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Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control

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Abstract Clinical outcome under adequacy control was studied in 10 pediatric patients under 5 years and 11 patients over 5 years of age on continuous peritoneal dialysis (PD). Outcome was compared between the age groups and with our previous results in patients under 5 years of age. Peritoneal equilibration test and 24-h dialysate collection were performed. Laboratory data, clinical status, and diet were recorded. PD prescription was adjusted for these parameters. The mean weekly urea Kt/V was similar and stable in the two age groups (3.1±0.6 vs. 3.2±0.4 at baseline). The mean weekly creatinine clearance (C_{Cr}) was at baseline significantly lower in the younger age group (58.7±11.9 vs. 78.0±14.9 l/week per 1.73 m^2, P=0.004), but later similar. Urea Kt/V and C_{Cr} correlated significantly. Hematological and biochemical parameters were stable, and catch-up growth was observed in 62% of the patients during 9 months of follow-up. The outcome for children under and over 5 years of age did not differ significantly. The clinical outcome in patients under 5 years of age improved under adequacy control, when compared with our previous results in patients of the same age. This suggests a positive effect of adequacy control on clinical outcome.

Key words Peritoneal dialysis · Dialysis adequacy · Peritonitis · Growth · Hospitalization

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Introduction

In infants and young children on continuous peritoneal dialysis (CPD), control of blood volume and maintenance of normal growth are hard to achieve, and mortality and the number of infectious complications are higher than in older children and adults [1–4]. Detailed information about dialysis outcome in young children is still sparse. During recent years, consensus has been reached about how to measure individual peritoneal transport kinetics in children of various sizes. Several studies have been published on peritoneal transport or the dose of dialysis delivered by a given prescription [5–11]. However, there are few data on the effects on clinical outcome using measurements of peritoneal transport properties or dialysis doses delivered [12]. In adult patients, mortality is often used as a criterion for dialysis adequacy [13], but it is harder to define adequate dialysis in children, and this has led to difficulties in setting guidelines based on clinical evidence for dialysis prescription targets in pediatric patients.

We previously reported our experience of CPD in children under 5 years of age between 1986 and 1994 [14]. During the 1980s, the mean time spent in hospital for children under 5 years of age was 270 days per year, which decreased to 150 days per year during 1990–1994. Metabolic control was acceptable and mean height standard deviation score (hSDS) increased from –2.1 at onset of PD to –1.7 at 6 months. We also suggested that peritoneal transport kinetics are age independent in children and that peritoneal equilibration tests (PET), when used regularly, might further help to individualize PD treatment and improve outcome [8]. Thus, we included regular PETs and 24-h dialysate collections in our dialysis program in 1995. Otherwise the same guidelines for treatment were used and the same team cared for the patients. The PD prescription was individually adjusted on the basis of clinical condition, laboratory data, dietary records, PET, and dose of dialysis delivered in previous dialysis prescriptions. In this report, the results for children under 5 years of age, treated after 1995, were com-

pared with those of older children treated during the same period and with our previous results for children of the same age.

Materials and methods

Patients

The 21 patients studied had chronic renal failure and were on maintenance PD. The mean age of the 10 children under 5 years of age was 1.0±0.6 years at the beginning of the study (range 0.3–2.3 years), and of the 11 children aged 5–15 years it was 9.6±3.4 years (range 4.8–14.4 years). The corresponding ages at the end of the study were 1.8±0.8 and 10.4±3.4 years, respectively. The primary renal diseases leading to CPD in the children under 5 years included congenital nephrotic syndrome with mutation in the nephrin gene (*NPHS1*) [15] in 9 patients and prune-belly syndrome in 1 patient. The primary renal diseases in the children aged 5–15 years included obstructive uropathy in 3 patients, and *NPHS1* mutation, polycystic kidney disease, Wegener's granulomatosis, Denys-Drash syndrome, Alport syndrome, rapidly progressive glomerulonephritis, nephronophthisis, and reflux nephropathy in 1 patient each. Of the 21 patients, 71% were male; 9 of the 10 children (90%) aged under 5 years and 3 of the 11 children (27%) aged 5–15 years had undergone bilateral nephrectomy. The nephrectomized children with NPHS1 mutation had the severe type of nephrotic syndrome type 1 (NPHS1), which is also called congenital nephrotic syndrome of the Finnish type (CNF).

Follow-up

Treatment was started at the Hospital for Children and Adolescents, University of Helsinki. The observation period was up to 12 months if renal transplantation was not performed earlier. The mean follow-up time was relatively short because the mean waiting time for renal transplantation at our institution is 9 months. All patients were seen every 3 months for clinical and dietary examinations, laboratory tests, dialysate collection, and PETs. Between these visits, the patients visited their local hospitals every 2–4 weeks.

Adherence to diet was checked using a 3-day food record. Height and weight were measured at every visit by the same trained observers. Height was measured in the supine position until 2 years of age, and later with a stadiometer. The hSDS was calculated according to the following equation: hSDS = (observed value – mean value)/SD, where SD represents the standard deviation for the normal population of the same chronological age and gender [16]. Hospital days during the study were computed from the total number of hospital days divided by the total number of patient-years at risk.

