

The present study is a double blinded, randomized clinical trial based on hospital records of Clients referred to the Ahvaz Razi hospital in 1397. The sample size considered in this study based on similar studies, [4] with alpha coefficient of 0.5 and $\beta<0.2$, was 157 subjects.

The inclusion criteria for the studied were as follow:

- Age over 18
- new poisoning with lead
- lead poisoning signs using laboratory data and symptoms and clinical manifestations
- lack of treatment for lead poisoning in the last 6 months
- Patient satisfaction.

On the other hand, the exclusion criteria for present study were:

- history of hypersensitivity reaction to garlic or penicillin family drugs,
- peptic ulcer disease
- taking anticoagulant
- antimalarial or gold salt medications
- anemia and agranulocytosis following treatment with D-penicillamine
- Finally those with a history of renal, heart and liver failure.

For the present study, necessary information of patients including demographic data, past medical histories and clinical manifestations of lead poisoning in 157 clients were recorded.

All patients were randomly divided into two groups: "D-penicillamine placebo treatment" and "D- penicillamine and garlic".

Ethical issues

The experimental procedures of the present study including interventions, data collections, and clinical assessments were approved by the local ethics committee of AJUMS (Ethic's Code: IR.AJUMS.REC.1397.427), which were in complete agreement with the ethical regulations of human studies.

Data analysis

The normality of the data in two genders was confirmed using the Kolmogorov–Smirnov test. Mann-Whitney, fisher-exact tests, chi-squared test and Wilcoxon test were used for analyzing the data as mono-variables. Also, multiple linear regression was used to analyze the data. The data were statistically analyzed in SPSS 22. The significance level was considered to be 0.05.

Results

A total amount of 157 (78 in the D-penicillamine and 79 in the garlic group) were investigated in this study. Their ages were ranged from 38.97 ± 10.47 years (range 21 to 86 years). The baseline characteristics of the patients studied in the two groups are presented in Table 1. There was no significant difference in the level of Hb in the group before the treatment ($P = 0.177$). However, BLL was significantly higher in the garlic treatment group than in the placebo group ($P = 0.002$). In this study, signs of lead poisoning in two groups are presented in Table 2. The two groups did not show any significant difference in terms of early symptoms, constipation, muscular problems, medical records and admissions in ICU ($P < 0.05$). Only types of digestive problems were different in two groups ($P = 0.1010$).

The results of the comparison of hemoglobin before and after treatment in both groups are shown in Table 3. As seen in the garlic treatment group, after 4 weeks of treatment, there was a significant difference in the Hb level of the patients ($P = 0.0001$), but no significant difference was observed in the placebo group after treatment ($P = 0.091$). Also, the Hb level after treatment in both groups showed a significant difference ($P = 0.002$).

The results of comparing blood lead levels before and after treatment in both groups are shown in Table 4. As seen, in the two groups of garlic and placebo treatment, there was a significant difference in BLL level after 4 weeks of treatment ($P < 0.05$). However, the BLL levels of the two groups showed a significant difference before the treatment, so that the blood lead level of the garlic treatment group was higher than the placebo group ($P = 0.002$).

On the other hand, comparison the level of lead in patients (difference between primary and secondary lead) showed that BLL reduction in garlic treatment group was significantly more than placebo group. The results of comparing lead changes before and after treatment in both groups are shown in Table 4.

In the end, the results of regression test showed that with the control of pre-treatment variables, age, level of literacy, place

of residence and route of administration, there was a significant relationship between garlic treatment with Hb and BLL.

