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Research Paper

Aluminium Toxicity in Chronic Kidney Disease Patients on Maintenance Hemodialysis

Medical Science

KEYWORDS : aluminium toxicity, hemodialysis, dementia, bone disease, anemia, chronic kidney disease

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ABSTRACT

Aims: Aluminium toxicity is encountered in chronic kidney disease patients who are on regular hemodialysis. It presents as dialysis encephalopathy, bone disease, microcytic anemia etc. This study was undertaken to compare the serum aluminium levels in chronic kidney disease patients on maintenance hemodialysis with that of apparently healthy individuals.

Methodology: It is a Case-Control Study consisting of 50 chronic kidney disease patients who were undergoing low-flux hemodialysis in Nephrology department of Sri Ramachandra Medical College, Chennai, for atleast 6 months and 50 apparently healthy individuals with normal kidney functions. Aluminium was estimated in Inductively Coupled Plasma – Optical Emission Spectrometer (ICP-OES) of Perkin Elmer Optima 5300DV.

Results: The mean and SD in control and case groups were 31.14 ± 4.46 µg/L and 56.93 ± 21.90 µg/L respectively with p value < .0001 showing that there is significant increase in serum aluminium levels in chronic kidney disease patients on maintenance hemodialysis.

Conclusion: Aluminium toxicity is encountered in patients undergoing hemodialysis, which might be due to increased aluminium content in water supply, defect in water/dialysate fluid purification and distribution system within the individual dialyzers. Aluminium toxicity is one of the factors in increasing the morbidity in chronic kidney disease patients.

INTRODUCTION

Chronic kidney disease (CKD) is on the increase due to rising prevalence of hypertension, diabetes mellitus, obesity, as well as to increase intake of nonstreoidal anti-inflammatory drugs and infections. CKD patients who are on maintenance hemodialysis are at increased risk for aluminium toxicity. Dietary ingestion of aluminium is 5-10mg/day; derived from food, drinking water, cooking utensils etc. Commercial preparations like antacids and albumin also have high level of aluminium (1). Normally it is completely excreted by the kidneys. In patients with CKD it is partially removed by dialysis, since 90% of aluminium is bound to plasma proteins especially transferrin. Aluminium accumulates in bone, brain, parathyroid glands and other tissues. Symptoms vary according to the rate and magnitude of aluminium accumulation. Aluminium accumulates along the mineralization surface of osteoid leading to low-turnover bone disease and interferes with the action of parathyroid hormone (PTH) and calcitriol on bones resulting in defective mineralization of bones. Aluminium gets accumulated in any parts of the body over time leading to hypochromic microcytic anemia, encephalopathy, abnormal speech, myoclonic jerks and convulsions (3)

Normal serum aluminium concentration is <6µg/L (4). In the dialysate fluid the aluminium concentration can be upto 10µg/L. Patients with no clinical features of osteomalacia or encephalopathy have aluminium and PTH levels of <20µg/L and 150-300ng/L respectively. Patients with osteomalacia have aluminium and PTH levels >60µg/L and <65ng/L respectively; PTH is being reduced due to aluminium related bone disease. Patients with aluminium levels >20µg/L but <65µg/L are asymptomatic; likely candidates to manifest as toxicity (5). Generally blood test for diagnosing aluminium toxicity is unreliable; since most of the body stores of aluminium are found in bone and tissue which is not reflected in the serum value. Desferrioxamine infusion is used in diagnosing and treating aluminium overload disease(6). Desferrioxamine –stimulation test is done in patients with serum aluminium levels >60µg/L and who are asymptomatic. Desferrioxamine induces mobilization of aluminium deposited in the tissues, leading to transient increase in aluminium concentration (7). The risk of aluminium-induced osteomalacia is greater in diabetic patients, compared with nondiabetic patients which may be related decreased bone turnover and decreased serum PTH levels(8,9). Aluminium accumulates in the neurofibrillary tangles leading to the degeneration of hippocampus in patients with Alzheimer's Disease(10).

