ORIGINAL ARTICLE

Relationship between the Use of Aluminum Utensils for Cooking Meals and Chronic Aluminum Toxicity in Patients on Maintenance Hemodialysis: A Case Control Study

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Abstract

Background: Chronic aluminum toxicity (CAT) in end stage kidney disease (ESKD) patients is now a rare clinical disorder, unlike in the past, because of improvements in hemodialysis water purification systems and discontinuation of use of aluminum hydroxide as a phosphate binder. The use of aluminum utensils for cooking could be an unrecognised cause of the CAT.

Objective: To assess the association between aluminum kitchen utensils used for cooking meals and chronic aluminum toxicity (CAT) in patients on maintenance hemodialysis (MHD)

Material and Methods: In this case control study, a total of 31 (cases n=10; controls n=21) patients on MHD for more than one year were included. Cases were defined as patients with clinical manifestations (including laboratory parameters) of CAT and high (>200 mcg/L) serum aluminum levels. Control group was chosen from the same hemodialysis facilities. Association between use of aluminum utensils for cooking and occurrence of CAT was assessed.

Results: The mean age of patients in the cases and the control group was 52.90 and 52.95 years respectively with on significant difference (p=0.99). There was no difference in mean duration of dialysis (p=0.78), serum calcium level (p=0.06), serum phosphate level (p=0.19), serum albumin level (p=0.06), history of hypertension (p=1.00) and history of diabetes (n=0.12) between two groups. Mean haemoglobin (p<0.05) and mean iPTH (p<0.05) was significantly lower in the cases as compared to control group. Thirteen patients had history of use of aluminum utensils [cases 10 (76.90%) and control 3 (23.10%); p<0.05]. All cases i.e. 10 (100%) had exposure to aluminum utensils whereas three (14.3%) patients in the control group had exposure to aluminum utensils whereas 18 (85.7%) patients had no exposure. The relative risk of having CAT because of use of aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd's ratio estimated was 120 (5.45 to 2642).

Conclusion: Use of aluminum utensils for cooking meals is associated with CAT. Larger studies are required to confirm these findings.

Introduction

Chronic aluminum toxicity (CAT) is a debilitating disorder seen in patients with end stage kidney disease (ESKD) on maintenance hemodialysis (MHD). With CAT, patients develop bone and muscle pain, proximal muscle weakness, joint pain, hypercalcemia, iron and erythropoietin resistant microcytic anaemia, osteomalacia and fractures, hypercalcemia and slowly progressive dementia.[1] Acute aluminum toxicity (AAT) occurs with sudden exposure to very high concentrations of aluminum resulting in life threatening acute encephalopathy manifested as altered consciousness, seizures and coma.[2] Major sources of aluminum are water used for making dialysate and oral aluminum hydroxide which was widely used as a phosphate binder in chronic kidney disease (CKD) patients in the past. Unlike two decades ago, with the advent of modern water purification systems for making dialysate and availability of newer non-aluminum phosphate binders, CAT is now very uncommon.[3] In fact, some authors have questioned the utility of routinely measuring serum aluminum levels in patients on MHD.[3,4] However, clusters of cases of AAT caused by defects in the water purification or distribution system are occasionally reported.[2,5]

We diagnosed a few patients with CAT which was confirmed by very high serum aluminum levels (>200 mcg/L). None of these patients was on aluminum hydroxide and the aluminum levels in the treated water in the two dialysis facilities where the patients received MHD treatment were conforming to the Association for the Advancement of Medical Instrumentation (AAMI) hemodialysis standard.[6] A review of clinical history revealed that all these patients were using aluminum utensils for cooking all their meals. Aluminum utensils are commonly used particularly in developing nations. However, there is no published data on association between the use of aluminum utensils and CAT in MHD patients. Hence, we decided to conduct this study.

Objective

To assess the association between

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use of aluminum utensils for cooking and CAT in patients on MHD. To look for other factors influencing serum aluminium levels in patients on MHD.

Materials and Methods

In this non-interventional, observational, case control study, 10 cases of CAT and 21 controls were included. Cases were retrospectively enrolled, and controls were enrolled prospectively. All cases were on MHD at two busy dialysis facilities in South Mumbai, each conducting around 2000 hemodialysis sessions a month. One is a part of a tertiary care hospital and the other is a stand-alone dialysis facility. Controls were selected from the same two hemodialysis facilities.

Cases were defined as those patients on MHD having any or all the following three clinical manifestations – a. chronic persistent bone pain, proximal muscle weakness and joint pain, b. microcytic anaemia and c. memory disturbance and cognitive impairment.