Diet and medication

All patients under 5 years of age were fed through a nasogastric tube, because their spontaneous protein and energy intake was clearly below our target for chronological age. One patient aged 8.0 years received additional nutrition through a nasogastric tube after 3 months on PD. Tube feeding was based on infant milk and cereal formulae, supplemented with a casein-based protein product and glucose polymers. Rape seed oil and glucose polymer were added to the diet if additional energy was needed. The protein allowance was restricted only if blood urea nitrogen (BUN) rose over 40 mmol/l. Additional changes in diet were made if the serum phosphorus concentration rose above the reference values.

Water-soluble vitamins were added to the diet and vitamin D was given as oral alphacalcidol pulse therapy [17]. The alphacalcidol dose was adjusted to maintain the serum intact parathyroid hormone (iPTH) concentration between 80 and 150 ng/l. Calcium carbonate was used as a calcium supplement and phosphate binder. Sodium polystyrene sulfonate resin was given, if needed, for hyperkalemia. All patients received recombinant human erythropoietin (rHuEPO) subcutaneously. Our starting dose was 50 U/kg three times weekly. The dose was later adjusted to maintain the blood hemoglobin (Hb) concentration at about 110 g/l. During rHuEPO therapy, the patients received iron (Fe^{2+}) supplementation, with a starting dose of 5 mg/kg per day. One patient received recombinant human growth hormone (rhGH). This patient was 7.6 years at the beginning of the study. rhGH therapy was started before initiation of PD, at the age of 3.6 years, because his hSDS had decreased to –4.6.

Dialysis

All patients received nightly automated PD (APD) with a long daytime exchange, and in all anephric children two additional exchanges were performed in the afternoon. The dialysate volume was recalculated at every visit according to the patient's body surface area (BSA); a nightly exchange volume of 1,000 ml/m^2 of BSA and a last fill of 500 ml/m^2 were targeted. The target volume of the additional day-time exchange was 500 ml/m^2 of BSA per exchange. Weight limits were given for the use of different glucose concentrations, according to the estimated dry weight of the patient at every check-up. During the night, as previously described [14], mixed glucose concentrations were also used (e.g., heater bag 2.27% glucose, solution supply bag 1.36%). At the beginning of the study, 19 patients were on continuous cycling PD (CCPD) and two on tidal PD (TPD). Curled, single-cuff Tenckhoff catheters (Quinton Instruments, Seattle, Wash., USA) were used. The tunnel was straight and the exit site lateral and pointed up in all patients. The cycler machines used were PAC X, PAC Xtra, Home Choice (Baxter Healthcare, Ill., USA), PD 100 (Gambro, Lund, Sweden), and PD-Night (Fresenius AG, Schweinfurt, Germany).

Dialysate collection and PET

A complete 24-h dialysate and urine collection was obtained from each patient every 3 months. The 24-h dialysate collection was modified to make it possible to detain the patients for only 2 days in hospital. A modified 24-h dialysate collection was started at noon on day 1, with replacement of the last fill volume after complete dwell; possible day exchanges were performed as usual. Night dialysis was performed 2–4 h earlier than for the patient's normal dialysis program. After night dialysis, an 8-h dwell was performed with 1,000 ml/m^2 of 2.27% glucose dialysate. Immediately after dialysate collection, a 4-h PET was performed with similar dialysate to the 8-h dwell.

Blood samples were collected immediately after completing the dialysate collection, and after 2 h (during PET). Serum concentrations of urea, glucose, and creatinine were corrected for the effective volume of plasma water in the samples [18]. Dialysate creatinine assays were corrected for glucose interference, using a correction factor of 0.51 specific to our laboratory [19]. Blood and dialysate urea were measured by the urease method, creatinine by the kinetic Jaffe method, and blood glucose using a glucose oxidase electrode and enzymatically in the dialysate. Total body water was estimated from height and body weight, using the child-specific equation of Friis-Hansen [20]. BSA was calculated using the child-specific equation of Haycock et al. [21].

The 1.4 version of the PD ADEQUEST program (Baxter Healthcare) was used to calculate normalized total weekly creatinine clearance (C_{Cr}, l/week per 1.73 m^2) and total weekly urea Kt/V from the modified 24-h collection. In 1995, we used a urea Kt/V of >1.7 and a C_{Cr} of >40 l/week per 1.73 m^2 as target clearances [22]. In 1997 we adopted the new raised targets: a urea Kt/V of >2.0 and a C_{Cr} of >60 l/week per 1.73 m^2 [23]. The PD ADEQUEST program was also used to obtain mathematical simulation of the results of the patients' usual 24-h dialysis regimen. Changes in PD prescription were made according to patient's BSA, clinical fluid balance, and well-being. The PD ADEQUEST program was used for mathematical simulation of changes planned in PD prescription. If the clear-

ance targets were not reached, further simulation was performed to find the optimal prescription.

