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Factors on phosphorus clearance in hemodialysis

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SUMMARY

Background: *The sustained elevation of phosphorous among patients with end-stage renal failure is associated with elevated mortality rates. Phosphate binding agents are usually necessary to control serum phosphate levels. Phosphate removal during dialysis is limited largely due to the intracellular location of most inorganic phosphorous. The membrane surface, the frequency and the duration of therapy have proved to be very important factors in the serum phosphate control.*

The aim *of our work is to investigate the influence on phosphate removal of factors that normally participate in the haemodialysis session: Plasma phosphate level (Php), treatment duration, membrane surface, high or low-flux membranes, the vascular access, dialysate flux, the volume of blood passing through the dialyzer (L) in each dialysis session and the blood flow during the first hour of dialysis. On 16 patients, we also had the possibility of comparing phosphate removal with 1.8 m^2 high-flux haemodialysis, 1.8 m^2 on-line hemodiafiltration and the on-line technique with the new Helixone dialyzer Fresenius Fx100®.*

Methods: *108 haemodialysis patients, 62% men, 38% women aged 21-82 years (61 ± 14; mean ± sem), were selected for the study. Mean treatment time 4.14 ± 0.41 hours (range 3.5-5 hours).The vascular access was an arterio-venous fistula in eighty five (78%) and a double lumen tunnelled catheter 23 (22%). Patients were studied under their normal every day conditions. High-flux membrane was used by 31 (30%) patients and low-flux membrane by 77 (70%). Membrane surface was: 1.7 m^2: 17 (16%); 1.8 m^2: 77 (71%); 2,1 m^2: 14 (13%). Dialysate flux was: 500 ml/min 55 patients; 700 ml/min 53 patients.*

In 16 out of 108 patients we had the possibility of using on-line hemodiafiltration with ultrapure bicarbonate-buffered dialysate. Phosphate mass removal (MPO4) was calculated using the formula: MPO4 = 0.1 t-17 + 50 Cds 60 + 11 Cb 60 (1), where t is treatment time in minutes, Cds 60 and Cb 60 are phosphate concentrations in dialysate and plasma measured at 60 min from the beginning of hemodialysis in mg/dl, and MPO4 is the estimated phosphate removed in mg/treatment.

Results: *We found a good correlation between phosphate removal and serum phosphate levels (p = 0.01) , the volume of blood (L) that passed the dialyzer in each session (r = 0.01) and the AV fistula as vascular access (p = 0.05), but not with the membrane surface, KT/V, the dialysate flux, the ultra filtration or treatment duration. Phosphate removal was 640 ± 180 mg/session with low-flux membrane and 700 ± 170 mg/session with high-flux membrane (p = 0.280). The MPO4 was 720 ± 190 mg/treatment in patients with a AV fistula and 620 ± 180 in patients with a tunnelled catheter (p = 0.023). On-line technique did not increased*

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the MPO4 (733 ± 280 mg, p = 0.383). The on-line technique with the new dialyzer (Fresenius Fx100), increased the phosphate removal to 759 ± 199 mg/session (p = 0.057). On multivariate analysis, plasma phosphate and the volume of blood that passed the dialyzer in each session predicted phosphate removal.

Conclusion: *Phosphate removal during dialysis is influenced by Plasma phosphate levels and the volume of blood that passed the dialyzer. Uniformity on time and membrane surface could explain the abs cense of influence in our case. The ultra filtration, dialysate flux, membrane permeability or on-line hemodiafiltration does not influence the phosphate removal. The new membrane helixone with 2,1 m^2 (Fresenius Fx100) increases phosphate removal probably because the membrane surface is higher.*

