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소아복막투석환자에서 CKD-MBD와 중증 부갑상샘 기능항진증에서 비타민 D 치료

울산대학교 의과대학 서울아산병원 어린이병원 소아청소년과

강은구 · 이주훈 · 박영서

Eun Gu Kang, M.D.,
Joo Hoon Lee, M.D.,
and Young Seo Park, M.D.

Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Corresponding Author: Young Seo Park, M.D.
Department of Pediatrics, Asan Medical Center Children's Hospital, Ulsan University College of Medicine, Seoul, Korea
Tel: +82-2-3010-3386, Fax: +82-2-473-3725
E-mail: yspark@amc.seoul.kr

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Chronic Kidney Disease-mineral Bone Disorder and Active Vitamin D Analogs for Treating Severe Hyperparathyroidism in Children Receiving Chronic Peritoneal Dialysis

Purpose: The aims of this study were to assess the clinical and laboratory profiles of chronic kidney disease-mineral bone disorder (CKD-MBD) and to assess the effects of treatment of active vitamin D analogs on severe hyperparathyroidism (SHPT) in pediatric patients on chronic peritoneal dialysis.
Methods: This is a retrospective study included 53 patients who had been undergoing dialysis for more than 1 year, between January 2003 and December 2012.
Results: Even after treatment with phosphate binders and active vitamin D analogs, the mean±standard deviation of the percentage of time during peritoneal dialysis that the patients' serum concentrations of phosphorus, corrected total calcium, and parathyroid hormone (PTH) fell within the Kidney Disease Outcomes Quality Initiative recommended ranges was 25.06±17.47%, 53.30±23.03%, and 11.52±9.51%, respectively. Clinical symptoms or radiological signs of CKD-MBD were observed in 10 patients (18.9%). There were significant differences in percentage of time that the serum intact PTH concentration was outside of the recommended range between patients with and without symptoms or signs of CKD-MBD (below recommended range, 11.74±7.37% vs. 40.77±25.39%, $P<0.001$; above the recommended range, 63.79±27.86% vs. 37.09±27.76%, $P=0.022$). Of the 25 patients with SHPT, high-dose alfacalcidol treatment was required in 13 patients that controlled SHPT in 7 of these patients, without marked complications.
Conclusion: Despite our efforts to manage CKD-MBD, patients' met the recommended ranges from relevant guidelines at a low frequency. The treatment of high-dose active vitamin D analogs was required in about half of the patients with SHPT and effective in about half of them.

Key words: CKD-MBD, Peritoneal dialysis, Active vitamin D

Introduction

Many studies have indicated that chronic kidney disease-mineral bone disorder (CKD-MBD), which is a systemic disorder of mineral and bone metabolism that occurs in association with chronic kidney disease, is associated with an increased risk of musculoskeletal morbidities, cardiovascular events, and mortality [1-4]. Current guidelines for the management of CKD-MBD place emphasis on the control of serum levels of parathyroid hormone (PTH) and mineral electrolytes by using several types of phosphate binders and active vitamin D analogues [4-6]. Although abnormalities in serum phosphorus and calcium concentrations improved after the introduction of guidelines on mineral metabolism, such abnormalities remain common in CKD-MBD patients receiving dialysis [2, 7, 8].

Skeletal deformities and growth retardation can easily develop in infants and young children that are receiving chronic peritoneal dialysis. Malnutrition, metabolic acidosis, end-organ growth hormone resistance, and mineral disturbances are risk factors for these abnormalities. However, even after correction of these factors, the growth rate does not normalize in the majority of patients and secondary hyperparathyroidism contributes to persistent growth failure [7]. Secondary hyperparathyroidism is also associated with an increased prevalence of bone pain, fracture and extraskeletal calcification [9]. Treatment of secondary hyperparathyroidism includes maintaining the serum levels of calcium and phosphorus within normal ranges by dietary manipulation, phosphate binders, vitamin D analogues, calcimimetics, or parathyroidectomy. The most effective doses of active vitamin D analogues and calcimimetics are not clearly identified. Some studies showed that large doses over a long time are required and others that such treatments are less likely to achieve the targets in patients with severe hyperparathyroidism [10, 11].

The aims of this study were to assess the clinical and laboratory profiles of CKD-MBD with reference to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and to review the treatment of active vitamin D analogues on severe hyperparathyroidism in pediatric patients who underwent peritoneal dialysis for more than 1 year.

