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Evidence-Based Case Report

Examining The Chelating Effectiveness of Dimercaptosuccinic Acid and Ethylenediaminetetraacetic Acid Calcium Disodium in Patients with Lead Poisoning: An Evidence-Based Case Report

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ABSTRACT

Introduction. Lead environmental and occupational exposures harm workers' health, both acute and chronic lead poisoning. Chelation therapy is one of the treatments for lead poisoning using several chelating agents available, including ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonate (DMPS), and 2,3-dimercaptopropanol or British Anti Lewisite (BAL). However, the use of these chelating agents varies and lacks standardized guidelines for lead poisoning cases.
Objective. To determine whether DMSA can be a better chelating agent than EDTA in treating lead poisoning among workers.
Methods. This study conducted a literature search using evidence-based databases focusing on clinical questions using the "PICO" method. The author searched the relevant articles using the following databases: "PubMed," "Cochrane Library," and "EMBASE." The keywords used included "lead poisoning," "lead intoxication," "EDTA" (MESH Term), "Ethylenedinitrilotetraacetic," "edetic acid" (MESH Term), "succimer" (MESH Term), "Dimercaptosuccinic Acid," along with their synonyms combined with Boolean operators. Inclusion criteria comprised studies involving adult populations aged >18 years, non-pregnant individuals, therapeutic research areas, systematic reviews/meta-analyses of randomized controlled trials or clinical trials, written in English, and with full-text availability. Exclusion criteria included articles with incomplete data or inaccessible full text.
Results. Based on the analysis of two reviewed literature, the author obtained insights into the effectiveness of using DMSA compared to EDTA in cases of lead poisoning. DMSA can be administered orally, providing better chelation therapy efficacy than EDTA in treating lead poisoning. It effectively alleviates lead poisoning symptoms and reduces blood lead levels better than EDTA.
Conclusion. DMSA can be considered an alternative chelating agent of choice for treating lead poisoning in workers.

INTRODUCTION

Lead poisoning is a common health problem among mining workers, particularly in tin and zinc mines. Commonly, lead is dispersed throughout the soil layers and also present in contaminated water, although in relatively small quantities. However, it is highly toxic to humans and animals and has significant health impacts. Inhalation or ingestion of lead can cause damage to the haematopoetic system. The nervous system, kidneys, brain, and digestive system.[1]

The symptoms of lead poisoning in adults depend on the concentration and duration of exposure. Common symptoms include increased blood pressure, headaches, abdominal pain, muscle and joint pain, and chronic exposure can lead to anemia.[2] The main cause of lead poisoning in mining workers is excessive and continuous exposure to lead during their work.[3,4] Typically, mining workers are exposed to lead through contaminated air from dust or lead particles during mining or ore processing. Lead contamination can also occur through skin contact with soil or objects contaminated with lead.[2]

The prevalence of lead poisoning in Indonesia is currently unavailable, but according to CDC data, 15 out of 100,000 workers are exposed to lead.[1,2] Lead exposure is highest among tin and manganese mining workers.[1] Generally, patients with lead poisoning can have their lead levels in the blood, known as Blood Lead Levels (BLL). Blood samples can be taken from either venous or capillary blood vessels. Urine lead levels (ULL) can also be examined by collecting urine samples.[4,5]

To reduce lead levels in the body, chelating agents can be a treatment of choice. Chelating agents are chemical compounds that can bind to heavy metal ions in the body and form complex compounds easily soluble in water, facilitating their elimination through urine or feces. In cases of lead poisoning, chelating agents can be used to help remove lead from the body. Some examples of chelating agents used in the treatment of lead poisoning include ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonate (DMPS), and 2,3-dimercaptopropanol or British Anti Lewisite (BAL).[1,2]

CASE DESCRIPTION[6]

To explore the comparison of these treatments we use the case reported by Du et al[6] in 2020. A 56-year-old man came to the Emergency Department complaining of severe abdominal pain, vomiting, weakness, and headache. He experienced similar symptoms a year ago but not as severe as the current episode. Physical examination reveals a lead line on the gingiva, palpable hepatomegaly, and normal findings on other physical examinations.

The patient worked at a lead (Pb) and manganese (Mn) smelter from 2002 to 2016. He works 3-4 days a week, 12 hours a day, wearing protective clothing, gloves, and a dust mask. Laboratory findings show moderate microcytic hypochromic anemia with a Hemoglobin level of 7.1 g/dL, MCV of 69 fL, blood lead level (BLL) of 64.8 µg/dL, urinary lead level (ULL) of 38.3 µg/dL, and normal liver function test results. The patient is diagnosed with acute on chronic Lead Poisoning with severe hemolytic anemia.

