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Research Article

Acute Neurotoxicity and Hyperlactatemia Due to Hemodialysis Water System Contamination: A New Relationship

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Abstract

Objectives: Many acute complications may develop in hemodialysis (HD) patients. Among these, life-threatening poisoning due to HD water system contamination has an important place. In this study, we aimed to investigate the relationship between acute neurotoxicity and hyperlactatemia, which developed after HD in HD patients.

Methods: This retrospective study includes intoxication cases treated in two tertiary centers. The laboratory and clinical parameters, treatments and outcomes of the patients were recorded during their hospitalization.

Results: A total of 15 patients were included in the study. Almost all patients had headache, dizziness, and nausea. The mean lactate was 23.7±5 mmol/L. All patients underwent a mean of 5.6±0.8 HD session. Dimercaprol, a heavy metal chelator, was administered to one patient due to its severe clinical course. The same patient died on the 8th day of hospitalization. Other patients' neurotoxicity findings were mostly resolved.

Conclusion: HD patients have a high risk of heavy metal toxicity due to direct blood contact. We report the association of neurotoxicity and hyperlactatemia for the first time in this patient group.

Keywords: Hemodialysis, hemodialysis water system, neurotoxicity, hyperlactatemia, heavy metal

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The most commonly used renal replacement therapy (RRT) in chronic kidney disease is hemodialysis (HD). According to the Turkish Society of Nephrology's 2021 registry report, the prevalence of in-center HD patients among the RRT options is 70% (https://nefroloji.org.tr/uploads/files/REGISTRY_2022.PDF). Many acute and chronic complications can be seen in HD. Water system contamination has an important place in acute and chronic complications seen in HD patients.[1-5] While a healthy individual consumes 15-20 liters of water per week, a standard HD patient (3 days a week, 4 hour-session, dialysate flow rate 500 ml/min) is exposed to 500 liters of water directly through blood.[6] For this reason, pollutants such as trace elements, toxins, bacteria, viruses and endotoxins that are easily tolerated in healthy people cause significant problems in HD patients.[6-8]

HD water is mostly supplied from municipal drinking water or well water and must meet minimum standards. Due to its potential risks, HD water is given to the patients after being subjected to specific and strictly controlled HD water purification systems.[6,8]

The aim of our study is to present the clinical and laboratory characteristics of cases who developed acute neurotoxicity and hyperlactatemia after HD treatment in the same center.

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Methods

This retrospective study was conducted between May-July 2023 at a tertiary care university hospital and a tertiary state hospital. All patients who applied to the emergency department after entering HD in the 2nd and 3rd sessions on the same day in the district state hospital and were hospitalized by being referred to the two centers where our study was conducted were included in the study.

Data Collection

Patient data were obtained from hospital automation systems and patient files. The following information of the patients were recorded; age, gender, weight, primary kidney disease etiology (diabetes mellitus (DM), hypertension (HT), chronic glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD), urinary tract anomaly), comorbid diseases (DM, HT, coronary artery disease, heart failure, peripheral arterial disease), HD access type, HD duration, systolic and diastolic blood pressures.

Patients with symptoms and findings of admission; Headache, dizziness, nausea, abdominal pain, drowsiness, confusion, balance disorder were recorded in the patient files. Laboratory data at the first application and during the follow-up period, such as white blood cell (WBC) count, hemoglobin (Hg) level, platelet count (PLT), urea, creatinine, sodium, potassium, calcium, lactate dehydrogenase (LDH), C-reactive protein (CRP), pH, bicarbonate, and lactate values were recorded. Intubation requirement and patient survival were evaluated during the follow-up period. The number of hemodialysis sessions applied during the patients' hospitalization and the blood lactate levels after the hemodialysis sessions were recorded.

Hemodialysis Water Contamination Data

Bacterial endotoxin (Limulus amebocyte Lysate (LAL)) test, hardness, conductivity, pH, chlorine, and boron levels obtained from the dialysate sample were recorded. Iron and nickel levels obtained from municipal drinking water were recorded.