Discussion

In the present study, the most common signs of lead poisoning were neuromuscular symptoms, especially myalgia, which after 4 weeks showed significant improvement in these symptoms in both groups. In the study of Kianoush et al., [13] the most common signs and symptoms in patients with mild to moderate lead toxicity were neuromuscular events that improved significantly in the garlic treatment group after four weeks of treatment. These results are consistent with the findings of our study. Naarala et al. [26] indicates that lead may cause neurotoxicity by producing reactive oxygen species and reducing cellular glutathione. Wang et al. [27] showed that oxidative stress caused by significant accumulation of aminolevulinic acid plays an important role in lead-induced neurotoxicity in mice. They also showed that exposure to low concentrations of lead induces tubular cell apoptosis, which is primarily mediated by oxidative stress. [27, 28] In addition, studies have shown that lead can cause oxidative damage to the liver. [29, 30] According to our result in this study we find that although standard de pene-silymin and placebo treatment also reduced BLL, the BLL reduction in the garlic-treated group was significantly higher than in the placebo group.

Allicin (diallyl thiosulfinate) is the main biologically active compound of garlic, which produces alliin by alliinase after the garlic is chopped, crushed or chewed. It is the cause of the strong smell of fresh garlic. [31]

The results of the study, El-Khishin et al., [32] in 2015 also indicated that garlic extract treatment reduced lead in the blood and kidney tissues of lead-induced mice, and its efficacy was comparable to dimercaptosuccinic acid (DMSA). The reduction of hemoglobin in lead poisoning is probably due to the effect of lead on hemoglobin biosynthesis or hemoglobin degradation to its components. [33] Chung [34] evaluated the antioxidant activity of garlic compounds on free radical damage in vivo and showed that allicin and alliin resist superoxide. In addition, alliin can scavenge hydroxyl radicals. In addition, Prasad et al. [35] showed that allicin can scavenge hydroxyl radicals because it prevents lipid peroxidation in the liver. Therefore, due to the antioxidant effects of garlic compounds, we believe that its antioxidant activity may help to alleviate the neuropsychiatric manifestations of lead poisoning in patients with chronic lead poisoning. In this study, garlic reduced BLCs. Therefore, it can be speculated that the garlic component (Allicin or Alliin) passes through its bioactive agent, such as thiosulfinate or amino functional group, by chelating agents such as DMSA, penicillamine, dimercaptopropionate and ethylene diamine. A similar mechanism of calcium tetraacetate (Ca-EDTA) works. Promote the excretion of lead in the body. Aslani et al. [2] showed that the blood and tissue lead concentrations of the mice decreased when treated with oral allicin and DMSA. They proposed that allicin can be used as a chelating agent for the treatment of lead poisoning. In another study by Najar-Nezhad et al., [21] the treatment of subacute lead toxicity by oral allicin resulted in a significant reduction in lead, kidney, bone and ovarian lead concentrations in sheep. These therapeutic effects of allicin can be attributed to chelation and elimination of lead in the body. Hanafy et al. [36] the therapeutic effect of garlic on lead poisoning in chickens was also studied, and it was claimed that garlic contained chelating compounds, which could reduce the lead content in chicken tissues. In addition, oral administration of three different doses of garlic extract (100, 200 and 400) mg / kg body weight for 6 weeks can effectively reduce the liver, kidney, brain and bone lead concentrations in rats. [37] Pourjafar et al. [38] showed that garlic extract reduced the blood and tissue lead concentrations almost identically to garlic slices. When the amount of garlic tablets was 100, 50 and 25 mg / kg body weight for 8 weeks, the lead load was effectively reduced. However, the study by Kilikdar et al. indicated that pretreatment with aqueous garlic extract would maintain Hb levels and prevent its reduction in lead-induced mice.

The first step in the treatment of lead poisoning should be to reduce exposure to lead sources. Then, chelators are used to facilitate the removal of lead from the body. Therefore, in the present study, all patients were advised and consulted about the need to avoid exposure to lead sources. Standard antidote to lead poisoning has side effects, [14, 39] which are expensive or require hospitalization. Shannon et al. [40] demonstrates that although low doses of D-penicillamine effectively reduce BLC in children, side effects are unavoidable. They gave D-penicillamine at a dose of 15 mg / kg body weight. In fact, the World Health Organization recently removed D-penicillamine from the list of lead antidote because it has serious side effects for children but not for adults. Although the exact mechanism by which garlic reduces BLC remains unknown, it prevents lead-induced oxidative stress, sequesters lead and inhibits its absorption from the gastrointestinal tract. Therefore, garlic can be considered a safer drug than D-penicillamine for the treatment of mild to moderate lead poisoning.