MATERIALS AND METHODS

The study is conducted in 100 subjects in the age group 25 to 75 years which includes both males and females. The case group included end-stage renal disease patients undergoing chronic hemodialysis for more than 6 months. The normal subjects (control) included apparently normal individuals who came for regular master health check up and had normal renal functions. All measures were taken to maintain strict confidentiality about the personal details of the participants of the study. This study was in conformity with the Declaration of Helsinki and was approved by Sri Ramachandra University Institutional Ethics Committee. All subjects gave written consent form.

Group A: consists of 50 end-stage renal disease (ESRD) subjects on MHD(maintenance hemodialysis) from the Department of Nephrology in Sri Ramachandra Medical College and Research Institute. All patients were on low-flux bicarbonate hemodialysis for more than 6 months using polysulfone membrane dialyzer; 4 hours per session for three times per week, with a dialysis fluid calcium concentration of 3.0 mEq/L, and there was no difference in dialysis frequency and efficiency among patients (Urea Reduction Ratio- >65%). 1-α-(OH) D3 in a dose of 0.25 µg – 0.75 µg daily and erythropoietin weekly were given to all patients.

Inclusion criteria:

ESRD patients on MHD

Exclusion Criteria:

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1. Patients on hemodialysis for < 6 months and for causes other than ESRD.
2. Any kind of acute illness/ Active infection
3. Those with malignancies
4. Use of any nephrotoxic drugs, hormone replacement therapy, aluminium hydroxide, steroids.

Group B: 50 subjects who are apparently healthy attending master attended routine health check-up were selected randomly.

Inclusion criteria:
1. Normal renal function (Blood urea: 15-45mg/dl & serum Creatinine:0.6-1.2mg/dl).
2. Clinically healthy individuals with no associated medical problems/illnesses.

Exclusion criteria:
1. Individuals with Liver and Cardiac diseases
2. Persons with Acute illnesses/Active infections
3. Use of any nephrotoxic drugs, hormone replacement therapy, aluminium hydroxide, steroids.

Study Protocol & Methodology adopted:
Blood samples were drawn from the individuals of both the groups for estimation of serum urea, creatinine and aluminium. For serum aluminium the samples were collected in royal blue topped BD vacutainer for element analysis. The serum was separated and stored at -20˚C until analysis.

Analysis of aluminium:
The samples were analyzed using inductively coupled plasma-optical emission spectrophotometer (ICP-OES) of Perkin Elmer Optima 5300 DV. Calibration curve was plotted before running each batch.

Table No.1 : Test Conditions

Sample aspiration volume per analysis	500 µL
Analysis time per sample	3 minutes
Test temperature	6000 K
Plasma used	Argon
Wavelength used	396.153nm
Lower limit of detection	28µg/L
Linearity	2mg/L

Mechanism of operation: An ICP requires the elements to be analyzed in solution. The nebulizer transforms the aqueous solution into an aerosol. The light emitted by the atoms of an element in the ICP is converted into electrical signals by the photomultiplier in the spectrometer.

Results:
The SPSS version 15 statistical software tool was used for data processing. The difference in the mean values between the group A and group B was analyzed using Student's t-test. A p-value of < 0.05 was considered statistically significant.

Table 2: Clinical characteristics of study groups

	GROUP A (cases)	GROUP B (control)
Age (years) (mean ± SD)	52.18 ± 9.85	52.44 ± 8.79
n(male/female)	50(31/19)	50 (29/21))
MHD duration (months)	6 to 24	0
Diabetes (yes/no)	50/0	0
Hypertension (yes/no)	45/5	0
Ingestion of Erythropoietin Lipid lowering agents	50 10	0 0

Table3: showing the values of biochemical parameters groups A and B

Parameters	Case group –A (n=50)	Control group – B (n=50)	*p* value
Serum urea (mg/dl)	78.62 ± 5.12	17.00 ± 2.01	.0001
Serum creatinine (mg/dl)	8.13 ± 1.69	0.70 ± 0.15	.0001
Serum Aluminium(µg/L)	56.93 ± 21.90	31.14 ± 4.46	.0001

