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What can we do with sodium retention in peritoneal dialysis patients?

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SUMMARY

Salt intake in XXI century in an average person exeeds 10-15 grams per day. The key organ responsible for sodium regulation is kidney and renal failure patients present with positive sodium balance. In peritoneal dialysis (PD) patients rising hypertension is often connected with volume overload and sodium retention. The reasons for inadequate sodium removal in PD patients are: too small gradient between standard 134 mmol/l sodium PD solutions, sodium seiving effect and lack of residual renal function. APD patients are at higher risk of sodium overload in comparison to CAPD ones. As it has been shown that a degree of sodium removal correlates with survivial, sodium management appears to be crucial in these patients. The concept of low sodium solutions has been developed over the years with single-dwell ultra-low solutions and recently with low sodium balance solution given as a continuous treatment in CAPD patients. Preliminary results show that low sodium solutions may be a safe and viable option of treatment of PD patients with sodium and fluid overload.

Key words: Peritoneal dialysis. Sodium retention. Low sodium solutions.

RESUMEN

El consumo de sal por una persona media en el siglo XXI supera los 10-15 gramos al día. El órgano fundamental responsable de la regulación del sodio es el riñón y los pacientes con insuficiencia renal presentan un balance de sodio positivo. En los pacientes sometidos a diálisis peritoneal (DP), la hipertensión creciente suele guardar relación con sobrecarga de volumen y retención de sodio. Los motivos de la insuficiente eliminación de sodio en los pacientes sometidos a DP son los siguientes: gradiente demasiado pequeño entre las soluciones convencionales para DP con 134 mmol/l de sodio, el efecto de filtrado del sodio y la ausencia de función renal residual. Los pacientes sometidos a DPA tienen mayor riesgo de sobrecarga de sodio que los sometidos a DPAC. Como se ha demostrado que el grado de eliminación de sodio se correlaciona con la supervivencia, el control del sodio parece ser esencial en estos pacientes. Se ha desarrollado el concepto de soluciones hiposódicas a lo largo de los años con soluciones ultrahiposódicas para una sola permanencia y, recientemente, la solución de equilibrio hiposódica administrada como un tratamiento continuo a los pacientes sometidos a DPAC. Los resultados preliminares han demostrado que las soluciones hiposódicas pueden ser una opción segura y viable de tratamiento de los pacientes sometidos a DP con sobrecarga de sodio y líquidos.

Palabras clave: Diálisis peritoneal. Retención de sodio. Soluciones bajas en sodio.

SALT AND BLOOD PRESSURE

Salt ingestion has been systematically increasing over the years. Homo erectus living 1,850,000-40,000 BC was taking 1 g of salt daily while our predecessor Homo sapiens 4 times more. In the XXI century we have to acknowledge the fact that in the civilized societies salt intake for an adult person is 10-15 grams per day and one double-burger contains 4.8 g of salt which accounts for 79% of recommended daily intake.

Amount of salt ingestion corresponds with sodium intake. Ten grams of NaCl contains 160 mmol of sodium. Healthy human being has got mechanisms responsible for sodium and chloride balance within wide variety of dietary salt intake. The regulatory hormones are: sodium-saving (aldosterone, sympathetic discharge) and sodium-loosing (catecholamines and natriuretic peptides) and the key organ responsible for sodium regulation is kidney. Sweat glands, exocrinic glands, respiratory epithelium and colonic crypts participate in this process in the smaller amount. 99% of filtered NaCl from 170 l of primary urine is reabsorbed daily by proximal tubule, thick ascending limb of Henle's loop, distal tubule and collecting duct. An individual with healthy kidneys excretes 10 g of NaCl daily in 1.0 to 1.5 l of urine. It appears that the kidney protects sodium loss more readily than it manages sodium overload.[1]

Over-consumption of salt increases blood pressure and the risk of cardiovascular disease. On the other hand the restriction in dietary salt reduces blood pressure. It was shown that with increasing age urinary sodium excretion goes along with the blood pressure. In addition there is a strong correlation between salt intake and left ventricular mass. Left ventricular

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hypertrophy is a prognostic factor for cardiovascular morbidity and mortality e.g. myocardial infarction, congestive heart failure, sudden death and stroke.[2,3]

High blood pressure is present in the vast majority of patients with chronic kidney disease. Moreover, it has been proven that hypertension is one of the major risk factors for the progression of the kidney disease as well as for the cardiovascular mortality in renal failure patients.[4] In peritoneal dialysis (PD) patients rising hypertension is often connected with volume overload and sodium retention. The volume-independent effect of sodium chloride on arterial blood pressure regulation is still under investigation.[5]