Key words: ***Phosphate removal. Hemodialysis.***

FACTORES EN LA ELIMINACIÓN DE FÓSFORO EN HEMODIÁLISIS

RESUMEN

La elevación de los niveles plasmáticos de fósforo se asocia a tasas elevadas de mortalidad en los pacientes en diálisis. La eliminación de fósforo con la hemodiálisis es limitada, debido a la localización intracelular del mismo. La superficie de la membrana del dializador, el tiempo y la frecuencia de la diálisis influyen claramente en su eliminación. El objetivo de este trabajo es analizar la influencia en la eliminación de fósforo de los factores relacionados con la sesión de hemodiálisis: El fósforo plasmático (Pp), la duración de la sesión, la superficie del dializador, la permeabilidad de la membrana, la naturaleza del acceso vascular, el flujo de sangre en la primera hora, el volumen de sangre depurado (L), la ultra filtración, el KT/V de urea y la técnica de hemodiafiltración on-line.

Métodos: *Se seleccionaron 108 pacientes en hemodiálisis. El 78% disponía de FAVI y 22% de catéter tunelizado. La membrana del dializador fue de polisulfona de alta permeabilidad en 31 (30%) y de permeabilidad media en 77 (70%). La superficie del dializador fue: 1,7 m^2: 17 (16%); 1,8 m^2: 77 (71%); 2,1 m^2: 14 (13%). Flujo del líquido de diálisis: 500 ml/min: 55 pacientes; 700 ml/min: 53 pacientes. Duración de la sesión: 4,14 ± 0,41 (Rango 3,5-5 horas). El 85% se dializaban entre 4 y 5 horas.*

Se realizó un corte transversal en el que se determinó la eliminación de fósforo en una sesión de mitad de semana simultáneamente a la realización del KT/V de urea (Bicompartimental). En la misma sesión se determinó la eliminación de fósforo (MPO4), utilizando la fórmula: MPO4 = 0,1 t-17 + 50 Cds 60 + 11 Cb 60 (1). Se analizó su relación con los parámetros señalados anteriormente. En un segundo tiempo, a 63 pacientes se les modificó únicamente la permeabilidad del dializador cambiando los de alta a media permeabilidad y viceversa de modo que cada uno era su propio control. La MPO4 se calculó y comparó en ambas situaciones. En 16 pacientes en los que tuvimos tecnología para realizar hemodiafiltración on-line, se comparó la eliminación de fósforo con hemodiálisis de alto flujo, hemodialiltración on-line con la misma membrana y hemodiafiltración on-line con la membrana Helixona de 2,1 m^2 de superficie.

Resultados: *La eliminación de fósforo (MPO4) guarda una buena correlación con los niveles plasmáticos del mismo (p = 0,01) , con los litros de sangre depurados (p = 0,01) y con la existencia de una fistula (p = 0,05), pero no observamos relación con la duración de la sesión, con el flujo del líquido de diálisis, con el KT/V de urea ni con la ultra filtración o la superficie de la membrana del dializador en nuestro caso. Fue de 700 ± 170 mg / sesión con membrana de alta permeabilidad y de 640 ± 180 mg / sesión con membrana de media permeabilidad (p = 0,280).*

Al modificar la permeabilidad de la membrana siendo el paciente su propio control, tampoco hubo diferencias en la eliminación. La MPO4 es de 720 ± 190 mg/ tratamiento en los pacientes que disponen de una FAVI y de 620 ± 180 mg /tratamiento en los pacientes que disponen de un catéter (p = 0,023). Las diferencias en los pacientes con FAVI o catéter se deben fundamentalmente al flujo de sangre tanto en la 1ª hora de diálisis como al total de litros depurados (p = 0,001). Sin embargo al realizar un analisis multivariante, son los niveles de fósforo plasmático y los litros de sangre depurada los que predicen la eliminación de fósforo. En los pacientes en que se pudo realizar hemofiltración on-line, la eliminación de fósforo fue de 725 ± 202 mg/sesión de HD de alto flujo, 733 ± 280 mg/ sesión de hemodiafiltración con reposición de 18L postdilución (p = 0,383) y de 759 ± 199 mg/sesión con hemodiafiltración con membrana de helixona de 2,1 m² (p = 0,057). ***En conclusión*** *en nuestra experiencia, en la depuración de fósforo en un sesión de diálisis intervienen además del fósforo plasmático, la cantidad de sangre depurada que es en general superior cuando el acceso vascular es una FAVI. Otros factores como la duración de la sesión y la superficie del dializador eran muy homogéneos y no han podido por tanto mostrar diferencias. La ultrafiltración, el flujo del líquido de diálisis, la permeabiliad de la membrana o la técnica de hemodiafiltración on-line no la incrementa de forma significativa.*