The results of arsenic, copper, mercury, zinc, selenium, chromium, lead, manganese, nickel, cadmium levels obtained from the blood of the patients were recorded.

Statistical Analysis

Descriptive data were recorded as frequencies and percentages for categorical variables. Continuous variables were presented mean±standard deviation (SD). The normality of the data was tested by the Shapiro-Wilks test. The paired-samples t test or Wilcoxon signed-ranks test were used to determine any significant differences between repeated measures. Categorical variables were compared with Fisher's exact test. Statistical analyses were performed using IBM SPSS for Windows v.22 software.

Results

Occurrence of Cases and Baseline Characteristics of the Study Population

Although the patients in the first HD session in the center where the patients entered HD had no symptoms, a total of 15 patients who entered HD in the second and third sessions applied to the emergency department with similar symptoms. Baseline demographic, clinical, and laboratory findings of patients are presented at Table 1. The mean

Table 1. Baseline demographic, clinical, and laboratory findings of patients.

Variabilite	n=15
Age, (years) Mean±SD	60.2±18.6
Male, %	60
Primary kidney disease, %	
Diabetes mellitus	26.7
Unknown	26.7
ADPKD	20
Hypertension	13.3
Urinary tract abnormalities	13.3
HD access type, %	
Arteriovenous fistula	60
Tunneled central venous catheter	20
Non-tunneled central venous catheter	13.3
Arteriovenous graft	6.7
HD duration, (month) Mean±SD	49.6±58.4
Systolic blood pressure, (mm Hg) Mean±SD	138±24.8
Diastolic blood pressure, (mm Hg) Mean±SD	84±16
Weight, kg	62.4±11.5
Application complaints, %	
Headache	100
Dizziness	100
Nausea	93.3
Balance disorder	80
Drowsiness	66.7
Confusion	53.3
Abdominal pain	33.3
White Blood Cell Count (10^3/mm^3) Mean ±SD	7895±2024
Hemoglobin (g/dL) Mean±SD	12.6±1.5
Serum creatinine, (mg/dL) Mean±SD	4.4±1.4
Sodium, (mEq/L) Mean±SD	139.3±3.7
Potassium, (mEq/L) Mean±SD	4.3±0.8
Calcium, mg/dL Mean±SD	9.3±0.8
Lactat dehydrogenase, U/L Mean±SD	214.3±40.6
C-reactive protein, mg/L Mean±SD	18.1±28.2
pH, Mean±SD	7.3±0.05
Bicarbonate, (mEq/L) Mean±SD	17.2±3.7
Lactate, (mmol/L) Mean±SD	23.7±5

ADPKD: Autosomal dominant polycystic kidney disease; HD: Hemodialysis; SD: Standart deviation.

age of our study group was 60.2±18.6 years, and 60% of the patients were male. The most common etiology of primary kidney disease was DM (4 patients). However, it was remarkable that 3 patients (20%) had ADPKD. HD access type was mostly arteriovenous fistula (9 patients). The mean duration of HD was 49.6±58.4 months. Systolic and diastolic blood pressures were 138±24.8 mm Hg and 84±16 mm Hg, respectively. The mean weight of the study group was 62.4±11.5 kgs. None of the patients had fever, dyspnea or low oxygen saturation. Almost of the patients had headache, dizziness, and nausea. Other symptoms and findings are listed in order of frequency: balance disorder 80%, drowsiness 66.7%, confusion 53.3%, and abdominal pain 33.3%. Baseline clinical features of each patient are presented in Table 2.

WBC, sodium, potassium, calcium, LDH levels of our study group were within the normal range. The mean Hgb value was 12.6±1.5 g/dL and there were no patients with <10 g/dL. The mean CRP was 8.1±28.2 mg/L. In venous blood gas evaluation, mean pH was 7.3±0.05, bicarbonate was 17.2±3.7 mEq/L, and lactate was 23.7±5 mmol/L. Lactate levels were remarkable. The baseline laboratory characteristics of each patient are presented in Table 3.