In this case, lead intoxication was linked to the previous of his employment history in Lead and Mangan Smelter from 2002-2016. The patient received the chelation therapy with calcium disodium ethylene-diaminetetraacetate (CaNa2EDTA) started on the first day of admission with a 3-day-on and 4-day-off CaNa2EDTA regimen as one course, for three courses. This regimen has been registered in the “WHO Model List of Essential Medicines” in 2017.

However, there is no clear data about the dosage given to the patient. After three courses of CaNa2EDTA chelation, all of his symptoms were alleviated; BLL decreased and Hb increased. BLL decreased from 64.8 µg/dL to 40 µg/dL and Hb increased from 7.1 g/dL to 9 g/dL. There was no side effect from the treatment. There was no data related to the cause of recurent intoxications and also his working history after being discharged from the hospital. This patient was later on diagnosed with lung cancer and transferred to the Oncology Unit in a Cancer Hospital for further treatment.

Based on the case, to explore the comparison of other chelating treatments versus EDTA, the authors seek scientific evidence regarding whether DMSA demonstrates better effectiveness as a chelating agent in alleviating lead poisoning symptoms compared to EDTA. The goal of this study is to provide a scientific evidence-based chelation therapy option for patients with lead poisoning.

PROBLEM FORMULATION

In workers with lead poisoning, does DMSA demonstrate superior effectiveness as a chelating agent compared to EDTA?

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EVIDENCE SEARCH STRATEGY

The search for articles was conducted to address the problem formulation using three electronic databases of PubMed, EMBASE, and Cochrane Library.

To search for journals, the authors used the advanced search mode in the databases using keywords such as "Lead Poisoning", "Lead Intoxication", "EDTA", "Ethylenedinitrilotetraacetic", "Edetic Acid", "Succimer", "Dimercaptosuccinic Acid", or their synonyms as determined by the authors. The search utilized MeSH terms and title/abstract fields, combined with Boolean operators "OR" and "AND". The preferred study designs expected were a Systematic Review/Meta-Analysis of RCTs and clinical trials focusing on therapy. This research used the inclusion criteria of adult populations aged 18 years and above, excluding pregnant women, the research area of therapy with study design of systematic reviews/meta-analysis of RCT or clinical trials, and English full-text articles while the exclusion criteria were articles with incomplete data or inaccessible full text. The literature search was completed on March 29, 2023. The obtained literature was critically appraised using the validity-importance-applicability (VIA) framework, utilizing the therapy worksheet from the Oxford Centre for Evidence-Based Medicine. The level of evidence was determined using the Oxford Centre for Evidence-Based Medicine 2011 guidelines.

RESULTS AND DISCUSSION

Evidence Search Result

The literature search was conducted on March 29, 2023, using the following electronic databases: PubMed, Cochrane Library, and EMBASE. (See **Table 1**)

Table 1. Articles searching strategy

Database	Search Strategy	Hits	Selected Article
Pubmed	((((lead intoxication[Title/Abstract]) OR (poisoning, lead[MeSH Terms]))) AND ((succimer[Title/Abstract]) OR (Dimercaptosuccinic Acid[MeSH Terms]))) AND (((((EDTA[Title/Abstract]) OR (Ethylenedinitrilotetraacetic Acid[Title/Abstract])) OR (Ethylenedinitrilotetraacetic Acid[MeSH Terms])) OR (Edetate, Calcium Disodium[MeSH Terms])) OR (edetic acid*[MeSH Terms]))	57	2
Cochrane Library	(lead poisoning OR lead intoxication in Title Abstract Keyword) AND (succimer OR Dimercaptosuccinic Acid in Title Abstract Keyword) AND (EDTA OR Ethylenedinitrilotetraacetic Acid OR Edetate Calcium Disodium OR edetic acid in Title Abstract Keyword)	5	0
EMBASE	('lead poisoning'/exp OR 'lead poisoning' OR 'lead intoxication'/exp OR 'lead intoxication') AND ('succimer'/exp OR 'succimer' OR 'dimercaptosuccinic acid'/exp OR 'dimercaptosuccinic acid') AND ('edta'/exp OR 'edta' OR 'ethylenedinitrilotetraacetic acid'/exp OR 'ethylenedinitrilotetraacetic acid' OR 'edetate calcium disodium'/exp OR 'edetate calcium disodium' OR 'edetic acid'/exp OR 'edetic acid')	279	1

The literature selection process involved screening the titles/abstracts from the three electronic databases, and after checking for duplicates, a total of 258 articles were identified. Subsequently, title and abstract screening was conducted by reading the article titles and abstracts, resulting in 15 articles that will be further filtered based on eligibility criteria.