Palabras clave: ***Depuración de fósforo. Hemodiálisis.***

INTRODUCTION

Phosphorus retention is an early event in chronic renal failure (CRF) and is closely related to the development of secondary hyperparathyroidism.[2] Besides, is constitutes the main determinant factor in calcium-phosphorus product increase that leads to the onset of metastatic calcifications and in its severest form to calciphylaxis.[3,4]

At the vascular level, phosphorus overload in CRF patients acts stimulating accelerated deposition of calcium within the smooth muscle cell of the vascular wall.[5] From an epidemiological perspective, sustained hyperphosphatemia is associated to high mortality indexes,[6] related to calcifications of the coronary arteries,[7] arterial hypertension (AHT), and left ventricular hypertrophy.[8,9]

Management of phosphorus plasma levels in a CRF patient should be approached at three levels: low phosphorus diet, phosphorus intestinal absorption chelating agents, and dialysis.

Phosphorus clearance during the hemodialysis session is mainly limited by the intracellular location of most of inorganic phosphorus. Cleared amounts, with either three weekly hemodialysis sessions (2400 mg/week) or peritoneal dialysis (2100-2800 mg/week) are far from the 800-1200 mg daily ingested with patients' diet.[10,11]

Among factors contributing to phosphorus clearance during hemodialysis, the classical ones are phosphorus plasma levels as well as the surface area of the dialyzer membrane.[12] Frequency and duration of dialysis seem, however, to be currently the most important factors.[10,11,12,13] For obvious reasons, general implementation of both factors is difficult.

The aim of this study was to analyze the influence of the following factors related with hemodialysis session in phosphorus clearance: plasmatic phosphorus (Pp), session duration, surface area of the dialyzer membrane, permeability of the membrane, type of vascular access, blood flow within the first hour, volume of depurated blood (L), ultrafiltration and on-line ultrafiltration technique.

METHODS

Patients

A cohort of 108 patients on HD, 62% men, 38% women, aged 21-82 years (61 ± 14, mean ± SD) was selected for a cross-sectional study. Patients were studied under usual conditions. Seventy-five (78%) had an arterial-venous fistula (GAVF) and 23 (22%) a double-lumen funneled catheter. The membrane used was: high-permeability polysulphone (Ultrafiltration coefficient: 55 mL/h.mmHg): 31 (30%); intermediate-permeability polysulfone (Ultrafiltration coefficient 11,1 mL/h.mmHg): 77(70%). The dialyzer surface area was: 1.7 m²: 17 patients (16%); 1.8 m²: 77 patients (71%); 2.1 m²: 14 (13%). The dialysis fluid flow was 500 mL/min in 55 patients and 700 mL/min in

53. In all cases, the buffer used was bicarbonate. The dialysis session duration was 4.14 ± 0.41 hours (range 3.5-5 hours). Only 15 patients dialyzed for less than 4 hours; 48 (44%) dialyzed 4 hours, and 45 (41%) between 4 and 5 hours.