Materials and methods

1. Patients

Patients who underwent chronic peritoneal dialysis for more than 1 year at Asan Medical Center Children's Hospital between January 2003 and December 2012 were included. Data were collected by retrospective review of medical records and included the basic characteristics, medical history, and medications of the patients, as well as their biochemical results during the follow-up.

2. Variables of interest and methods of measurement

The percentage of time throughout the follow-up that the biochemical results were within, below, and above the range recommended by the KDOQI guidelines was calculated for each patient. The target serum concentrations of phosphorus were 4.5-6.5 mg/dL for children aged 1-5 years, 3.6-5.8 mg/dL for children aged 6-12 years, and 2.3-4.5 mg/dL for adolescents aged over 12 years. The target serum concentrations of corrected total calcium were 9.4-10.8 mg/dL for children aged 1-5 years, 9.4-10.3 mg/dL for children aged 6-12 years, and 8.8-10.2 mg/dL for adolescents aged over 12 years [5]. Total calcium concentration was corrected for serum albumin using the following equation: Total calcium concentration=calcium concentration+0.8 (4.0-albumin concentration), if the albumin concentration is $<$4.0 g/dL.

Vitamin D status was assessed according to the mean 25(OH) vitamin D concentration in each year. According to the KDOQI guidelines, vitamin D deficiency was defined as a 25(OH) vitamin D concentration of $\leq$15 ng/mL, severe vitamin D deficiency as $<$5 ng/mL, vitamin D insufficiency as 16-30 ng/mL, and vitamin D sufficiency as $>$30 ng/mL. The target concentration of intact PTH was 200-300 pg/mL and severe hyperparathyroidism

was defined as an intact PTH concentration of >1,000 pg/mL, according to the KDOQI guidelines.

Both calcitriol and alfacalcidol are widely used as active vitamin D analogues, having been shown to be effective in suppressing PTH. Alfacalcidol has been more frequently prescribed in our center. There is no consensus regarding the optimal dosage of active vitamin D analogues; we defined high-dose active vitamin D treatment as a dosage of alfacalcidol greater than 0.05 mcg/kg/QOD and usual dose as a dosage of alfacalcidol less than 0.05 mcg/kg/QOD. Control of severe hyperparathyroidism was defined as maintaining a serum concentration of intact PTH less than 300 pg/mL.

Routine biochemical variables, such as calcium, phosphorus, alkaline phosphatase, albumin, and total CO_2 levels, were measured by standard automated methods. The serum intact PTH concentration was measured by an immunoradiometric assay. Serum 25(OH) vitamin D and 1,25$(OH)_2$ vitamin D concentrations were measured by radioimmunoassays.

3. Statistical analyses

Descriptive statistics of continuous variables are presented as the mean and standard deviation for normally distributed parameters or as the median (range) for skewed parameters. Categorical variables are presented as frequencies. Subgroups were compared using the t-test for continuous variables and the chi-square test for categorical variables with a P value of <0.05 considered significant. Associations between the intact PTH serum concentration and other variables were tested by linear regression analysis with a P value of <0.05 considered significant. All statistical analyses were performed using IBM SPSS software, version 21 (IBM, Armonk, NY, USA).

Results

1. Patient characteristics

Between January 2003 and December 2012, 53 patients (35 boys and18 girls) underwent peritoneal dialysis in our center and were included in this study. The age at initiation of peritoneal dialysis was 1-17 years (median, 10 years) and the duration of peritoneal dialysis was 12-132 months (median, 33 months). Twenty-five patients (47.2%) received a kidney transplant and the median duration from initiation of peritoneal dialysis to kidney transplantation was 31 months (range, 14-112 months). The most common primary cause of end-stage renal disease was focal segmental glomerulosclerosis (18.9%) (Table 1).