The endotoxin LAL test was run twice from HD water and the results were negative. Water hardness, water conductivity, pH (6.8), chlorine, copper, aluminum, iron, and zinc levels were within the normal range. On the other hand, boron levels were high (3.5 ppb, upper limit was 1 ppb), nickel levels were high (33 ppb, upper limit was 20 ppb). Working from municipal drinking water; iron levels were high (208 ppb, upper limit was 200 ppb), nickel levels were high (93 ppb, upper limit were 20 ppb).

The patients were referred to tertiary centers due to intoxication caused by the HD water system.

Patient Follow-Ups and Treatments in Tertiary Centers

Patients numbered 1-8 were followed in the university hospital, patients numbered 9-15 were followed in the state hospital. None of the patients had signs of methemoglobinemia, hemolytic and endotoxic reactions. Lactate levels were re-examined in the university hospital. According to the re-examination, the mean lactate values were 4.7±6.9. After that, all patients entered HD due to its potential benefits. It was observed that the initial symptoms of some of the patients improved even without receiving HD. A mean number of 5.6±0.8 HD sessions was applied to the patients. Figure 1 shows that lactate levels decreased statistically significant with HD sessions ($p<0.001$). Patient number 2 was intubated during the first HD due to deterioration in general condition. After the first HD session, blood samples were taken from the patients and trace element levels were studied (Table 4). It is noteworthy that all patients had high levels of lead, manganese and nickel in common. Due to the severe clinical course, dimercaprol, a heavy metal chelator, was administered to patient number 2 for 3 days. The changes of blood trace element levels in patient number 2 after dimercaprol treatment are presented in Table 4. Despite these changes, there was no change in the clinical condition of patient number 2. During her follow-ups,

Table 2. The characteristic clinical features of each patient

Patient Number	Gender (m/f)	Age (years)	Headache (Y/N)	Dizziness (Y/N)	Nausea (Y/N)	Abdominal pain (Y/N)	Drowsiness (Y/N)	Confusion (Y/N)	Balance disorder (Y/N)	Intubation (Y/N)	Survivor (Y/N)
1	m	81	Y	Y	Y	N	Y	Y	Y	N	Y
2	f	30	Y	Y	Y	N	Y	Y	Y	Y	N
3	m	74	Y	Y	Y	N	N	N	N	N	Y
4	m	42	Y	Y	Y	N	Y	Y	Y	N	Y
5	m	72	Y	Y	Y	N	Y	Y	Y	N	Y
6	m	74	Y	Y	Y	N	Y	Y	Y	N	Y
7	m	84	Y	Y	Y	N	Y	Y	Y	N	Y
8	f	52	Y	Y	Y	N	Y	Y	Y	N	Y
9	f	49	Y	Y	Y	N	N	N	N	N	Y
10	m	49	Y	Y	Y	N	N	N	Y	N	Y
11	m	37	Y	Y	N	N	N	N	N	N	Y
12	f	37	Y	Y	Y	Y	N	N	Y	N	Y
13	f	67	Y	Y	Y	Y	Y	Y	Y	N	Y
14	f	84	Y	Y	Y	Y	N	N	Y	N	Y
15	m	70	Y	Y	Y	N	N	N	Y	N	Y

m: Male; f: Female; Y: Yes; N: No.

Table 3. The characteristic baseline laboratory features of each patient

Patient number	Hgb (g/dL)	Serum creatinine (mg/dL)	Ca (mg/dL)	LDH (U/L)	CRP (mg/L)	pH	Bicarbonate (mEq/L)	Lactate (mmol/L)
1	14.1	5.9	9.9	184	5	7.33	18.1	30
2	11.2	5	9.9	196	2	7.23	11.9	16
3	10.9	3.5	8.9	203	2	7.29	18	25
4	11.7	4.2	7.9	245	8	7.32	15.3	23
5	10.9	2.7	7.7	271	62	7.36	19.4	22
6	12.7	4.1	8.8	199	2	7.27	17.8	30
7	15.5	6.1	9	155	3	7.32	17	25
8	11.6	7.4	10	262	16	7.29	14.5	26
9	11.3	4.4	10.3	N/A	4	7.23	14.8	26
10	13.7	3.5	10.3	N/A	62	7.31	23.8	16
11	14.6	4.4	10.1	N/A	2	7.43	26	16
12	12.8	4.5	9.5	N/A	3	7.32	15.7	21
13	12.2	2.5	9.7	N/A	2	7.29	14.4	N/A
14	11.3	2.4	8.8	N/A	89	7.4	17.9	30
15	14.7	6.2	9.9	N/A	9	7.32	14.3	26