All values in Mean ± SD

Discussion:
Aluminium toxicity is found to be a potential hazard in all patients, more so in patients with ESRD; even though the magnitude of increase in aluminium may not be very high. Aluminium has a cumulative effect (11); elimination half-life from brain being 7 years. In patients with normal renal function increased ingestion of aluminium is implicated in amyotrophic lateral sclerosis and dementia as occurring in patients with parkinsonism(12). Aluminium is found to be low in ground water but high in surface water(13). Domestic tap water can derive aluminium directly from the water source or from aluminium sulfate added as a flocculant during the process of purification. In patients with chronic renal failure, serum aluminium concentration increases due to the ingestion of aluminium containing phosphate binders (14) as well as due to the presence of aluminium in the dialysate(15) and parenterally from immunizations(16) and total parenteral nutrition(17) and from antiperspirants. Lactate, phosphate and citrate facilitate absorption. The transfer of aluminium during dialysis depends on the pH and concentration of aluminium in the dialysate as well as on the serum aluminium concentration. In this study there is significant increase (p .0001) in serum urea, Creatinine and aluminium in chronic renal patients who are on maintenance hemodialysis were compared with that of normal individuals.

Aluminium toxicity depends on the species of aluminium (halides, oxides, hydroxide, carbide, nitride, acetylide and phosphide) in the dialysate which may affect the dialyzability of aluminium. Aluminium in blood is tightly bound to serum proteins as well as to some lower molecular weight species(18). It gets deposited in gray-matter of brain, muscle, liver, spleen, heart and bone. Aluminium is believed to act as a neurotoxin by inhibiting dihydropteridine reductase (19), causing alteration in cholinergic neurotransmission (20). It inhibits protein synthesis, alters nucleic acid function and cell membrane permeability. It causes alterations in cognitive function and dementia(21, 22, 23). It disrupts neurofilament axonal transport and neurofilament assesmbly(24). Aluminum brain concentrations should be lower than 2µg/g. Aluminium is a competitive inhibitor of calcium, magnesium and iron. It causes anemia through decreased heme and globulin synthesis and increased hemolysis. Patients have increased reticulocyte count, decreased mean corpuscular volume, and mean corpuscular hemoglobin. Aluminium inhibits hexokinase leading to decreased glucose utilization(25). Aluminium by forming aluminium citrate complexes interferes with bone mineralization(26-28). There is alteration in the activities of acid and alkaline phosphatases, as well as in the response of parathyroid hormone and calcitriol on bone(29, 30). Aluminium interferes with both bone formation and resorption leading to osteomalacia, bone pain, multiple nonhealing fractures and premature osteoporosis. Deposition of aluminium in the parathyroid gland prevents the release of the hormone(31-34). Removal of aluminium from water can be done by use of water softener (removes only 50%) and incorporation of reverse osmosis which bring down the concentration to 10µg/L (35).

Low flux or high flux membranes can be applied for hemodialysis. High-flux dialysis is defined as a β2- microglobulin clearance

of over 20 mL/min (36, 37). Compared with low-flux dialysis, high-flux dialysis more efficiently removes middle molecules ranging in size from 1000 to >15,000 D. These molecules include β_2-microglobulin (β_2M) (11,800D), which was the marker, used for the flux evaluations in the HEMO Study. Substances with lower molecular masses might behave kinetically as middle molecules because of properties such as steric configuration, electric charge, hydrophobicity, or binding to plasma proteins. High flux membranes have large pores and allow diffusion of greater amount of uremic toxins and middle molecules such as β2-microglobuline and may, therefore, decrease the risk of dialysis-related amyloidosis (38), reduced morbidity and mortality (39-42). Also they cause few activations of coagulation, complement and inflammatory systems (43), lower leukocytosis, improve neutrophil function, decrease cytokine secretion, remove endotoxins, improve lipid profile (44), reduce infection risk, aluminum toxicity and better preservation of renal function.

Potential disadvantages of high-flux dialyzers include loss of albumin into the dialysate when bleach is used for reprocessing (45) and back-transfer of dialysate contaminants into the blood, although some high-flux membranes also adsorb and thus inhibit the back-transfer of endotoxins(46). Many previous studies, however, exclusively compared a synthetic high-flux membrane with an unsubstituted cellulosic low-flux membrane, thus confounding the effects of middle-molecule clearance with those of membrane biocompatibility. Furthermore, there have been no randomized trials examining the effects of membrane flux on long-term clinical outcomes.

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