ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 01 | January - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SIGNIFICANCE OF SERUM PHOSPHATE AS A MARKER FOR INITIATING DIALYSIS IN CKD PATIENTS IN A TERTIARY CARE CENTRE

Nephrology

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ABSTRACT

Guidelines for Chronic Kidney Disease (CKD) suggest initiation of dialysis when a patient experiences symptoms or signs of kidney failure. More objective laboratory parameters are needed to help decide when to initiate dialysis. Significant hyperphosphatemia occurred in CKD patients who chose to delay initiation of dialysis. So evaluation of potential role of hyperphosphatemia as a marker to initiate dialysis in CKD is necessary. 110 CKD patients were selected for initiation of dialysis according to existing protocols. A control group of 110 matched CKD patients not selected for initiation of dialysis was taken. Mean serum phosphate was found to be higher (6.02+2.15 mmol/l) in the study group, in contrast to the control group (3.44+0.54 mmol/l). This result was statistically significant, with a p-value of 5.7×10-09. Serum phosphate also correlated positively with serum urea(r=+0.367) and serum creatinine(r=+0.278). Hyperphosphatemia may be a useful marker to determine initiation of hemodialysis in patients with advanced CKD, and correlates well with existing indicators for dialysis.

KEYWORDS

Phosphate, Dialysis, Chronic Kidney Disease

1. INTRODUCTION: -

Chronic Kidney Disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as abnormalities of kidney structure or function, present for ≥3 months, with implications for health [1].It is a rapidly growing global health problem. International Society of Nephrology's Kidney Disease Data Centre Study reported a prevalence of 17% of CKD [2].

Renal replacement therapy (RRT) is indicated in CKD patients when the benefits of treatment outweigh the risks of therapeutic complications, the psychosocial inconvenience, and the financial burden. The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for CKD suggest initiation of dialysis when a patient experiences uremic symptoms or signs attributable to kidney failure, an inability to control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary intervention, or cognitive impairment [2].

However, this evaluation of patients in the context of deciding whether to initiate dialysis or not, is partially based on patient perceptions and subjective physician judgments. This decision, if delayed, may result in significant morbidity and mortality. So more objective laboratory parameters, in addition to the existing ones, are needed to help decide when to initiate dialysis in advanced CKD patients, especially in countries or areas where practicing nephrologists are scarce.

Patients with advanced CKD are known to retain phosphate, and thus develop hyperphosphatemia. Previous studies have shown that significant hyperphosphatemia occurred in patients who chose to delay initiation of dialysis [3]. Hyperphosphatemia is also known to be associated with mineral and bone disorders, vascular calcification, accelerated progression to ESRD, cardiovascular events, and increase in all-cause mortality in CKD [4]-[7]. One previous study in 2015 by Lu et al studied the importance of phosphate in advanced CKD and its role as a guide towards initiating dialysis, but could not arrive at a cut-off value [8].

This study attempts to study the correlation of serum phosphate levels with existing clinical and biochemical indications of dialysis. It also aims to establish the importance of serum phosphate as a marker for initiating dialysis in CKD patients.

2. Materials and methods:-

2.1 Place and period of Study:

This study was carried out in the Department of Medicine and Nephrology, VIMSAR, Burla, over a period of 24 months, from November 2018 to October 2020.

2.2 Study design:

The study was designed to be a cross-sectional analytical study.

2.3 Study population:

The study group consisted of 110 CKD Patients having been selected for initiation of dialysis according to existing protocols, while the control group consisted of 110 age, sex, and socio-economic status matched CKD patients not selected for initiation of dialysis

2.4 Sampling method:

The sampling method used was convenience sampling of cases.

2.5 Sample Size:

Sample size was calculated by the formula: -

$$\text{Sample size} = \frac{2SD^2 (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

Where

SD (standard deviation) = taken from previous published study

d= Expected mean difference between 2 groups taken from previous study

Z_{β} = Standard normal variate for power (for 80% power its value is 0.84)

$Z_{\alpha/2}$ = Standard normal variate for level of significance = 1.96

Using these parameters, the minimum sample size for the study as determined to be **12**. Sample size was fixed at 110 for each group.