Peritonitis and exit-site infection care

As the criteria for peritonitis, cloudy peritoneal fluid and an elevated dialysate white cell count >100/mm^3 with >50% polymorphonuclear cells were used. Facultative findings were abdominal pain and/or fever. Peritonitis therapy outside our institution consisted of loading doses of vancomycin (15 mg/kg) and netilmicin (1.8 mg/kg) intraperitoneally for 2 h, followed by 8–12 daily exchanges of dialysate containing 30 mg/l vancomycin and 8 mg/l netilmicin. Patients treated at our institution received intermittent intraperitoneal antibiotic treatment: vancomycin at a dose of 30 mg/kg in one 6-h exchange and netilmicin 20 mg/l using once daily dosing. The serum vancomycin concentration was followed, and the dose was repeated in 7 days or as soon as the serum concentration fell below 5 µg/ml. Antibiotics were later adjusted according to the microbial findings and continued for 8–10 days. Heparin (500 U/l) was added to the dialysate until the effluent was clear.

A decision to give antibiotic treatment was used as the criterion for exit-site and tunnel infections. The clinical findings of exit-site infection were redness and/or the presence of extuberant granulation tissue, and a purulent discharge from the exit site. The typical findings of tunnel infection were redness and induration above the tunnel, and purulent discharge on compression of the tunnel. Exit-site infections were treated with local antiseptics and oral antibiotics, and tunnel infections with parenteral antibiotics.

Table 1 Hospital days during peritoneal dialysis (PD) therapy per patient-year related to causality, for different age groups (<5 and 5–15 years) (*ESI* exit-site infection)

Cause of hospital stay	Hospital days per patient-year		
	All patients *n*=21	<5 years *n*=10	5–15 years *n*=11
Control	22	25	19
Peritonitis/ESI	9	14	5
Other infection	6	12	0
Hypertension	6	8	5
Other[a]	17	36	1
Overall	60	95	30

[a] Social problems, urodynamic investigations

Statistics

Comparisons of two groups at baseline and at later time points were performed using the unpaired *t*-test and the Mann-Whitney U test for nonparametric data. Analysis of variance with repeated measures was used to determine whether time affected the studied parameters, and Bonferroni's method was used for correction of simultaneous multiple comparisons. For significant interactions, the paired *t*-test was used for comparison with the baseline values within the groups. The Wilcoxon signed rank test was used for comparison of nonparametric data. Pearson's correlation coefficient was used to evaluate correlations between parametric data, and the Spearman rank correlation coefficient between nonparametric data. Simple regression analysis was used to identify the independent predictors of hSDS, $C_{Cr,}$ and urea Kt/V. *P* values less than 0.05 were considered significant.

Results

Modality outcome

The mean time spent on dialysis during the study was 0.8±0.2 years (a total of 209 patient-months), and the mean dialysis time prior to the study was 0.4±0.5 years (range 0.0–1.7 years). The hospitalization rate was 60 days per patient-year; 95 and 30 days per year for children under 5 and 5–15 years of age, respectively (*P*=0.02, Mann-Whitney U test). Hospital days related to causality are listed in Table 1. The peritoneal catheter was replaced only once because of a peritoneal fluid leak. Of the 21 patients, 1 died (5%). The cause of death was sudden cerebral hemorrhage of unknown etiology in a 1.2-year-old boy with the *NPHS1* mutation after 8 months on PD. Clinical data of the 9 patients with the *NPHS1* mutation after 6 months of controlled PD are given in Table 2.

At the beginning of the study, the CCPD regimen included an average of 9±2 exchanges and the TPD regimen 21±1 exchanges, with a tidal inflow of 50%. The number of nightly exchanges remained unchanged during the study period, but was higher in younger patients during CCPD, and the same for both age groups during TPD. The mean nightly dialysis time was 9.6±0.8 h, 7

Table 2 Clinical data of 9 patients with congenital nephrotic syndrome with a mutation in the nephrin gene (*NPHS1*) after 6 months of controlled continuous PD (*hSDS* height standard deviation score, C_{Cr} creatinine clearance, *BUN* blood urea nitrogen, *D/P* dialysate/plasma)

	Age (years)	Weight (kg)	Height (cm)	(hSDS)	Protein intake (g/kg per day)	Daily dialysate volume (ml)	Weekly Kt/V	C_{Cr} (l/week per 1.73 m^2)	4-h D/P urea	4-h D/P creatinine	BUN (mmol/l)
1.	2.8	15.6	95	(+0.4)	2.5	6250	3.2	68.4	0.96	0.94	48.0
2.	2.2	11.0	80	(–2.9)	3.0	4600	3.1	53.7	1.00	0.74	31.0
3.	2.3	10.2	84	(–1.9)	3.5	4750	3.9	70.2	0.99	0.83	37.0
4.	1.0	10.4	78	(+0.4)	3.0	4600	3.0	54.7	0.95	0.68	42.0
5.	1.2	10.8	76	(–0.8)	2.2	4100	2.8	50.1	1.00	0.70	42.0
6.	1.1	10.4	75	(–0.2)	2.4	4600	3.7	59.2	1.00	0.77	35.0
7.	1.2	11.4	78	(–0.4)	2.5	4750	3.0	53.5	1.00	0.85	43.0
8.	1.2	11.7	77	(–0.2)	1.9	5800[a]	2.4	85.8	0.85	0.87	37.0
9.	1.2	9.6	74	(–2.1)	2.0	4870	2.7	53.3	0.87	0.74	34.0
Mean±1SDS	1.6±0.6	11.2±1.8	80±7	(–0.9±1.2)	2.5±0.5	4924±669	3.1±0.5	61.0±11.6	0.96±0.06	0.79±0.09	38.8±5.3