SODIUM BALANCE IN PERITONEAL DIALYSIS PATIENTS-THEORETICAL BACKGROUND AND PRACTICAL IMPLICATIONS

Sodium elimination during peritoneal dialysis occurs due to sodium gradient between dialysate and plasma. Standard PD solutions present with sodium concentration of 132-134 mmol/l and this gradient may be too small to adequately decrease sodium overload. Another reason for sodium accumulation is sodium sieving effect which means that transport of sodium is slower than free-water transport across the peritoneal membrane. A discrepancy between sodium and water transport can be observed especially during short dwells when hypernatremia together with volume depletion and hyperosmolality may develop. Another powerful mean of sodium elimination in PD patients is residual renal function. Model CAPD patient on four 2 L exchanges per day of 1.5% glucose and sodium of 134 mmol/l with 800 ml of ultrafiltration per day will need another 400 ml of urine per day to achieve sodium elimination of 100 mmol/day. In patients loosing residual renal function the problem of sodium retention is obvious.[6]

In a prospective observational study of Ortega et al. the peritoneal sodium removal during a 24-hour period was compared in 16 CAPD and 20 APD patients and its possible influence on blood pressure control was analysed.[7] In particular, in single regression analysis, the 24-hour peritoneal sodium removal strongly correlated with net ultrafiltration. In addition peritoneal sodium removal was significantly higher in CAPD than in APD patients. The residual renal function, serum sodium, peritoneal urea and creatinine clearances, 4-hour dialysate/plasma creatinine ratio, or proportion of hypertonic solutions did not differ significantly between groups. The systolic blood pressure and the proportion of patients with antihypertensive therapy was significantly higher in APD patients, although no significant relationship between blood pressure values and amount of peritoneal sodium removal was found. Although small number of patients was observed, this study showed that peritoneal sodium removal is higher in CAPD than in APD patients, is correlated with ultrafiltration volume, and there is a trend towards improved control of blood pressure in CAPD patients. In another work comparing sodium removal in CAPD and APD, Rodríguez-Carmona et al. identified CAPD modality, ultrafiltration and urine output as independent predictors of sodium elimination.[8] For any degree of ultrafiltration, sodium removal was better in CAPD than in APD.

In another study of Ates et al. 125 PD patients were monitored prospectively over 3 years for the effects on mortality of demographic features, comorbidity, peritonitis rate, blood pressure, medications, blood biochemistry, peritoneal membrane transport characteristics, residual renal function (RRF), Kt/V, creatinine clearance, normalized protein nitrogen appearance and sodium removal.[9] In the Cox model, total sodium and fluid removal, hypertensive status, serum creatinine and RRF were independent factors affecting survival. Total sodium removal and hypertensive status also significantly affected the hospitalization rate. Systolic and diastolic blood pressure were negatively correlated with total sodium removal and total fluid removal. Sodium and fluid removal are both predictors of mortality in PD patients. Inadequate elimination of both of them may contribute to cardiovascular mortality in these patients.

The aim of the prospective, interventional study of Gunal et al. was to investigate whether normal blood pressure can be achieved in hypertensive CAPD patients by salt restriction. and volume control without the use of antihypertensive drugs[10] Of 47 patients, a strong dietary salt restriction led to blood pressure normalisation in 20 of them.

Of further 24 patients, 17 became normotensive with strict dietary salt restriction together with increased ultrafiltration. The authors showed clearly that normal blood pressure can be achieved by severe salt restriction combined with increased ultrafiltration in the majority of CAPD patients. In another study of Gunal et al. in 19 patients starting hemodialysis, it was shown that salt restriction alone achieved substantial improvement in blood pressure control and cardiovascular markers like cardiothoracic index.[11] Salt restriction and volume control allowed for better blood pressure control and improvement of left ventricular hypertrophy, ejection fraction, left ventricular mass index and cardiothoracic index. Intensified blood pressure medications without salt restriction and strict volume control did not sufficiently control hypertension and improve cardiovascular parameters.

These clinical studies clearly show that dialysis patients have a positive sodium balance and sodium and water elimination is crucial for their management especially in view of cardiovascular mortality which is 10 to 100 fold higher than in the age matched general population.[4]

DEVELOPMENT OF CONCEPT OF LOW SODIUM PD SOLUTIONS

Over the last ten years the research went into developing PD solutions that would help volume control. For some years polyglucose seemed to have dominated overall clinical research in PD. From the results of clinical studies mentioned above, it appears that sodium elimination is a prerequisite to be addressed in PD patients and in order to avoid oedema, hypertension and thirst. In standard PD solutions (Na 132 to 134 mmol/L) peritoneal sodium removal greatly depends on the drained ultrafiltration volume (convective effect of sodium elimination). Sodium removal can be increased by enhancement of diffusive transport via a low sodium PD solutions.