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Two study articles were identified for critical appraisal to address the clinical question. The search strategy scheme can be found in the following **Figure 1**.

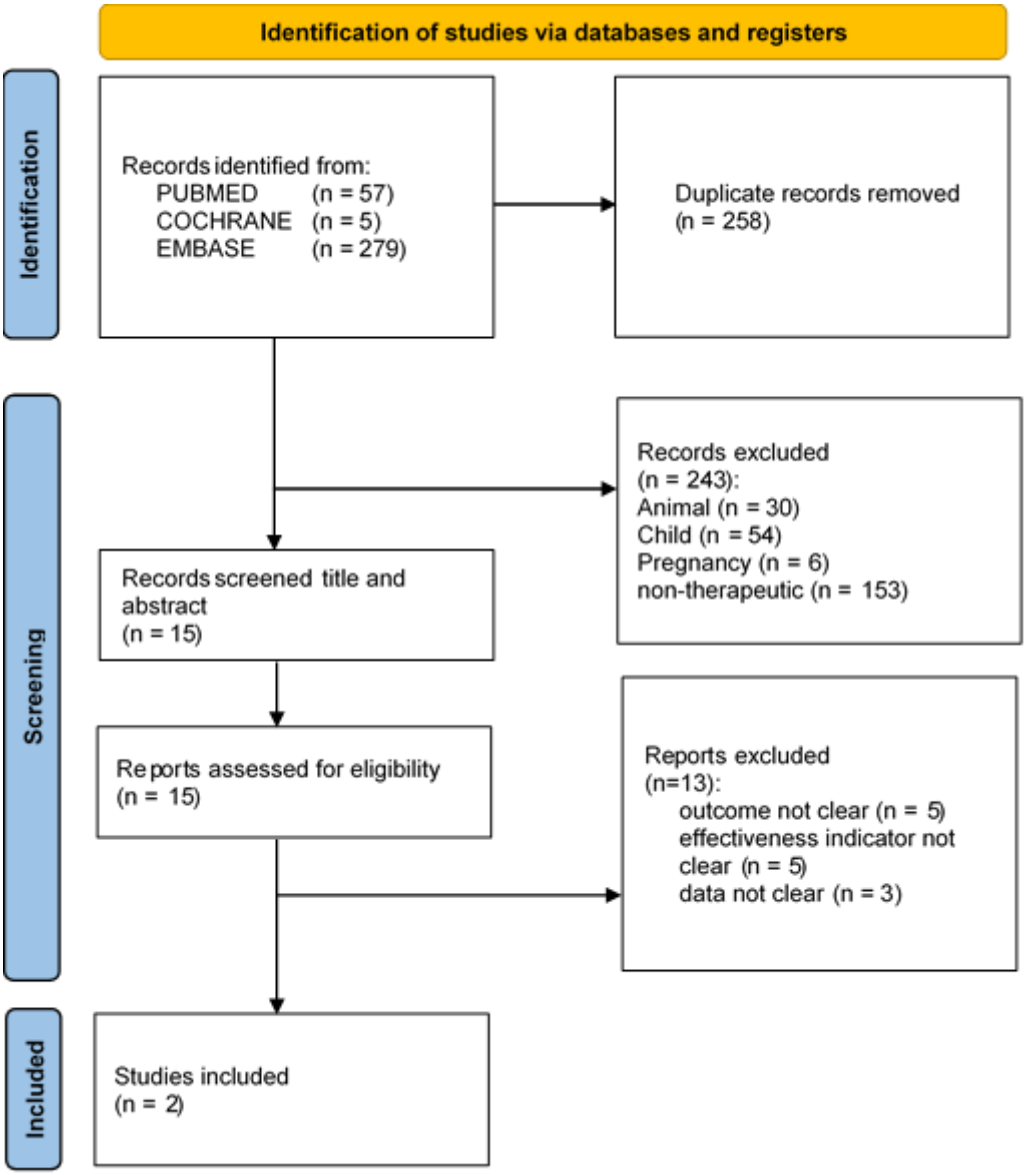

Figure 1. PRISMA flow chart article search

The two selected articles are studied by Sakthithasana et al. and Georgieva et al., which will be further reviewed using the therapy worksheet from the Oxford Centre for Evidence-Based Medicine. For more details on study characteristics, please refer to **Table 2**.