[a] With tidal PD

nights a week, with a mean inflow volume of 855±188 ml/m^2. The nightly dialysis time remained unchanged over the study period, but was significantly longer in the younger patients than in the older patients (P=0.03 at baseline, unpaired t-test). The nightly inflow volume (ml/m^2) correlated positively with age (r=0.78, P=0.0005 at baseline, Spearman rank correlation). The nightly inflow volume was significantly increased during the study period in the younger patients (from 716±95 ml/m^2 to 838±94 ml/m^2, P=0.018, Wilcoxon signed rank test), but still remained significantly lower than in the older patients. In the older patients, the corresponding volumes were 982±161 and 1,045±131 ml/m^2 (P=0.17, Wilcoxon signed rank test). The average glucose concentration was 1.8±0.5% and the average ultrafiltration 544±288 ml/m^2. In 48% of the children, two exchanges were performed in the late afternoon, with inflow volumes of 382±71 ml/m^2.

The mean urea Kt/V from the 24-h dialysate collection did not change during the 9-month observation period (3.2±0.5, Table 3), nor was any significant difference found between the two age groups. All patients reached urea Kt/V >2.0. The mean C_{Cr} increased slightly during the 9-month period. It differed significantly between the age groups only at baseline. At baseline, C_{Cr} was <60 l/week per 1.73 m^2 in 70% of the patients under 5 years of age, and at 9 months in only 29%. All the older patients attained a C_{Cr} >60 l/week per 1.73 m^2. The residual renal clearance decreased slightly during the study period in the non-nephrectomized patients (from 2.9 to 2.4 ml/min per 1.73 m^2). Urea Kt/V and C_{Cr} correlated significantly (r=0.61, P<0.05 at baseline, Spearman rank correlation). A weak correlation was found between residual renal clearance and C_{Cr} (r=0.87–0.50, P=0.05–0.13, Spearman rank correlation), and urea Kt/V (r=0.89–0.48, P=0.05–0.17, Spearman rank correlation). Age, BUN, serum albumin, protein intake, or energy intake did not predict Kt/V or C_{Cr} in simple regression analysis. Total daily dialysate volume (ml/m^2) showed a weak positive prediction of Kt/V and C_{Cr} (NS).

Table 3 The mean weekly urea Kt/V and C_{Cr} at the beginning of the study and after 9 months on PD. Values are expressed as means±1SD

	All patients n=21	<5 years n=10	5–15 years n=11	P
Kt/V				
Baseline	3.2±0.5	3.1±0.6	3.2±0.4	NS
9 months	3.2±0.5	3.3±0.5	3.0±0.4	NS
C_{Cr} (l/week per 1.73 m^2)				
Baseline	68.8±16.6	58.7±11.9	78.0±14.9	0.004*
9 months	71.3±14.0	71.2±19.9	71.5±7.3	NS

* Comparison of different age groups, Mann-Whitney U test

Laboratory outcome and medication

Hematological and biochemical parameters remained stable throughout the study (Table 4). At baseline, serum prealbumin, albumin, and protein concentrations were significantly lower in the younger patients (P=0.006, 0.03, and 0.01, respectively, unpaired t-test). However, their prealbumin and protein concentrations rose after 3 months (P=0.03 and P=0.05, respectively, paired t-test), and were subsequently stable and comparable with the results from the older patients. Serum albumin remained significantly lower in the younger patients than the older patients (P=0.0005 at 3 months, and 0.03 at 6 and 9 months, unpaired t-test).

Table 4 Laboratory variables of 21 patients on continuous PD for 9 months (mean±SD). Numbers of patients are given in parentheses