Study design

1. During a dialysis session in the mid-week, the Kt/V for urea was determined (bi-compartimental model). At the same session, phosphorus clearance (MPO4) was determined by using the following calculation: MPO4 = 0.1 t–17 + 50 Cds60 + 11 Cb60,[1] where t is treatment time in minutes, Cds60 and Cb60 phosphorus concentration, in mg/dL, in dialysis fluid and in blood within the 60 first minutes of dialysis, and MPO4 is depurated phosphorus by treatment in mg/treatment. MPO4 was analyzed in relation to phosphorus plasma levels, dialysis duration and dialyzer surface area, ultrafiltration, urea Kt/V, membrane permeability, type of vascular access, as well as blood flow at the first hour, liters of depurated blood, and dialysis fluid flow. Pp levels were analyzed in relation to weight, age, and some nutritional parameters (plasma albumin, prealbumin, and transferrin). The relationship between phosphorus MPO4 with urea Kt/V.

2. At a second step, in 63 patients only dialyzer permeability was modified, changing those of high permeability by intermediate ones, and vice versa, so that each patient acted as his/her own control. MPO4 was calculated and compared in both situations.

3. In 16 patients we had available the necessary technology to perform on-line hemodiafiltration. In this group we compared MPO4 with high-flow conventional HD with polysulfone dialyzer surface area of 1.8 m^2. On-line hemodiafiltration with post-dilution reposition of 18 L and the same dialyzer, and finally, on-line hemodiafiltration with the same reposition volume but using helixone membrane of 2.1 m^2 surface area (Fresenius F x 100), which theoretically yields better phosphorus clearance.[14,15]

Biochemical analysis

Plasma was obtained by centrifugation within the first hour after collection. Phosphorus at the dialysis fluid was determined in a sample obtained at the first dialysis hour. The method for inorganic phosphorus determination is based on the reaction of phosphorus with ammonia molibdate yielding ammonia phosphomolibdate without reduction. By adding an accelerator (Roche), the results are more accurate. The analysis is done with Hitachi 717.

Statistical analysis

Normally distributed quantitative variables are presented as mean ± standard deviation. The student's t test has been used to analyze the differences between groups for quantitative variables, and the Student's t test for paired samples when each patient was his/her own control. Simple regression has been used to relate quantitative variables. The results were considered to be statistically significant when the probability of type I error was less than 0.05.

Multivariate analysis has been done introducing into the model only those variables that were related with phosphorus clearance in the univariate analysis. This has been a stepwise backwards analysis in a multi-colinearity study.

RESULTS

Phosphorus clearance (MPO4) is related with phosphorus plasma levels ($p = 0.01$) (Fig. 1), liters of depurated blood ($p = 0.01$) (Fig. 2) and the existence of a GAVF as the vascular access type ($p = 0.05$), but we did not observe a relationship with session duration, surface area of the dialyzer membrane, urea Kt/V, blood flow at the first hour, dialysis fluid flow, plasmatic calcium, or ultrafiltration. Plasma phosphorus levels were negatively correlated with age ($p = 0.05$), but not with other nutritional parameters (prealbumin, transferrin or albumin).

MPO4 was 720 ± 190 mg/treatment in patients with GAVF and 620 ± 180 mg/treatment in patients with a catheter ($p = 0.023$). When analyzing the differences between patients with a GAVF or a catheter (Table I), these seem to be essentially due to both blood flow at the first dialysis hour and total number of depurated liters.

In patients with high-permeability membrane, phosphorus clearance was 700 ± 170 mg/session versus 640 ± 180 mg/session with intermediate-permeability membranes ($p = 0.280$). When changing the membrane permeability, the patient being his/her own control, we did not observe differences in clearance either ($p = 0.259$).

In the multivariate analysis, the predictive variables for phosphorus clearance were: plasmatic phosphorus, liters of depurated blood, and GAVF. The latter disappears when a multi-colinearity analysis is preformed.

In patients in whom on-line hemodiafiltration could be done, phosphorus clearance was 725 ± 202 mg/high-flow HD session, 733 ± 280 mg/session of hemodiafiltration with post-dilution reposition of 18 L ($p = 0.383$), and 759 ± 199 mg/hemodiafiltration session with helixone membrane of 2.1 m^2 ($p = 0.057$).