2. Biochemical outcomes and vitamin D status

To maintain serum concentrations of calcium, pho-

Table 1. Basic Characteristics of the Patients

Variable	Value (N=53)
Age at initiation of peritoneal dialysis	10 years (1-17 years)
Duration of peritoneal dialysis	33 months (12-132 months)
Outcome	
Continued peritoneal dialysis	24 (45.3%)
Received kidney transplantation	25 (47.2%)
Changed to hemodialysis	3 (5.7%)
Death	1 (1.9%)
Sex	
Boy	35 (66%)
Girl	18 (34%)
Primary cause of end-stage renal disease	
Focal segmental glomerulosclerosis	10 (18.9%)
Reflux nephropathy	4 (7.5%)
Renal dysplasia	3 (5.7%)
IgA nephropathy	3 (5.7%)
Alport's syndrome	2 (3.8%)
Membranoproliferative glomerulonephritis	2 (3.8%)
Nephronophthisis	2 (3.8%)
Others*	11 (20.8%)
Unknown	16 (30.2%)
Serum intact parathyroid hormone concentration (pg/mL)	296 (7.9-4,240)
Serum corrected calcium concentration (mg/dL)	9.75 (5.0-13.3)
Serum phosphorus concentration (mg/dL)	6.3±1.86
Calcium-phosphorus product concentration (mg^2/dL^2)	60.4±18.9
25-OH-vitamin D concentration (ng/mL)	6.1 (1.8-64.1)
1,25-OH-vitamin D concentration (pg/mL)	7.7 (8-127)

*Others: bilateral angiomyolipoma, Caroli disease, congenital chloride diarrhea, Fechtner syndrome, Henoch-Schonlein nephritis, hyperuricemic nephropathy, infantile nephrotic syndrome, Joubert syndrome, lupus nephritis, primary oxalosis, and posterior urethral valve syndrome. Mean±standard deviation for normally distributed parameters and median (range) for skewed parameters.

sphorus, and PTH within the recommended ranges, patients were treated with calcium-containing phosphate binders (calcium carbonate or calcium acetate), calcium-free phosphate binders (sevelamer hydrochloride or lanthanum carbonate), and active vitamin D analogues (alfacalcidol) for 75.33±3.14%, 23.30±24.00%, and 58.69 ±25.82% of the time they were receiving peritoneal dialysis, respectively. The type of phosphate binder (calcium-containing or calcium-free) was determined by the serum calcium concentration. Despite the treatment with these medications, the mean±standard deviation of the percentage of time during peritoneal dialysis that the patients' serum concentrations of phosphorus, corrected total calcium, and PTH were within the recommended ranges was 25.06±17.47%, 53.30±23.03%, and 11.52±9.51%, respectively.

There were no significant differences between boys and girls in relation to the percentage of time during peritoneal dialysis that the biochemical results were within the recommended ranges. Peritoneal dialysis for a longer amount of time was associated with patients showing hypercalcemia for a higher percentage of time (r=0.439, *P*=0.001), but was not associated with the percentage of time that patients exhibited hyperparathyroidism or hyperphosphatemia.

At 1 year after peritoneal dialysis initiation, 6 (17.1%) of the 38 patients in whom the 25(OH) vitamin D concentration had been measured at least once had a mean 25(OH) vitamin D concentration of greater than 30 ng/mL. At 2 years after peritoneal dialysis initiation, 1 patient (2.9%) had vitamin D sufficiency. At 3 years after peritoneal dialysis initiation, no patients had vitamin D sufficiency.

An increased serum PTH concentration was significantly associated with a decreased serum corrected total calcium concentration and an increased serum phosphorus concentration, but was not significantly associated with decreased serum concentrations of 25(OH) vitamin D or $1,25(OH)_2$ vitamin D.

3. Clinical symptoms and/or radiological signs of CKD-MBD

Clinical symptoms or radiological signs of CKD-MBD were observed in 10 patients (18.9%). Bone pain or osteopenia was observed in 4 patients, skeletal deformities in 2 patients, tissue calcification in 2 patients, rickets in 1 patient, and a fracture in 1 patient. Three patients developed these symptoms or signs prior to the initiation of peritoneal dialysis. There were significant differences between patients without and with symptoms or signs of CKD-MBD in terms of the percentage of time during peritoneal dialysis that the intact PTH concentration was below the guideline (40.77± 25.39% vs.11.74±7.37%, *P*<0.001) and above the guideline (37.09±27.76% vs. 63.79±27.86%, *P*=0.022). The percentage of time during peritoneal dialysis that the other biochemical results were outside the recommended guidelines did not significantly differ between these two groups of patients. Clinical symptoms or radiological signs of CKD-MBD were associated with severe hyperparathyroidism (*P*=0.002) (Table 2).

4. Treatment of high dose active vitamin D analogues on severe hyperparathyroidism

Of the 25 patients (47.2%) who showed severe hyperparathyroidism more than once during the follow-up, severe hyperparathyroidism was controlled in 12 patients by treatment with alfacalcidol at a dosage of less than 0.05 mcg/kg/QOD. Among the 13 patients who were treated with alfacalcidol at a dosage of greater than 0.05 mcg/kg/QOD, severe hyperparathyroidism was controlled by using high dose alfacalcidol alone in 5 patients and by using high dose alfacacidol plus cinacalcet (dose; 25-50 mg daily) in 2 patients. In these patients, the mean duration of high dose alfacalcidol treatment was 5.5±4.4 months (maximum, 12.3 months) and the mean dose of alfacalcidol was 0.109±0.032 mcg/kg/QOD (maximum, 0.158 mcg/kg/QOD).