2.6 Selection criteria:

Patients of chronic kidney disease of age ≥14 years admitted to General medicine and Nephrology wards, who had not undergone dialysis previously, were included in the study. Patients with acute kidney injury, malignancies (tumor lysis syndrome), parathyroid disorders, acromegaly, hyperglobulinemia, hyperlipidemia, hemolytic anemia or hyperbilirubinemia were excluded. Patients on phosphate-containing medications (e.g. laxatives) / bisphosphonates/ cinacalcet, medications causing pseudohyperphosphatemia (Amphotericin B, heparin, tissue plasminogen activator), or patients with extensive cellular injuries (crush injuries/ rhabdomyolysis/ hyperthermia/ fulminant hepatitis/ cytotoxic therapy) were also excluded.

2.7 Data Collection Methods

Detailed history was taken regarding the characteristics and duration

of the presenting symptoms like fatigue, nausea, vomiting, loss of appetite, decreased urination, swelling of feet or generalised swelling, and changes in mental state. Relevant past history of hypertension, diabetes mellitus, malignancy, and parathyroid disorders was taken. History of phosphate containing medications or use of phosphate binders was taken. Treatment with medications causing hyperphosphatemia, or anticancer drugs, was ruled out by detailed history-taking. Any history of recent traumatic injuries was taken. Detailed systemic examination was done in all patients and data was entered into a pre-structured format. Complete blood counts, serum urea, creatinine, electrolytes, blood glucose, and liver function tests were carried out for all patients. Serum phosphate was measured by the **Vitros DT II system**. A 10 µl drop of sample was deposited on **Vitros PHOS DT slides**, and evenly distributed. Phosphorus, in the form of inorganic phosphate, was allowed to complex with ammonium molybdate at acid pH. p-Methylaminophenol reduced the complex to produce a stable blue colour. An analyser calculated the amount of phosphate by measuring the amount of light reflected from the dye layer after a fixed incubation period. The reference range for serum phosphate was 2.5-4.5 mg/dl.

2.8 Statistical Analysis

Data management and statistical analysis were done using Microsoft Excel 2016. Results were expressed in terms of mean, standard deviation and percentages.

3. RESULTS:

220 patients satisfying the inclusion criteria were taken in the study. The mean age of the patients in the study was 54.05 ± 11.77 years. 130 patients were male and 90 were female. Majority were in the age group of 50-59 years (40.4%), followed by 40-49 years (23.2%). The male to female ratio was 1.44:1.

Table 1: Clinical features in study subjects (n=220)

Presenting Complaints	No. of cases	Percentage
Vomiting	54	24.55%
Decreased Urination	40	18.18%
Head Reeling	22	10.00%
Altered Sensorium	46	20.91%
Generalized Swelling	65	29.55%
Fatigue	77	35.00%
Breathlessness	42	19.09%
Cough	26	11.82%
Bodyache	30	13.64%
Loss of appetite	55	25.00%

Fatigue was the most common clinical feature seen in 77 cases (35%), followed by generalised swelling, seen in 63 of the CKD patients (29.5%). The other common complaints that the patients involved in the study presented with, include loss of appetite (25%), nausea/vomiting (24.5%), altered sensorium (20.9%) and breathlessness (19.1%).

The overall incidence of anemia in the study group was found to be 95.45% in the study sample. Common electrolyte abnormalities were looked for. The incidence of hyponatremia was found to be 75% in the study sample. The overall incidence of hyperkalemia in the study sample was found to be 6.81%, while the incidence of hypokalemia was found to be 55.45%. Hypocalcemia was found in 55.45% of the population studied.

The mean values of different parameters were calculated, along with their standard deviation in both study and control group. P-values for the comparisons were also estimated.

Table 2: Mean values of parameters in study (n=110) and control group (n=110)

Criteria	Mean + SD (Not dialysed)	Mean + SD (Dialysed)	p-value
SBP (in mm Hg)	123.27 + 21.78	143.27+32.56	0.7474
DBP (in mm Hg)	78.18+8.33	87.64+13.26	0.0021
Hemoglobin (g/dL)	8.35+1.36	7.99+1.45	0.77909
Urea (mg/dl)	66.18+46.47	160.64+38.53	0.00015
Creatinine (mg/dl)	4.00+2.54	9.10+4.36	0.1842
Sodium (mmol/l)	128.73+9.20	124.82+11.53	0.024
Potassium (mmol/l)	3.80+0.97	3.95+1.06	5.7×10-09
Calcium (mmol/l)	1.11+0.21	0.91+0.32	0.0006
Phosphate (mmol/l)	3.44+0.54	6.02+2.15	5.9×10-08
Urine output (ml/day)	1163.64+214.36	572.73+310.69	1.9×10-09

The average values of all important parameters were calculated in both the control group (not on dialysis) as well as the study group (dialysed). The results were as follows.