	Baseline		3 months		6 months		9 months	
	<5 years (10)	5–15 years (11)	<5 years (10)	5–15 years (11)	<5 years (10)	5–15 years (9)	<5 years (7)	5–15 years (9)
BUN (mmol/l)	43.1±10.8	31.6±7.2*	41.9±8.2	36.1±7.8	39.7±5.8	36.1±8.5	40.3±6.6	40.4±9.8
Creatinine (µmol/l)	435±106	700±177*	425±114	718±213*	451±126	801±181*	480±158	757±162*
Sodium (mmol/l)	141±4	142±2	141±5	141±3	139±4	140±2	139±2	139±3
Potassium (mmol/l)	4.9±1	4.8±0.6	5.4±0.8	4.8±0.6	4.6±0.6	5.2±0.9	4.9±0.8	5.2±1.1
Chloride (mmol/l)	102±8	102±4	96±7	102±3*	93±6	101±4*	96±5	100±4
Ionized calcium (mmol/l)	1.33±0.10	1.29±0.07	1.33±0.16	1.24±0.05	1.24±0.05	1.27±0.06	1.29±0.07	1.25±0.06
Bicarbonate (mmol/l)	25±4	25±4	25±4	24±3	28±5	24±3	29±3	25±3
Intact parathyroid hormone (ng/l)	59±43	90±105	229±196	221±275	389±345	163±202	217±345	128±99
Phosphorus (mmol/l)	1.74±0.42	1.76±0.57	1.81±0.67	1.84±0.46	1.51±0.48	1.73±0.34	1.22±0.47	1.85±0.48*
Prealbumin (mg/l)	298±78	414±82*	427±93	432±81	449±77	431±70	411±94	433±56
Albumin (g/l)	29±5	33±5*	28±2	33±3*	30±4	34±4*	30±5	36±3
Protein (g/l)	54±6	62±7*	61±6	63±3	60±2	63±5	59±4	63±4*
Hemoglobin (g/l)	105±13	107±12	118±23	104±10	104±11	118±12	105±15	106±11
Hematocrit (%)	32±4	32±3	36±7	32±3	32±3	36±3	32±4	33±3
Cholesterol (mmol/l)	4.5±1.2	4.8±1.1	5.8±1.2	5.6±1.2	6.1±1.3	5.2±0.9	5.3±1.4	4.9±0.9
Triglycerides (mmol/l)	2.55±0.91	1.99±0.72	3.30±1.03	2.10±1.18*	3.51±1.74	2.04±0.94*	3.09±1.62	1.97±0.95

* P<0.05 when comparing different age groups

The serum iPTH concentration was initially lower in the younger patients, increased significantly within 3 months (P=0.03, Wilcoxon signed rank test), and remained higher (NS) than in the older patients. The mean serum alkaline phosphatase concentration was initially 722± 432 U/l in children under 5 years, rose within 3 months to 1,022 U/l, and remained at this high-normal level. In the older children, it remained significantly lower from the beginning (P=0.02 at baseline, Mann-Whitney U test). Serum phosphorus and ionized calcium remained within normal limits. Serum cholesterol and triglyceride values increased during the first 6 months in both age groups, and triglycerides were significantly higher in the tube-fed younger children at 3 and 6 months (P=0.03 and P=0.047, respectively, Mann-Whitney U test).

All patients received human recombinant erythropoietin. The rHuEPO dose was higher at baseline in the younger patients (202±91 vs. 139±101 U/kg per week, respectively), and remained higher (P=0.005, 0.001, and 0.003 at 3, 6, and at 9 months, Mann-Whitney U test). rHuEPO was given in one to three doses per week. The ionized iron dose was 4 mg/kg in both groups. Alphacalcidol was given at baseline at a dose of 1.0 µg/week to patients under 5 years, and gradually increased to 2.2 µg/week at 9 months. The corresponding doses for patients aged 5–15 years were 1.6 and 1.3 µg/week. Alphacalcidol was given in two to three doses a week. The mean calcium substitution varied from 557 mg/day at initiation to 776 mg/day at 9 months in patients under 5 years, and from 3,107 to 1,820 mg/day in patients 5–15 years of age, respectively. Sodium polystyrene sulfonate resin was given at initiation to 50% of the younger patients and to 45% of the older patients, with mean doses of 3.2±4.2 g/day (range 0–12 g/day) and 4.5±7.8 g/day (range 0–20 g/day), respectively. The corresponding doses at 9 months were 2.0±2.2 g/day in 57% of the younger patients and 1.2±1.8 g/day in 67% of the older patients.

Nutrition and growth

The total energy intake (dietary intake and dialysate glucose absorption) was 90%–110% of the recommended dietary allowance (RDA) for children of the same age [24], and protein intake 170%–190% of the RDA (Table 5). Both energy intake as a percentage of RDA and as kilocalories per kilogram per day, and protein intake as a percentage of RDA and as grams per kilogram per day, were higher in the younger patients. Most children showed catch-up growth during peritoneal dialysis. The mean hSDS increased from –1.3±1.2 at baseline to –0.8±1.0 at 9 months (P=0.04, Wilcoxon signed rank test) (Table 5, Fig. 1). The 9-month change in hSDS in patients under 5 years of age was significantly better (P=0.001, Mann-Whitney U test) than in the older patients. In simple regression analysis hSDS was not significantly predicted by urea Kt/V, C_{Cr}, energy or protein intake (/kg, /m^2, or percentage of RDA), serum albumin, serum protein, phosphorus, BUN, iPTH, or serum alkaline phosphatase. However, there was a trend for positive prediction of hSDS by C_{Cr}, and negative prediction by serum alkaline phosphatase.