Six patients had persistent severe hyperparathyroidism despite high dose alfacalcidol treatment. In 2 of these patients, severe hyperparathyroidism was controlled

Table 2. Comparison of Patients with and without Symptoms or Signs of Chronic Kidney Disease-mineral Bone Disorderin Terms of the Percentage of Time During Peritoneal Dialysis that Biochemical Results were within, Below, and Above the Range Recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines

		Clinical symptoms or radiological signs of chronic kidney disease-mineral bone disorder		*P* value
		Yes (N=7)	No (N=43)	
PTH	% of time below the guideline	11.74±7.37	40.77±25.39	<0.001
	% of time within the guideline	24.47±21.92	22.13±16.71	0.744
	% of time above the guideline	63.79±27.86	37.09±27.76	0.022
Phosphorus	% of time below the guideline	7.85±14.44	5.57±9.31	0.583
	% of time within the guideline	18.97±22.74	25.80±17.54	0.364
	% of time above the guideline	73.18±26.62	68.63±21.22	0.614
Calcium	% of time below the guideline	17.08±21.54	16.75±18.05	0.965
	% of time within the guideline	49.30±29.26	56.64±25.35	0.490
	% of time above the guideline	33.62±28.11	26.61±24.20	0.490
Ca*P	% of time below the guideline	32.34±23.16	47.22±21.61	0.103
SHPT	Yes	7 (14%)	15 (30%)	0.002
	No	0 (0%)	28 (56%)	

Abbreviations: SHPT, severe hyperparathyroidism; PTH, parathyroid hormone; Ca*P, Calcium-phosphorus product.

after kidney transplantation or parathyroidectomy. Another 2 patients in whom the intact PTH concentration has recently increased continue to receive a high dose of alfacalcidol. The other 2 patients persistently had an intact PTH concentration of greater than 1000 pg/mL despite the treatment with a combination of high dose alfacalcidol, cinacalcet (dose; 50 mg daily) and parathyroidectomy.

During high dose alfacalcidol treatment, 4 patients experienced hypercalcemia and 10 patients experienced hyperphosphatemia, but this phenomenon was normalized after alfacalcidol treatment was discontinued or the dosage was reduced. After high dose active vitamin D treatment, the serum 1,25 $(OH)_2$ vitamin D concentration remained below the normal range. Although none of the patients in this study underwent a bone biopsy, no patients showed biochemical features consistent with adynamic bone such as persistent hypercalcemia, low serum PTH or alkaline phosphatase level.

Discussion

This study shows that CKD-MBD remains a significant problem in children receiving chronic peritoneal dialysis, despite efforts to meet the KDOQI guidelines. Most studies concerning CKD-MBD reported cross-sectional data in adult patients receiving dialysis and there are few studies of pediatric patients. This study was a retrospective study that assessed CKD-MBD by determining the percentage of time during chronic peritoneal dialysis that mineral electrolytes were imbalanced in pediatric patients. Although most patients received phosphate binders and active vitamin D analogues, the percentage of time during peritoneal dialysis that serum phosphorus, calcium, and intact PTH concentrations were within the recommended ranges was low. The median percentage of time during peritoneal dialysis that patients exhibited hyperphosphatemia was 73% and the serum phosphorus concentration was above the recommended range throughout the entire follow-up period in 4 patients. The median percentage of time during peritoneal dialysis that patients exhibited hyperparathyroidism was 37% and 3 patients had persistent hyperparathyroidism throughout the entire follow-up period. The International Pediatric Peritoneal Dialysis Network (IPPN) study showed a similar result that the KDOQI guidelines were achieved in a relatively low percentage of patients [12]. There was a limitation to assess whether enough doses of phosphate binders were administered because the doses of phosphate binders were not collected in this study. The compliance and dietary restrictionof the patients should also be considered.