Table 2. Study characteristics

Researcher & year of study	Country	Study design	Populations	Number of subjects	Intervention	Comparator	Outcome
Sakthithasan, et.al. (2018)[7]	France	Clinical Trial	Lead poisoning workers at Widal Hospital in Paris, France	34	DMSA	EDTA	Workers who experience lead poisoning experience clinical improvement in the form of loss of clinical symptoms after DMSA or EDTA administration. DMSA administration is able to eliminate clinical symptoms better than EDTA although not statistically significant. (Level of Evidence IIB)
Georgieva et.al. (2015)[8]	Bulgaria	Clinical Trial	Workers at a metallurgical plant hospitalised in Bulgaria for lead poisoning	35	DMSA	EDTA	Workers who received treatment with DMSA showed as well reduced blood lead levels as EDTA, but DMSA administration prevented the release of the mineral zinc in the blood compared to EDTA. (Level of Evidence IIB)

Critical appraisal was conducted in terms of the validity, importance, and applicability of each previously identified study. The following are the results of the critical appraisal of the literature used to address the clinical question. A detailed description of the journal appraisal will be provided in Table 3 and Table 4.

Table 3. Critical appraisal of Sakthithasan, et al[7]

Author(s)	Sakthithasana et.al. (2018)
Title	A comparative study of edetate calcium disodium and dimercaptosuccinic acid in the treatment of lead poisoning in adults
Study Design	Randomized Clinical Trial
Population	Patient > 18 years old, not pregnant with lead poisoning
Intervention	DMSA
Comparison	EDTA
Outcome	Improvement of clinical symptoms and Decreased BLL (*Blood Lead Level*)
Are the results of the trial valid?	
What question did the study ask	· Population: Patient > 18 years old, not pregnant with lead poisoning · Intervention: DMSA · Comparison: EDTA · Outcome: Improvement of clinical symptoms and Decreased BLL (Blood Lead Level)
Was the assignment of patients to treatment randomised?	It is unclear, the patients were randomized into 2 groups but the randomization method is not described in detail, the first group (n = 21) received DMSA (1050 mg / m2 / day divided into 3 doses). While the second group (n = 16) received EDTA 500 mg / m2 / day in 1-hour infusion of 250 ml dextrose 5%. The intervention is administered in 2 cycles.
Where the groups similar at the start of the trial?	Yes, baseline characteristics in groups 1 and 2 do not have significant differences in characteristics
Aside from the allocated treatment, were groups treated equally ?	Yes, both the group that got the intervention and the one that didn't get the same action
Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?	No, there are 3 people who lost to follow-up (8%)
Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No, researchers say the study is open-label
What were the results?	
How large was the treatment effect?	* Significant improvement in symptoms was found in the group that received DMSA administration but did not show a statistically significant difference. * RR = (7/20) / (9/14) = 0.35 / 0.64 = 0.65 * EER = 0.35 * CER = 0.64 * RRR = (CER-EER)/CER = (0.64-0.35)/0.64 = 45% * ARR = CER-EER = 0.29 * NNT = 1/ARR = 1/0.29 = 3.44
How prescise was the estimate of the treatment effect?	The study used a p-value <0.05 as a significant criterion. In this study, there were no RR or NNT values reported in the research results. However, we manually calculate and get the RR value of 0.65 and NNT value of 3.44.
Is my patient so different to those in the study that the results cannot apply?	No, the characteristics of the patient are the same as the patient in the scenario
Is the treatment feasible in my setting?	Yes, DMSA is available in hospitals in Indonesia.
Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	Yes, in this study, no symptoms of significant side effects occurred. Even the use of DMSA does not cause loss of zinc minerals in the body

Table 4. Critical appraisal of Georgieva, et al[8]