Hgb: Hemoglobin; Ca: Calcium; LHD: Lactate dehydrogenase; CRP: C-reactive protein.

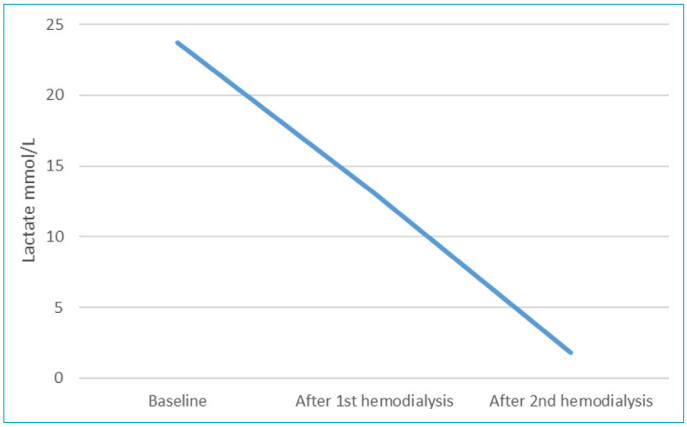

Figure 1. Serum lactate change by Hemodialysis.

brain death occurred and she died on the 8th day of hospitalization. Other patients were discharged on the 6th day of their follow-ups, with significant decrease of neurotoxicity findings.

Discussion

To the best of our knowledge, our study is the first to reveal the relationship of neurotoxicity and hyperlactatemia in intoxications caused by HD components in HD patients. While no symptoms developed in the patients in the first HD session at the center on the day the cases emerged, the development of acute neurotoxicity and hyperlactatemia in the patients in the second and third HD sessions is remarkable. This allowed us to focus on the common touchpoint. Water system may affect all patients in HD units.[6] Many life-threatening intoxications associated with HD water system contaminants have been described.[1-5] Some of these occur in the acute phase and some in the chronic phase. Our study group reveals an acute life-threatening condition. At this point, the main focus of our study will be hyperlactatemia and neurotoxicity.

Lactate is widely produced in the body, especially in the skeletal muscles. It is rapidly eliminated from the liver in normal physiology.[9] Therefore, decrease in lactate levels measured in the university hospital in this study was inevitable. D-lactate is not measured by routine biochemical methods but is produced by colon bacteria during intestinal transit of large amounts of unabsorbed carbohydrates and is potentially neurotoxic.[10] As in our study, L-lactate measured by routine biochemical methods does not have neurotoxic effects.[11] It is not considered a HD indication alone. Hyperlactatemia is traditionally divided into Type A hyperlactatemia in which tissue hypoxia/hyperfusion predominates, and Type B hyperlactatemia, which is mostly mitochondrial dysfunction without tissue hypoxia. Since there were no signs of tissue hypoxia in our study group, we were faced with Type B hyperlactatemia. Many factors have been defined for type B hyperlactatemia.[11] Since more than one patient in our study group were affected at the same time, we were withdrawn from medication use. Alcohols (ethanol, methanol, propylene glycol)[12,13] carbon monoxide[14], and cyanide[15] are among the possible factors. Carbon monoxide intoxication was clinically excluded. However, analysis was not performed for alcohols and cyanide.