In the pilot study of Nakayama et al. a low sodium PD solution (Na 120 mmol/l, Cl 84 mmol/l) was developed to incre-

ase transperitoneal sodium removal through diffusive forces and to study the clinical effects of this solution over continuous 4 week application in CAPD patients with volume overload and hypertension.[12] From nine patients, two patients dropped out due to overhydration caused by inadequate ultrafiltration and due to hyponatremia with general fatigue. The remaining seven patients presented with highly significant increase in sodium removal while using the low sodium solution and showed no adverse symptoms. There were no changes in body weight and ultrafiltration but blood pressure significantly decreased over a 4-week treatment time. This and subsequent studies demonstrated that a solution with a lower sodium concentration than the conventional solution, can be effectively used to increase transperitoneal sodium elimination, thereby controlling hypertension in patients with sodium overload.[13,14]

In the 8 week study done by Vrtovsnik et al. with a single-bag per day of ultralow sodium 102 mmol/L, despite lower ultrafiltration, the low sodium PD solution was well tolerated and led to more efficient control of blood pressure, extracellular water and sodium balance.[15] No side effects were reported and one low sodium bag generated a lower ultrafiltration than standard glucose 3.86%, but a higher sodium extraction (80 versus 56 mmol). In addition thirst was also reduced with the low sodium solution. Other single dwell studies with ultra-low sodium concentration in CAPD patients (102 and 105 mmol/l) showed vigorous sodium and chloride removal with low sodium solution in comparison to standard fluids and increase of net ultrafiltration with alleviation of symptoms of fluid overload.[16,17] There is only one single-dwell study which reported immediate complaints of drowsiness and lethargy in CAPD patients treated with 126 mmol/l sodium solution.[18]

A multicentre study with a PD low sodium solution in hypertensive or antihypertensively-medicated balance patients was developed by Fresenius Medical Care as a prospective, controlled, randomised, double-blind, parallel-group study. The study group of CAPD patients was treated with 4-5 exchanges of balance low sodium (125 mmol/l) solution per day for 6 months with the parallel group of CAPD patients treated with control balance solution in a double-blinded approach. Primary hypothesis was that the use of a balance low sodium solution compared to balance solution causes no relevant effect on total weekly Kt/V after a 3 months treatment (non-inferiority). The objectives of the study were to evaluate: efficacy and safety of the investigational CAPD solution balance low sodium when compared to the registered CAPD solution balance as an active control, in double-blinded testing. The secondary end-points included cardiovascular effects of balance low sodium solution as defined by changes in blood pressure, changes of the number or dosage of anti-hypertensive drugs as well as changes in serum markers related to the cardiovascular system. Effects of balance low sodium solution on sodium balance and quality of life were the other secondary objectives of the study. Adult patients of more than 18 years of age were included into the study and the main exclusion criterium was serum sodium concentration less than 130 mmol/l or known medical history of recurrent severe hyponatremia < 130 mmol/l. The data of preliminary safety evaluation, crucial to this trial in the context of reducing sodium below physiological concentrations, were presented during ISPD meeting in Hong Kong in 2006.[19] There were 5 events regarding volume status (overhydration and dehydration). Transient hyponatremia was reported in 3 out of 108 patients, one of which was erroneously included with preexisting hyponatremia. None of these patients presented with serious adverse clinical signs or symptoms. In conclusion this was the first trial to evaluate long-term effects of low sodium solution in chronic PD patients following prospective, randomized, double-blind design. Low sodium fluid had benign risk profile and the application of these solutions is practical and clinically safe. We are awaiting final results of the trial. It appears that the balance low sodium solution may prolong time on PD due to preservation of peritoneal membrane function (balance solution = no GDP, physiological pH).[20] It may also positively influence quality of life due to lack of pain at installation and reduction of the blood pressure and fluid overload. The main advantage of it can be prolonged survival of PD patients due to the increase of sodium removal and reduction of cardiovascular mortality.

In summary, positive sodium balance in PD patients is common especially in patients without residual renal function and treated with APD. These patients frequently present with high fluid intake, thirst, oedema and high blood pressure which are the risk factors for cardiovascular mortality. Low sodium PD solutions enhance diffusive transport of sodium and thus can be efficient in reducing overhydration and hypertension-risk factors for decreased survivial of these patients.

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Conflict of interes statement

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Gdańsk PD Unit was taking part in the Low Sodium Study developed by Fresenius. Members of Research and Development Department of Fresenius Medical Care provided information concerning Low Sodium Study.

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