Other causes for all these three manifestations were ruled out. Patients were diagnosed to have low turnover bone disease based on low serum intact parathyroid hormone (iPTH) and alkaline phosphatase levels and X-Ray findings. Although diagnostic, bone biopsy was not done as this requires special equipment and expertise which were not available. Patients with a haemoglobin persistently below 10 gm/dl despite adequate doses of erythropoietin and normal iron stores, had a peripheral blood smear, reticulocyte count, serum haptoglobin, serum LDH, serum vitamin B12 and folic acid levels, to rule out other causes of anaemia. Stool was screened for occult blood. Patients with memory impairment and cognitive disturbance underwent thyroid function tests, vitamin B12 level, biochemistry, brain imaging and a neurology consultation.

In addition to the clinical manifestations, an elevated serum aluminum level of over 200 mcg/L was a mandatory criterion to confirm CAT.

For the controls, the inclusion and exclusion criteria were as follows -

Inclusion criteria

1. Patients from the same two dialysis centres as the cases.
2. Patients on hemodialysis for more than one year.
3. Patients receiving thrice a week, low flux dialysis.
4. Patients who consented for participation in the study.
5. Patients having serum aluminum levels of less than 60 mcg/L.

Exclusion criteria

1. Patients on hemodialysis for less than one year.
2. Patients who were not willing to give consent or not capable of giving consent.
3. Patients with noncompliance with dialysis treatment.
4. Patients receiving less than or more than three times a week dialysis.
5. Patients receiving high flux dialysis.
6. Patients with aluminum containing prosthetic devices like metallic valves or joints.
7. Patients who have received aluminum hydroxide in the last 12 months.
8. Patients who had undergone iodine contrast study in the past 3 months.
9. Patients who have serum aluminum levels of more than 60 mcg/L.

All cases and controls were receiving three times a week hemodialysis with low flux dialysers. All received unfractionated heparin during dialysis. All cases and controls received erythropoietin and intravenous iron supplementations as guided by haematocrit, serum ferritin and serum transferrin saturation. None of the cases or controls received oral aluminum hydroxide and none had aluminum containing prosthetic devices like valves or joints. All patients and controls were on dialysis for more than one year.

All cases and controls were questioned about the history of use of aluminum utensils for cooking meals. The number of utensils used, and the duration of use was documented along with what food was cooked or stored. All controls were questioned about the symptoms of CAT.

Cases were compared with controls for the following parameters – age, gender, dialysis vintage, medications, symptoms of CAT and laboratory parameters (hemoglobin, serum calcium, serum albumin, serum phosphorus, serum iPTH, alkaline phosphatase and serum aluminum level)

Serum aluminum was analysed by inductively coupled plasma – mass spectrometry (ICP-MS) technology. Treated water for hemodialysis was checked for aluminum content as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)™ guidelines and the results were conforming to the AAMI standard.[6]

Statistical methods

Data was entered in Microsoft excel® and then imported to SPSS for analysis (version 16). For the quantitative variables such as age, calcium level, iPTH level, duration of dialysis, serum phosphate, serum albumin, etc., descriptive statistics was calculated. The difference between the mean of these variables, between cases and controls was compared by unpaired t test. The frequency base variables such as gender, chronic aluminium toxicity, use of drugs, hypertension and diabetes, descriptive statistics proportion or percentages were calculated and difference between proportions (for cases and control) were compared by Fisher exact test. Risk of CAT due to use of aluminum utensils was estimated by means of statistical measure like relative risk and odd's ratio value.

Results

A total of 31 patients were included in the study. The enrolled patients were divided into two groups; cases (n=10) and controls (n=21). Baseline characteristics in patients in case and control groups are shown in table 1. The mean age of patients in the cases and the control group was 52.90 and 52.95 years respectively. There was no difference in the age (p=0.99), mean duration of dialysis (p=0.78), serum calcium level (p=0.06), serum phosphate level (p=0.19), serum albumin level (p=0.06), history of hypertension (p=1.00) and history of diabetes (n=0.12) between two groups (table 1). Mean haemoglobin ($p<0.05$) and mean iPTH ($p<0.05$) was significantly lower in the cases compared to control group (Table 1).