The mean systolic blood pressure (SBP) in the study group (dialysed) was significantly higher (143.27±32.56 mm Hg) than in the control group (123.27 ± 21.78 mm Hg). Likewise, the mean diastolic blood pressure (DBP) in the study group (dialysed) was also relatively higher (87.64±13.26 mm Hg) than in the control group (78.18±8.33 mm Hg).

The mean haemoglobin concentration was lower in the study group (7.99±1.45 g/dl) than in the control group (8.35±1.36 g/dl). This confirmed that advanced CKD patients requiring dialysis presented with more severe anemia than those not requiring dialysis.

The mean serum urea in the dialysed group was found to be 160.64 ±38.53 mg/dl, which is significantly higher than the mean urea in the control group (66.18 ±46.47 mg/dl). Similarly, the mean serum creatinine in the dialysed group is 9.10 ±4.36 mg/dl, while it is 4.00 ±2.54 mg/dl in the control group. This is an understandable trend as serum creatinine is one of the indicators for dialysis. Also, CKD patients requiring dialysis usually present with uremic symptoms, which explains the trend of serum urea.

The mean sodium levels were 124.82 ±11.53 mmol/l in the dialysed study group, while it was 128.73 ±9.20 mmol/l in the control group. While sodium levels across both groups was found to be low, the study showed a significantly high incidence of hyponatremia in patients selected for dialysis. The mean serum potassium levels in the dialysed group were found to be 3.95±1.06 mmol/l, while mean serum potassium levels were found to be slightly lower in the control group (3.80±0.97 mmol/l). Understandably, there was a higher incidence of hyperkalemia, and a higher chance of cardiac complications in the patients selected for dialysis. There was higher incidence of hypocalcemia in the study group with a mean calcium level of 0.91±0.32 mmol/l. The control group had a relatively higher serum calcium on an average (1.11±0.21 mmol/l).

Serum phosphate, the primary parameter in question, was found to be significantly higher in the study group, with a mean value of 6.02±2.15 mmol/l. In the undialysed group, mean serum phosphate was found to be consistently lower, with a value of 3.44±0.54 mmol/l. This result was found to be statistically significant, with a p-value of 5.7×10^{-09}.

Urine output had a very predictable trend, with the study group selected for dialysis displaying considerably lower daily urine output. The mean urine output in the study group was 572.73±310.69 ml, while the mean urine output in the control group was 1163.64±214.36 ml.

Each of the variables was correlated with serum phosphate, and their correlation coefficients were calculated. The following results were observed. Serum urea, serum creatinine, systolic and diastolic blood pressure, all correlated positively with serum phosphate values. Correlation co-efficient of serum creatinine with phosphate was 0.278. This positive correlation is significant as serum creatinine is an important existing indicator for the initiation of dialysis in CKD patients. Urine output, serum sodium and serum calcium correlated negatively with serum phosphate. This implied that with rising serum phosphate levels, urine output began to show a decreasing trend, and incidence of hypocalcemia and hyponatremia began to increase. All these trends correspond to progressive stages of CKD.

4. DISCUSSION:

The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for CKD suggest initiation of dialysis when a patient experiences uremic symptoms or signs attributable to kidney failure, an inability to control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary intervention, or cognitive impairment. [2] However, evaluation of these symptoms are partially based on patient perceptions and subjective physician judgments. So more objective laboratory parameters, in addition to the existing ones, are needed to help decide when to initiate dialysis in advanced CKD patients, especially in countries or areas where practicing nephrologists are scarce.

Thus, establishing the role of serum phosphate as a marker for

initiating dialysis in CKD patients assumes significance. In a previous study, Lu et al studied the importance of serum phosphate in CKD patients in a centre in Taiwan in this regard. They enrolled 292 participants in a retrospective study, with 209 of them ultimately undergoing dialysis. The difference in laboratory parameters, with emphasis on serum phosphate and its correlation with existing indicators for dialysis, was studied by Lu et al.

The present study consisted of 220 patients divided into two groups. The study group consisted of 110 CKD patients having been selected for initiation of dialysis according to existing protocols, while the control group was formed by 110 age, sex, and socio-economic status matched CKD patients not selected for initiation of dialysis. In both the groups, all clinical and laboratory values were recorded, and the primary parameter, serum phosphate, was recorded in both groups before any intervention. Data was collected at the time of admission and patients were followed up till the duration of their hospital stay.