Table 4. Blood trace element levels of each patient

Patient number	Arsenic (0-12) µg/L	Copper (800-1550) µg/L	Mercury (0-10) µg/L	Zinc (400-860) µg/L	Selenium (23-190) µg/L	Chromium (0.7-28) µg/L	Lead (0-49) µg/L	Manganese (4.2-16.5) µg/L	Nickel (0-10) µg/L	Cadmium (0-5) µg/L
1	0.22	946	9.8	565	81.8	19.2	169.2	42.2	42.6	0.7
2	0.22	896.8	92.5	548	38.1	32.9	128.6	51.4	81.8	0.7
3	0.79	1184	8.7	571	55.3	19.5	86.7	31.9	51.3	0.6
4	0.24	1486	1	550	91.6	26.3	90.7	57.2	46.9	0.2
5	0.32	1029	2.2	479	52.1	108.4	50.6	85.9	26.3	1.9
6	0.05	1055	20	712	51	28	128.9	46.5	65.5	0.9
7	14.8	773.9	28.5	1165	50.9	124.4	258.7	987	80	5.2
8	1.6	1360	199.2	2931	74.8	117.8	385.7	321.1	81.5	4.1
9	0.7	999.8	55.7	537	61.3	32	100.7	36.9	88.6	0.7
10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11	0.5	870	5.5	516	81.3	35.7	167.4	104.5	77.5	0.7
12	0.4	933.5	12.4	573	61.4	25	106.8	30.7	57	1.3
13	0.05	1239	0.9	451	81.6	32.5	109.2	41.9	76.4	0.6
14	1.2	181.5	118	631	38.1	44.8	162.7	28	81.9	2.4
15	0.4	1392	17.4	924	80.7	47.6	138.5	43.9	158.6	1
2*	N/A	N/A	6.9	N/A	N/A	24	97.4	11.9	6.4	N/A

* After dimercaprol treatment.

For any toxin to cause neurotoxicity, it or its metabolite should pass through the cerebrospinal fluid and affect the central nervous system. Aluminum is a heavy metal that can cause fatal encephalopathies in HD patients.[16] Although aluminum was not detected in dialysate in our study group, it was not studied from patient blood. We could not find data in the literature that aluminum causes hyperlactatemia. All patients had high blood lead, manganese and nickel levels. Lead can leak from the metal plumbing into the drinking water network. It may cause encephalopathy with severe acute toxicity in HD patients. In the literature, it has been reported that blood lead level is >80 mcg/dL in acute lead toxicity and >100 mcg/dL in encephalopathy.[17-19] Since the blood lead unit used in our study was µg/L, these values were >800 µg/L for acute toxicity and >1000 µg/L for encephalopathy. All patients in our study group were far away from these levels. In addition, we could not detect a relationship between lead levels and hyperlactatemia. Manganese can cause neurotoxicity, which is dominated by extrapyramidal side effects, through contaminated well water and in metalworkers.[20] Manganese-related toxicity has not been reported in HD patients in the literature. We could not detect a relationship between manganese levels and hyperlactatemia. Nickel-induced neurotoxicity has not been reported in HD patients in the literature. We could not see a relationship between nickel levels and hyperlactatemia.

The neurotoxic and neurodegenerative effects of heavy metals have been known for a long time. Astrocytes protect neurons against harmful effects by accumulating heavy metals. However, this makes them the main target cells for heavy metal toxicity.[21] The specific treatment of heavy metal poisoning is chelator administration. In severe cases, HD may be an option.[22]

Our study has some limitations. First, we have missing data due to the retrospective design of our study. Secondly, potential contaminants such as iron and aluminum levels were not studied. Third, we do not have information about possible recent changes in the drinking water supply to the center where the cases occurred. Finally, we do not have the autopsy information of the deceased patient and therefore cannot make a definitive judgement.

In conclusion, HD patients are exposed to hundreds of times the water that a normal healthy person is exposed to through blood, with only a semi-permeable membrane in between. This exposure is much more risky than oral contact with any toxin. Therefore, strict control of the HD water system and cooperation with drinking water providers is a very important issue that nephrologists should care about. Increasing environmental pollution poses a serious risk for heavy metal intoxication. HD patients are at high risk because of their intense contact with pollutants. Comprehensive studies are needed to protect HD patients from this exposure.