To the best of the authors' knowledge, this double-blind clinical trial was the first study in which the therapeutic effect of garlic was investigated in human individuals and compared with D-penicillamine as a well-known antidote to the treatment of lead poisoning. However, there have been more studies on the efficacy of using allicin alone or in combination with other standard lead poisoning treatments. Since In this study, most of the subjects studied were male, it is recommended that women and children with lead poisoning be studied in larger populations.

Conclusion

According to the results of this study, garlic is as effective as D-penicillamine in significantly reducing BLCs. In addition, garlic showed less side effects and more clinical improvement than D-penicillamine. Therefore, garlic can be considered as a substitute for D-penicillamine in the treatment of mild to moderate occupational lead poisoning.

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"Disclosure of interest."

The authors report no conflicts of interest.

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Appendix:

Table 1: Demographic data of patients

Variables		Garlet	Placebo	P-value	Test
sex	Male	77	77	1	Fisher-exact
	Female	2	1		
Age	(mean±SD)	38.99±28.99	38.13±50.23	0.851	Mann-Whitney
	Median(Iqr)	34(12.75)	34(13)		
Job (%)	workless	18(22.5)	26(33.3)	0.108	Fisher-exact
	self-employment	48(60)	39(50)		
	Employee	14(17.5)	10(12.8)		
	Other	0(0)	3(3.8)		
Way.Opiuom	Oral only	51(63.8)	51(65.4)	0.409	Chi-square
	Edible soluble	11(13.7)	15(19.2)		
	Edible processing	18(22.5)	12(15.4)		
Hb_1 (mean±SD)		9±50.85	9±35.75	0.141	Mann-Whitney
Median(Iqr)		9.8(1)	9.5(0.9)		
BLL_1 (mean±SD)		99.17±49.58	99.14±33.92	0.706	Mann-Whitney
Median(Iqr)		98.5(21)	97(20.5)		

Table 2: Study of symptoms and complications of lead poisoning in two groups

Complication		Garlet N (%)	Placebo N (%)	P-value	Test
First symptom	Digestion	57(71.3)	58(74.3)	0.634	Chi-square
	Weakness and anxiety	12(15)	13(16.7)		
	Myalgia	11(13.7)	7(9)		
Constipation	Yes	61(76.3)	62(79.5)	0.711	Fisher- exact
	No	2(2.5)	3(3.8)		
	Periodic	17(21.2)	13(16.7)		
Muscle. Problem	Myalgia	56(70)	49(62.8)	0.662	Chi-square
	decrease of power	7(8.8)	11(14.1)		
	Sense decrease	10(12.4)	12(15.4)		
	Motion disorder	7(8.8)	6(7.7)		
ICU. admission	Yes	24(30)	30(38.5)	0.262	Chi-square
	No	56(70)	48(61.5)		

Table 3: Comparison of Hemoglobin (Hb) changes in the two groups

	Garlet	Placebo	P-value	Test
Before	9±50.85	9±30.75	0.141	Mann-Whitney
	9.8(1)	9.5(9)		
After	9±74.87	9±36.72	0.001	Mann-Whitney
	9.91(1.08)	9.45(0.95)		
P-value	<0.001	0.033		
Test	Wilcoxon	Wilcoxon		

Table 4: Comparison of blood lead (BLL) changes before and after treatment in two groups

	Garlet	Placebo	P-value	Test
Before	99.17±49.58	99.14±33.92	0.706	Mann-Whitney
After	80.13±76.70	87.14±95.35	0.002	Mann-Whitney
P-value	<0.001	<0.001		
Test	Wilcoxon	Wilcoxon		