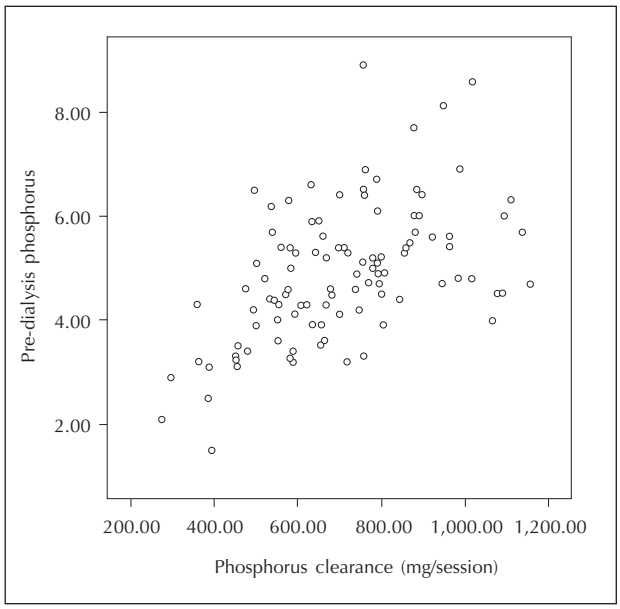

Fig. 1.—Phosphorus clearance in relation to plasmatic phosphorus (mg/dL).

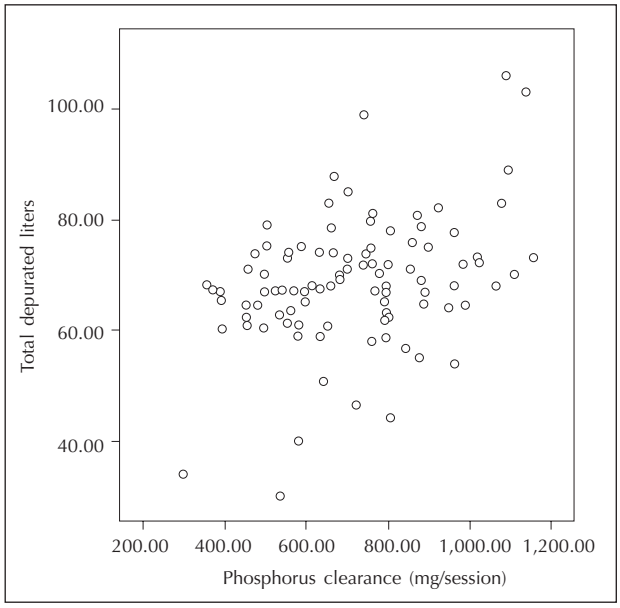

Fig. 2.—Phosphorus clearance in relation to depurated blood volume (L).

DISCUSSION

Among factors contributing in phosphorus clearance, besides phosphorus plasma levels, it seems that frequency[12] and duration[13] of the dialysis sessions are the most important ones. It is currently known that a slow and long dialysis (24 hours/week), that is to say time, is clearly related with an excellent patient's survival, even in those with associated comorbidity factors.[16] It is also known that hyperphosphatemia is associated with higher mortality,[6] and that phosphorus serum levels may be controlled without using chelating agents in patients with daily nocturnal hemodialysis.[17] We have found a correlation between phosphorus clearance and phosphorus plasma levels, but not with duration of the dialysis session, likely because the dialysis duration was very similar (85% of the patients dialyzed 4-5 hours). Phosphorus location within the intracellular space[18] and its clearance kinetics may explain why long and frequent dialyses improve its depuration and also the lack of a correlation between phosphorus clearance and urea Kt/V in our own and some other authors' experience.[1,19]

Jindal *et al.*[20] already showed that the increase in surface area of the dialyzer membrane increased phosphorus depuration although other authors[21] have observed that this increase is limited with surface areas higher than 2 m^2. In our series, 84% of the patients