Disclosures

Ethics Committee Approval: The study was approved by the local ethics committee (number 384581) and conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Saha M, Allon M. Diagnosis, Treatment, and Prevention of Hemodialysis Emergencies. Clin J Am Soc Nephrol. 2017;12(2):357-69.
2. Manuel J. Nutrient pollution: a persistent threat to waterways. Environ Health Perspect. 2014;122(11):A304-9.
3. Davis TW, Watson SB, Rozmarynowycz MJ, Ciborowski JJ, McKay RM, Bullerjahn GS. Phylogenies of microcystin-producing cyanobacteria in the lower Laurentian Great Lakes suggest extensive genetic connectivity. PLoS One. 2014;9(9):e106093.
4. Selenic D, Alvarado-Ramy F, Arduino M, Holt S, Cardinali F, Blount B, et al. Epidemic parenteral exposure to volatile sulfur-containing compounds at a hemodialysis center. Infect Control Hosp Epidemiol. 2004;25(3):256-61.
5. de Torres JP, Strom JA, Jaber BL, Hendra KP. Hemodialysis-associated methemoglobinemia in acute renal failure. Am J Kidney Dis. 2002;39(6):1307-9.
6. Kasparek T, Rodriguez OE. What Medical Directors Need to Know about Dialysis Facility Water Management. Clin J Am Soc Nephrol. 2015;10(6):1061-71.
7. Ward RA. Water processing for hemodialysis. Part I: a historical perspective. Semin Dial. 1997;10(1):26-31.
8. Layman-Amato R, Curtis J, Payne GM. Water treatment for hemodialysis: an update. Nephrol Nurs J. 2013;40(5):383-404, 65 quiz 5.
9. Consoli A, Nurjhan N, Reilly JJ, Jr., Bier DM, Gerich JE. Contribution of liver and skeletal muscle to alanine and lactate metabolism in humans. Am J Physiol. 1990;259(5 Pt 1):E677-84.
10. Petersen C. D-lactic acidosis. Nutr Clin Pract. 2005;20(6):634-45.
11. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc. 2013;88(10):1127-40.
12. MacDonald L, Kruse JA, Levy DB, Marulendra S, Sweeny PJ. Lactic acidosis and acute ethanol intoxication. Am J Emerg Med. 1994;12(1):32-5.
13. Halperin ML, Hammeke M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic: a pathophysiologic approach. Metabolism. 1983;32(3):308-15.
14. Moon JM, Shin MH, Chun BJ. The value of initial lactate in patients with carbon monoxide intoxication: in the emergency department. Hum Exp Toxicol. 2011;30(8):836-43.
15. Reade MC, Davies SR, Morley PT, Dennett J, Jacobs IC, Australian Resuscitation C. Review article: management of cyanide poisoning. Emerg Med Australas. 2012;24(3):225-38.
16. Berend K, van der Voet G, Boer WH. Acute aluminum encephalopathy in a dialysis center caused by a cement mortar water distribution pipe. Kidney Int. 2001;59(2):746-53.
17. Wani AL, Ara A, Usmani JA. Lead toxicity: a review. Interdiscip Toxicol. 2015;8(2):55-64.
18. Cullen MR, Robins JM, Eskenazi B. Adult inorganic lead intoxication: presentation of 31 new cases and a review of recent advances in the literature. Medicine (Baltimore). 1983;62(4):221-47.
19. Frith D, Yeung K, Thrush S, Hunt BJ, Hubbard JG. Lead poisoning--a differential diagnosis for abdominal pain. Lancet. 2005;366(9503):2146.
20. Evans GR, Masullo LN. Manganese Toxicity. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Lawrence Masullo declares no relevant financial relationships with ineligible companies.2023.
21. Li B, Xia M, Zorec R, Parpura V, Verkhratsky A. Astrocytes in heavy metal neurotoxicity and neurodegeneration. Brain Res. 2021;1752:147234.
22. Kim JJ, Kim YS, Kumar V. Heavy metal toxicity: An update of chelating therapeutic strategies. J Trace Elem Med Biol. 2019;54:226-31.