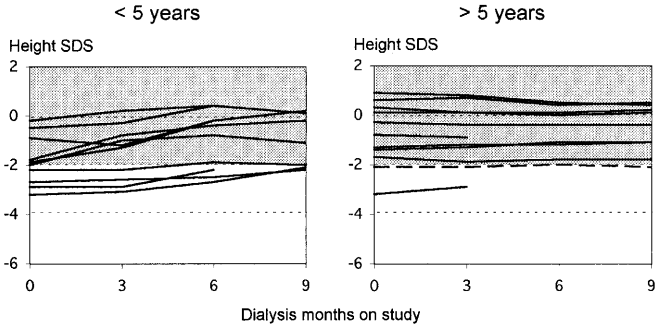

Fig. 1 Height standard deviation score (*SDS*) for 10 children <5 years and 11 children >5 years of age on peritoneal dialysis (PD). Time on PD represents the treatment period during the study up to 9 months. The *broken line* represents the patient who was treated with growth hormone and the *shaded area* the normal range (±2SD) for Finnish children

Table 5 Mean hSDS, energy and protein intake at the initiation of the study and after 9 months on continuous PD

	All patients n=21/16[a]	<5 years n=10/7[a]	5–15 years n=11/9[a]
hSDS			
Baseline	–1.3±1.2	–1.8±1.0	–0.8±1.3
9 months	–0.8±1.0*	–1.0±1.1*	–0.6±1.0
Energy intake (% RDA)[b]			
Baseline	101±18	109±14	92±19
9 months	92±24	87±24	98±31
Energy intake (kcal/kg per day)[b]			
Baseline	89±27	107±18	66±17
3 months	78±25	88±18	66±29
Protein intake (% RDA)			
Baseline	177±28	185±26	167±28
9 months	189±52	194±37	184±68
Protein intake (g/kg per day)			
Baseline	2.3±0.6	2.8±0.2	1.7±0.4
9 months	2.1±0.6	2.3±0.4	1.8±0.8

* P<0.05 baseline compared with 9 months
[a] Number of patients at baseline/9 months
[b] Includes estimated calories from dialysate glucose

Peritonitis and catheter infections

There were 18 episodes of peritonitis during the study (209 months). The overall frequency of peritonitis was 1 episode per 11.6 patient-months. The frequency was higher in the younger patients than in the older patients (1 in 9.4 vs. 1 in 15.8 patient-months). Fifty-seven percent of the patients had no episodes of peritonitis during the study (40% of the younger and 72% of the older patients). Gram-positive bacteria accounted for the majori-

Table 6 Causative organisms in 18 episodes of peritonitis documented during the 209 patient-months

	Number of cases	Frequency (%)
Causative organism		
Gram-positive	13	72
Staphylococcus aureus	(8)	
Coagulase-negative *staphylococcus*	(1)	
Streptococcus viridans	(1)	
Enterococcus	(1)	
Brevibacterium	(2)	
Gram-negative	4	22
Enterobacter cloacae	(1)	
Acinetobacter calcoaceticus	(1)	
Klebsiella oxytoca	(1)	
Escherichia coli	(1)	
Culture-negative	1	6

ty of the episodes and no fungal peritonitis was diagnosed (Table 6). Thirty-one percent of the episodes were treated with intermittent intraperitoneal antibiotic therapy, and the rest was treated continuously. There were no relapses documented after intermittent intraperitoneal antibiotic therapy. The overall frequency of exit-site infections was 1 episode per 34.8 patient-months. The corresponding frequencies in patients under 5 and 5–15 years were 1 in 49.1 and 1 in 27.6 patient-months, respectively. The overall frequency of tunnel infections was 1 in 34.8 patient-months.

Noninfectious complications

Medical treatment for hypertension was given to 10 patients (48%) at some time during the study. At initiation, 38% of the patients (20% and 54% of the patients under and over 5 years of age, respectively) were on antihypertensive medication. At 3, 6, and 9 months, the percentages were 38% (20% and 54%), 32% (20% and 44%), and 21% (14% and 44%), respectively. Severe hypertension was diagnosed mostly in non-nephrectomized patients, which was seen as a clearly higher prevalence of hypertension in the older age group (73% non-nephrectomized patients). Six patients had only moderate hypertension (0–1 antihypertensive drugs during at least one 3-month observation period) and 5 of these were nephrectomized. Four patients had severe hypertension (2–3 antihypertensive drugs) and only 1 of these was nephrectomized. The mean number of antihypertensive drugs per patient was 1.4 at initiation and 0.7 at 9-month follow-up. No episodes of dialysis-related pulmonary edema or dialysis-related seizures were diagnosed.

Discussion

This is one of the first detailed prospective studies of the effects of PD adequacy measurements on clinical outcome in children. The only extensive prospective pediatric report on the effects of PD adequacy control contains 51 children with a mean age of 8.0 years [12]. In that study Schaefer et al. [12] provided evidence that the peritoneal transporter state was an independent determinant of growth and body mass acquisition in children on chronic PD. High transporters were found to be at increased risk for growing poorly and becoming obese. The general outline of our treatment of uremia and the guidelines for nutrition were not changed, the only difference being the regular use of adequacy measurements and the regular use of rHuEPO in this study. The doctors responsible for the patients were also the same as before 1994. Although many factors may have improved outcome, we feel that the introduction of regular PETs, 24-h dialysate collections, and simulations with the PD ADEQUEST program contributed to the results. Hospital days decreased by 37%, fewer complications were documented, and metabolic control and growth were better. This is illustrated in Table 7, which compares the essential data from our previous study and the present study for children under 5 years of age. Both studies contained a comparable number of NPHS1 and nephrectomized children.