Have received dialysis with a surface area of 1.8-2.1 m^2, i.e. a very homogeneous one, which may explain the lack of a relationship with phosphorus clearance. Similarly to our experience, other authors have not found, however, an evidence showing that high-permeability membranes increase it in a clinically relevant way.[16] Some works have found an improvement in phosphorus clearance with hemodiafiltration[22] or with new helicoidal-shaped membranes.[23] Our data do not show a benefit in phosphorus clearance with high-permeability membranes with regards to intermediate-permeability ones, nor with the use of the on-line hemodiafiltration technique with post-dilution reposition of 18 liters, although in this regard, our experience may be too short and this benefit might be shown with a larger sample size. The increase in phosphorus depuration produced by helixone membranes may be attributed, in our study, to the higher membrane surface area, besides the membrane characteristics themselves. Other membrane types have not shown to have an influence on phosphorus depuration.[24]

The most relevant results in our study are that phosphorus clearance specially depends on phosphorus plasma levels and on the total number of liters of depurated blood during the dialysis session, regardless the urea Kt/V, and that both this and phosphorus depuration are higher in patients carrying a fistula. However, when performing the multi-colinearity analysis, the GAVF vanishes as an influencing factor, only remaining plasmatic phosphorus and liters of depurated blood. Although urea Kt/V levels may be acceptable, patients carrying a catheter usually have lower blood

Table I. Characteristics by type of vascular access

	AV Fistula	Catheter	p value
Age	60.90 ± 14.99	64.21 ± 14.01	0.329
Weight (kg)	64.80 ± 11.58	59.58 ± 11.02	0.074
Phosphorus clearance	720 ± 190 mg/Tto.	620 ± 180 mg/Tto.	0.023
Membrane SA	1.82 ± 0.10	1.80 ± 0.10	0.270
Session duration (hours)	4.12 ± 0.36	4.21 ± 0.56	0.474
Urea KT/V	1.50 ± 0.19	1.46 ± 0.22	0.570
Depurated liters/Session	70.00 ± 10.00	58.00 ± 12	0.001
Blood flow (mL/min)	313.20 ± 26.26	274.61 ± 35.96	0.002
Fluid flow (mL/min)	605.88 ± 100.41	569.56 ± 97.39	0.124
Plasmatic phosphorus (mg/dL)	5.00 ± 1.31	4.55 ± 1.42	0.079

flow and, as observed in Table I, the total number of depurated liters of blood is lower. Although other authors have not found the blood flow improvement increases phosphorus clearance,[19] frankly speaking that study referred to a blood flow increase above 250 mL/min, which is not easily to achieve and maintain throughout the whole dialysis session with a catheter. In our case, blood flow at the first hour was not correlated with phosphorus clearance but the total number of liters of depurated blood did. This is likely due to the fact that blood flow may vary throughout the dialysis session. Although double-lumen catheters are widely used in a satisfactory way, recent studies have shown a better survival in patients with GAVF.[25] In the case of catheters with insufficient flow, the clinician may consider, provided there is no other choice, the option of increasing the dialyzer surface area (and maybe using a helixone membrane), the dialysis duration or frequency so that a minimum of liters of depurated blood is achieved in order to better manage phosphorus in spite of a "sufficient" urea Kt/V. In our case, higher flow of the dialysis fluid does not increase phosphorus clearance, similarly to what has been reported elsewhere.[21]

To conclude, to our experience, besides plasmatic phosphorus the volume of depurated blood, which is generally greater when the vascular access is a GAVF, also has an influence in phosphorus depuration during a dialysis session. Other factors such as session duration and dialyzer surface area, were highly homogenous so that they were not able to show any difference. Ultrafiltration, dialysis fluid flow, membrane permeability, or the on-line hemodiafiltration technique, do not significantly increase phosphorus clearance.

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