There was no significant difference in the use of calcium carbonate (p=0.51), calcitriol (p=0.09) and insulin (n=0.35) between cases and control group (Table

Table 1: Baseline characteristics of patients in the case and control groups

	Cases (n=10)	Control (n=21)	P value
Age	52.90 (±10.27)	52.95 (±9.89)	0.99
Gender (males, females)	4, 6	14, 7	
Duration of dialysis in months	59.90 (±11.83)	58.19 (±17.14)	0.78
Hemoglobin (gm%)	9.12 (±0.76)	11.03 (±0.76)	<0.05
Serum calcium (mg/dl)	8.46 (±0.52)	8.81 (±0.46)	0.06
Serum phosphate (mg/dl)	4.24 (±0.73)	4.76 (±1.09)	0.19
Serum albumin (gm/dl)	3.32 (±0.34)	3.58 (±0.34)	0.06
iPTH level (pg/ml)	74.02 (±55.49)	372.60 (±190.15)	<0.05
History of hypertension n (%)	9 (90.0%)	19 (90.5%)	1.00
History of diabetes n (%)	3 (39%)	14 (66.7%)	0.12
Cause of Chronic Kidney Disease:			
Chronic glomerulonephritis	4	6	
CTID	1	-	
Diabetic nephropathy	3	11	
Renal calculus disease/obstructive Nephropathy	1	1	
Unknown	1	3	

Hemoglobin, serum calicum, phosphorus, albumin and iPTH – mean(±SD); Cause of CKD – number of patients.

2).

Association between use of aluminum utensils for cooking and CAT –

The relative risk of having CAT by using aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd's ratio estimated was 120 (5.45 to 2642). A correction factor of 0.5 was used as there was not a single patient without a history of use of aluminum utensils in the case group. A total of 13 patients from both the groups had history of use of aluminum utensils. Among these 10 (76.90%) and three (23.10%) were from the cases and control group respectively. This difference was statistically significant (p<0.05). All cases i.e. 10 (100%) had a history of use of aluminum utensils whereas three (14.3%) patients in the control group had a history of use of aluminum utensils.

There was no significant difference between the serum aluminum levels of patients not exposed to aluminum utensils, who received calcium carbonate (p=0.41), calcitriol (p=0.99) or insulin (p=0.96) and who did not (Table 3).

Discussion

World Health Organization states that the provisional tolerable weekly intake of aluminum for people with normal kidney function is 2 mgs per kg body weight.[7,8] Most healthy adults tolerate larger daily oral aluminum exposures without any adverse effect. However susceptible population like pre-term infants, children and patients with renal insufficiency can be at risk of CAT even at lower doses (8). Aluminum being a ubiquitous element and as its use in industry and daily life is rising, exposure to aluminum sources is unavoidable for patients on MHD.[9,10]

In the past, two major sources of aluminum in patients on MHD were the water needed for making dialysate and oral aluminum hydroxide prescribed as a phosphate binder. Some other medications used in ESKD patients such as erythropoietin, intravenous iron preparations, oral iron sulphate, calcitriol, calcium carbonate and insulin contain minute amounts of aluminum.[11,12] Many studies have documented leaching of aluminum into food while cooking in aluminum utensils.[13-16] In one study the mean exposure estimate for aluminum was 125 mg per serving, more than six times the World Health Organization's provisional tolerable daily intake of 20 mg/day for a 70 years old person with normal kidney function.[7,16]

Since the last 2 decades CAT in patients with MHD has become a rare clinical entity because of major improvements in the water purification and distribution systems and use of non-aluminum phosphate binders.[3] Hence, when we encountered a few cases with CAT with a history of use of aluminum utensils for cooking, a case-control study was designed to ascertain the relative risk of CAT with the use of aluminum utensils in patients with ESKD on MHD.

Of the 10 cases of CAT, all had musculoskeletal manifestations and anaemia. The mean haemoglobin (p<0.05) and the mean iPTH (p<0.05) were significantly lower in the cases as compared to the control group. Four cases had minor memory disturbances and three had cognitive disturbance out of which one had an episode of unexplained encephalopathy which resolved with supportive care.

Table 2: Comparison of use of aluminum containing drugs in cases and controls

	Cases (n=10)	Control (n=21)	P value
Calcium carbonate	4 (40%)	7 (33.3%)	0.51
Calcitriol	2 (20%)	11 (52.4%)	0.09
Insulin	1 (10%)	5 (23.8%)	0.35

Table 3: Effect of aluminum containing drugs on serum aluminum levels of patients not using aluminum utensils

	Yes	No	P value
Calcium carbonate	25.16 (9.93)	21.61 (7.66)	0.41
Calcitriol	23.44 (8.57)	23.36 (9.19)	0.99
Insulin	23.14 (10.04)	23.44 (8.89)	0.96

Serum aluminum levels mcg/L, Mean (SD)

Confounding factors were matched in both groups. The control group (n=21) and case group (n=10) had no statistically significant difference in mean age (p = 0.99) and duration on MHD (p=0.779). All cases and controls were from same ethnic background and cooking customs. Dialysis water quality was matched as the patients in both the groups were from the same two dialysis facilities. None from both groups was prescribed aluminum hydroxide in the past. All patients in both groups received low flux dialysis three times a week. Of the medications that contain aluminum, all received intravenous iron preparation and erythropoietin. There was no statistically significant difference in patients receiving other preparations like calcium carbonate (p=0.51), calcitriol (p=0.092) and insulin (p=0.35) in the two groups. None of the patients in both groups received oral iron sulphate or ferric citrate (as phosphate binder).