We targeted weekly clearances of urea Kt/V of >2.0 and creatinine of >60 l/week per 1.73 m^2. If recent adult recommendations for dialysis adequacy for CCPD (weekly urea Kt/V ≥2.1 and C_{Cr} ≥63 l/week per 1.73 m^2) are considered to be the minimal values acceptable for children [13], the mean urea Kt/V and C_{Cr} values of our patients were within this acceptable range. However, a C_{Cr} >63 l/week per 1.73 m^2 was difficult to achieve in our young nephrectomized patients. Schaefer et al. [12] reported lower weekly C_{Cr} (58±29 l/week per 1.73 m^2) and urea Kt/V (2.75±0.97) in their APD patients. Walk et al. [11] reported similar C_{Cr} as in our patients in their 19 pediatric patients in 1997, but their urea Kt/V values were lower, with a mean weekly urea Kt/V of 2.3. In the latter study the patients were on continuous ambulatory PD (CAPD) or nightly intermittent PD with fewer exchanges, which would explain this difference. However, one has to remember that our urea Kt/V values are approximately 13% higher, and C_{Cr} values 15% higher, than during the patients' regular dialysis program, because we modified the 24-h dialysate collection. After recalculation of Kt/V and C_{Cr} values, our results were similar to those of Schaefer et al. [12]. Our Kt/V and C_{Cr} showed no significant correlation with residual renal function, although a clear relationship was found. The lack of statistical significance was probably a manifestation of the small number of non-nephrectomized patients.

Patients with the *NPHS1* mutation have muscular hypotonia and are more prone to fluid leaks, which explains the lower exchange volumes at baseline. The dialysis dose was then increased gradually, which would explain the positive prediction of C_{Cr} by age at baseline and at 3 months, as well as the increase in peritoneal clearances during the study period in the younger patients. Our younger patients also had lower exchange volumes

Table 7 PD outcome measures at 6 months follow-up in PD patients under 5 years of age. Comparison of previous results (Hölttä et al. [14]) with the present data. Percentage represents the proportion of patients with diagnosed and treated hypertension, seizures, or pulmonary edema during at least one 3-month observation period

	Hölttä et al. [14] (*n*=27)	Present study (*n*=10)	*P*
Age at onset	1.6±1.0 (0.6–4.3)	1.0±0.6 (0.3–2.3)	0.09
Hospitalization (days/patient-year)	150[a]	95	0.12
Peritonitis frequency	1 in 7.3 months	1 in 9.4 months	
Hypertension	64%	30%	
Seizures	26%	0%	
Pulmonary edema	41%	0%	
Nutrition and growth at 6 months			
Protein intake (% RDA)	140–200%[b]	209±42%	
Energy intake (% RDA)	110–120%[b]	93±16%	
hSDS	–1.7±1.5	–1.1±1.1	0.26
ΔhSDS[c] (0–6 months)	0.6±0.6	0.8±0.6	0.43
Laboratory parameters at 6 months			
Hemoglobin (g/l)	91±12[d]	104±11	0.009
Hematocrit (%)	0.27±0.04[d]	0.32±0.03	0.009
BUN (mmol/l)	47±15	39±6	0.13
Prealbumin (mg/l)	391±80	449±77	0.32
Albumin (g/l)	29±5	30±4	0.99
Protein (g/l)	54±8	60±2	0.06
Ionized calcium (mmol/l)	1.27±0.07[e]	1.24±0.05	0.28
Phosphorus (mmol/l)	2.01±0.42	1.51±0.48	0.004
Medication at 6 months			
Alphacalcidol (µg/week)	1.1±2.0[f]	1.8±1.5	0.41
Calcium substitute (mg/day)	3,641±1718	836±558	<0.0001

[a] Hospitalization (days/patient-year) between 1990 and 1994
[b] Analyzed through years 1989–1992
[c] 6-month change in hSDS
[d] Patients without erythropoietin were excluded
[e] Analyzed in 8 patients
[f] Used since 1991 in 8 patients

per dwell, but more often day-dwells than the older patients. This certainly further increased their weekly clearances to levels comparable with those of the older patients.

Hospitalization time is a crude but extremely important measure of patient outcome. Although treated by the same team as before 1994, hospitalization time in the youngest patients (under 5 years) has fallen substantially (Table 7), but it is still high compared with the reference data for older patients, with hospitalization rates of only 15–29 days/patient-year [4, 25]. The time spent in hospital was significantly shorter in our older patients. The higher hospitalization rate in our young patients was greatly affected by 2 patients with social problems: 1 patient had to spend the whole dialysis period (11.2 months) in hospital, and the other, half of the week for over 12 months. If these 2 children are excluded, the hospitalization time for the younger children is reduced to 55 days/patient-year, and the total hospitalization time to 40 days/patient-year.