Author(s)	Georgieva et.al. (2015)
Title	Antidotal Effect of Succimer and CaNa2 EDTA on Workers Exposed to Lead, Cadmium and Arsenic
Study Design	Clinical Trial
Population	Worker who work at metallurgy factory
Intervention	DMSA
Comparison	EDTA
Outcome	Decreased blood lead level
Are the results of the trial valid?	
What question did the study ask	· Population : worker who work at Metallurgy factory · Intervention : DMSA · Comparison : EDTA · Outcome : decreased BLL (Blood Lead Level)
Was the assignment of patients to treatment randomised?	No, there is no explanation in this study whether randomisation was carried out
Where the groups similar at the start of the trial?	It is unclear though the average age in both groups was mentioned, but there was no comparison of table characteristics of the study sample
Aside from the allocated treatment, were groups treated equally ?	Yes, both the group that got the intervention and the one that didn't got the same action
Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?	Yes, all research samples complete a series of studies
Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No, the researcher did not mention the presence of blinds when the study was conducted
What were the results?	
How large was the treatment effect?	There was a decrease in blood lead levels in both DMSA and EDTA groups, but in the DMSA group, the effect was better because it did not cause zinc deficiency at the end of the study. Average decrease in blood lead levels on day 5 after therapy with P<0.05 where lead levels in the DMSA group were 0.71 ± 0.4 and the EDTA group was 0.73 ± 0.09 µmol/l
How prescise was the estimate of the treatment effect?	The study used p value <0.05 as a significant criterion. In the study, there was no mention of RR or NNT values in the research results.
Is my patient so different to those in the study that the results cannot apply?	No, the characteristics of the patient are the same as the patient in the scenario
Is the treatment feasible in my setting?	Yes, DMSA availability in Indonesia is available in hospitals
Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	Yes, in this study, no symptoms of significant side effects occurred. Even the use of DMSA does not cause loss of zinc minerals in the body

In summary, the overview of each study can be seen in **Table 5** below.

Table 5. The summary of critical appraisal importance, applicability dan level of evidence

Parameter		Study	
		Sakthithasan, et.al.[7]	**Georgieva et.al.[8]**
Validity	Was the assignment of patients to treatment randomized?	Unclear	No
	Were the groups similar at the start of the trial?	Yes	Unclear
	Aside From the allocated treatment, were groups treated equally?	Yes	Yes
	Were all patients who entered the trial accounted for? And were they analyzed in the groups to which they were randomized?	No	Yes
	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No	No
Importance	How large was the treatment effect?	$p < 0.05$, RR =0.65, NNT = 3.44	The outcome is the blood lead level ($p < 0.05$)
	How precise was the estimate of the treatment effect?	There was an improvement in clinical symptoms but not statistically significant	There is a statistically significant decrease in blood lead levels in DMSA
Applicability	Is my patient so different from those in the study that the results cannot apply?	No	No
	Is the treatment feasible in my setting?	Yes	Yes
	Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	Yes	Yes
Level of evidence		3	3

DISCUSSION

Lead poisoning is a prevalent health issue among miners, particularly in tin and zinc mines. Lead is a highly toxic heavy metal that can cause damage to the nervous system, kidneys, brain, and digestive system when inhaled or ingested. Lead poisoning can be acute or chronic and commonly affects workers in the mining and metal processing sectors. According to the Sakthithasan et.al.[7] study, lead poisoning presents various clinical symptoms, and assessing blood lead levels serves as an initial indicator for guiding lead poisoning treatment. [7] The study also mentions that despite the availability of various chelating agents for managing lead poisoning, their usage varies, and there is no specific indicator. The easiest indicator of treatment success is the improvement of clinical symptoms accompanied by a decrease in blood lead levels. The use of DMSA has proven effective in improving clinical symptoms, although there was no significant statistical difference observed.

EDTA is the standard chelation therapy for lead poisoning. However, a study conducted by Boyadzhieva et.a.l[8] states that the use of EDTA can lead to zinc and other mineral deficiencies, making it unsuitable for long-term use. Conversely, DMSA, which has similar effectiveness to EDTA in reducing blood lead levels, can also prevent the occurrence of zinc and other mineral deficiencies.

The weaknesses of both studies lie in the limited clinical trials conducted, as there was no clear randomization and blinding process applied to the research samples, which may introduce bias. However, considering the limited studies on lead management, especially in workers and adults, the results of both studies can serve as a good starting point for assessing chelation therapy for lead poisoning. The use of DMSA can be considered as an alternative for lead poisoning, as it can be taken orally and has comparable effectiveness to EDTA. DMSA may also be preferred to avoid the risk of zinc and other mineral deficiencies associated with EDTA administration or when long-term treatment of lead poisoning is required.

CONCLUSION

The use of DMSA has no superiority of effectiveness compared to EDTA in managing lead poisoning. The use of DMSA can be considered as an alternative treatment option, especially for patients with mineral deficiencies or when long-term chelation therapy is required.

DECLARATION

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