Vitamin D insufficiency and deficiency were common

and the proportion of patients who showed vitamin D insufficiency or deficiency increased with the duration of peritoneal dialysis. In pediatric patients treated with dialysis, the prevalence of vitamin D insufficiency and deficiency was reportedly 83-98%. Many studies suggested that suboptimal serum vitamin D levels were associated with higher serum PTH levels, contributed to the development of secondary hyperparathyroidism, and were associated with increased risks of cardiovascular events and death [13-15].

Approximately 19% of patients showed clinical symptoms or radiological signs of CKB-MBD and these were associated with severe hyperparathyroidism. Information about the growth of patients was not collected in this study, although growth failure is a common feature of pediatric patients with CKD-MBD. In the IPPN registry, the prevalence of clinical symptoms or radiological signs of bone disease was 15%, and the height of below the third percentile was 39% of children [12]. Among young Dutch adults who received dialysis before the age of 14 years, 61% had severe growth retardation, 36.8% had clinical symptoms of bone disease, and 17.8% had disabilities owing to bone disease [16].

In the current study, about half of patients who showed severe hyperparathyroidism required higher than usual doses of alfacalcidol. Among these, 7 patients had a decreased serum intact PTH concentration and achieved the KDOQI target intact PTH concentration by taking an increased dose of alfacalcidol with or without cinacalcet. In a recent meta-analysis, receiving vitamin D therapies in the form of alfacalcidol, calcitriol, or analogues was significantly associated with reduced risks of all-cause mortality and cardiovascular mortality. The effect of 1,25 $(OH)_2$ vitamin D concentration on the reduced risk of mortality is not only owing to the alleviation of hyperparathyroidism but also to PTH-independent biological activity [17]. It is uncertain whether the benefits of active vitamin D analogues are reduced when they are prescribed at high doses or whether such high doses are insufficient in patients with severe hyperparathyroidism [18, 19]. Adynamic bone disease is a side-effect of intermittent treatment with active vitamin D analogues [20]. Although none of the patients in this study underwent a bone biopsy, no patient showed biochemical features consistent with adynamic bone disease. The percentage of time during dialysis that patients exhibited hypercalcemia was not higher in patients that were treated with high doses of alfacalcidol than in patients that were treated with lower doses of alfacalcidol. Furthermore, during high-dose alfacalcidol treatment, the serum 1,25 $(OH)_2$ vitamin D concentration remained below the normal range.

In conclusion, despite our efforts to manage CKD-MBD in pediatric patients receiving dialysis, the proportions of time that patients met the relevant guidelines were low. In addition, severe hyperparathyoroidism, which was associated with clinical symptoms and radiological signs of CKD-MBD, was observed in half of patients. High dose of active vitamin D analogues was required in 13 patients with severe hyperparathyroidism and controlled severe hyperparathyroidism was observed in 7 patients without marked complications.

한글요약

목적: 본 연구는 만성복막투석환자에서 만성 신부전 무기질 골 장애의 목표 달성 정도의 평가와 중증 부갑상선기능항진증에서 비타민 D 치료에 대해 검토하였다.

방법: 본 연구는 2003년 1월부터 2012년 12월까지 1년 이상 복막투석을 시행한 53명의 환자를대상으로 한 후향적 연구이다.

결과: 인산염 결합제제와 비타민 D 치료에도 불구하고 투석기간 중 인, 칼슘, PTH가 KDOQI의 목표치 내에 있었던 비율의 평균±표준편차 값은 각각 25.06±17.47%, 53.30±23.03%, 11.52±9.51%이었다. 10명(18.9%)의 환자에서 CKD-MBD의 임상적 증상 혹은 영상의학적 징후가 있었고, 이는 증상 혹은 징후가 없었던 군과 비교하여 PTH가 목표치보다 높았던 시간의 비율이 길고(63.79±27.86% vs. 37.09±27.76%, P=0.022) PTH가 목표치보다 낮았던 시간의 비율이 짧은 것(11.74±7.37% vs 40.77±25.39%, P<0.001)과 유의한 상관관계가 있었다. 중증 부갑상선기능항진증이 있었던 25명의 환자 중 고용량비타민 D 치료를 받은 환자는 13명이었고 이 중 7명의 환자가 특별한 합병증 없이 부갑상선기능항진증이 조절되었다.

결론: 만성복막투석에서 CKD-MBD를 조절하기 위한

노력에도 불구하고 칼슘, 인, 비타민 D, PTH가 목표치를 만족하는 기간의 비율은 낮은편이다. 중증 부갑상선기능항진증 환자의 반 정도에서 고용량 비타민 D 치료가 필요하였고 이 중 50% 정도에서 효과가 있었다.

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