Ninety percent of the younger patients had congenital nephrotic syndrome with the *NPHS1* mutation as the primary renal disease. These patients are not uremic before nephrectomy, and have low serum BUN, creatinine, and iPTH levels. Because of renal protein wasting, their serum prealbumin, albumin, and protein levels are low before nephrectomy [26]. Of 10 patients under 5 years of age, 6 were nephrectomized bilaterally 1–2 weeks before the study and 3 patients 8–20 months before the study. Thus, 60% of the young patients were bilaterally nephrectomized shortly before the start of the study, which would explain the lower prealbumin, albumin, protein, and iPTH levels in the younger patients at baseline. BUN tended to be higher in the younger patients. This may have been caused by their higher protein intake (g/kg body weight). After the first 3 months, iPTH tended to be higher in the younger patients, as well as alkaline phosphatase. Alphacalcidol was given to these patients in higher doses than to the older patients, but obviously not enough was given. Serum albumin was consistently lower in the younger patients. This may have been due to a higher albumin loss into the dialysate [27].

If we compare the present results for the 10 children under 5 years of age with our previous results from 27 children of the same age, there has been improvement in metabolic control under adequacy control: the laboratory parameters are better and the need for medication lower [14] (Table 7). The mean protein intake was slightly higher and the energy intake comparable or even somewhat lower in the present study. Despite the higher protein intake, the mean BUN at 6 months was lower. Serum prealbumin was higher and serum protein almost significantly higher. The rHuEPO dose was significantly higher in the present study, because there was a higher target Hb concentration. Despite significantly lower calcium supplementation, the mean serum phosphorus concentration at 6 months was significantly lower and the serum ionized calcium was similar.

Low protein and energy intake, acidosis, disturbed calcium/phosphorus balance, and uremia are believed to impair growth and cause malnutrition in children on renal replacement therapy [28]. Despite improved control of these factors, poor growth has remained a major problem during PD treatment [1, 4]. Catch-up growth is rare,

but has been achieved with growth hormone therapy, which is recommended during PD to prevent further loss of height [4, 29]. In the first prospective study dealing with the effects of PD adequacy on growth, Schaefer et al. [12] did not observe catch-up growth in their patients over 18 months, although 37% were treated with rhGH. We have previously reported significant catch-up growth during PD without rhGH in 27 patients under 5 years of age [14]. The follow-up period in the present study was 9 months, similar to the mean waiting time for renal transplantation at our institution. This is shorter than the recommended follow-up period for growth studies (12 months). However, we consider it important to analyze and report available growth data to provide a complete picture of PD outcome in our patients. All the younger patients and 33% of the older patients showed catch-up growth. A positive, but not significant prediction of hSDS by C_{Cr} was found. Growth was significantly better in the younger than in the older patients, which is partly a result of the normalization of protein balance after nephrectomy in patients with the *NPHS1* mutation. However, compared with our previous results, the hSDS at 6 months and the change in hSDS at 6 months in patients under 5 years of age were better in the present study (NS) (Table 7), although the number of patients with the *NPHS1* mutation and nephrectomized patients was similar in both studies. This suggests a positive effect of adequacy control on growth, bearing in mind that the number of patients and the follow-up period were limited. Schaefer et al. [12] failed to demonstrate a major impact of the dialysis dose or total small solute clearance on growth in their univariate data analysis, but found a positive effect of the mean total C_{Cr} on growth rates when they controlled for the PET transporter state in multivariate analysis, supporting our results.

Our patients still demonstrate a relatively high overall frequency of peritonitis compared with the frequency of 1 episode per 7.1–28.6 patient-months reported in recent years [1, 4, 30]. In the annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) for 1995, the peritonitis rate in 212 children aged 0–1 years was 1 per 10.1 patient-months, compared with 1 per 15.7 patient-months in patients over 12 years of age [1]. Our results are similar, although all our patients have single-cuff Tenckhoff catheters pointed up, which has been suggested to increase the risk of peritonitis [31]. However, compared with our previous results, we have managed to reduce the frequency of peritonitis in children under 5 years of age (Table 7). In 1 patient, peritonitis was twice due to *Brevibacterium*. This is a fast-growing, strictly aerobic, nonmotile, gram-negative rod. We have considered it a real pathogen. According to the literature, it has pathogenic potential for humans and should be included in the list of uncommon organisms in a variety of clinical conditions, such as CAPD peritonitis [32].

Hypertension remained an important complication in our patients, but higher incidences have been reported. According to the 1995 annual report of the NAPRTCS, 49% of PD patients were receiving antihypertensive drugs at 12 months [1]. If we compare the incidence of hypertension in our patients under 5 years of age with our previous results, the incidence and the number of antihypertensive drugs used are lower. Seizures were documented in the 1995 NAPRTCS report in 2.4%–4.7% of the PD patients. The incidence of overhydration-related seizures, and especially of pulmonary edema, was previously higher in our patients. However, since 1995, control of blood volume has been better, and these complications have been avoided in both age groups. One patient died, giving a mortality rate similar to previous reports [1, 30, 33].

Although our study suggests a positive effect of adequacy control on clinical outcome, the number of patients and the limited follow-up period do not provide definitive evidence. Additional prospective studies will be required to further evaluate the effects of the increased dose of dialysis in children on PD. However, the clinical outcome of our patients under 5 years of age was at least as good as in our previous study of patients of the same age. The outcome for children under and over 5 years of age did not differ significantly, which is encouraging for the long-term outcome in the infant and toddler with end-stage renal disease.

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