All cases had a serum aluminum level of >200 mcg/L. A mean could not be calculated as the laboratory does not routinely report the exact values above 200 mcg/L. As the cases were enrolled retrospectively, exact values could not be obtained on request. In the control group the mean aluminum level was 24.84 (±9.59) mcg/L.

All cases had a history of aluminum utensils usage for a minimum of more than ten years. Aluminum utensils were used to cook all the meals. 3 (14.28%) of the 21 patients, in the control group used aluminum utensils in a limited way i.e. only for boiling milk, making tea, coffee, curds and butter milk and for steam pressuried cooking ("pressure-cooker"). For cooking all other meals, stainless steel utensils were used by these patients. These three patients in control group too used aluminum utensils for a minimum of more than ten years.

The relative risk of having CAT because of use of aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd's ratio estimated was 120 (5.45 to 2642). Of all the patients (n=31) included in the study, 13 (41.9%) used aluminum utensils. Of these 10 (76.9%) had CAT whereas 3(23.1%) did not have CAT. This difference is statistically significant ($p<0.05$). Of all the patients included in the study, 18 (58.1%) did not use aluminum utensils. Of these none had CAT ($p<0.05$). A Taiwanese study looked at the effect of aluminum utensils in CKD patients not yet on dialysis and found that replacing aluminum utensils by stainless steel ones significantly decreased serum aluminum levels.[17] Results of the current study suggest a strong association between use of aluminum utensils and CAT in patients on MHD. Observations from the current study and the Taiwanese study suggest that aluminum kitchen utensils is a significant source of aluminum in patients with renal insufficiency.

In patients not using aluminum utensils (n=18), the effect of use of aluminum containing medications on serum aluminum levels was studied. In this group there was no significant difference in serum aluminum levels in patients taking or not taking calcitriol ($p=0.47$), calcium carbonate ($p=0.99$) or insulin ($p=0.96$). Intravenous iron and erythropoietin were used by all patients and oral iron preparation was used by none. A Spanish study found significantly higher aluminum levels in those consuming antianemics ($p=0.007$), anti-hyperphosphatemics ($p=0.021$) or hypercalcemics ($p=0.012$).[18] Another study found significant higher aluminium levels (22.1 ± 9.0 mcg/L versus 6.7 ± 2.4 mcg/L, $p<0.05$) in those on intravenous iron, erythropoietin and insulin.[12]

According to the KDOQI guidelines the serum aluminum level in patients on MHD should be maintained below 20mcg/L.[19] This is an opinion and not based on evidence. The mean serum aluminum levels amongst nonusers of aluminum utensils in the current study was 23.39 (± 8.77). In a study from the United States which looked at serum aluminum levels of 755 patients, done routinely, the mean value was 11.05 (± 8.07) which is significantly lower ($p<0.05$) than that in the nonusers of aluminum utensils in the current study.[3] However, in a Spanish study which looked at serum aluminum levels of 116 patients, done routinely, the mean value was 39.9 (±23.1) which is significantly higher($p=0.004$) than that in the nonusers of aluminum utensils in the current study.[18] The reason for these differences is not clear. Whether these are related to differences in the amount of aluminum contaminants in medications mentioned above or there are any unknown sources of aluminum or there are any geographical differences leading to this observation needs to be studied in larger prospective studies.

KDOQI guidelines recommend monitoring serum aluminum level once a year in all patients on MHD.[19] Several large studies from the United States have questioned this as only about 2 to 3 percent of the patients on MHD have a level above 20mcg/L in these studies.[3,4] Indian Society of Nephrology guidelines on hemodialysis do not have a mention on monitoring serum aluminum levels probably considering these studies.[20] However, the current study and the Spanish study bring forth the need for a larger prospective study from India to make a recommendation.[18]

The limitation of this study is its retrospective nature and the small number of cases and controls.

Conclusion

Use of aluminum utensils is very common in India and developing world. Use of aluminum utensils for cooking food is associated with CAT in patients on MHD. Patients on MHD should be counselled to stop using aluminum utensils and to replace them with stainless steel ones. This simple measure will help prevent this debilitating clinical disorder which is difficult to treat and cure.

A significant higher level of serum aluminium in patients not using aluminum utensils in the current study, highlights the pressing need for a large prospective trial from this region to confirm this observation and find the cause or recommend a higher acceptable value.

CAT, although reportedly rare, should be ruled out in all ESKD patients who use aluminum utensils and present with persistent bone and joint pains, unexplained anaemia or memory disturbances. Eliciting history of use of aluminum utensils should be routinely practised.

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