The previous study showed a mean age of 62.7± 11.7 years in the control group, and 63,1 ± 14.8 years in the study group that was selected for dialysis. In comparison, mean age of the patients in the present study was found to be a relatively lower 54.05 ± 11.77 years. Lu et al carried out the study on 141 females out of 292 participants (48.28%), while males were 151 in number (51.72%), with a male to female ratio of 1.07:1. Comparatively, in the present study, out of 220 patients, 130 were male and 90 were female, with a male to female ratio of 1.44:1.

The previous study reported a mean hemoglobin level of 8.5 $\pm$1.4 g/dl in the dialysed study group, with a relatively higher mean level in the control group of 9.2 $\pm$1.4 g/dl. The present study reports significantly lower levels of hemoglobin, with a mean haemoglobin concentration of 7.99$\pm$1.45 g/dl in the study group, and 8.35$\pm$1.36 g/dl in the control group. This higher incidence of anemia probably signifies a poorer nutritional status and general health in western Odisha, the zone to which this tertiary health centre belongs.

The previous study reported a mean creatinine level of 11.3 $\pm$4.1 mg/dl in the study group, and 8.1 $\pm$ 1.9 mg/dl in the control group. The present study, in comparison, estimated lower levels of serum creatinine at presentation to the hospital, with a mean serum creatinine of 9.10 $\pm$4.36 mg/dl in the dialysed group, while it was found to be 4.00 $\pm$2.54 mg/dl in the control group. This probably signifies development of uremic symptoms at lower levels of serum creatinine in Odisha than in the previous study at Taiwan.

Lu et al reported mean serum sodium levels in the normal range for both study and control groups, while the present study reports a significantly higher incidence of hyponatremia in both groups, with mean sodium levels of 124.82 $\pm$11.53 mmol/l in the dialysed study group, and 128.73 $\pm$9.20 mmol/l in the control group. This may be due to the relatively different type of CKD reported in Odisha called CKDu, or CKD with unspecified nephropathy.

In the present study, the mean serum potassium levels in the dialysed group were found to be 3.95$\pm$1.06 mmol/l, while mean serum potassium levels were found to be slightly lower in the control group (3.80$\pm$0.97 mmol/l). The previous study reported slightly higher levels of potassium, albeit in the normal range. Both studies showed very less incidence of hyperkalemia.

The present study revealed serum phosphate, the primary parameter in question, to be significantly higher in the study group, with a mean value of 6.02$\pm$2.15 mmol/l. In the control group, mean serum phosphate was found to be consistently lower, with a value of 3.44$\pm$0.54 mmol/l. This difference was calculated to be statistically significant, with a p-value of 5.9×10^{-08}. This was in agreement with the study by Lu et al, who found a mean serum phosphate of 7.0 $\pm$ 2.4 mmol/l in the study group, with a much lower mean of 4.9 $\pm$ 0.8 mmol/l in the control group.

Furthermore, serum phosphate was found to correlate positively with serum urea, serum creatinine, systolic and diastolic blood pressure. Positive correlation with serum creatinine was significant, as serum creatinine is an existing indicator for initiation of dialysis.

5. LIMITATIONS:

As serum phosphate has diurnal variation, and is prone to be influenced by multiple factors, it is difficult to recommend a single cut-off value for initiation of dialysis. Other limitations include a single-hospital study, and a small sample size.

A multi-centre study with a larger sample size, along with more meticulous monitoring of serum phosphate after exclusion of associated factors may help decide a specific cut-off value of serum phosphate and help physicians take better objective decisions regarding initiation of dialysis in CKD patients.

6. CONCLUSION:

Chronic kidney disease is a commonly encountered entity in the current scenario, with an incidence that has been progressively increasing at a rate of 7% per year. Hyperphosphatemia as a derangement is frequently detected in CKD. Hyperphosphatemia is also known to be associated with mineral and bone disorders, vascular calcification, accelerated progression to ESRD, cardiovascular events, and increase in all-cause mortality in CKD. [9] This study attempted to study the correlation of serum phosphate levels with existing clinical and biochemical indications of dialysis.

The results have demonstrated statistically significant and consistent hyperphosphatemia in the study group that was selected for dialysis. Simultaneously, serum phosphate correlated well with existing indicators of dialysis.

In conclusion, serum phosphate can potentially be used as an additional marker to take an objective decision regarding initiation of dialysis in advanced CKD patients.

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